Cardiovascular Catheterization and Intervention
A Textbook of Coronary, Peripheral, and Structural Heart Disease

About the book
The field of invasive and interventional cardiology is dynamic with frequent advances in both technique and technology. An internationally renowned team of editors and over 100 contributors have shaped this textbook to provide clinicians with a thorough guide that covers the procedural and peri-procedural aspects of coronary, peripheral, and structural heart disease diagnostics and interventions.

This comprehensive and highly illustrated textbook presents critical information for anyone active in the field of cardiovascular interventions, including:

• Practical suggestions on how to set up a cardiovascular catheterization laboratory, choose the right equipment and minimize radiation exposure.
• A careful analysis of the general principles of percutaneous coronary interventions, the specific knowledge needed in different clinical scenarios, as well as the patient selection criteria for each invasive procedure.
• In-depth coverage of non-coronary interventions, including 13 chapters on peripheral vascular interventions, including carotid artery stenting, as well as newer procedures for intracranial stenosis treatment, septal defect repair, and left atrial appendage closure.
• An incorporation of emerging procedures in structural heart disease, such as percutaneous aortic valve replacement and mitral valve repair, that although not presently mainstream, will likely become an important domain of interventional cardiologists.

Given the importance of appropriate training and credentialing for clinicians, the textbook also includes current national guidelines and policies on the performance of the various procedures.

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A Textbook of Coronary, Peripheral, and Structural Heart Disease

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To all the contributors for their hard work, insight, and wisdom in making this book a great resource for cardiologists, my parents for their infinite patience, love, and understanding, and who continue to be my source of inspiration, and to my wonderful wife, Suchandra, for her love and support.

—Debabrata Mukherjee

I would like to thank my wife Nancy and children Andrew, Lyndsay, Alexis, and Evan for all their love and support during the writing of this book.

—Eric R. Bates

To my spouse Muriel and my children Emma, Thomas, and Giulia with love and gratitude.

—Marco Roffi

To all the terrific faculty and fellows with whom I have worked in the catheterization laboratory through the years. For sharing their thoughts, time, and talents, I am grateful.

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Preface

The field of interventional cardiovascular medicine continues to rapidly evolve in both diagnostic and therapeutic arenas. Over the past decade, substantial advances have been made on many fronts including the development and utilization of techniques and devices for intravascular and intracardiac imaging, percutaneous hemodynamic support, drug-eluting stents, embolic protection, mechanical thrombectomy, and percutaneous valve repair and replacement. The evolution of newer drugs and devices challenges the cardiologist to stay abreast of cutting-edge pharmacological and mechanical strategies for optimal patient care. The *Cardiovascular Catheterization and Intervention: A Textbook of Coronary, Peripheral, and Structural Heart Disease* aims to provide clinicians with comprehensive guidance on the preprocedural, procedural, and postprocedural aspects of coronary, peripheral, and structural heart disease interventions in general situations and in various clinical settings. The text features evidence-based discussions on patient selection, vascular access, general principles of interventional cardiology, and postprocedure management of these patients and serves as a comprehensive, easily accessible reference for busy practitioners and cardiovascular trainees.

Of foremost importance, the topic areas covered are relevant to the daily practice of interventional cardiology. The book begins with several chapters dedicated to the general concepts associated with cardiac catheterization and interventional cardiovascular medicine. The subsequent chapters focus on hemodynamic assessment and coronary angiography in general and in specific situations such as those in pediatric patients and in adults with congenital heart disease. The bulk of the text addresses coronary and noncoronary interventions including structural heart disease interventions. Finally, we have included dedicated chapters on credentialing and organizing prehospital and hospital systems of cardiovascular care. A large number of high-quality illustrations make this textbook particularly attractive to the practitioner.

Essential to the quality and appropriateness of the text is the expertise of the chapter authors. We are fortunate to have assembled a stellar roster of interventional cardiovascular experts to create this book. The contributing authors from leading medical centers around the world have collectively performed hundreds of thousands of procedures and published thousands of peer-reviewed manuscripts. We are greatly indebted to them. The practice of interventional cardiovascular medicine is exciting, rewarding, and a privilege each of us enjoys. Likewise, it has been our personal privilege to work with these superb contributors, our colleagues in interventional cardiology, as well as the editorial team at Informa Healthcare. It is our hope that you will enjoy this book and that it will be a valuable resource to you in providing the highest quality care to your patients.

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Introduction to cardiac catheterization

Richard A. Lange, Steven R. Bailey, and L. David Hillis

INTRODUCTION
Cardiac catheterization is one of the most frequently performed procedures in the United States. Over the past 25 years, the number of procedures has increased 3.5-fold because of expanded indications and improvements in techniques and equipment (1). In 2005, an estimated 1,322,000 inpatient left heart diagnostic catheterizations and 1,271,000 inpatient percutaneous coronary interventional (PCI) procedures were performed in the United States (1). According to the most recent American Hospital Association survey, 36% of the 4836 hospitals in the United States have adult diagnostic catheterization laboratories. Of the 1728 hospital-centered adult diagnostic laboratories, 78% are PCI capable (2).

HISTORICAL PERSPECTIVE
The Early Years of Catheterization: Animal and Cadaveric Studies (1711–1927)
The earliest known cardiac catheterization of an animal was performed in 1710 by Reverend Stephen Hales, an English physiologist and parson, when he “bled a sheep to death and then led a gun-barrel from the neck vessels into the still-beating heart. Through this, he filled the hollow chambers with molten wax and then measured from the resultant cast the volume of the heartbeat and the minute-volume of the heart” (3). There is no indication that Hales actually performed catheterization procedures, but in 1727 he measured the rise in a column of blood in a long glass tube secured in an artery (Fig. 1.1). Brass pipes placed in the carotid artery and jugular vein of a horse were connected to an 11-ft-high glass tube for pressure measurements, with the trachea of a goose used as a flexible connector. Hales astutely noted that the pressure was different in arteries and veins (blood from the carotid artery rose to a height of >8 ft in the glass tube, whereas blood from the jugular vein rose <1 ft) and between contractions and relaxations of the heart.

In 1844, the term cardiac catheterization was coined by Claude Bernard, a French physiologist who inserted long glass thermometers into a horse’s right and left ventricles from its jugular vein and carotid artery, respectively. By demonstrating that blood temperature was higher in the right ventricle than in the left, he established that “chemical reactions” (i.e., metabolism) occurred in the body rather than the lungs. Subsequently, he used this technique to acquire blood samples from various arterial and venous sites for metabolic studies, and he performed intracardiac pressure recordings in dogs and sheep to study the regulation of systemic arterial pressure by the nervous system. He was the first to describe right and left heart catheterization via the femoral vein and artery (5,6). Although Bernard was not the first to perform catheterization, his careful application of scientific methods to the study of cardiac physiology demonstrated the potential importance of cardiac catheterization and initiated an era of cardiovascular physiologic investigation.

In 1861, Etienne Jules Marey, another French physicist and physiologist, in collaboration with Jean Baptiste Aguste Chauveau, a veterinarian, elucidated the nature of the apex beat by simultaneously recording its movement and the right atrial and right ventricular pressures of a conscious horse (7). Their observation that the apical impulse was caused by early forceful ventricular contraction remains a milestone as the first graphic recording of intracardiac events in a conscious animal (Fig. 1.2) (8). Gaining access to the left ventricle via the carotid artery, they studied left ventricular pressure waveforms and characterized various phases of the cardiac cycle, and they were the first to obtain simultaneous recordings of left ventricular and aortic pressures. In addition, Marey and Chauveau invented the double-lumen catheter, with which they simultaneously measured pressures in contiguous cardiac chambers in horses and dogs. Decades later, Andre Cournand (see following text) utilized this catheter design to perform similar studies in humans.

In 1870, Adolph Fick (Fig. 1.3), a German physicist and physiologist, proposed a direct method of measuring cardiac output. In a commentary to his local medical society that resulted in a publication less than one page long (the Fick principle, 1870), Fick proposed that the cardiac output could be measured by dividing the oxygen uptake by the corresponding arteriovenous oxygen content difference (9). Interestingly, in 1873 Fick published the results of right and left heart catheterizations that he performed in animals, but he did not utilize or validate his method (10). Only two decades later did physiologists begin to apply the Fick principle in animals. Although Grehant and Quinquand published a brief report describing the use of the technique in dogs in 1886, it was not until 1898, when Zuntz and Hageman made a detailed study of cardiac output in the horse at rest and during exercise, that the Fick method was established as reliable and reproducible (11). Application of the Fick principle in humans was hindered by the difficulty of obtaining samples of mixed venous blood. Invasive catheterization was thought to be too dangerous to be applied to human subjects, because of excessive blood loss and the risk of infection. Furthermore, radiography was not yet available, so attempts to obtain samples of mixed venous blood were made by such avante-garde interventions as direct transhoracic needle puncture of the right ventricle (12).

With the discovery of X rays in 1895 by William Roentgen, radiographic equipment was quickly introduced into laboratories in universities and medical schools throughout Europe and North America (13). Within a month of the publication of Roentgen’s paper, two European physicians published
the first arteriogram, which was obtained by injecting chalk into the brachial artery of a cadaver and observing the arterial supply of the hand with a roentgenogram (14). In October 1896, Francis Williams, a radiologist at Boston City Hospital, published his observations on the use of the fluoroscope to evaluate the beating heart (15). A decade later, Friedrich Jamin and Hermann Merkel, German physicians, published the first roentgenographic atlas of human coronary arteries (16). In their 1907 description of 29 excised hearts, coronary arteries were injected with a suspension of red lead in gelatin, after which stereoscopic roentgenograms were obtained (Fig. 1.4) (13). In some of the specimens, coronary arterial obstructions and collateral blood vessels were noted, which helped form the basis of James Herrick’s seminal 1912 paper, titled “Certain Clinical Features of Sudden Obstruction of the Coronary Arteries.” His observations served to advance our understanding of the pathophysiology of coronary artery disease, angina pectoris, and myocardial infarction (MI) (17,18).

For angiography to be safe and practical in a living human subject, several developments were necessary, including the availability of a nontoxic radiopaque material that could be safely injected intravascularly. In this regard, an important advance occurred in 1921 with the introduction of lipiodol, a 40% solution of iodine in poppy oil (19). The injection of
lipiodol into an antecubital vein permitted roentgenographic visualization of the pulmonary circulation. Sodium iodid, originally introduced as a urographic contrast agent in 1918, was first administered intravascularly by Osborne and colleagues at the Mayo Clinic in 1923 (20). The following year, Barney Brooks, a vascular surgeon at Washington University, described the intraarterial injection of sodium iodid in patients with suspected peripheral vascular disease (21). The application of vascular roentgenography to the coronary arteries did not take place in the 1920s, in large part because the technique for human heart catheterization had not yet been described.

Cardiac Catheterization Performed in Humans (1928–1929)
In 1929, Werner Forssmann (Fig. 1.5) first reported the passage of a catheter into the heart of a living subject: himself (22). As a medical student, Forssmann learned of the work of Bernard, Chauveau, and Marey, and he became interested in using catheterization for the intracardiac administration of drugs for attempted cardiac resuscitation (4). Believing that catheterization could be applied as safely in humans as in animals, he performed the self-catheterization during his surgical residency at the Auguste-Viktoira Hospital in Eberswalde, Germany (Fig. 1.6). According to Forssmann’s daughter (23),

he inserted the [ureteral] catheter through a vena sectio of the left cubital vein and pushed it up to about 65 cm—the estimated distance to the right heart. He experienced a sensation of warmth on the wall of the vein when he moved the catheter and a slight cough, which he attributed to stimulating the vagus nerve. With the catheter in his heart, he walked from the operating room downstairs to the X-ray room. He took X rays [Fig. 1.7] while moving the catheter with the help of a nurse. This nurse held a mirror in front of Forssmann so that he could observe the position of the catheter and take X rays when

Forsmann’s successful procedure was performed under inauspicious circumstances. He had discussed his ideas about heart catheterization with the chief of surgery, who forbade him from performing studies in humans without preliminary research in experimental animals to demonstrate the procedure’s safety. To procure the surgical instruments for the vena sectio, Forssmann assuaged the scrub nurse’s concerns about the procedure’s safety by agreeing to allow her to be the subject, as she had requested (24). He had her lie down on the operating table and then strapped her arms and legs. While distracting her by applying iodine to her elbow, he anesthetized his own arm, performed a cutdown of the antecubital vein, and inserted a ureteral catheter into it. At that point, he released her and
enlisted her help in assisting him down the stairs to the X-ray room to perform fluoroscopy. When word of Forssmann’s self-catheterization reached the chief of surgery, Forssmann was reprimanded for his disobedience and promptly fired. When his work was published the following year (1929), it was acclaimed by the popular press but ridiculed and vilified by the medical community (22). He was immediately dismissed from his new position at a Berlin hospital and informed that “he could lecture in a circus, but never in a respectable German university” (23). Before being dismissed, he performed experiments in animals to demonstrate the value of contrast angiography as a diagnostic tool. He used rabbits in his first experiments and later confessed that “if he had started experimenting with rabbits, he would never have experimented on himself. When the tip of catheter touched the rabbit’s endocardium, the electrocardiogram showed temporary cardiac arrest” (23).

Forssmann ultimately continued his studies in dogs at another institution and reported in 1931 that angiography was a safe and useful diagnostic procedure (25). During this time period, he catheterized himself nine more times in an attempt to obtain a publishable angiogram of his heart, but he was unsuccessful. “The response of the academic community ranged from laughter and disbelief to admiration” (23). He left academic medicine in 1932 to practice urology, remaining in obscurity until he, Andre Cournand, and Dickinson Richards were awarded the 1956 Nobel Prize for Physiology or Medicine, he for pioneering the procedure and the others for developing its application. Although Forssmann is credited with being the first to report heart catheterization in human subjects, Otto Klein, in fact, should be recognized for performing the first diagnostic right heart catheterizations. In 1929, Klein performed 11 successful right heart catheterizations, including passage of a catheter into the right atrium and right ventricle, and he estimated the cardiac output in his human subjects using the Fick principle (26).

The Era of Hemodynamic Cardiac Studies (1930–1940s)

Although isolated reports of pulmonary (27, 28) and right heart angiography via right atrial injection (29) appeared soon after Forssmann’s publication, cardiac catheterization progressed slowly in the 1930s because of the poor quality of the radiographic images and concerns about safety. In a 1932 book on the measurement of cardiac output, Forssmann’s technique was considered “not only dangerous to the subject, but useless as far as cardiac output determinations are concerned . . . . This method must thus be considered merely a clinical curiosity” (30). In addition, progress in the field was hindered by the events leading to World War II that interrupted biomedical research in Europe. However, in the Western Hemisphere, Castellano (in Cuba) and Rob and Steinberg (in New York) obtained high-quality images of all four cardiac chambers and the great vessels using a rapid intravenous injection of radiographic contrast material (31, 32).

As Forssmann noted in his Nobel Prize acceptance speech in 1956, “A turning point in the history of cardiology is the year 1941, when Cournand and Ranges made known their first experiments with the heart catheter as a clinical method of investigation” (4). They showed that “consistent values for blood gases could be obtained from the right atrium, that with this, cardiac output could be reliably and fairly accurately determined by the Fick principle, and furthermore that the catheter could be left in place for considerable periods without harm” (33). Prior to their published studies, cardiac catheterization was not routinely considered “a safe and sound procedure to study cardiac physiology” (34), so their article served as a breakthrough.

The development of pressure manometers and the double-lumen catheter, through which simultaneous pressures in two contiguous heart chambers and large vessels could be recorded, served as important advances that allowed Cournand and colleagues to obtain the first tracings of pressures recorded simultaneously from the right ventricle and pulmonary artery (Fig. 1.8) (35). Their “tracing holds a unique place, since it is the first demonstration that the tip of a catheter was placed in the pulmonary artery of man in order to record pressure pulses” (35). Cournand and his colleague Dickinson W. Richards developed the technique of heart catheterization for safe and widespread use “not only to normal man but to patients even in the most severe and acute stages of decompensation” (33). As a result of their efforts, cardiopulmonary physiologic investigation accelerated rapidly. As noted previously, their seminal work was acknowledged when they (along with Werner Forssmann) received the 1956 Nobel Prize for Physiology or Medicine (Fig. 1.9).
While Courand and Richards used right heart and pulmonary arterial catheterization primarily to study the pulmonary circulation, Lewis Dexter refined its use in patients with heart disease. In 1946, he described the placement of a stiff catheter in the pulmonary capillary “wedge” position, where he obtained blood samples for determination of oxygen saturation; the following year, he reported hemodynamic and oximetric data from normal subjects and those with congenital heart disease (36,37).

The development of new synthetic catheter material in the 1940s (including polyethylene, nylon, woven Dacron, polyurethane, and metal braiding) facilitated heart catheterization, which was previously performed with modified rubber urologic catheters. In part, the development of such synthetic material resulted from the difficulty of obtaining rubber during World War II. Concomitantly, improvements in radiographic equipment and techniques (e.g., rapid series “cut films,” image intensifiers, cineangiography, etc.) paved the way for the subsequent development of diagnostic and therapeutic left heart catheterization and coronary angiography. Finally, safer and more widely applicable techniques with which to gain access to the aorta were developed during this time. Direct needle access of the aorta was abandoned in favor of retrograde catheterization of the femoral, brachial, or radial arteries via cutdown or percutaneous puncture (6). Although aortography had been performed in the late 1940s, the passage of a catheter in a retrograde fashion across the aortic valve into the left ventricle was considered to be excessively dangerous. Instead, left ventriculography was performed via direct left ventricular transthoracic needle puncture (6).

**Left Heart Catheterization and Coronary Angiography (1950–1960s)**

Retrograde left heart catheterization was initially reported in 1950 by Zimmerman, who performed “pull-back” pressure measurements in a patient with aortic regurgitation (38). Although enthusiasm for left heart catheterization escalated, the lack of safe and reliable access to the arterial system tempered its use. In 1953, Sven-Ivar Seldinger, a Swedish radiologist, developed a technique of introducing catheters into the arterial circulation. “A needle is introduced, a guidewire is pushed into it, and the needle is removed. The catheter then is guided in over the wire, which also is removed” (39,40). This technique, which bears his name (the “Seldinger technique”), continues to be used in virtually all catheterization procedures.

A new era in cardiovascular medicine began in 1958 when selective coronary angiography was performed in a patient undergoing left heart catheterization. Previously, visualization of the coronary arterial system was obtained nonselectively by a variety of techniques, including the following:  

1. Balloon occlusion of the ascending aorta during aortic root injection of contrast material (41)  
2. Aortic root injection of contrast material enhanced by acetylcholine-induced ventricular arrest (42)  
3. Phasic injections of contrast material timed to occur during ventricular diastole (43)  
4. Use of various catheters designed to opacify the coronary sinuses while directing jets of contrast material toward the coronary arterial ostia (44)  

Selective coronary angiography was not attempted because of concerns that it would cause myocardial hypoxia, which might lead to an electrical imbalance and a resultant fatal ventricular arrhythmia. In support of these concerns, Nobel Laureate André Courand reported “his personal experience of a 100% fatality rate when contrast was selectively injected in the coronary arteries of dogs” (45).

On October 30, 1958, Mason Sones, a pediatric cardiologist, inadvertently performed the first selective coronary angiogram in a 26-year-old patient with aortic regurgitation (46). After performing left ventriculography, Sones reported (47):

I asked my associate to withdraw the catheter tip across the aortic valve into the ascending aorta so that we could complete the procedure by performing an aortogram with the catheter tip in the ascending aorta. My associate complied and we relied on the pressure change from the left ventricle to the ascending aorta without sliding the table top back under the 5 inch amplifier to confirm the exact location of the tip. I didn’t think this was necessary because I was quite certain that the catheter tip lay in the ascending aorta just above the aortic valve. My associate, Dr. Royston Lewis, made an injection of 40 cc of 90% Hypaque through the catheter. About one second before the injection was initiated, I had the switch to initiate a cine run. When the injection began, I was horrified to see the right coronary artery become heavily opacified and realize the catheter tip was actually inside the orifice of the dominant right coronary artery. I shouted, “Pull it out.” Our combined reaction times to accomplish withdrawal of the catheter consumed from 3–4 seconds which meant that approximately 30 cc of 90% Hypaque had been delivered into the right coronary artery. I was of course horrified because I was certain the patient would develop ventricular fibrillation. At that time we did not have direct current defibrillators and knew nothing about the application of closed chest cardiac massage. I climbed out of the hole and ran around the table looking for a scalpel to open his chest in order to defibrillate him by direct application of the paddles of an alternating current defibrillator. I looked at the oscilloscope tracing of his electrocardiogram and it was evident that he was in asystole rather than in ventricular fibrillation. I knew that an explosive cough could produce a very effective pressure pulse in the aorta and hoped that this might push the contrast media through his myocardial capillary bed. Fortunately, he was still conscious and responded to my demand that he cough repeatedly. After three to four explosive coughs, his heart began to beat again with initially a sinus bradycardia which accelerated into a sinus tachycardia within 15 to 20 seconds. He then made a perfectly uneventful recovery with no neurological deficit or other sequelae.

The failure of ventricular arrhythmias to materialize during this inadvertent selective coronary arterial opacification convinced Sones that the human coronary circulation was different from that of dogs, so he continued to perform selective coronary angiography in patients, with access to the arterial system obtained via a brachial artery cutdown. Sones’ seminal discovery eventually opened the door to coronary artery bypass surgery and interventional cardiology. The development of preformed coronary catheters by Judkins, Amplatzer, Schoonmaker, and others (6,48–50); a percutaneous femoral
arterial approach (51); and sheaths with a hemostatic valve (52)
further refined the technique, which has become standard in
thousands of catheterization laboratories around the world.

Shortly after selective coronary angiography was
adopted, quantitation of left ventricular function and correla-
tion with coronary anatomy transpired. In 1960, Dodge and
coworkers reported methods to determine left ventricular vol-
umes via “angiocardiology” and to quantitate global func-
tion by introducing the concept of ejection fraction (53).
Subsequently, their work provided the basis for the quantita-
tive assessment of regional wall motion.

Concomitant with the development of selective coronary
angiography and quantitative ventriculography, the early foun-
dations for coronary intervention were laid by Charles Dotter, a
radiologist in Portland, Oregon. In 1963, he inadvertently
recanalized an occluded right iliac artery by passing a catheter
through the site of occlusion (54). The following year, Dotter
and his trainee, Melvin Judkins, performed the first intentional
percutaneous transluminal angioplasty on the popliteal artery
of an 82-year-old woman with gangrene who refused amputa-
tion. The site of severe obstruction was dilated with rigid
catheters of increasing diameter, the patient’s leg was salvaged,
and angiography two years later demonstrated a patent vessel
(Fig. 1.10) (54). The “Dotter technique” was not widely
embraced in the United States, since it was considered to be
crude, technically cumbersome, and associated with a high
incidence of failure and complications. However, it was widely
employed in Germany, where Andreas Gruentzig, a young
German angiology fellow, learned the technique in 1969 and
conceived of adding a balloon to the Dotter catheter so that it
could be applied to other arterial systems.

The Age of Percutaneous Coronary
Revascularization (1970–1980s)
Attempts to improve on Dotter’s techniques by adding a bal-
loon to the dilatation catheter were met with limited success, in
large part because the balloon material was too fragile or too
compliant for dilatation of rigid plaques. Gruentzig set out to
develop a suitable catheter with a nondistensible balloon for
use in narrowed coronary arteries. He chose polyvinyl chloride
at the suggestion of a professor emeritus of chemistry who was
working across the street from Gruentzig’s institution, the
University Hospital of Zurich (55). Using heat molding and
compressed air, he manufactured balloon catheters in his
kitchen at night and on weekends with the help of his wife
and friends (6). After testing these balloon catheters in animals,
he performed the first of several hundred successful percuta-
neous balloon angioplasties of peripheral arteries in human
subjects in February 1974 (56). Subsequently, he refined and
miniaturized his balloon catheters so that they could be used in
the coronary arterial circulation. Although he conducted exten-
sive studies in animals and human cadavers (Fig. 1.11), skepti-
cism concerning the utility of coronary balloon angioplasty was
widespread. After successful coronary angioplasty in a dog (57),
the pathologist wrote in his report that Gruentzig should
stop doing whatever he was doing and certainly never
come close to a human being with this terrible balloon
instrument because the canine heart and coronary
arteries looked terrible.

Despite widespread skepticism, Gruentzig performed the
first successful percutaneous transluminal coronary angiop-
plasty (PTCA) in a human subject in Zurich, Switzerland, on
September 16, 1977. The patient, a 38-year-old man, had unsta-
able angina and a discrete stenosis in his proximal left anterior
descending coronary artery. Following two balloon dilatations,
he became free of angina, and when he underwent catheter-
ization at Emory University on September 16, 1987—precisely 10
years after his original procedure—his left anterior descending
coronary artery was widely patent. In 2000, repeat catheterization
performed for chest pain thought to be atypical for angina
showed that “the dilated area was pristine” (Fig. 1.12) (55).
PTCA was first performed in the United States on March
1, 1978, simultaneously by Richard Myler in San Francisco and
Simon Stertzer in New York (6). It was rapidly adopted by
American cardiologists, but in Europe it was received with
skepticism. Gruentzig encountered obstacles that prevented him from developing the technique in Zurich, so in 1980 he moved to Emory University in Atlanta, Georgia, where he continued to refine the procedure until his untimely death in 1985 in an airplane crash. Several technical developments led to the widespread use of PTCA, the most important of which was the introduction of steerable guidewires, which allowed the application of PTCA to distal coronary arterial stenoses and tortuous vessels. At the same time, softer, smaller-diameter guiding catheters and lower-profile, more flexible balloons were manufactured. Altogether, these technologic advances resulted in higher rates of success and lower rates of complications, even though PTCA was being used in patients with more technically difficult stenoses and in those with multi-vessel coronary artery disease.

Throughout the 1980s, the balloon catheter remained the primary device for performing angioplasty, but by the late 1980s, new equipments began to emerge. The first addition, the directional atherectomy device developed by John Simpson, was based on the idea that removal of atherosclerotic tissue would be superior to simple dilation of the artery. Peripheral arterial atherectomy was first reported in 1985 (58), and the following year the device was successfully applied to coronary arteries (59). Although higher procedural success rates were noted with atherectomy than with balloon angioplasty in randomized comparisons, atherectomy was not widely adopted, since it was more tedious and expensive and was associated with a higher rate of non-Q wave MIs. Subsequently, other atherectomy (extraction, rotational, thermal, laser) and thrombectomy devices were developed. In randomized comparisons with balloon angioplasty or stenting (see following text), many of the atherectomy devices were associated with higher acute complication rates without improving late results. Therefore, their use is currently restricted to coronary arterial stenoses that are not thought to be amenable to balloon angioplasty or stenting.

The Stent Era (1990s–2000s)
The derivation of the term “stent” is attributed to Dr Charles Stent (1807–1885) (Fig. 1.13) who developed a material that enabled him to secure better dental molds (60). The concept of endovascular stents is attributed to Alexis Carrel, 1912 Nobel laureate and vascular surgeon, who implanted glass and metal tubes into the aorta of dogs (61). Fifty years later, Charles Dotter developed “sleeve” graft devices and metallic coils, which he used in experimental animals, but he never implanted them in patients (6). The recognition that PTCA resulted in acute vessel...
closure in ~5% of patients and restenosis in >30% in those in whom it was attempted accelerated the development of an endoprosthetic device (e.g., stent) to enhance procedural results, avert vessel closure, and prevent restenosis. The first implantation of coronary arterial stents in humans occurred in 1986 in Europe, with insertion of the spring-loaded, self-expanding Wallstent (6). The following year, a balloon-mounted, wire coil stent designed by Cesar Gianturco was implanted at Emory University Hospital in Atlanta, Georgia, and a slotted tube stent designed by Julio Palmaz was inserted in a patient in Sao Paulo, Brazil. The Gianturco-Roubin stent was approved for use by the Food and Drug Administration (FDA) in 1993 in subjects with abrupt and threatened arterial closure. In 1994, the Palmaz-Schatz stent was approved by the FDA (Fig. 1.14) (62).

Initially, intensive anticoagulation and antiplatelet therapy were administered to patients in whom intracoronary stents were deployed to prevent acute (in-hospital) and subacute (within 30 days of implantation) stent thrombosis. As a result, bleeding complications at the peripheral arterial puncture site were common. Two major developments advanced the use of stents. First, the abandonment of warfarin in favor of dual antiplatelet therapy (aspirin and ticlopidine) substantially reduced the incidence of the aforementioned bleeding complications. Second, the discovery (with intravascular ultrasound) that stents were often not fully expanded and in poor apposition against the coronary arterial wall led to the use of high pressure balloon inflations to achieve more complete stent expansion. Both advances improved the acute and chronic success rates of stents.

Soon after coronary stents were introduced, it was recognized that in-stent restenosis from neointimal hyperplasia occurs in ~20% to 25% of patients with discrete, short de novo stenoses and in as many as 60% of those with small caliber vessels, long lesions, bifurcation lesions, or diabetes mellitus. Furthermore, in contradistinction to the discrete restenotic lesions that sometimes occurred following balloon angioplasty, in-stent restenosis was noted often to be a much more diffuse lesion that was not readily amenable to repeat dilatation or atherectomy. Extensive research was performed in the late 1990s to seek a solution to the problem of in-stent restenosis. Numerous immunosuppressive and antiplatelet regimens were evaluated but were unsuccessful in reducing its incidence. In 2001, intracoronary radiation (i.e., brachytherapy) after balloon dilatation was reported to be moderately successful in treating in-stent restenosis, but its limitations, including late thrombosis, limited applicability, high cost, and the required presence of a radiation oncologist during the procedure, rendered it unsuitable for widespread, routine clinical practice.

In early 2000, stents that eluted antiproliferative pharmacologic agents directly into the vessel wall were developed. The antiproliferative drug was bound to the stent via a polymer coating, which permitted controlled release of the drug for days, weeks, or months after stent implantation. A sirolimus-coated (CYPHER®) stent was approved for clinical use in Europe in April 2002, and in the United States in May 2003, following randomized studies, which demonstrated a marked reduction in restenosis when compared with uncoated (bare metal) stents (63). A paclitaxel-coated stent (TAXUS®) was approved for use in Europe in January 2003 and in the United States in March 2004 following studies that demonstrated that it too was accompanied by a lower incidence of restenosis in comparison with bare metal stents. Subsequently, additional drug-eluting stents (DES) have been developed, each varying in its delivery platform, polymer coating, and antiproliferative agent. At present, DES are utilized for the majority of patients undergoing stent implantation for coronary artery disease because of their expected very low incidence of in-stent restenosis.

At the same time, devices were developed to improve the evaluation of arteries, selection of therapies, and success of the procedures described above. Intravascular ultrasound was developed in the late 1980s but did not achieve widespread use until the 1990s. Although it had long been known to provide an image of the arterial wall that was not available with angiography, its use became commonplace with the development of atherectomy devices and intracoronary stenting, with which operators needed to evaluate vessel characteristics, including lumen size, extent and location of plaque, and

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**Figure 1.14** (A) Spring-loaded, self-expanding stent (Sigwart Wallstent, Medinvent SA, Lausanne, Switzerland); (B) prototype of the Palmaz stent (Johnson and Johnson Interventional Systems, Warren, New Jersey, U.S.); (C) balloon-expandable flexible coil stent (Gianturco-Roubin Flex-Stent, Cook, Inc., Bloomington, Indiana, U.S.). Source: From Ref. 62.
presence and distribution of calcium deposits within the arterial wall. For patients with coronary luminal narrowings of indeterminate hemodynamic significance, methods to assess the physiology of coronary flow were developed, including (i) the Doppler flow wire, which can record the velocity of blood flow in the coronary artery and thereby determine if a stenosis is impeding flow, and (ii) the pressure wire, which can be used to assess the presence or absence of a pressure decline across a coronary stenosis at rest or after the administration of a vasodilator.

INDICATIONS AND CONTRAINDICATIONS

During its early years, cardiac catheterization was performed sparingly and with substantial risk. As time has elapsed, considerable advances have occurred, and the associated morbidity and mortality have fallen precipitously. Today, diagnostic cardiac catheterization is performed with minimal risk, and therapeutic catheterization (i.e., PCI and valvuloplasty) is performed without incident in most patients. Cardiac catheterization now plays a central role in the diagnostic evaluation of the patient with suspected or known cardiac disease, and it offers percutaneous therapeutic possibilities in many individuals.

Diagnostic cardiac catheterization is appropriate in several circumstances. First, it is indicated to confirm or to exclude the presence of a condition already suspected from the history, physical examination, and/or noninvasive evaluation. In such a circumstance, it allows physicians to both establish the presence and to assess the severity of cardiac disease. Second, catheterization is indicated to clarify a confusing or obscure clinical picture in a patient whose clinical findings and noninvasive data are inconclusive. Third, it is performed in some patients for whom corrective cardiac surgery is contemplated to confirm the suspected abnormality and to exclude associated abnormalities that might require the surgeon’s attention. Fourth, catheterization occasionally is performed purely as a research procedure.

Therapeutic catheterization is appropriate in several circumstances. Percutaneous coronary revascularization (e.g., angioplasty, rotational atherectomy, or endovascular stenting) may be indicated in the patient with symptomatic atherosclerotic coronary artery disease whose coronary anatomy is suitable for the procedure. Valvuloplasty is indicated in the subject undergoing PCI, it is 2.1% (1,65), with the latter being higher in patients undergoing diagnostic catheterization or PCI occur in 1.3% of patients undergoing a diagnostic study and in 2.3% of those undergoing PCI (1). MI during or immediately following diagnostic catheterization occurs in about 0.07% of patients, but most are small and uncomplicated. Cerebrovascular accidents in the pericatheterization period may be (i) embolic (from the arterial catheter, guidewire, left ventricular or atrial thrombus, or dislodged atherosclerotic plaque) or (ii) ischemic (i.e., existence of extensive cerebrovascular disease that, in association with the hemodynamic alterations induced by angiography, leads to inadequate cerebral perfusion).

Catheterization may result in vascular complications, such as bleeding at the entry site, retroperitoneal bleeding, vascular access occlusion at the entry site, peripheral embolization, vascular dissection, pseudoaneurysm, and arteriovenous fistula. The incidence of vascular complications in patients undergoing diagnostic catheterization is <0.5%, and in those undergoing PCI it is 2.1% (1,65), with the latter being higher because of the use of intensive antiplatelet and anticoagulant therapy and larger lumen catheters than those used in diagnostic catheterization.

RISKS AND COMPLICATIONS

As cardiac catheterization has been more frequently performed, the incidence of complications has diminished (Table 1.1). However, even in skilled hands, the procedure is not without risk. The overall incidence of in-hospital mortality is 0.09% for diagnostic catheterization and 0.8% for PCI (1). Such deaths may be caused by perforation of the heart or great vessels, cardiac arrhythmias, acute MI, or anaphylaxis to radiographic contrast material. Individuals with an increased risk of death include those with (i) advanced (>70-year-old) or very young (<1-year-old) age, (ii) marked functional impairment (class IV angina or heart failure), (iii) severe left ventricular dysfunction or coronary artery disease (particularly left main disease), (iv) severe valvular disease, (v) severe comorbid medical conditions (i.e., renal, hepatic, or pulmonary disease), or (vi) history of an allergy to radiographic contrast material. Patients with significant narrowing of the left main coronary artery have a substantially greater risk of periprocedural death (2.8%) compared with those without left main stenosis (0.1%) (64).

Major complications (allergic reaction to radiographic contrast media, cardiogenic shock, cerebrovascular accident, congestive heart failure, cardiac tamponade, and renal failure) occurring during or within 24 hours of diagnostic catheterization or PCI occur in 1.3% of patients undergoing a diagnostic study and in 2.3% of those undergoing PCI (1). MI during or immediately following diagnostic catheterization occurs in about 0.07% of patients, but most are small and uncomplicated. Cerebrovascular accidents in the pericatheterization period may be (i) embolic (from the arterial catheter, guidewire, left ventricular or atrial thrombus, or dislodged atherosclerotic plaque) or (ii) ischemic (i.e., existence of extensive cerebrovascular disease that, in association with the hemodynamic alterations induced by angiography, leads to inadequate cerebral perfusion).

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Numerous minor complications may cause morbidity but exert no effect on mortality. Local vascular complications occur in 0.5% to 2.0% of patients. The incidence is similar for the brachial and femoral approaches and somewhat higher for the radial approach. Following arterial catheterization by the brachial or radial approach, thrombosis, dissection, intimal flap formation, or subintimal hemorrhage may compromise blood flow to the hand or arm, and the patient may require thrombectomy or surgical exploration after catheterization. With the
percutaneous femoral approach, hemorrhage and/or hematoma formation at the arterial puncture site are the most common problems and, if severe, may require limited surgical exploration. Arteriovenous fistulae or pseudoaneurysm formation may occur, especially if protracted bleeding at the puncture site occurs after sheath removal, as may result from inadequate compression of the femoral vessel, insertion of large sheaths, severe systemic arterial hypertension, prolonged heparinization, or administration of thrombolytic or antiplatelet agents. Less commonly, femoral arterial thrombosis occurs, which requires immediate thrombectomy. Compression by a large hematoma or groin clamp may cause local nerve damage. Local infection may occur at the site of catheter insertion and manipulation, but this can usually be treated with meticulous wound care and antibiotics.

The administration of radiographic contrast material may cause nausea and vomiting as well as a transient fall in systemic arterial pressure. Occasionally, such injections are associated with allergic reactions of varying severity, and a rare individual has anaphylaxis. Interestingly, only 15% of individuals with a previous allergic reaction to contrast material have another adverse reaction with repeat administration, and most of these are minor (urticaria, nausea, vomiting) (66). In most patients with a history of contrast allergy, angiography can be performed safely; however, premedication with glucocorticosteroids and antihistamines as well as use of a different contrast agent are usually recommended. The endocardial injection of contrast material during ventriculography (so-called endocardial staining) may cause ventricular irritability. Finally, use of excessive quantities of radiographic contrast material may cause renal insufficiency, which is usually transient. This is particularly likely to occur in patients with preexisting renal dysfunction and diabetes mellitus, and its occurrence can be minimized by (i) limiting the amount of contrast material used during catheterization on the basis of the patient’s weight and serum creatinine (67), (ii) administering sufficient oral and intravenous fluids during and after the procedure to insure that the osmotic diuresis caused by the hyperosmolar contrast material does not induce intravascular volume depletion, and (iii) perhaps by administering nephroprotective agents (i.e., N-acetylcysteine) before the procedure (68).

CARDIAC CATHETERIZATION SETTINGS

Cardiac catheterization procedures were originally only performed on inpatients. Nowadays, however, most elective diagnostic catheterizations are performed in outpatients in laboratories based at a hospital with available cardiovascular surgery. These laboratories may be fixed or mobile, with the latter being located on the hospital premises. Outpatient catheterization is widely accepted because of its excellent safety record when performed in properly selected patients (see following text). In 16 studies reporting the results of 20,129 individuals who underwent diagnostic catheterization at a hospital outpatient laboratory, mortality rates ranged from 0% to 0.3%, MI rates from 0% to 0.7%, the rate of stroke or transient ischemic attack from 0% to 0.4%, the incidence of vascular complications from 0% to 2%, and the rate of bleeding or hematoma from 0% to 7% (69). These complication rates are similar to those reported in a very large multicenter registry of 222,553 patients who had inpatient diagnostic catheterization (70).

For patients considered to be at low risk of suffering a complication or having extensive coronary artery disease, the procedure may be performed at a community hospital without cardiovascular surgical capability or in a freestanding catheterization facility, which may be a fixed structure or a mobile unit. Since a freestanding laboratory is not physically attached to a hospital, quick transportation of a patient by stretcher to a hospital is usually not possible. The most recent Society of Cardiac Angiography and Intervention survey of cardiac catheterization laboratories (published in 2007) identified 75 non-hospital-based laboratories in the United States, up from 58 in the 1999 survey (71).

Some freestanding catheterization laboratories are privately owned by physicians. Regardless of who owns and operates them, all freestanding laboratories should have a clearly defined working relationship with one or more nearby hospitals to facilitate emergency transfer of patients when required. Such freestanding facilities must be able to stabilize the occasional patient who has a complication, and they must have the equipment required for endotracheal intubation and ventilator support. The physicians using such facilities should be facile in performing endotracheal intubation (since on-site anesthesiologists are not available) and intra-aortic balloon insertion. Quality assurance and quality improvement programs should be in place and reviewed regularly by an outside consultant. Currently, only diagnostic procedures (i.e., left or right heart catheterization, ventriculography, and coronary angiography) are performed in freestanding laboratories; performance of PCI is restricted by state edict only to hospital-based laboratories.

By providing a setting exclusively for low-risk diagnostic procedures, freestanding facilities can eliminate the long waiting periods that sometimes occur with inpatient facilities. In addition, cost savings are touted as one of the advantages of such freestanding facilities (69). In many circumstances, however, the growth of freestanding laboratories has been driven by a desire to “capture market share” rather than to improve patient access to expert catheterization. Since most of these facilities are physician owned, the potential exists for financial incentives that inappropriately influence the decision to perform the procedure at such a facility. Other concerns associated with freestanding facilities include the ability to perform an adequate caseload to maintain the operators’ skills, limited experience with recognition and management of complications, inadequate regulation and quality control, and the time required to transfer patients to nearby hospitals in the event of an emergency.

The authors of the American College of Cardiology/Society for Cardiac Angiography and Interventions (ACC/SCAI) Clinical Expert Consensus Document on Cardiac Catheterization Laboratory Standards (72) recommended patient selection criteria for individuals deemed suitable for consideration of diagnostic catheterization in an outpatient facility. They recommended the following exclusion criteria for adult patients:

1. Age >75 years
2. NYHA class III or IV heart failure
3. Acute intermediate- or high-risk ischemic syndromes
4. Recent MI with postinfarction ischemia
5. Pulmonary edema thought to be caused by ischemia
6. Markedly abnormal noninvasive test indicating a high likelihood of left main or severe multivessel coronary artery disease
7. Known left main coronary artery disease
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8. Severe valvular dysfunction, especially in the setting of depressed left ventricular systolic performance
9. Patients at increased risk for vascular complications
10. Complex adult congenital heart disease

Patients with any of these exclusion criteria would not be candidates for catheterization in a freestanding facility, nor would any patients considered to be at high risk because of the presence of comorbid conditions, including the need for anticoagulation therapy, poorly controlled hypertension or diabetes mellitus, allergy to radiographic contrast material, or renal insufficiency.

Although several case series have reported the rate of complications of diagnostic catheterization in freestanding facilities, no randomized trials have compared the complication rates in freestanding facilities with those in hospital-based laboratories. The rates of mortality, MI, stroke, and vascular complications in these case series are comparable to those observed in hospital outpatient facilities (69). In recent years, diagnostic catheterization procedures have been combined with PCI if the diagnostic study indicates a need for intervention. Combining the two procedures may lower the overall cost. Patients who undergo diagnostic catheterization at a freestanding facility or a diagnostic-only hospital do not have the option of a combined procedure if PCI is deemed appropriate; for these individuals, the PCI must be performed at a different institution at a separate time. Approximately 30% of patients who undergo diagnostic catheterization in an outpatient setting are referred for subsequent PCI (69).

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12 CARDIOVASCULAR CATHETERIZATION AND INTERVENTION


Setting up a catheterization laboratory and equipment considerations

John W. Hirshfeld, Jr.

OVERVIEW
A cardiac catheterization laboratory is a complex facility that integrates multiple items of equipment and a group of clinical personnel who have differing skill sets and responsibilities. It is a component of a hospital that relates to multiple facilities within the overall umbrella of the hospital system. In addition, the laboratory facility has the potential to be a large hospital cost center as it utilizes expensive equipment and supplies. Consequently, it is important that a cardiac catheterization laboratory be operated efficiently. This requires careful thought and planning in developing its architectural design, selecting and integrating its equipment, and developing its operating procedures and protocols.

ARCHITECTURAL CONSIDERATIONS

General Considerations
A cardiac catheterization laboratory suite is an integrated facility that provides care to a variety of patients ranging from stable outpatients undergoing diagnostic procedures to critically ill patients presenting to the emergency room with ST elevation myocardial infarctions requiring emergent interventional procedures. This complement of services requires that it be architecturally configured to accommodate the broad range of patients.

Facilities required in a cardiac catheterization suite include the following:
1. Procedure rooms with attached control rooms and X-ray equipment electronics rooms
2. Patient pre- and postprocedural care area including patient changing areas and lockers
3. Equipment and supply storage area
4. Patient registration and family waiting area
5. Data review and report-generating area
6. Office space for facility administrative personnel
7. Relationship to other hospital facilities

The design of a cardiac catheterization suite should include development of programmatic requirements that specify the number of procedure rooms needed and the space to be allocated to each out of procedure room function (1). An additional architectural challenge is to arrange the components of the suite so that they relate well to each other and provide for efficient circulation between them.

The cardiac catheterization suite also interacts closely with other hospital facilities. These include critical care units, the emergency department, and cardiac operating rooms. Ideal architectural relationships place the cardiac catheterization suite in close proximity to these facilities.

There are three basic reasons for which these architectural relationships are important.
1. Patients are frequently transported between these facilities. Many of these patients are critically ill and medically unstable. Short transportation distances and minimal elevator rides are important safety considerations.
2. Patients who have recently undergone invasive diagnostic and therapeutic procedures are frequently cared for in critical care units. In the event that they develop a problem post procedure, if they are located in close proximity to the cardiac catheterization suite, the cardiac catheterization laboratory staff can check on them promptly and efficiently.
3. Supporting staff needed to respond to emergencies occurring in the cardiac catheterization suite such as anesthesiologists, and respiratory therapists are frequently located in the operating rooms and critical care units. Thus, if these units are in close proximity to the cardiac catheterization laboratory suite, the support personnel will be able to respond more promptly.

Procedure Room Design
The procedure room is the core of the facility, and its design should not be compromised by competing architectural considerations. The first consideration is to provide adequate floor space. Many state departments of health codes specify minimal floor areas. In addition, the X-ray equipment manufacturers specify minimum room sizes and minimum clearances between equipment items and adjacent walls. However, irrespective of whatever code requirements exist, a minimal procedure room size should be 500 ft² (more if the room contains a biplane X-ray system).

In laying out the procedure room, particular attention should be paid to circulation, sight lines, and relationships with supporting utilities.

Patient entry locations and circulation space around the procedure table should be designed to facilitate ease of patient entry and transfer to the procedure table. In planning circulation, one should consider the worst-case scenario of getting a patient who is in an oversized hospital bed on mechanical ventilation, and circulatory support in and out of the procedure room.

Sight line considerations are important to facilitate communications and interactions between the procedure room staff and the control room staff. Thus, the location of the control room, its window to the procedure room, and the provision for audio communication between the control room and the procedure room are an important consideration.
The X-ray imaging system has four groups of components. 

1. The X-ray gantry supporting the X-ray tube and imaging system and the patient procedure table
2. The X-ray video monitors mounted on a ceiling-suspended monitor boom in the procedure room
3. The X-ray system’s supporting electronic equipment, which should be housed in a separate climate-controlled room adjacent to the procedure room
4. The X-ray control system, which is housed in the control room along with a duplicate set of video monitors

The procedure room, control room, and X-ray electronics equipment room should be designed with adequate space, physical relationships, and sight lines to optimize the positioning and configuration of the X-ray system.

**Procedure Room Utilities**

The procedure room has important utility requirements for electrical power, oxygen, vacuum, and lighting.

The X-ray system is powered by its own dedicated electrical power source. This is typically 480-V three-phase power that is routed separately to the X-ray system. This power is required to operate the X-ray generator, which typically requires as much as 150 KW. Most X-ray systems contain transformers that step electrical power down to lower voltages to power components of the X-ray unit such as the procedure table and the monitors.

It is important to provide ample receptacles for standard 110-V single-phase electrical power in both the procedure room and the control room. These receptacles are needed to power portable equipment such as the defibrillator, mechanical ventilators, ultrasound machines, and other portable items that may be used regularly or intermittently in the procedure room. A basic axiom is that it is impossible to furnish too many electrical receptacles as the need for portable devices appears to be inexhaustible. It is also important that receptacles be located throughout the room on all walls, above counter tops and, importantly, in the procedure table pedestal. Floor-mounted receptacles are undesirable because the floor is frequently wet.

One important consideration in the design of a laboratory’s electrical power system is the provision of uninterruptable or emergency power capability. Superficially, it would seem appropriate to have all electrical power supported by the hospital’s emergency power system. However, this approach may require a larger-capacity emergency generator than would otherwise be required. In addition, consideration must be given to the response time for switchover to emergency power. Current X-ray and physiologic monitoring systems require long initialization procedures (some as long as 10 minutes). Thus, if power is interrupted long enough to require that the system reinitialize, it is possible that a laboratory X-ray system will be inoperable for as long as 10 minutes after switchover to emergency power.

Oxygen and vacuum are essential components of the laboratory’s emergency response system. The outlets for these utilities should be positioned close to the head end of the procedure table to be readily available to apply to a patient. One location for positioning these utilities is on the wall closest to the patient’s head. There they are typically grouped with some other emergency resuscitation equipment. An alternative location is on a ceiling-mounted anesthesia column. This latter location offers the benefit of being closer to the patient. However, if employed, it must be positioned carefully so that it does not conflict with the movements of X-ray system components.

Procedure room lighting is another important consideration. Considerable attention should be devoted to the type of lighting employed and its control system. The laboratory operates under several different lighting conditions. During setup, patient entry, and patient preparation, a high lighting level is needed. During procedures, dimmer lighting is desirable to facilitate viewing the X-ray image monitors. During dim lighting conditions, it is desirable to have brighter spot lighting in selected locations such as the catheter entry site area and the instrument table. Ideally, lighting controls that can be operated by the physicians performing the procedure should be furnished at the procedure table. This facilitates selecting the optimal lighting level for a given procedure phase.

The procedure room also needs to be able to accommodate items of ancillary portable equipment. This includes portable imaging equipment (including intravascular and intracardiac ultrasound), portable physiologic monitoring equipment (including pressure wire and flow wire consoles), and circulatory support equipment (including intraaortic balloon pump, Impella and various extracorporeal circulatory support devices). Each of these units requires space when in use and utility connections. Some require connection to dedicated monitors located on the X-ray imaging monitor boom. Some require connection to the laboratory’s physiologic monitoring system to send signals to it or receive signals from it (i.e., ECG signals for intraaortic balloon pump and ultrasound machines). Each of these utility connections and monitor connections should be specified at the time of procedure room design so that the appropriate connectors and cabling are designed into the room at the time of construction.

Since the procedure room is a source of diagnostic X radiation, its walls must be shielded. State departments of health construction codes specify the type and extent of shielding required as well as the X-ray signage requirements.

**Control Room Design**

The design and layout of the control room are among the most complex and are most frequently overlooked when designing a cardiac catheterization laboratory suite. The challenge is to arrange all of the equipment needed in the control room (frequently provided by different manufacturers) with appropriate cabling and ergonomic arrangement to facilitate control room operations. In addition, the design should provide for future changes in equipment configuration. The control room requires a seating area for the staff monitoring the procedure that has good sight lines to the procedure room and to the physiologic monitoring and X-ray equipment. There are numerous computer cases and monitors associated with these functions that need to be arranged and cabled appropriately. Cabling includes dedicated signal cables from the procedure room and the X-ray equipment control room as well as hospital network connections and electrical power connections. In addition, the room design needs to provide the flexibility to accommodate future changes in X-ray imaging or physiologic monitoring equipment.

**Pre- and Postprocedure Care Area Design**

The pre- and postprocedure care area must provide comfortable private areas for individual patients with appropriate staff access and monitoring capabilities. The overall purpose and functions provided by these units influence design considerations. At a
minimum, these units provide a facility for the intake of patients before procedure and for their short-term aftercare post procedure. Some units also function as 23-hour stay facilities for patients undergoing interventional procedures. Thus, the particulars of design and capabilities provided will vary depending on the functionalities intended. Anticipated utilization levels will determine the total capacity designed into the unit.

**Supply Storage and Inventory Management**
A cardiac catheterization facility must maintain a large inventory of devices readily accessible on site, as it is not possible to anticipate and procure in advance all of the devices that may be required to complete a given procedure. Thus, the facility needs to have a supply storage area located in close proximity to the procedure room(s) so that needed devices can be obtained promptly as the need arises. The overall scale of operation of the laboratory facility determines the size of this facility.

Inventory management is a complex challenge for a cardiac catheterization laboratory. The facility must inventory a large range of devices and supplies, some of which are used regularly with almost every case, while others are used only sporadically in unusual circumstances. It is important not to run out of either commonly or infrequently used items because, in a particular situation, availability of a given item may make the difference between success and failure in completing a case. One of the challenges of maintaining the inventory of infrequently used items, in addition to replenishing supplies when used, is to monitor expiration dates.

Inventory management begins with establishment of a comprehensive list of items to be inventoried and establishment of par levels for each item on the basis of its anticipated usage pattern and resupply times and reliability. A variety of inventory management systems are available to facilitate this process. Some cardiac catheterization laboratory physiologic recorder/monitor systems (see below in this chapter) have the capability to record device usage and generate reordering lists. Other options include computerized device storage cabinets, which can be interfaced with computer systems to tabulate device usage. These systems are expensive and, while useful, are imperfect because they can easily be defeated by user errors. Thus, their value to the administrative operation of a laboratory facility is tightly linked to the rigor of the operating procedures employed.

**Ancillary Equipment Storage**
Cardiac catheterization suites acquire numerous small portable equipment items including ultrasound imaging machines, pressure and flow wire consoles, circulatory assistance machines, and others. These machines should be stored in a designated area in the suite outside of general circulation (not in the procedure rooms or in the corridors) where they can be appropriately supported (connected to line electrical power if necessary to maintain battery charge) and readily located when needed. The size of this facility is determined by the amount and type of equipment stored.

**HOSPITAL NETWORK CONSIDERATIONS**

General Considerations
Cardiac catheterization laboratories transmit and receive large quantities of computer network traffic. X-ray images are transmitted to and recalled from the laboratory’s archive server. Data from the physiologic monitoring system and report generation system are similarly transmitted to and from archive servers. The laboratory’s X-ray system and monitoring system read ADT (admissions, discharge, transfer) demographic and accounting data from the hospital information system and postaccounting data from completed procedures to it. The laboratory also, ideally, makes its reports available throughout the hospital network for access by physicians and clinical staff caring for the patient. Both the X-ray system and the physiologic monitoring system require maintenance and troubleshooting. This is frequently accomplished by vendor service personnel connecting remotely via network connections to the equipment in the procedure rooms.

A cardiac catheterization laboratory’s computer network demands, thus, are substantial. These demands must be considered in the design of the network backbone of the system. The network must have sufficient bandwidth to support real-time communications between the core systems in the procedure rooms, the archive servers, and the client terminals used to access images and procedure data outside of the procedure rooms. It must also be sufficiently secure to protect against the intrusion of viruses and other computer malware into the core system components. The bandwidth issue is particularly important given that hospital information networks experience large fluctuations in traffic volume. Consequently, a network design that is adequate for low traffic periods may choke during high traffic periods. One solution is to isolate the core network connecting the procedure rooms and the archive servers from the balance of the hospital network so that the LAN performance between procedure rooms and archive servers is not affected by traffic elsewhere in the hospital network.

Security is an important issue as well. As many X-ray and physiologic monitoring systems run under a Windows operating environment using open-source hardware, they are vulnerable to viruses and other malware. Systems should be configured to prohibit installation of unauthorized applications on any hardware. They should also, ideally, not have either a web browser or an e-mail client installed. Ideally, systems should be isolated from the Internet. However, the challenge in this area is that Internet-based connections are needed for remote monitoring and servicing of the system. Thus, the challenge is to provide remote monitoring and servicing access while excluding other potentially harmful Internet traffic.

**EQUIPMENT CONSIDERATIONS**

**System Integration**
A cardiac catheterization laboratory has two major equipment systems that work together.

1. The X-ray cinefluorographic unit
2. The physiologic monitoring system

The majority of current physiologic monitoring systems provide both physiologic signal conditioning and display functions for monitoring and recording purposes and also provide report generation and data archiving. The X-ray system and the physiologic monitoring system need to communicate with each other to link angiographic and physiologic data into a single procedure file and report document. The task of achieving this communication capability is variable. The X-ray system vendors also furnish physiologic monitoring systems and archiving systems. In this case, the communication protocols are built into the systems and should operate seamlessly. However,
there are also vendors that furnish stand-alone physiologic monitoring systems with varying angiographic image archiving capabilities. These vendors, who compete with the X-ray systems vendors by offering alternative functionality capabilities, must establish communications with the X-ray systems to transfer patient and procedure identifier data as well as angiographic image data if that is included in the system capability. Consequently, when selecting equipment, compatibility and communications between systems must be assured to avoid operational problems.

As discussed above, when selecting equipment, it is important to confirm that, in addition to communication between the X-ray system and physiologic monitoring system, working communications links can be established with the hospital information system to enable transmission of registration and accounting data and publishing of completed procedure reports. These capabilities should be specified contractually at the time the systems are ordered.

**X-Ray Cinefluorographic Unit**

**General Imaging Considerations**

The X-ray cinefluorographic unit is the core equipment around which the entire laboratory facility is based. The technology of these units has matured, and all of the vendors currently in the marketplace offer systems that are capable of generating excellent fluorographic images. X-ray generator and X-ray tube design have now become relatively uniform across vendors. Imaging chains have now migrated virtually completely from X-ray image intensifier/video camera systems to integrated flat-panel detector systems.

A major advantage of the migration to flat panel detector imaging chains is detector uniformity making the earlier quest for "the best image intensifier" a thing of the past. X-ray system manufacturers frequently make claims that flat panel detectors require smaller X-ray input doses. However, in practice, this turns out not to be the case.

With current systems, X-ray image quality is much more determined by the interaction of X-ray input dose and image processing software than by the actual hardware components. Consequently, any quality current system should be capable of generating high-quality images if its X-ray–generating system, dose-modulating system, and image processing algorithms are optimally calibrated. Thus, if a system is generating poor images, the fault is likely with calibration rather than with defective components in the imaging chain.

The impact of current image processing algorithms on image characteristics cannot be overstated. In fact, many qualitative differences in default image appearance characteristics between different X-ray manufacturers are actually attributable to philosophical choices about the characteristics of an optimal image. While the raw initial image data generated by different X-ray vendors are quite similar, the final image displayed on the monitor is strongly influenced by image processing choices such as contrast ratio, white compression, and edge enhancement algorithms. Thus, ideally, the end user should collaborate with the X-ray system manufacturer’s imaging specialists to achieve the image quality that is optimal in the opinion of the end user physician.

It is important that the end user physician keep in mind the tradeoff between X-ray input dose and image quality. It is easy for an X-ray vendor, in response to a request for better image quality, to increase the X-ray input dose. This, while reducing image noise, increases radiation exposure to both the patient and to the laboratory clinical personnel. Consequently, it is important that the hospital’s radiological physicist and radiation safety officer oversee the calibration of the X-ray system to assure that optimal image quality is being generated at the lowest input doses achievable.

**Unit Configuration Issues**

A number of issues need to be considered when specifying the configuration of an X-ray unit. These include detector size, image processing capabilities, procedure table capabilities, and biplane configurations.

**Detector Size**

X-ray image detectors suitable for cardiovascular imaging come in two sizes 20 × 20 cm and 40 × 30 cm. The 20-cm detectors are square and have 1024 × 1024 pixel matrices. The 40 cm detectors are rectangular and have 2048 × 1536 pixel matrices. It is important to point out that flat panel detectors provide multiple image magnification modes. However, as these are digital devices, generation of a magnified image (e.g., a 20-cm) detector generally offers three image sizes. This is achieved by using only the detector’s central pixels and stretching their display to a larger size, thus magnifying the image. This stretching of pixels is accompanied by a commensurate increase in X-ray input dose, maintaining a constant dose-area product, to reduce image noise that would otherwise become evident in response to pixel magnification. Forty-centimeter detectors generate rectangular images in the 40-cm mode but change to square images in magnified modes.

Detector size is an important consideration that is based on the unit’s anticipated usage pattern. The 40-cm detectors offer the ability to achieve a larger image field of view but do so at the cost of greater bulk that impairs ability to achieve extreme degrees of cranial and caudal skew. The 40-cm detector is ideal for imaging large areas of the peripheral vasculature and also imaging substantially enlarged hearts (e.g., imaging the left atrium and left ventricle in a patient with severe enlargement of both chambers due to chronic mitral regurgitation, or imaging the left ventricle and aortic aorta in a patient with severe left ventricular enlargement due to severe aortic regurgitation secondary to a thoracic aortic aneurysm). Thus, a 20-cm detector is ideal for a laboratory that will be doing mostly coronary imaging in patients with normal sized or only moderately enlarged hearts. A 40-cm detector will prove to be more cumbersome for coronary imaging and may actually preclude achieving certain highly skewed projections but will be ideal for imaging enlarged hearts with valvular disease and angiography of the peripheral vasculature.

**Digital Subtraction and Table Stepping**

Peripheral angiography is facilitated by two additional capabilities in addition to detector size—digital subtraction and table stepping. Digital subtraction is very valuable when imaging below the diaphragm or in the neck. It frequently permits acquisition of diagnostic quality images with smaller contrast (but not X-ray) doses. Thus, it is a valuable adjunct for peripheral vascular work. Table stepping is useful principally to follow a contrast bolus injection below the inguinal ligament to the feet. Thus, it is of value for assessing infrainguinal arterial anatomy.
3-D Rotational Imaging

Another recently introduced capability of current digital X-ray units is rotational 3-D angiography. This technique rotates the gantry rapidly through a 180° arc during a coronary injection acquiring images of the opacified coronary artery in multiple projections. CT-type reconstruction algorithms are applied to the image data set to enable a 3-D reconstruction of the coronary anatomy. The potential of this technique is to enable generation of a comprehensive anatomic assessment of a coronary artery with a single contrast agent injection.

Biplane Configurations

Biplane configurations have attributes that are of value in three circumstances.

1. Patients with renal insufficiency in whom it is desirable to minimize contrast agent dose. In such patients, if an operator is skilled and experienced at performing biplane coronary angiography, a biplane X-ray unit offers the potential for substantial contrast agent dose reduction. It is possible that, in future, 3-D rotational angiography may superecede this particular indication for biplane angiography.

2. Patients with complex congenital heart disease who require multiple contrast injections with images acquired in multiple projections can also benefit from studies conducted on a biplane unit.

3. On occasion, biplane fluoroscopy is an adjunct when performing interventional cardiovascular procedures as it enables rapid switching between fluoroscopic views, which is sometimes helpful when conducting a complex interventional procedure.

A biplane X-ray unit costs nearly twice the price of a single-plane unit. As mentioned above, it also requires provision of a larger procedure room. The investment is wasted if the lateral imaging plane hangs unused in the corner of the procedure room. Thus, the choice to specify a biplane unit should be made carefully considering the uses intended for the particular laboratory. Many multiple procedure room facilities will equip one room with a biplane unit scheduling patients with the above-cited circumstances in it while equipping other rooms with single-plane units. Similarly, a multiroom facility may have a mixture of detector sizes in its different rooms using the rooms with large detectors for patients with severe cardiac enlargement and for peripheral vascular procedures while doing straightforward coronary work in rooms with 25-cm detectors.

Display Monitor Configuration

The configuration of the monitor displays is an important ergonomic feature of procedure room design. The ceiling-suspended monitor system should facilitate positioning the monitors where they can be easily viewed from all possible catheter entry site locations. Ceiling-suspended monitor support systems are available, which will support up to eight monitors. As a general rule, one should design for two monitors (live and roadmap) for each X-ray plane. In addition, the monitor configuration will include the monitor for the physiologic recorder/monitor system for monitoring the patient during the procedure. Consideration should be given to whether additional monitors should be provided for display of other data such as intracardiac and intravascular ultrasound images.

Physiologic Monitor, Recorder, and Database

In the past decade, the physiologic monitor and recorder system has undergone a major evolution. This component, which descended from a multichannel oscillograph with analog signal conditioning preamplifiers and an optical strip chart recorder, has evolved into a comprehensive cardiac catheterization laboratory information system. These systems now function as a digital recorder and monitor that also incorporate procedure logging, report generating, and database capabilities. The addition of these capabilities is the logical development of the progressive application of computer technology to what was originally an analog device.

A typical current system incorporates the basic pressure, ECG and other signal acquisition, display, and recording capability. The system has logic to measure digital values that characterize intracardiac and intravascular pressure wave forms as well as calculate valve pressure gradients, cardiac output, vascular resistance, valve orifice areas, and intracardiac shunt flows. In addition, the unit, through its user interface, records a time-stamped procedure log of all procedure events and tabulates devices used for reporting and for inventory maintenance purposes. The recorder system archives the physiologic data from the procedure including all of the physiologic signal data obtained during the procedure. In addition, the system has the ability to generate a clinical procedure report using its recorded data combined with physician interpretation of the angiographic image data.

The physiologic recorder/database interfaces with the procedure room X-ray system to establish links between the procedure’s physiologic data and its angiographic images. Some systems are comprehensive physiologic data and image archiving systems, while others do not archive the angiographic data. If the latter type of system is employed, a separate angiographic archive is needed.

Particular attention should be paid to the ability of the physiologic recorder/database to interface with and communicate with the X-ray system. The X-ray vendors supply physiologic recorder/database systems that are specifically designed to interface with their X-ray systems. In addition, there are third-party vendors that offer physiologic recorder/database systems and compete with the X-ray vendors on feature complement. A given cardiac catheterization suite may contain X-ray equipment from more than one vendor but should have a single physiologic recorder/database system if it intends to use the system for reporting. Thus, there is the potential depending on the supplier of the physiologic recorder/database system to need to interface one X-ray manufacturer’s physiologic recording system with another X-ray manufacturer’s X-ray unit. Given the potential for conflicts, considerable planning must be conducted to configure a blended manufacturer system. This should include contractual guarantees to achieve full interoperability of all linked systems.

Database Servers

The heart of the laboratory information system is its database server(s) (2). Depending on vendors used and configurations, the laboratory may have a single archive server that stores both angiographic image data and physiologic monitoring and report generation data. Alternatively, these functions may be supported by physically different servers depending on the particulars of equipment configuration and vendors supplying the systems. It is important to point out that these servers do
not need to be located physically in the laboratory suite provided that they have connections with sufficient bandwidth as discussed above. In fact, it is likely preferable that these servers be located in the hospital’s larger computer facility where they can be maintained by dedicated computer support staff rather than be an item that requires periodic attention from the laboratory’s clinical staff (who are less likely to be adept at these functions). The same considerations regarding Internet connections described for the X-ray systems and monitoring systems apply to the database servers.

Database server capacity is an important consideration with financial implications. The server system is generally a combination of three units. The server itself with an associated redundant array of inexpensive disks (RAID) storage system provides online storage available immediately. A server “juke box,” which contains an array of mountable removable media data storage units, provides near-line storage generally available automatically within several minutes of a request. Offline storage is removable media not stored in a “juke box” that must be physically mounted by an operator in a server drive in response to a request. Data in offline storage require variable amounts of time for retrieval. When specifying a database server configuration, there is an obvious financial tradeoff between the amount of online and near line capacity and the cost of the system. These are functionality considerations that should be made at that time of system specification.

Ancillary Diagnostic Equipment: Provision, Integration

Ultrasound

A cardiac catheterization laboratory may employ a variety of ultrasound equipment. This will entail portable consoles that drive transducers used for a variety of purposes.

A small duplex ultrasound machine is very useful for assisting with vascular access, particularly internal jugular access in which anatomy can be very variable with respect to external landmarks. This unit is also of value in assessing vascular access sites following catheter removal in case there is concern about vascular integrity.

Intravascular and intracardiac ultrasound imaging is a valuable adjunct to a variety of invasive and interventional procedures. Since this imaging is used to support intracardiac catheter and device manipulation, these machines are ideally interfaced with a monitor mounted on the main monitor boom so that the operators have ready access to both ultrasound and fluoroscopic images in the same location.

Guide Wire Pressure and Flow Velocity Transducers

These devices are used for assessment of intracoronary pressure and flow for measuring fractional flow reserve and coronary vasodilator reserve. The devices are driven by portable consoles that need to be interfaced with the physiologic recording system. This constitutes one of the requirements for procedure table pedestal input and output connections other than the standard pressure transducer input connections. These connection capabilities must be designed into the table pedestal and cabled appropriately at the time of construction and installation.

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Radiation safety principles in the cardiac catheterization laboratory

Thomas M. Bashore

INTRODUCTION
According to the most recent National Council on Radiation Protection and Measurements report (1), Americans were exposed to seven times as much ionizing radiation in 2006 than in the early 1980s. While much of this increase is the result of computed tomography (CT) and nuclear imaging, not an insignificant amount occurs in the cardiac catheterization laboratory. The general public has become increasing aware of the potential hazards of ionizing radiation (2). As a consequence, the use of as-low-as-reasonably-achievable (ALARA) has become a mantra for all healthcare providers to more carefully examine the use of medical radiation. A recent review from the American Heart Association Science Advisory committee has further emphasized the importance of paying attention to radiation effects in cardiac imaging (3). In general, the effects of ionizing radiation have been a much greater focus for the radiologist than the cardiologist. This overview will very briefly discuss the manner in which X-ray images are created to better understand the means by which a reduction in X-ray dose may be accomplished. The radiobiology of ionizing radiation will then be addressed to provide some insight into the consequences of X rays on biologic tissue and how the effects can be minimized.

THE BASICS OF X-RAY IMAGING IN THE CARDIAC CATHETERIZATION LABORATORY
Figure 3.1 outlines the basic operation of the digital X-ray systems using a conventional image intensifier compared with a flat panel system. The two systems have several commonalities. In both systems, the flow of energy begins in the generator where electrons are sent to the X-ray tube and converted into X rays. These X rays are emitted from the X-ray tube and diverge quickly as they are beamed through the patient toward either the image intensifier or the flat panel receptor. A grid filters out stray X rays and only allows direct X rays to hit a cesium iodide crystal, where they are converted to light photons.

In the traditional image intensifier, these light photons strike a photocathode and are converted back to electrons and accelerated toward an output phosphor by a voltage potential across the image intensifier of about 25,000 V. These electrons strike the output phosphor and produce a light image. The X-ray image can be seen by looking directly at the output phosphor. From there the image is captured on a silicon light-sensitive charge-coupled device chip and converted to a video signal. The video signal includes the amount of light that struck each tiny silicon square on the chip and the precise location of that square. This signal is then sent to an analog to digital converter, and the digital message is displayed on the computer monitor.

In the flat panel system, the light photons emitted from the cesium iodide crystal strike a series of thin-film transistors, rather than charge-coupled device silicon squares. The electron current produced is proportional to the number of light photons that hit each thin-film transistor. The video signal that emerges reflects the amount of energy at each thin-film transistor and its location much like the charge-coupled device chip. The signal is digitized (converted from analog to digital) on the flat panel itself, and the digitalized video signal is then sent directly to the computer monitor for display.

It is important to understand a couple of these steps in more depth to appreciate where radiation exposure might occur and how to best provide protection from it. The X-ray tube (Fig. 3.2) is a glass enclosed vacuum tube with a cathode filament or coil inside a focusing cup. This filament emits electrons when heated (thermionic emission). The temperature is >3000°F. The focusing cup is negatively charged to help direct the emitted electrons toward the spinning anode where either a large or a small focal spot area is targeted. The small focal spot provides better spatial resolution while the larger focal spot is used to provide more X rays for imaging larger patients. The number of electrons that leave the cathode and head toward the anode is referred to as the mA (milliamperes) of the system. These electrons are encouraged to jump to the anode by applying a voltage potential across the X-ray tube. This voltage potential is the kVp (peak kilowatts of voltage). The anode rotates to distribute the heat that would otherwise be striking a single spot. About 99% of the kinetic energy of the projectile electrons is converted to heat, so this is a very inefficient system. Adding filtration increases the average energy of the X-ray beam by getting rid of the lower-energy X rays—a process called beam hardening. Filtration thus improves the image and reduces the radiation emitted. The beam can also be shaped by collimators.

X rays are produced when the tungsten in the anode is struck by the projectile electrons in two different ways (Fig. 3.3). Bremsstrahlung or braking X rays are emitted as a spectrum of energies when the projectile electron approaches the tungsten atom, slows down, and changes its path. Most diagnostic X rays are formed by this method. If the projectile electron hits an inner shell electron of the tungsten atom and an outer shell electron then hops inward to fill the vacant spot, the excessive energy is released as a characteristic X ray. These have discrete energies and do not produce a continuous spectrum like the Bremsstrahlung variety. As shown in Figure 3.3, the kVp across the X-ray tube determines the maximal X-ray energy emitted. If the kVp of the system is increased, the amplitude of the emission spectrum...
shifts upward and to the right. If the kVp is kept the same but the mA of the system is increased, there is no right shift, but a major shift in the emission amplitude.

If the absorption spectrum of iodine is superimposed over the X-ray emission spectrum (Fig. 3.3), it becomes clear why iodine is used as an X-ray contrast agent—it absorbs the bulk of the energies emitted. As the intensity of the emitted X rays increases, the iodine initially absorbs less and less of the X-ray energies, then suddenly it absorbs most of them. This spike in iodine absorption of X rays is due to the fact that the K shell electron of iodine has an affinity for absorption of these particular X-ray energies; this is sometimes referred to as the K edge of iodine.

What is the relevance of all this? Understanding these issues helps the cardiologist understand how changes in the physical energy of the X-ray system affect the eventual image. To obtain the optimal image, the X-ray system is constantly trying to achieve a balance among all these factors by use of an exposure equation: \( \frac{kVp}{C^2} \times \frac{mA}{C^2} \times \text{pulse width} \). For instance, when the kVp is increased, the iodine will absorb less of the high-energy X rays emitted. This results in overpenetration of the iodine column and less contrast between the desired image and the background. Too high a kVp, thus washes out the image.

Keeping the kVp optimal and increasing the mA of the system produces better images, but at the cost of more energy and more radiation exposure. Increasing the pulse width results in a blurred image of the beating heart. Thus, it is difficult to increase either the kVp or the pulse width too much in acquiring images in the catheterization laboratory as the images would either be washed out or blurred. So when a greater dose of X ray is needed, the principle way to increase the dose is to increase the number of X rays sent (increase the mA).

The X-ray quantity is the number of X rays produced. When the mA is doubled, the number of X rays produced is doubled—a 1:1 relationship. The change in quantity is proportional to the square of the ratio of kVp, however. In other words, if the kVp is doubled, the quantity of X rays increases by a factor of 4—another reason to keep the kVp as low as possible.
for good image contrast. The X-ray intensity striking an object, such as a patient, also varies inversely by the square of the distance from the X-ray target—the inverse square law. Thus doubling the distance between the X-ray source and the patient reduces the intensity of the X rays by a factor of 4.

X-ray quality is similar to the penetrability or the ability of the X rays to penetrate through tissue. Distance and mA do not affect this, but, as outlined above, the kVp does. High-energy X rays penetrate tissue more than low energy. Filtration of the beam to get rid of low-energy X rays improves the quality. Barriers, such as a lead apron, reduce the penetration of X rays. The ability of these barriers to do their job is measured in the half-value layer (HVL). The HVL is the thickness of absorbing material necessary to reduce the X-ray intensity to half its original value.

**X-RAY INTERACTION WITH MATTER**

While X rays interact with matter in five basic ways: coherent scattering, the Compton effect, the photoelectric effect, pair production and photodisintegration, only the first three interactions are important in the cardiac catheterization laboratory. Electromagnetic radiation tends to interact with structures that are similar in size to the wavelengths of the radiation. X rays have very short wavelengths (from $10^{-8}$ to $10^{-9}$ m). The higher the energy, the shorter the wavelength. As a generality, low-energy electrons interact with atoms, moderate energy electrons interact with electrons and high-energy electrons interact with nuclei.

X-ray energy below about 10 keV interact with matter by coherent or classical scattering (Fig. 3.4A). In this situation the X ray interacts with an atom and it becomes excited, immediately releasing the same amount of excess energy but in a different direction from the incident X ray. This is simply scatter of energy with no ionization.

Both high- and low-energy X rays can interact with the outer shell electrons of an atom and not only ionize the atom, but can reduce its energy—the Compton effect. This occurs when the X ray knocks the outer shell electron from the atom (Fig. 3.4B). This scatters the X ray in a different direction and the ejected electron is referred to as a Compton electron. Both the scattered X ray and Compton electron may go on to interact with other atoms before they lose their energy. Scattered X rays provide no useful information and can produce a uniform haze on the image, resulting in loss of image contrast. They also are a major source of radiation hazard for both the patient and the operators.

Another interaction is the photoelectric effect wherein the X-ray photon is absorbed by an inner shell electron, ejecting the electron—now called a photoelectron (Fig. 3.4C). These photoelectrons may now interact with other atoms increasing scatter.

---

**Figure 3.4** X-ray interaction with matter. Shown is the classic Bohr atom. (A) **Coherent or classical scatter.** In this situation the energy of the incident X ray is diverted but loses no energy. The wavelength of the scattered X ray is the same as the incident X ray. (B) **Compton scatter.** In this situation the incident X ray knocks out the outer shell electron and ionizes the atom. The wavelength of the scattered X ray is greater than the incident X ray and a Compton electron is ejected. Both can now interact further with other atoms. (C) **Photoelectric scatter.** In this scenario the incident X ray is totally absorbed while knocking out an inner shell electron. The incident X ray disappears and the ejected electron is called a photoelectron and can now interact with other atoms.
Other interactions include pair production wherein an X ray interacts with the nuclear force field and two electrons of opposite charge are created. This interaction is not important in diagnostic X-ray imaging. Nor is photodisintegration, where high-energy X rays are directly absorbed by the nucleus and the excited nucleus releases a nucleon or other fragments.

The X-ray images you see is almost entirely created by how many X rays go through the patient unscathed and how many interact with matter by either the Compton or the photoelectric effect and are thus absorbed. The interaction of the X rays and tissue is proportional to the mass density of the tissue. Therefore bone absorbs more X rays than the lungs, and one must increase the X-ray dose to penetrate bone compared with the penetration of lungs.

In the end, only about 1% of the incident X rays from the X-ray tube make it through all this and reach the image intensifier or flat panel. Increasing the kVp of the system reduces the number of direct Compton scatter interactions but increases the photoelectric effect and the Compton scattering due to that. The result is that there is more X-ray scatter at high kVp, levels as mentioned above.

Grids are placed on the input of the image intensifier or flat panel to reduce imaging of scattered X rays. They improve image contrast, but the more the scatter, the higher the dose of X ray needed to obtain a satisfactory image. At the output of the image intensifier or flat panel, an automatic exposure control system analyzes the image produces and provides immediate feedback to the generator on whether the exposure equation has been fulfilled. The generator pulses the X rays and the fewer the frames/second used the lower the overall dose. Magnification occurs when only a central portion of the input face of the image intensifier is used or when the source-to-image distance (SID) is increased and many X-ray photons are lost because of the divergence of the X rays from the X-ray tube. Magnification always results in the need for a greater dose, therefore, and the avoidance of magnified views helps reduce X-ray radiation exposure.

RADIOBIOLOGY

It is clear that X rays are harmful to tissue. This is due to the interactions of X rays at the atomic level and the resulting ionization of the atoms or the deposition of the energy into the tissue. Deposited energy can result in a molecular change. Ionization changes the chemical bonding properties of the atom and can result in the molecule breaking up or the atom relocating within the molecule. This can result in the molecule no longer functioning and can impair or kill the cell.

The target radiosensitive molecule in the cell is the DNA. It is composed of a backbone of alternating segments of a sugar (deoxyribose) and a phosphate. Attached to the backbone is one of four nitrogenous bases (adenine, guanine, thymine or cytosine). The molecule is strung together in the familiar double helix ladder with the backbone of alternating sugar-phosphate molecules and the ladder rungs of the base pairs (adenine-thymine or guanine-cytosine). Mitosis is defined when the cell divides, and this is when the cell is most susceptible to radiation damage. Organs that are the most susceptible to radiation injury are therefore those that divide the most frequently (4) (Table 3.1). These tend to be bone marrow cells, lymphoid tissue and gonads. Stem cells are more radiosensitive than mature cells. Similarly, younger tissue, those with the highest metabolic rate and those with a high proliferation rate are the

### Table 3.1 Cell Type and Radiosensitivity

<table>
<thead>
<tr>
<th>Radiosensitivity</th>
<th>Cell type</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Lymphoid tissue</td>
</tr>
<tr>
<td></td>
<td>Bone marrow</td>
</tr>
<tr>
<td></td>
<td>Gonads</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Skin</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td></td>
<td>Cornea</td>
</tr>
<tr>
<td></td>
<td>Growing bone</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
</tr>
<tr>
<td></td>
<td>Thyroid</td>
</tr>
<tr>
<td>Low</td>
<td>Muscle</td>
</tr>
<tr>
<td></td>
<td>Brain</td>
</tr>
<tr>
<td></td>
<td>Spinal cord</td>
</tr>
</tbody>
</table>

Source: From Ref. 4.

most radiosensitive. Tissue is also more sensitive when irradiated in the oxygenated or aerobic state. Hyperbaric conditions have been used in radiation oncology to take advantage of this.

DNA injury from radiation can be either direct or indirect (Fig. 3.5A). Direct damage to the DNA backbone occurs when there is ionization of a backbone molecule and a break occurs.

Figure 3.5 DNA Injury. (A) Direct and indirect injury. DNA can be directly affected by the X-ray energy or may be injured by free radical formation. Two-thirds of injury is from free radicals. (B) Types of DNA injury. The injury to the DNA backbone can be a single break, a double break, a break and subsequent cross-linking or may be injury to the amino acid rungs of the DNA. Single breaks and noncontiguous breaks usually heal quickly. Source: From Ref. 5.
Indirect injury occurs when the X ray interacts with water producing electrically charged \( H_2O^+ + e^- \rightarrow H_2O + OH^- \). The free hydroxyl radical possesses nine electrons, so one of them is unpaired. It is highly reactive and can diffuse a short distance to reach DNA. About two-thirds of DNA injury is by free radical injury and about one-third by the direct effect of X rays.

When a DNA strand break occurs (Fig. 3.5B), it tends to be rapidly repaired using the opposite strand as a template. If the repair is incorrect (misrepair), it may result in a mutation. If both strands are broken but the places where the breaks occur are separated up and down the strand from each other, then healing tends to occur quickly. If both strands are broken in a similar place and the DNA breaks into two pieces, then the cell dies, a mutation is created or carcinogenesis occurs. Other types of DNA injury include a DNA break and then cross-linking with another piece of DNA or injury to the amino acid rungs of the DNA structure (rung breakage). These latter are also referred to as point mutations and can result in incorrect code being transferred to daughter cells. DNA damage can result in abnormal metabolic activity and uncontrolled growth of the tissue. For a chromosome break to be obvious a large amount of DNA must be destroyed.

A deterministic radiation injury is said to be present when a certain number of cells of an organ die following radiation injury, such as a skin burn. These types of injuries are dose dependent, and there is a threshold when the effects become obvious. A stochastic radiation injury results in radiation cancers or genetic effects and can occur with only a single DNA break. It, therefore, has no threshold dose, though the risk of a break increases linearly as the dose increases. Hormesis is a term used to describe the concept that a little radiation may be good for you (Fig. 3.6). The explanation is that a little radiation may stimulate hormonal or immune responses to other toxic environmental agents. The exact role of hormesis in reducing the risk of radiation has not been established and the concept remains controversial.

**RADIATION SAFETY ISSUES**

Definitions on how to describe the amount of radiation dose that is delivered to the tissue have varied over the years. The radiation absorbed dose (rad) is a measure of the energy absorbed per unit mass by an organ. It is expressed in units of mGy (milliGray). The absorbed dose depends on the absorbing material and the photon energy. One rad = 10 mGy. The effective dose (rem) strives to reflect the overall result of being exposed to ionizing radiation. It is an attempt to represent the amount of whole body radiation that occurs during radiation of only a portion of the body, such as in the catheterization laboratory. It is expressed in mSv (milliSieverts). The effective dose is derived from simulations of radiation exposure using mathematical models plus the radiation weighting factor (for X rays it is 1.0) plus tissue-specific weighting factors. One rem = 10 mSv.

Table 3.2 outlines the estimated effective dose for a variety of cardiovascular imaging procedures to order to put cardiac catheterization radiation dosage in perspective. We live on a radioactive planet and are exposed to cosmic radiation as well as man-made sources. Background radiation includes about 82% from natural resources and 18% from man-made radiation. Of the background radiation, the bulk (55%) comes from earth radon (α particle) exposure, with the average total background radiation exposure in the United States around 3.6 mSv. If a routine PA chest X ray results in 0.04 mSv of exposure, we therefore receive the equivalent of about 90 chest PA X rays per year from background radiation. Patient exposure in the cardiac catheterization laboratory amounts to about 7 mSv for a diagnostic catheterization (twice background) and around double that for a coronary interventional procedure.

To gauge how much radiation exposure the operator receives, a radionuclide badge of some sort is used—either a thermoluminescent dosimeter (TLD) or by an optical simulated luminescent (OSL) badge. TLD badges utilize a LiF crystal to absorb X rays and release light photons proportional to the absorbed dose. The absorbed dose is converted to mSv by a calibration factor. The calibration factor varies depending on the type of radiation, the material and the photon energy. One rad = 0.1 mSv.

### Table 3.2 Representative Values for the Effective Dose Estimates for Various Cardiovascular Imaging Studies

<table>
<thead>
<tr>
<th>Cardiovascular study</th>
<th>Representative effective dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background radiation</td>
<td>3.6</td>
</tr>
<tr>
<td>Chest X ray (PA and lateral)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diagnostic cardiac catheterization</td>
<td>7</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>15</td>
</tr>
<tr>
<td>Coronary calcium computed tomography</td>
<td>3</td>
</tr>
<tr>
<td>Coronary CTA (unigated)</td>
<td>15</td>
</tr>
<tr>
<td>Coronary CTA (triggered)</td>
<td>3</td>
</tr>
<tr>
<td>Myocardial perfusion</td>
<td>3</td>
</tr>
<tr>
<td>Sestamibi (99mTc 1-day protocol)</td>
<td>9</td>
</tr>
<tr>
<td>Sestamibi (99mTc 2-day protocol)</td>
<td>13</td>
</tr>
<tr>
<td>Thallium-201</td>
<td>41</td>
</tr>
<tr>
<td>F-18 FDG</td>
<td>14</td>
</tr>
<tr>
<td>Rubidium-82</td>
<td>5</td>
</tr>
<tr>
<td>MUGA (99mTc-labeled RBCs)</td>
<td>8</td>
</tr>
</tbody>
</table>

**Source:** From Refs. 3, 7, and 8.

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![Figure 3.6](image) The concept of hormesis. A radiation dose-response curve is shown suggesting a reduced response at low doses of radiation exposure. **Source:** From Ref. 6.
X rays absorbed when heated. The OSL badge contains an aluminum oxide doped with carbon and releases light in proportion to the X rays absorbed when later struck with a laser. Differing filters mimic attenuation one might expect for shallow, lens or deep exposure. Proper use of radiation badges is to wear them exposed on the thyroid collar and under the lead apron at the waist. Unfortunately, few wear the waist badge, so most data related to exposure is derived from the thyroid collar badge.

Radiation to the patient is difficult to quantitate. It can be estimated using the DAP (dose-area-product) and/or the interventional reference point (IRP). These concepts are shown in Figure 3.7. The DAP is measured by means of an ionization chamber placed at the output of the X-ray tube. It is the absorbed radiation dose to air kerma multiplied by the X-ray beam cross-sectional area at the point of measurement. It is expressed in Gy/cm². It is an attempt to estimate how much X-ray dose exited the X-ray tube during the study. An average value for a diagnostic catheterization is about 45 Gy/cm² and for an interventional procedure about 75 Gy/cm² (9), though recent values of much higher values have also been reported (10). Values of DAP over 300 Gy/cm² are more likely to result in skin injury to the patient (11). In pediatrics, the values have been much lower than in adults, with diagnostic DAP values of 7.77 Gy/cm² and even PDA closure values of only 23.21 Gy/cm² (12). Because stochastic effects are cumulative, some have suggested the DAP be a permanent part of each patient’s record (13). It is only a surrogate, though, for the total amount of radiation actually delivered to the patient.

The IRP is an attempt to figure out how much dose was delivered to the patient’s skin. It is determined by assuming the patient’s skin is about 15 cm from the isocenter (9,14). If one knows the distance from the X-ray tube to the isocenter, then the distance to the skin facing the X-ray tube is presumed 15 cm toward the X-ray tube. The delivered X-ray dose at that point can then be estimated from the DAP and the distance to the skin (1/d²). If the calculated value is >4 Gy, it is likely the patient may develop a skin rash (9).

**Figure 3.7** The dose-area-product (DAP) and the IRP. The DAP is calculated from the output of the X-ray tube by use of an ionizing chamber. It represents total X-ray energy emitted from the X-ray tube. The IRP is determined by assuming the skin of the patient is 150 mm from the isocenter of the patient’s body. Abbreviation: IRP, interventional reference point.

RISKS FROM IONIZING RADIATION

The health effects from radiation has been the subject of much debate over the years. The Committee on the Biological Effects of Ionizing Radiation (BEIR), an arm of the National Academy of Sciences recently published the seventh in a series of reports on the issue (BEIR VII) (15). In it they support the concept of a “linear-no-threshold” model for cancer risk. This assumes that even the smallest dose of ionizing radiation carries a tiny, but potential risk. The committee pointed out the risk is a function of age at exposure, the known gap between exposure and manifestation of disease and whether the response was absolute or relative. There is a latent period after exposure before the risk of cancer is manifest. The magnitude of this risk is strikingly low, however, and for most occupational radiation exposure the chances of dying in a year is about equivalent to the risk of air travel.

Linear energy transfer (LET) is a measure of the rate at which energy is transferred from ionizing radiation to tissue. Alpha particles (such as radon) have a high value for LET (100 keV/µm) while diagnostic X rays have a low value (3 keV/µm). Low LET results in less damage to the tissues. The BEIR VII report defines low doses in the range of near zero to about 100 mSv of low LET radiation (15). Using data from the Japanese atomic bomb survivors, about 60% of survivors were exposed to less than 100 mSv. On average, assuming a sex and age distribution similar to the U.S. population, 1 in 100 persons would be expected to develop cancer from exposure of 100 mSv while 42 in 100 would develop cancer from other causes. At doses less than 100 mSv, the BEIR VII committee concluded that the risk would be extremely low and would drop linearly with no threshold (15) as demonstrated in Figure 3.8. The BEIR committee did not feel there was evidence to support any benefit from low doses of radiation—the hormesis described above.

**Figure 3.8** Linear risk of cancer. While there are both linear and nonlinear models for cancer risk from radiation, the latest BEIR VII consensus report suggest a linear model is appropriate for low-dose exposure. The graph, however, is derived from high-dose single exposures experienced in Japan and Chernobyl after nuclear accidents, and the ability to extrapolate to the low levels used in medical imaging remains controversial. Source: From Ref. 6.
PATIENT RISKS
As shown in Figure 3.1, as X rays leave the X-ray tube and traverse the patient, they are absorbed and scattered. When only local tissue is irradiated, it takes a higher dose to produce an adverse response, as opposed to the risk from whole body irradiation. The effect on any particular organ is individual cell death and shrinkage of that organ or tissue. It also takes a threshold level to produce a noticeable change in the organ’s function— a deterministic response to radiation. Once the threshold has been reached, then the severity of the adverse response increases with dose.

The patient’s skin first greets X rays in the catheterization laboratory and receives the brunt of the radiation injury during cardiac catheterization. Table 3.3 outlines the threshold doses for skin injury and the timing when these injuries become evident after exposure. Certain diseases appear to predispose the patient to skin injury from radiation, including collagen vascular disease, diabetes mellitus, hyperthyroidism, ataxia telangiectasia and prior exposure to radiation (9,18,19).

The risk of a stochastic skin effect (cancer) is difficult to estimate, but the relative risk of 4:1 has been reported from exposure of 5 to 20 Gy, 14:1 from 40 to 60 Gy, and 27:1 from 60 to 100 Gy (20). Stochastic effects are cumulative; though it is very unlikely patients would receive doses of this magnitude from low radiation studies such as cardiac catheterization.

The risk of stochastic effects to other organs in the patient is incompletely known, but there may be a small but detectable increase in solid tumors at doses as low as 100 mSv (21). The general risk of a fatal cancer has been estimated at 0.004% to 0.12% for each 10 mSv exposure (9). Newborns are estimated to be 10 to 30 times more sensitive to radiation and females appear more susceptible than males (22).

Pregnancy is a special situation. Fetal risk is greatest during the first trimester. The risk of leukemia has been estimated at 0.06% per 10 mSv exposure. The risk of later adult cancer is unknown. Neurologic tissue appears to be at greatest risk and mental retardation after the atomic bomb survivors was observed. Pregnancy is not an absolute contraindication to cardiac catheterization. Shielding from direct X-ray exposure is relatively effective when the heart is imaged, and it has been estimated that less than 2% of the delivered dose scatters to reach the uterus (9).

OCCUPATIONAL RISKS
Occupational risks from radiation in the cardiac catheterization laboratory are poorly understood, but by all measures they are quite low. One way to look at this is shown in Table 3.4 where it is suggested that a radiation worker can expect to lose only 12 days from his lifespan compared with heart disease that would result in 2100 days lost, for instance.

Despite these reassuring data, a recent consensus statement from the major American societies of physicians who work in the interventional laboratory environment sends an alarm that the risk is simply not well defined (23). The group notes the epidemic of orthopedic issues in these environments, and cites case reports of increased cancers, particularly of the brain (24) and bone marrow (25). They point out that there is no shielding of the central nervous system, and that radiation exposure has been associated with neural tumors. The also suggest that cataract formation may be a stochastic and not deterministic effect, and that the dose upper limits may currently be too high to protect. Finally they lament that many interventional cardiologists may be exposed to over 30 years of radiation with no real data to know the actual risks involved.

Table 3.3 Threshold Skin Entry Doses That Result in Skin Injury

<table>
<thead>
<tr>
<th>Dose (2000 mSv)</th>
<th>Effect</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Gy</td>
<td>Erythema</td>
<td>1 hr</td>
</tr>
<tr>
<td>4–6 Gy</td>
<td>Late erythema</td>
<td>10 days to 10 wk</td>
</tr>
<tr>
<td>7 Gy</td>
<td>Hair loss</td>
<td>3 wk</td>
</tr>
<tr>
<td>10 Gy</td>
<td>Atrophy, fibrosis</td>
<td>14 wk to 1 yr</td>
</tr>
<tr>
<td>6–18 Gy</td>
<td>Necrosis</td>
<td>10 wk to 1 yr</td>
</tr>
<tr>
<td>Unknown</td>
<td>Skin cancer</td>
<td>&gt;5 yr</td>
</tr>
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</table>

Source: From Refs. 9 and 17.

Table 3.4 Days of Life Lost as a Consequence of Occupation, Disease, or Other Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Expected days of life lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Being male (vs. female)</td>
<td>2800</td>
</tr>
<tr>
<td>Heart disease</td>
<td>2100</td>
</tr>
<tr>
<td>Being unmarried</td>
<td>2000</td>
</tr>
<tr>
<td>One pack of cigarettes a day</td>
<td>1600</td>
</tr>
<tr>
<td>Coal mining</td>
<td>1100</td>
</tr>
<tr>
<td>Cancer</td>
<td>980</td>
</tr>
<tr>
<td>30 lb overweight</td>
<td>900</td>
</tr>
<tr>
<td>All accidents</td>
<td>435</td>
</tr>
<tr>
<td>Radiation worker</td>
<td>12</td>
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<tr>
<td>Airplane crashes</td>
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Source: From Ref. 20.

Table 3.5 Recommended Radiation Effective Dose Limits

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<th>Source</th>
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<tr>
<td>Airplane crashes</td>
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<tr>
<td>One pack of cigarettes a day</td>
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<tr>
<td>Coal mining</td>
<td>1100</td>
</tr>
<tr>
<td>Cancer</td>
<td>980</td>
</tr>
<tr>
<td>30 lb overweight</td>
<td>900</td>
</tr>
<tr>
<td>All accidents</td>
<td>435</td>
</tr>
<tr>
<td>Radiation worker</td>
<td>12</td>
</tr>
<tr>
<td>Airplane crashes</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: From Refs. 26 and 27.
considerable variability in the estimated dose (29), further adding to the uncertainty of these guidelines. This has contributed to the wide variations in the radiation doses to operators that have been reported (28).

Exposure is highest on the left side of the body because of the relationship of the operator to the X-ray tube and patient (28). Indeed the location of the operator to the X-ray tube is critical. In an LAO cranial view, the X-ray tube is closest to the operator and the dose received may be six times that from the 30° RAO view where the X-ray tube is on the opposite side of the table (16) (Fig. 3.9). Studies performed by the radial method may result in a substantial increase in operator radiation exposure (30).

Operator exposure comes from both scattered radiation from the patient and directly from the X-ray tube (including leakage). As a general rule, the closer you are to the X-ray tube itself, the greater your radiation exposure. Similarly, the greater the dose used, the greater your exposure. Thus, when the SID is wide, the divergence of X rays means that many X rays will not strike the receiving image device and many will be lost. A wide SID therefore requires more X-ray dose and results in more exposure to both the patient and the operator. The use of magnified views also results in the need for more dose to satisfy the exposure equation and more radiation to both the patient and the operator as well. Pulsed fluoroscopy at rates below 25 pulses/sec reduces dosage, but not at higher rates (31). Table 3.6 outlines the various means by which one can reduce radiation to the patient and to the operator during cardiac catheterization. As one editorial pleaded: “Shielding really works when you use it” (35). It is important to remember that not only are operators exposed over a long period, many patients will have multiple procedures using ionizing radiation over a lifetime, and stochastic risks are cumulative. Also recall that obese patients require greater doses as well, and with the epidemic of overweight people in this country, the average X-ray dose per patient has gone up.

In the end, remember the ALARA principle: (i) assume there is no absolutely safe dose of ionizing radiation; (ii) recall the smaller the dose, the less risk of an adverse event; and (iii) incremental radiation doses have a cumulative effect.

Table 3.6 Ways to Reduce Radiation Exposure in the Cardiac Catheterization Laboratory

<table>
<thead>
<tr>
<th>Patient specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vary views to minimize dose to any specific skin area</td>
</tr>
<tr>
<td>Shielding of gonads</td>
</tr>
<tr>
<td>Use of the interventional reference point to estimate skin deterministic risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>To both the patient and operator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proper collimation of the X-ray beam</td>
</tr>
<tr>
<td>Use of filters at the output of the X-ray tube</td>
</tr>
<tr>
<td>Keep the image intensifier as close to the patient as possible (minimize the source-to-image distance)</td>
</tr>
<tr>
<td>Use the lowest framing rate possible</td>
</tr>
<tr>
<td>Use high-dose fluoroscopy only when absolutely necessary</td>
</tr>
<tr>
<td>Use pulsed fluoroscopy</td>
</tr>
<tr>
<td>Keep magnified views to a minimum</td>
</tr>
<tr>
<td>Use the minimum number of views</td>
</tr>
<tr>
<td>Pay attention to angulated views</td>
</tr>
<tr>
<td>Record the dose-area-product to look for ways to minimize dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operator specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remember: time/distance/barriers</td>
</tr>
<tr>
<td>Stay as far from X-ray source and patient scatter as possible</td>
</tr>
<tr>
<td>Use all available shielding, barriers and eyewear</td>
</tr>
<tr>
<td>Keep track of exposure by use of radiation badges</td>
</tr>
<tr>
<td>Pay attention to relationship of patient, the X-ray source and you</td>
</tr>
</tbody>
</table>

Source: From Refs. 9 and 32–34.

REFERENCES


Contrast agents

Michael C. Reed and Hitinder S. Gurm

INTRODUCTION

Contrast agents used in the cardiac catheterization laboratory are effective in the radiographic visualization of the cardiac chambers and/or the coronary and peripheral vasculature. However, these agents are associated with potential adverse effects. Therefore, they have been modified over the years to allow for the most effective imaging at the lowest potential toxicity. This chapter will discuss the types of contrast agents, their toxicity, and the evidence-based methods designed to prevent adverse effects.

TYPES OF CONTRAST AGENTS

Various formulations of contrast agents containing iodine have been used over the years to visualize the vasculature. All of these formulations have similar concentrations of iodine, but differ significantly in their structure, osmolality, and viscosity (Table 4.1 and Fig. 4.1).

First-generation, high-osmolality contrast media (HOCM) are ionic monomers, which consist of a single, negatively charged tri-iodinated benzene ring attached to sodium or another cation. As ionic media, they dissociate in solution and can cause cardiotoxicity related to calcium binding and repolarization changes during coronary angiography (2). Included in this category are diatrizoate (Hypaque, Angiovisat, Renografin), metrizoate (Isopaque), and iothalamate (Conray). First-generation agents have a sodium concentration similar to blood, but are hyper-osmolar relative to blood. Osmolality is typically >1400 mOsm/kg compared with 290 mOsm/kg found in blood. Both the ionicity and hyperosmolality of these agents contribute to significant volume shifts and to direct toxic effects on the left ventricle and other organs.

Second-generation, low-osmolality contrast media (LOCM) were designed, in part, to minimize side effects related to hypertonicity. Among the first such agents was the ionic dimer ioxaglate (Hexabrix). Ioxaglate is a monoacidic double benzene ring with a total of six molecules of iodine at the 2, 4, and 6 positions on each ring. This agent can be used to visualize the vasculature at an osmolality of 600 mOsm/kg, twice that of blood, but less than half that of HOCM. Early studies confirmed that ioxaglate was associated with fewer side effects compared with HOCM (3).

LOCM were further developed in the nonionic form. Monomeric forms of nonionic contrast agents are tri-iodinated with many hydrophilic hydroxyl groups and have an osmolality between 500 and 850 mOsm/kg, two to three times that of blood. These include iopamidol (Isovue), iohexol (Omnipaque), iopromide (Ultravist),ioxilan (Oxilan), and ioversol (Optiray). Water soluble and without charge, the nonionic LOCM could cause less ventricular irritability than its ionic predecessors, but generally have a higher viscosity. Nevertheless, there appears to be no increased risk of thrombotic events compared with ionic agents (4). Additionally, nonionic LOCM are associated with less nephrotoxicity and fewer allergic reactions compared with HOCM (5–7).

There is some evidence that a nonionic contrast agent with an osmolality similar to blood may be safer than LOCM. Iodixanol (Visipaque) is a nonionic dimer which consists of two tri-iodinated benzene rings. It has an osmolality the same as blood (290 mOsm/kg). Iso-osmolar contrast media (IOCM) have a higher viscosity than HOCM and LOCM, but have been shown in some studies to cause fewer allergic reactions and are not associated with increased adverse coronary events (4,8). Iodixanol was associated with less nephropathy than ioxaglate in one randomized trial, and a meta-analysis of multiple small trials comparing LOCM and iodixanol suggests iodixanol is less nephrotoxic (9,10). More recent randomized trials, however, have not shown a reduced incidence of contrast-induced nephrotoxicity due to iodixanol compared with other LOCM (11,12). However, multiple trials have shown a reduction in patient symptoms, allergic reactions, and organ toxicity with LOCM or IOCM compared with HOCM.

CHEMOTOXIC REACTIONS

Contrast reactions can be divided into two major categories: chemotoxic reactions and hypersensitivity reactions. Hypersensitivity reactions, or allergic reactions, are idiosyncratic and independent of rate or volume of contrast infusion. Chemotoxic reactions are related to the chemical properties of the agents and are dose and rate dependent. These include volume overload, vasovagal reactions, cardiotoxicity, and nephrotoxicity.

Volume Overload
Most contrast media used in contemporary cardiac catheterization are hyper-osmolar relative to blood. First-generation agents have an osmolality which is up to six times that of blood. Even LOCM have two to three times the osmolality of blood. Rapid infusion of large amounts of contrast can result in large fluid shifts from the extravascular to the intravascular space, causing elevated filling pressures or even cardiogenic pulmonary edema in the supine patient. Use of LOCM or IOCM, or minimization of contrast volume, or deferral of angiography altogether may be considered in patients with evidence of volume overload on history, physical exam, or direct measurement of left ventricular end-diastolic pressure or pulmonary capillary wedge pressure.
Vasovagal Reactions

It is very common for patients to experience a sensation of flushing, warmth, or nausea with the injection of contrast media. This is typically mild, transient, and self-limited. Rarely, this sensation can persist, and severe forms have been associated with hypotension and bradycardia. The mechanism of vasovagal reactions from contrast is not known. These reactions should be distinguished from hypersensitivity reactions prior to further injection of contrast media. Vasovagal reactions do not preclude further injection of contrast media, and slowing the rate of injection may ameliorate further symptoms. Because patients rarely can have prolonged bradycardia or severe hypotension related to increased vagal tone, it is advisable to disconnect the catheter from the power injector and reconnect to the manifold to assess hemodynamics after a large, rapidly-infused bolus of contrast media, such as with ventriculography.

Cardiotoxicity

Cardiotoxicity is less common with the introduction of non-ionic LOCM and IOCM. The mechanism of direct cardiotoxicity is not well understood, but may involve the hypertonicity of these agents or calcium-chelation of anions which dissociate from ionic contrast compounds. Observed electrocardiographic changes include sinus bradycardia, heart block, QRS widening, QT prolongation, ST segment changes, and giant T wave inversion. Ventricular tachycardia and ventricular fibrillation may also rarely occur, especially when injecting into a dampened (ventriculized) coronary catheter. Transient left ventricular systolic dysfunction and elevated left ventricular end-diastolic pressure have also been observed after contrast exposure. Strategies to minimize contrast toxicity include using a ramped coronary injection, using the least amount of contrast possible to fill the coronary artery, and counseling the patient to cough to clear contrast from the coronary tree in the event of an arrhythmia.

Nephrotoxicity

A common and important chemotoxic contrast reaction is contrast-induced nephropathy (CIN). In some patients, particularly those with preexisting chronic renal insufficiency, contrast media causes a significant rise of serum creatinine in the first few days after exposure. It typically begins in the first 12 to 24 hours, peaks at two to three days, and resolves over five to seven days following exposure. The renal failure is typically
nonoliguric, and the need for dialysis is highly uncommon (<0.1%) (13).

The exact change in creatinine that defines CIN has varied from study to study, but the conventional definition is an absolute rise of serum creatinine of >0.5 mg/dL or a 25% increase from baseline serum creatinine.

Epidemiology
Nephrotoxicity from contrast media is a common cause of acute renal failure in hospitalized patients. The incidence of CIN varies depending on the presence of risk factors, the type of contrast media, and the volume of contrast media. The incidence is 1.2% to 1.6% (14,15). In patients with mild to moderate renal insufficiency (serum creatinine 1.5–4 mg/dL), the incidence is 4% to 11% (6,14,16,17). This increases to 10% to 40% in patients with mild to moderate renal dysfunction and diabetes mellitus, and approaches 50% in patients with severe renal insufficiency (serum creatinine of 4–5 mg/dL) (6,14,18). In a Mayo Clinic registry of 7586 patients undergoing percutaneous coronary intervention (PCI), the incidence of renal insufficiency (defined as a rise in creatinine of 0.5 mg/dL) was 3.3% overall and 25% in patients with a baseline serum creatinine >2.0 mg/dL (19). It should be noted that this study did not separate causes of renal failure, and likely included some cases of renal failure related to atheroemboli or hemodynamic instability.

Prognosis
Very few patients with CIN require hemodialysis (<0.1%), but CIN does increase hospital stay and is associated with worse short-term and long-term prognosis (13). In the Mayo Clinic registry, the mortality was 22% in those patients with acute renal failure following PCI compared with 1.4% in those without renal failure (19). In a similar retrospective analysis of 9067 post-PCI patients, the one-year survival of patients with renal failure was 70.3% versus 93.6% without renal failure (20). Although a creatinine rise of 0.5 mg/dL may not seem significant, a retrospective analysis of 16,248 patients showed that even small rises in creatinine were associated with increased mortality risk (21,22).

Pathophysiology
The exact pathophysiology of CIN is not clear, although many potential mechanisms have been implicated. Because of the typically transient and self-limited nature of CIN and because of the frequent presence of concomitant etiologies of chronic kidney disease, renal biopsy is rarely performed. Animal models have shown changes consistent with acute tubular necrosis (ATN) (23,24). However, recovery from CIN is faster than the two to three weeks expected after other types of ATN. This suggests less severe or less permanent damage to tubular cells, analogous to that observed with myocardial stunning after an ischemic event. In addition, the fractional excretion of sodium (FENa) observed in CIN is often <1%, which suggests prerenal hypoperfusion, as opposed to frank tubular necrosis.

One proposed mechanism of contrast nephrotoxicity is renal artery vasoconstriction. A transient increase in renal blood flow, followed by a prolonged decrease has been observed in CIN (25). The outer medulla seems particularly vulnerable to damage from decreases in renal blood flow. There is evidence for decreased nitric oxide (NO) and increased adenosine and endothelin levels in subjects exposed to contrast media (26–28). NO is necessary for renal artery and arteriolar vasodilation. In comparison, increased levels of endothelin and adenosine may promote vasoconstriction (29). This forms the rationale for the experimental prophylactic drug theophylline, an adenosine receptor antagonist.

Reduction in blood flow to the renal tubules and to the renal medulla may also be related to the hyperviscosity of contrast media. The renal medulla is supplied by the vasa recta, a collection of long, narrow-caliber vessels. Blood flow through these small-diameter vessels may be particularly susceptible to changes in viscosity.

In addition to medullary hypoxic ischemia from decreased renal blood flow, there may be direct cytotoxic effects of contrast media on renal cells (24). There is some evidence that oxygen free radical generation may be increased after contrast media exposure. On the basis of this line of reasoning, the antioxidant acetylcysteine has been investigated for prophylaxis of CIN.

Risk Factors
There are modifiable and nonmodifiable risk factors that predispose patients to CIN. These risk factors are likely additive. Identification and modification of risk factors is crucial to minimizing nephrotoxicity.

Age is an independent predictor of CIN in observational studies and by multivariable analysis (30). The incidence of CIN in patients greater than 70 years is approximately 11% (15). This likely reflects the fact that elderly patients tend to have a lower glomerular filtration rate (GFR) and more medical comorbidities. In addition, the elderly are more likely to have multivessel coronary artery disease and to require PCI, which translates to more contrast media exposure.

The most important predictor of CIN is the presence of underlying renal insufficiency. Chronic renal insufficiency (creatinine >1.5 mg/dL or GFR <60 mL/min/1.73 m squared) is consistently shown to increase the risk of CIN (15,19,31). In addition, the incidence of CIN increases dramatically with the severity of chronic renal insufficiency. This is especially true when underlying renal insufficiency is due to diabetes mellitus.

Inadequate renal perfusion in the setting of congestive heart failure or hemodynamic instability is also associated with increased risk for CIN. This is particularly true in the setting of a large anterior myocardial infarction or the need for intra-aortic balloon counterpulsation (15,32). Anemia has also been identified as an independent risk factor in multivariable analysis, perhaps related to decreased oxygen delivery to tubular cells (33).

It is intuitive that nephrotoxic drugs would further increase the risk of CIN. Nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, and other nephrotoxins should ideally be avoided. The use of ACE inhibitors is controversial, and studies examining whether these medications increase risk have had mixed results (34,35).

Multiple myeloma has been associated with increased risk of CIN. This is particularly true with HOCM. The incidence is likely <1.5% with newer agents. There may be an interaction between contrast media and light chains, promoting deposits in the tubules. Volume depletion, in particular, tends to cause tubular precipitation of light chains after contrast media exposure. The dose and the type of contrast medium used also influences the likelihood of CIN.

Cumulative risk prediction models have been designed to help predict the risk in a given patient (32). Freeman et al. developed a method of calculating a maximum predicted
Use of low-osmolar or sodium bicarbonate 3 mL/hr IV for 1 hr prior to procedure. Minimize contrast volume. Biplane imaging, limited injections, staged procedures.

Table 4.2 Prevention of Contrast-Induced Nephropathy

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Proven efficacy?</th>
<th>Recommended?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% saline</td>
<td>1 L IV prior to procedure</td>
<td>Dilution</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Minimize contrast volume</td>
<td></td>
<td>Biplane imaging, limited</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>injections, staged</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of low-osmolar or iso-osmolar</td>
<td>600 mg PO BID day prior and</td>
<td>Antioxidant</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>contract contrast</td>
<td>day of procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcysteine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>3 mL/hr IV for 1 hr prior and</td>
<td>Alkalization</td>
<td>Controversial</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 mL/hr IV for 6 hr after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td></td>
<td>Antioxidant</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Fenoldopam, dopamine,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prostaglandin E1, or theophylline</td>
<td></td>
<td>Improved renal artery</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td></td>
<td>perfusion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: IV, intravenous.

Contrast media dose (MRCD = 5 mL × body weight (kg)/serum creatinine (mg/dL)). Exceeding this threshold was determined to be the strongest independent predictor of CIN requiring hemodialysis after PCI.

Clinical Features

CIN typically begins in the first 12 to 24 hours after contrast media exposure. Creatinine usually peaks between 48 and 72 hours, and renal function typically improves over the next five to seven days. Renal failure is typically nonoliguric, mild, and transient. The need for hemodialysis is only 0.8% in patients who develop CIN after PCI (31). Not surprisingly, the need for hemodialysis translates into a bad outcome, with an in-hospital mortality 36% (versus 1% of patients without hemodialysis) and a two-year mortality of 81% (31).

It is important to consider other causes of renal insufficiency after contrast exposure. These include, but are not limited to renal hypoperfusion or even ATN in the setting of congestive heart failure, volume depletion, or sepsis; atheroemboli; interstitial nephritis; or obstructive uropathy. Renal failure related to atheroemboli is highest in patients with peripheral vascular and/or abdominal aortic aneurysmal disease who undergo cardiac catheterization. Unlike CIN, it may have a delayed onset, days or even weeks after catheterization. Atheroemboli are associated with blue toes, livedo reticularis, fever, hypeereosinophilia, hypocomplementemia, and ghost-like clefts on renal biopsy from vacated cholesterol crystals. Unlike CIN, a high percentage of patients with atheroemboli-related renal insufficiency require hemodialysis, and recovery of renal function is minimal (36).

Urinalysis in CIN may reveal either low or elevated FENa, presumably depending on degree of prerenal hypoperfusion versus actual tubular injury. Urine protein may be elevated for the first 24 hours after contrast media exposure. Biopsy is rarely performed. By and large, the diagnosis of CIN is a clinical diagnosis with the characteristic features described above.

Prevention

The treatment of CIN is essentially supportive care for acute renal insufficiency, with attention paid to electrolyte and volume abnormalities. The most effective treatment for CIN is prevention. Recognition of patients at risk is the first step. Identification of risk factors, and measurement of serum creatinine with estimation of GFR or creatinine clearance prior to contrast exposure is essential. Use of an alternative diagnostic modality such as ultrasound or magnetic resonance imaging when possible is optimal, especially in those patients identified to be at high risk. Nephrotoxic medications should be held, when possible. In addition to these general tactics, there are specific preprocedural and procedural methods which are effective in minimizing the risk of CIN (Table 4.2).

Hydration

There are no prospective randomized trials comparing hydration with no hydration, but there is universal consensus that hydration is beneficial. The efficacy of hydration in minimizing CIN may be related to dilution of contrast. In addition, there is evidence that hydration minimizes the reduction of nitrous oxide in the renal circulation. In an early study evaluating various methods of prophylaxis against CIN in patients with chronic renal insufficiency, 0.45% saline was associated with a significantly lower incidence of CIN (11%) than 0.45% saline + mannitol (28%) or 0.45% saline + furosemide (40%) (37). Mueller et al. established that 0.9% saline reduced CIN by more than half compared with 0.45% saline in patients who received angioplasty (38). Finally, two trials helped establish that intravenous (IV) saline was superior to oral hydration with salt tablets (39,40). The optimal dose of hydration is not clear, and regimens may need to be modified in patients with impaired left ventricular function or evidence of preexisting volume overload on physical exam.

Isotonic sodium bicarbonate has been proposed as an alternative form of hydration for prevention of CIN. Alkalization may further protect from free radical-induced tubular injury or may decrease the viscosity of contrast agents passing through the vasa recta of the kidney. A reduction in CIN (defined as a 25% increase in serum creatinine) was found in a small study of 119 patients randomized to isotonic sodium bicarbonate (CIN incidence 1.7%) versus normal saline (CIN incidence 13.6%) (41). Several subsequent trials have demonstrated mixed results. The REMEDIAL trial showed a significant reduction in the incidence of CIN in 326 patients with mild to moderate baseline renal insufficiency (serum creatinine > 2.0 mg/dL) treated with isotonic sodium bicarbonate +...
acetylcysteine (1.9%) versus normal saline + acetylcysteine (9.9%) versus normal saline + acetylcysteine + vitamin C (10.3%) (42). A subsequent trial of 356 high-risk patients, however, revealed no benefit of isotonic sodium bicarbonate compared with isotonic saline alone (43). Two recent meta-analyses of sodium bicarbonate studies concluded that it probably does reduce the incidence of CIN compared with saline alone, but the results may be exaggerated by publication bias (44,45). Nevertheless, routine prophylactic use of sodium bicarbonate for prevention of CIN remains controversial.

**Type of contrast** Some LOMC have been shown to reduce the incidence of CIN in patients with preexisting mild to moderate renal insufficiency when compared with HOMC (5,7,16,46). A randomized trial of more than 1100 patients referred for coronary angiography compared the LOMC iohexol with the HOMC diatrizoate (16). In patients with baseline serum creatinine > 1.4 mg/dL, the incidence of CIN (defined as a rise in creatinine of 1.0 mg/dL) was significantly lower with iohexol compared with diatrizoate (7.2% vs. 15.8%). This difference was even more profound in diabetic patients (11.8% vs. 27%).

The nonionic, IOMC ioxilan, has been compared with various types of LOMC in a number of randomized trials. Some randomized trials have shown a reduced incidence of CIN with ioxilan, while others have not (9,11,12,47). A meta-analysis of 16 trials comparing ioxilan with LOMC concluded that ioxilan was less nephrotoxic, but many of the trials were not designed with CIN as the primary endpoint, and thus the analysis may have suffered from ascertainment bias (10). In addition, the difference was driven primarily by a large trial which compared ioxilan with the LOMC ioxaglate, which is generally considered to be inferior to other, nonionic LOMC. A more recent meta-analysis of 17 trials specifically showed no difference CIN between ioxilan and a pool of various LOMC (48). At this point, it is not clear that ioxilan is superior to all nonionic LOMC, so large prospective randomized trials are needed.

In the highest risk patients, there is some experience with using gadolium-containing contrast agents as a substitute for iodinated contrast (49–51). Gadolinium has rarely been associated with nephrotoxicity, but it should be used with caution in patients with moderate to severe renal failure, given the increased risk of nephrogenic systemic fibrosis. CO2 has also been used in the peripheral vasculature, but it must be limited to below the diaphragm because of the potential risk of cerebral embolization, and digital subtraction angiography must be used (52,53).

**Volume of contrast** Volume of contrast administered is crucial to the development of CIN, and minimization of contrast volume is of utmost importance in its prevention (54,55). The mean volume of contrast administered during cardiac catheterization is 130 mL for diagnostic procedures and 191 mL for interventional procedures (56). In patients with chronic renal insufficiency or other conditions which put them at risk for CIN, techniques such as use of biplane cameras, limiting contrast puffs, minimizing cine runs, or staging interventional procedures until at least 72 hours after a diagnostic procedure can be useful.

**Potential Prophylactic Therapy**

**Antioxidant therapy** Given the possibility of contrast-mediated oxidative kidney injury in CIN, prophylactic use of the antioxidant, acetylcysteine has been evaluated. An early randomized trial showed a marked reduction in CIN in 83 patients randomized to saline + 600 mg twice daily acetylcysteine versus saline alone (2% vs. 21%) (57). Further studies suggest that 1200 mg twice daily may be superior to 600 mg twice daily, with a reported CIN incidence of 8% versus 15% (58). Some trials have shown equal benefit of IV and oral acetylcysteine, but there is a risk of anaphylaxis with the IV form (58,59). Since the promising original trial, several randomized prospective trials have shown no benefit for acetylcysteine compared with hydration alone (60–62). Meta-analysis have demonstrated trends toward overall benefit, but the trials are heterogeneous and the results are inconsistent (63). Given that the agent is well-tolerated and may have benefit, the use of acetylcysteine for prevention of CIN in patients with chronic renal insufficiency is routine at most centers.

**Inhibition of renal artery vasoconstriction** Fenoldopam is a selective D-1 receptor agonist. In theory, it could improve renal artery perfusion and attenuate the deleterious effects of contrast media on the kidney. However, systemic infusions of fenoldopam + saline have failed to reduce CIN compared with saline alone in two controlled studies (64,65). Intravenous fenoldopam using a bifurcated renal artery infusion catheter may be more effective than IV fenoldopam in improving GFR and reducing the incidence of systemic hypotension and is currently undergoing evaluation in randomised controlled trials (66). Another renal artery vasodilator, dopamine, has likewise showed inconsistent promise in reducing CIN (67–69). Theophylline, an adenosine A-1 receptor antagonist has had mixed results in randomized trials (70,71). One randomized trial showed a significantly-reduced rise in creatinine of three different doses of prostaaglandin E1 compared with placebo (72). None of these measures have an evidence base to support their routine clinical use.

**Other agents** After an initial small randomized trial of patients undergoing cardiac catheterization showed a reduced incidence in CIN in patients who received oral vitamin C (9%) versus placebo (20%), a larger trial showed no difference in saline + acetylcysteine versus saline + acetylcysteine + vitamin C (42). Recently, the cellular anti-ischemic agent trimetazidine reduced CIN in a small randomized trial (73).

**Hemodialysis and hemofiltration** Prophylactic hemodialysis does not appear to diminish the incidence of CIN in patients with preexisting renal insufficiency (74). A meta-analysis of 412 patients from six studies with a creatinine ranging from 2.5 to 4.0 mg/dL showed no benefit and there was a suggestion of harm (75). Prophylactic continuous venovenous hemofiltration (CVVH) in moderate to severe renal insufficiency (mean creatinine 3.0 mg/dL) results in a lower creatinine and a lower mortality compared with standard of care, but the outcomes may have resulted from the fact that CVVH removes creatinine and those patients in the CVVH arm were all treated in the intensive care unit; their greater intensity of care compared with the control arm may have explained their improved short- and long-term survival (76). A recent trial in patients with severe chronic kidney disease (serum creatinine 4.9 mg/dL) referred for cardiac catheterization found a reduced incidence of long-term need for hemodialysis in those who received immediate hemodialysis compared with the control group (0% vs. 13%, respectively) (77). There may be a role for prophylactic hemodialysis in a subpopulation of patients who are at the highest risk of CIN but more studies are warranted before routine use of this strategy can be recommended.
HYPERSENSITIVITY REACTIONS

Unlike chemotoxic contrast reactions, hypersensitivity reactions are independent of the rate or volume of contrast infusion. Immediate hypersensitivity reactions typically occur within seconds to an hour after contrast exposure. Delayed hypersensitivity reactions can occur between one hour and one week, but this is much less common. Hypersensitivity reactions typically present with some combination of pruritus, urticaria, rash, angioedema, laryngospasm, bronchospasm, hypotension, syncope, shock, or even death. Most such reactions are mild, but they can (rarely) be fatal.

Epidemiology

The incidence of hypersensitivity reactions has been as high as 13% in past analyses, but is much lower with newer agents (78,79). Overall, the incidence of mild reactions is approximately 9%, and severe reactions 0.2% to 1.6% (80,81). The mortality is <1/100,000 patients (82). It is seven times higher in the elderly, in part related to comorbidities (83).

Pathophysiology

The pathophysiology of hypersensitivity reactions is poorly understood. The clinical manifestations may be similar to that of anaphylaxis, but unlike anaphylaxis, the vast majority of contrast hypersensitivity reactions are not IgE-mediated (84,85). The most likely etiology is an anaphylactoid reaction involving direct mast cell activation and massive degranulation of histamine. Activation of the coagulation cascade and kinin, release of serotonin, and inhibition of platelets may also play a role (86-88).

Risk Factors

The type of contrast media used impacts the likelihood of a hypersensitivity reaction. Ionic HOCM cause mild to moderate reactions in as many as 12% of patients, compared with less than 3% with nonionic LOCM (89). Severe reactions occur in 0.22% to 0.04% with ionic HOCM, compared with 0.04% to 0.004% with nonionic LOCM. The incidence of hypersensitivity reactions may be even lower with the nonionic ICM ioxitanol (78,79).

The most important risk factor for the development of an anaphylactoid reaction is a prior anaphylactoid reaction to contrast media, with repeat unpremedicated reaction rates as high as 50% in some observational studies (89,90). Other risk factors include asthma or an allergic disease history (89).

It has been proposed that shellfish allergy confers a higher risk of contrast allergy because shellfish contain iodine (91,92). This is likely not the case. In fact, the allergen in shellfish is the protein tropomyosin, not iodine. However, atopic individuals are commonly allergic to seafood, and atopic individuals tend to be at higher risk of a contrast reaction. In addition, patients who react to topical iodine are not at increased risk of an anaphylactoid reaction to contrast media.

It has been proposed that certain medications, such as β-blockers and NSAIDs, may increase the risk of a contrast reaction, but this has not been definitively established (90,93).

Clinical Features

Hypersensitivity reactions are not related to the dose or the injection rate of contrast medium. In fact, fatal reactions have been reported with only 2 mL of contrast (94). Symptoms typically begin within minutes up to one hour after contrast infusion. Reactions which occur within seconds after contrast exposure may initially seem mild but tend to progress rapidly. Typical manifestations include pruritus and urticaria. More severe reactions may include angioedema, laryngospasm, bronchospasm, loss of consciousness, and even death. Danger signs are rapid progression of symptoms, respiratory distress, stri- dor, hypotension, arrhythmia, or chest pain.

It is important to distinguish an anaphylactoid reaction from other complications of contrast injection, such as vasovagal reactions or cardiogenic pulmonary edema. Like an anaphylactoid reaction, a vasovagal reaction can result in acute hypotension, but typically involves bradycardia and nausea, and patients will not have pruritus, urticaria, angioedema, stridor, or wheezing. Rapid volume expansion after contrast bolus can cause respiratory distress and wheezing from cardiogenic pulmonary edema, but this syndrome likewise will not be associated with puritus, urticaria, or angioedema.

Lab testing for anaphylactoid reactions is not routinely done, but there are two tests that may help indicate that an anaphylactoid reaction has occurred: serum tryptase, and 24-hour urine histamine. Tryptase is a mast cell proteinase which is released in large quantities in the setting of massive mast cell activation and degranulation such as anaphylaxis, anaphylactoid reactions, and systemic mastocytosis (84,95). It has a 90-minute half-life and is only detectable for a couple of hours after an anaphylactoid reaction. Histamine has an even shorter half-life. Elevated histamine levels can be detected on a 24-hour urine collection, which is begun soon after an anaphylactoid reaction.

Routine skin testing has not proven to be beneficial in predicting the recurrence of a hypersensitivity reaction to contrast media, although there may be a very small subset of patients with true IgE-mediated anaphylaxis who can be detected with skin testing (85).

Treatment

The initial step in the treatment of a presumed anaphylactoid contrast reaction is to stop injecting contrast medium (Table 4.3). Mild reactions, such as simple pruritus, may be treated with antihistamines and observation. However, it should be noted that mild reactions can quickly progress, and the clinician should anticipate and respond to a severe reaction when needed.

The first and most important active treatment of a severe anaphylactoid reaction is epinephrine. Other therapies take time to work, and may not be effective in reversing the underlying reaction. Aqueous intramuscular epinephrine 0.3 to 0.5 mg in the anterolateral thigh can be given. Alternatively, a 0.1 mg vial of epinephrine from the crash cart can be diluted in 10 mL of saline and given 1 mL (10 mcg) at a time intravenously. If symptoms persist despite epinephrine boluses, then an IV drip at 2 to 10 mcg/min can be infused. Patients on β-blockers may not respond adequately to epinephrine. In this setting, glucagonons 1 to 2 mg IV can be given over five minutes, followed by an infusion of 5 to 15 mcg/min.

In addition to oxygen, albuterol nebulizer may be given to relieve bronchospasm. If there is evidence of impending airway obstruction from angioedema or stridor, immediate endotracheal intubation should take place. Delay may result in complete obstruction requiring cricothyroidotomy.
Adjunctive antihistamine therapy with IV diphenhydramine 50 mg, an H1 blocker and ranitidine 50 mg, an H2 blocker, may improve symptoms and help prevent short-term recurrence. Glucocorticoids have little immediate benefit, but methylprednisolone 125 mg IV can be given to prevent a recurrent reaction several hours later.

Prevention
As indicated earlier, the most important risk factor for a contrast reaction is a history of previous reactions. Premedication is crucial to preventing a repeat reaction. The combination of prednisone, diphenhydramine, and LOCM lowers the risk of a recurrent reaction to less than 1%. The exact dosing of glucocorticoids is not known, but glucocorticoids need to be taken hours in advance to have the maximum effect. A validated protocol is prednisone 50 mg by mouth at 13 hours, 7 hours, and 1 hour prior to the procedure (96,97). In addition, diphenhydramine 50 mg should be given one hour prior to the procedure.

In the case of an emergency procedure, a rapid premedication protocol may include hydrocortisone 200 mg IV once and then every four hours until the procedure is complete, diphenhydramine 50 mg IV or orally, and LOCM.

There is no clear benefit or harm with prophylactic H2 blockers (90,98). Ephedrine has been shown to be useful, but this drug is relatively contraindicated in patients with coronary artery disease and may promote coronary vasospasm.

Use of LOCM reduces the chance of recurrence compared with HOCM. Use of the IOCM ioxaglate, may reduce this risk even further. The incidence of a repeat contrast reaction using ioxaglate was 0.7%, compared with 2% when using the ionic, LOCM ioxaglate (4).

Gadolinium is even less likely to cause a repeat contrast reaction, with the incidence ranging from 1/100,000 to 1/500,000 cases and essentially confined to rare case reports (99). In addition, CO2 can be used for peripheral interventions, but must be confined to injections below the diaphragm given the risk of cerebral embolization.

There are no routine empiric medications which are recommended for prevention of first-time reactions. If not already a routine practice, one may consider using LOCM in patients with asthma or with any history of other serious allergic reactions. Most prevention is directed at minimizing recurrent reactions.

SUMMARY
Contrast agents allow visualization of the cardiac anatomy. Many different formulations have been introduced in an attempt to minimize adverse side. In general, LOCM and IOCM are equally as effective as and are associated with less toxicity than the HOCM. It is not entirely clear whether IOCM are safer than LOCM in the prevention of CIN. Many evidence-based methods have been developed to prevent anaphylactoid contrast reactions and CIN, particularly in patients considered to be at higher risk. These methods should be used on a routine basis in the cardiac catheterization laboratory.

REFERENCES


Patient selection, preparation, risks, and informed consent

David O. Williams and J. Dawn Abbott

INTRODUCTION
Cardiac catheterization is one of the most common in-hospital procedures performed in the United States with an annual volume of over one million and the number is expected to increase as the population ages. The procedures performed in the cardiac catheterization laboratory have expanded over time to include the diagnosis and treatment of a wide range of cardiac and vascular diseases. Independent of the type or complexity, all procedures involve the insertion of catheters into the circulatory system guided by a combination of fluoroscopy, hemodynamic monitoring, and contrast media injection. Paramount to patient safety is an experienced and competent catheterization laboratory team. The physician performing the procedure in each case is responsible for determining the potential risks and benefits of a given procedure on the basis of both patient and technical factors. Proper patient selection and preparation can minimize the occurrence or severity of complications. The risks of angiography should be understood by all members of the catheterization laboratory team so that complications can be anticipated and responded to in a rapid and coordinated manner. An in-depth knowledge of the risks of each procedure is also required to obtain appropriate informed consent from the patient. The preprocedural aspects of cardiac catheterization deserve special review and are the basis for this chapter.

PATIENT SELECTION

Procedural Indications
Before a decision to recommend cardiac catheterization is made the indication for and alternatives to the procedure should be clear. The patient should know what clinical information is desired and how the findings will be used. An invasive study should be performed for diagnostic or prognostic indications when incremental to a noninvasive evaluation or for therapeutic purposes. A thorough review of the patient’s medical history, physical exam, electrocardiogram, and laboratory and cardiac testing results is required to determine the appropriateness of and type of procedure planned. Left heart catheterization is commonly performed for coronary artery disease and includes aortic and left ventricular pressures, left ventriculography, and coronary angiography. The practice guidelines for coronary angiography are detailed in a report from the American College of Cardiology and American Heart Association (ACC/AHA) and are summarized in Table 5.1 (1).

In many clinical scenarios such as valvular, myocardial, and congenital heart disease, one or more additional procedures such as aortography, right heart catheterization, or oximetry are required for a complete diagnostic study. The operator must, therefore, have the expertise to determine and perform the necessary procedural components. For patients that subsequently require interventional procedures including those detailed in the following chapters of this book, clinical guidelines from the ACC/AHA exist for many diseases and procedures and can serve as a framework for making clinical decisions.

Cardiac catheterization may be performed as part of a diagnostic or therapeutic research study, or solely for research purposes. In these circumstances, the protocol must be approved by the local Institutional Review Board, the patient informed of the investigative nature of the study, and informed consent obtained.

Procedural Contraindications
As the field of interventional cardiology has evolved to routinely care for critically ill patients such as those with myocardial infarction (MI) and cardiogenic shock, the number of absolute contraindications to cardiac catheterization has decreased. The majority of procedures are still done on an elective or urgent, nonemergent basis and a number of relative contraindications to the procedure have been reported that can often be addressed prior to the procedure to improve safety (Table 5.2). When possible, procedures should be delayed until all relative contraindications are evaluated and treated.

The list of relative contraindications includes severe contrast allergy, which is uncommon but potentially life-threatening. Proper pretreatment, discussed below, can reduce the incidence and severity of recurrent reactions. Acute or chronic kidney disease may alter the risk/benefit ratio of cardiac catheterization or may result in the requirement for hemodialysis. Measures such as ensuring adequate volume status before treatment to prevent contrast nephropathy, and consultation with a nephrologist may be required in such cases. Uncontrolled ventricular irritability may increase the incidence of ventricular tachycardia or fibrillation. Electrolyte imbalances should be corrected, diagnosis and treatment of potential drug toxicity should be sought, and medical therapy for ischemia optimized. Attention to control of hypertension can reduce the potential for ischemia, congestive heart failure, and bleeding related to angiography. Patients with decompensated congestive heart failure in the absence of acute myocardial ischemia or the need for hemodynamic support should be stabilized prior to catheterization when possible. Abnormal coagulation or blood counts should be corrected when feasible to reduce bleeding risk and ischemic complications. The presence of a febrile illness or bacteremia is an additional relative contraindication. Several of the relative contraindications will be determined and treatment optimized during patient preparation for cardiac catheterization.
Table 5.1 Indications for Coronary Angiography in Patients with Known or Suspected Coronary Artery Disease

<table>
<thead>
<tr>
<th>Asymptomatic or stable angina</th>
<th>Unstable coronary syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High-risk criteria on noninvasive testing</td>
<td>• Unstable angina refractory to medical therapy</td>
</tr>
<tr>
<td>• Sudden cardiac death survivors</td>
<td>• Unstable angina with intermediate to high short term risk</td>
</tr>
<tr>
<td>• Sustained monomorphic or polymorphic ventricular tachycardia</td>
<td>• Unstable angina with subsequent abnormal noninvasive testing</td>
</tr>
<tr>
<td>• Angina on medical treatment</td>
<td>• Suspected Prinzmetal variant angina</td>
</tr>
<tr>
<td>• Worsening abnormalities on serial noninvasive testing</td>
<td>• Suspected stent thrombosis</td>
</tr>
<tr>
<td>• Patients that cannot be adequately risk stratified by other means</td>
<td>• Patients with STEMI with the intent to perform primary or rescue percutaneous coronary intervention</td>
</tr>
<tr>
<td>• Individuals whose occupation involves the safety of others who have an abnormal stress test or high-risk clinical features</td>
<td>• Evaluation of non-STEMI</td>
</tr>
<tr>
<td>• Abnormal but not high-risk stress test in a patient with high likelihood of disease</td>
<td>• Cardiogenic shock</td>
</tr>
<tr>
<td>• Ischemia demonstrated by noninvasive testing in a patient with a prior myocardial infarction</td>
<td>• Post myocardial infarction with angina, congestive heart failure, ejection fraction &lt;40%, or ventricular arrhythmia</td>
</tr>
<tr>
<td>• Post-cardiac transplant evaluation</td>
<td>• Suspected or known mechanical complication post myocardial infarction</td>
</tr>
<tr>
<td>• Preoperation organ transplant in individuals ≥40 yr old</td>
<td>• Myocardial infarction suspected to be from nonatherothrombotic cause (i.e., spontaneous dissection, arteritis)</td>
</tr>
<tr>
<td>• Patients with equivocal or abnormal non–high risk findings on noninvasive testing with recurrent hospitalizations for chest pain</td>
<td>• Cardiac trauma</td>
</tr>
<tr>
<td>• Suspected in-stent restenosis or early bypass graft failure on the basis of symptoms or noninvasive testing</td>
<td></td>
</tr>
<tr>
<td>• Planned noncoronary cardiac surgery (valve surgery, hypertrophic cardiomyopathy, congenital heart disease)</td>
<td></td>
</tr>
<tr>
<td>• Before surgery for aortic aneurysm or dissection</td>
<td></td>
</tr>
<tr>
<td>• Unexplained systolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>• Suspicion for ischamically mediated diastolic dysfunction</td>
<td></td>
</tr>
<tr>
<td>• Prospective immediate cardiac transplant donor at risk for coronary disease</td>
<td></td>
</tr>
<tr>
<td>• Kawasaki disease with coronary artery aneurysms detected noninvasively</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: STEMI, ST segment elevation myocardial infarction.

Table 5.2 Relative Contraindications to Cardiac Catheterization

| • Severe contrast allergy |
| • Acute renal failure or advanced chronic kidney disease without the ability to perform hemodialysis |
| • Uncontrolled ventricular arrhythmia |
| • Metabolic derangements (electrolytes, acid-base abnormalities) |
| • Drug toxicity (digoxin) |
| • Malignant hypertension |
| • Active noncardiac problems (bacteremia, bleeding, stroke) |
| • Acute decompensated heart failure in the absence of ischemia |
| • Coagulopathy or bleeding diathesis |
| • Patient unable to cooperate with instructions |

Appropriateness Criteria
Marked variability in the use of coronary angiography and revascularization in and outside the United States have led to concerns about the appropriate use of cardiovascular procedures (2–4). In addition to regional variation in cost, both under- and overuse of invasive procedures have the potential to adversely impact patient outcomes. Appropriateness criteria for coronary revascularization were therefore developed in an effort to optimize the quality of cardiovascular care and develop a tool that can be used to measure variability and utilization patterns in the use of coronary revascularization. In determining whether coronary revascularization was appropriate, inappropriate or uncertain, the following definition was used, “Coronary revascularization is appropriate when the expected benefits, in terms of survival or health outcomes (symptoms, functional status, and/or quality of life) exceed the expected negative consequences of the procedure” (5). The appropriateness criteria apply to surgical and percutaneous coronary revascularization but do not address diagnostic cardiac catheterization.

In brief, indications for revascularization were developed considering the following common variables: clinical presentation, angina severity, extent of ischemia on noninvasive testing, the presence or absence of other prognostic factors, and the extent of anatomic disease. The technical panel scored each indication on a scale from 1 to 9. Indications that were scored 7 to 9 by the panel were termed appropriate, meaning coronary revascularization is generally acceptable, a reasonable approach, and likely to improve the patient’s health outcomes or survival. Indications with a score of 4 to 6 were termed uncertain, meaning coronary revascularization may be acceptable and a reasonable approach but with uncertainty implying that more research and/or patient information is needed to further classify the indication. Inappropriate indications for coronary revascularization, score of 1 to 3, are generally not acceptable and unlikely to improve the patient’s health outcomes or survival. In general, the technical panel rated the majority of clinical scenarios in patients with acute coronary syndromes and high-risk noninvasive findings as appropriate for revascularization.

Operators performing cardiac catheterization must be familiar with the appropriateness criteria. While the criteria are not meant to replace clinical judgment, they do provide guidance for decision making and supplement practice guidelines developed by the ACC/AHA. Importantly, the criteria will certainly be used by health care facilities and third-party payers and ultimately patients.
PREPARATION

Patient preparation is one of the most important aspects of cardiac catheterization. Each patient has unique issues that must be addressed, for example, a history of contrast reaction, coumadin therapy, or diabetes mellitus. In addition to clinical factors, the physician must ensure that the patient is mentally prepared, understands instructions, and knows what to expect before, during, and after the procedure. A well-informed patient will be less anxious and more cooperative. The circumstances of the procedure will dictate the pace of preparation, but even in emergent situations such as ST segment elevation myocardial infarction (STEMI) patient safety cannot be compromised by inadequate preprocedural assessment.

Preprocedural Assessment

A detailed medical history, pertinent physical examination, and review of allergies and ancillary studies should be performed within 30 days and updated the day of the procedure. In patients with known or suspected coronary artery disease, assessment of compliance and ability to take dual antiplatelet therapy should be made. Any upcoming noncardiac procedures and surgeries should also be discussed with the patients. The electrocardiogram should be reviewed and available at the time of the procedure for comparison. In some individuals a chest X ray may be warranted. Basic laboratories, including a complete blood count, glucose, electrolytes, blood urea nitrogen and creatinine should be obtained in all patients to assess the status of chronic diseases or to identify clinically silent comorbidities such as kidney disease and anemia. Patients with a personal or family history of a bleeding diathesis or anticoagulation should have coagulation studies. Abnormalities should be recorded and corrected if possible. The procedure, if elective, should be delayed when problems are identified that could influence treatment strategies, for example, unexplained anemia. Abnormalities such as an elevated creatinine or thrombocytopenia may not alter plans for diagnostic cardiac catheterization, but may require additional measures to reduce the risk of contrast nephropathy or bleeding, respectively.

For patients with prior cardiac catheterization, the approach, equipment, and findings including a review of the images should be performed whenever feasible. There is no use trying to engage the left coronary artery with a Judkins left 4 catheter when the previous operator was successful with a Judkins left 6 or to rediscover an anomalous coronary artery. For patients with prior coronary bypass surgery (CABG), the preoperative native coronary anatomy, operative report, and postoperative angiograms if performed, should be reviewed. Every effort should be made to review the original operative report rather than relying on a summary of the graft anatomy which may be misleading. Attention should be paid to the number and types of conduits and any special circumstances such as use of a free versus in situ left internal mammary graft, use of uncommon conduits such as a gastroepiploic graft, or placement of a saphenous vein graft off the descending aorta. When the operative report is unavailable and the procedure cannot be delayed, aortography and bilateral mammary injections should be considered to assist in locating grafts.

Access Considerations

Whether to use femoral, brachial, or radial access should be considered prior to the procedure (Table 5.3). While many operators and catheterization laboratories have a default strategy of using the right femoral artery approach, patient and lesion specific factors may obligate an alternative approach. A review of the patient’s comorbidities, need for left (vs. right and left) heart catheterization, and anticipated maximum sheath size can decrease the need for more than one access site. The femoral approach should be considered for procedures requiring a large sheath size, technical complexity, or simultaneous arterial and venous access. Radial access should be considered in patients unable to lay flat for prolonged periods because of pulmonary or musculoskeletal conditions, or patients with an increased risk of local vascular complications such as those with peripheral artery disease, aortic dissection or aneurysm, morbid obesity, or coagulopathy. In patients with a mammary graft, the ipsilateral side should be used if an arm approach is chosen to simplify selective mammary engagement. In a meta-analysis of randomized trials comparing radial with femoral access that included 3224 patients, the risk of access site complications was significantly less with the radial approach, whereas the risk of major adverse cardiac events was similar. The radial approach, however, was associated with a higher risk of procedural failure (6). Procedural success may depend in part on operator experience with the radial technique.

The palmar arch should be assessed prior to radial artery cannulation because there is a 5% to 19% occurrence of radial artery occlusion (7). In patients with an intact arch, extensive collaterals between the radial and ulnar arteries make this complication clinically irrelevant. Hand ischemia can occur with radial artery occlusion in patients that have incomplete palmar arches. The modified Allen test assesses the palmar arch and should be performed prior to radial artery catheterization. The test is performed by compressing both the radial and ulnar arteries while the patients hand is held high with the fist clenched. The hand is then lowered and opened and pressure over the ulnar artery released. If the superficial palmar arch is intact color should return to the hand within 6 seconds, and ≥10 seconds is considered abnormal. Since the Allen test is subject to inaccuracy, many centers use pulse oximetry and plethysmography as a more direct assessment of blood flow (8,9). Plethysmography is considered abnormal if during radial artery compression there is a loss of pulse tracing with no recovery during two minutes of observation. In 1010 consecutive patients referred for cardiac catheterization, the modified

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**Table 5.3 Arterial Access Considerations**

<table>
<thead>
<tr>
<th>Femoral approach</th>
<th>Brachial/ radial approach</th>
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</thead>
<tbody>
<tr>
<td>Requirement of a large sheath size (&gt;7F)</td>
<td>Aortic pathology (dissection, aneurysms, large atheroma)</td>
</tr>
<tr>
<td>Simultaneous arterial and venous access planned</td>
<td>Peripheral arterial disease (aortic or iliac occlusions, iliac tortuosity)</td>
</tr>
<tr>
<td>Abnormal Allen test or known subclavian/innominate artery disease</td>
<td>Morbid obesity</td>
</tr>
<tr>
<td>1. Aortic pathology (dissection, aneurysms, large atheroma)</td>
<td>Difficulty maintaining a supine position (back pain, lung disease)</td>
</tr>
<tr>
<td>2. Peripheral arterial disease (aortic or iliac occlusions, iliac tortuosity)</td>
<td>Coagulopathy</td>
</tr>
</tbody>
</table>

1. Aortic pathology (dissection, aneurysms, large atheroma)
2. Peripheral arterial disease (aortic or iliac occlusions, iliac tortuosity)
3. Morbid obesity
4. Difficulty maintaining a supine position (back pain, lung disease)
5. Coagulopathy
Allen test was abnormal in 6.3% and plethysmography in 1.5%, but the clinical implications of using a particular method are not clear (8).

An abnormal Allen test is observed in 6% to 27% of patients undergoing cardiac catheterization (8,10). A small study of patients undergoing coronary angiography showed that patients with an abnormal Allen test had decreased thumb blood flow and increased capillary lactate after 30 minutes of radial artery occlusion compared with patients with a normal Allen test (7). Given the potential risk of hand ischemia, the radial artery approach should not be used in patients with an abnormal modified Allen test unless the risks of alternative approaches are prohibitory.

**Conditions Requiring Special Preparations**

**Allergies**

A list of allergies should be recorded and patients should be specifically questioned regarding allergies to lidocaine, premedications (i.e., valium), and contrast media. An alternative local anesthetic, Marcaine (1 mg/mL), can be used in patients with an allergy to lidocaine. Sedatives can be withheld or alternatives substituted for patients with prior reactions to benzodiazepines or narcotics. The overall incidence of adverse reactions to intravascular contrast media is about 5%, but rates are higher in patients with a history of allergy, asthma, or prior contrast media reaction (11,12). Patients reporting contrast reactions require premedication prior to cardiac catheterization. Premedication should also be considered in patients with severe asthma or prior anaphylaxis. Pretreatment with corticosteroids, when given at least 12 hours before the procedure, significantly decreased contrast reactions with the exception of hives which had only a trend toward reduction. A single-dose regimen administered two hours prior to contrast exposure, however, did not reduce the incidence of reactions (13). On the basis of the limited data available, nonemergent procedures should be delayed until adequate premedication can be administered. An acceptable regimen is oral prednisone 40 mg every 6 hours starting at least 12 and up to 24 hours before procedure (see chap. 4 for different dosing schedule).

For emergent circumstances intravenous solumedrol can be given despite the lack of known efficacy. In addition to steroids, nonsteroidal anti-inflammatory agents should be considered. Patients with an elevated creatinine, metformin, should be held post procedure (18). Patients on metformin require special instructions and monitoring because of rare cases of metformin-associated lactic acidosis reported in patients with diabetes and chronic kidney disease (17). Metformin is excreted in the urine and 90% is eliminated within 24 hours, therefore it is contraindicated in patients with elevated creatinine. Since contrast studies can induce acute renal failure, there is a small risk of lactic acidosis in patients undergoing contrast administration. Nearly all the cases reported, however, were in individuals with preexistent renal impairment who were continued on the drug after contrast exposure (18). Patients with a creatinine >1.5 mg/dL can undergo cardiac catheterization without discontinuing metformin before the study. Metformin should be held post procedure and resumed in 48 hours in patients without signs of renal failure. In patients at high risk of renal failure due to concomitant mediation such as cyclosporine, volume depletion, or low output, the creatinine should be measured prior to resuming metformin. In patients with an elevated creatinine, metformin should be discontinued 48 hours prior to an elective procedure. In emergent situations, metformin should be discontinued at the time of the procedure, hydration administered, and renal function monitored closely (19).

**Anticoagulants**

Patients on oral anticoagulant therapy should be assessed for the ability to temporarily hold warfarin to decrease the bleeding risk associated with cardiac catheterization. When the risk of a subtherapeutic international normalized ratio (INR) is acceptable, warfarin can be held for several days to allow the INR to drift down to 1.5. For high-risk clinical situations such as recent pulmonary embolism, atrial fibrillation with prior embolic events, or mechanical mitral valve prosthesis, patients require perioperative heparin to bridge the discontinuation of warfarin. Low-molecular-weight heparin can be administered on an outpatient basis or the patient can be admitted for intravenous unfractionated heparin. In some circumstances, catheterization must be performed while a patient is fully anticoagulated. For these cases, a radial approach may be preferable and vitamin K+ and fresh frozen plasma can be transfused if bleeding complications occur. One study suggested that manual compression is an acceptable method of hemostasis in therapeutically anticoagulant patients with an INR of 2 to 3 (15).

**Diabetes Mellitus**

Patients with diabetes treated with oral agents or insulin require an adjustment in medication to prevent periprocedural hypoglycemia while fasting. Patients taking subcutaneous insulin should be instructed to take half doses of long-acting insulin preparations the morning of the procedure. Regular insulin should be held and a blood glucose level checked by the catheterization laboratory staff for symptoms of hypo- or hyperglycemia. Oral agents should be held the morning of the procedure as well. Patients with diabetes, particularly those taking neutral protamine Hagedorn (NPH) insulin, have an increased sensitivity to protamine, an agent used to reverse systemic heparinization. Major reactions to protamine including vasomotor collapse occur 50-fold more frequently in NPH insulin-dependent diabetes patients, therefore this drug should be used with caution in this patient subset (16).

Patients on metformin require special instructions and monitoring because of rare cases of metformin-associated lactic acidosis reported in patients with diabetes and chronic kidney disease (17). Metformin is excreted in the urine and 90% is eliminated within 24 hours, therefore it is contraindicated in patients with elevated creatinine. Since contrast studies can induce acute renal failure, there is a small risk of lactic acidosis in patients undergoing contrast administration. Nearly all the cases reported, however, were in individuals with preexistent renal impairment who were continued on the drug after contrast exposure (18). Patients with a creatinine >1.5 mg/dL can undergo cardiac catheterization without discontinuing metformin before the study. Metformin should be held post procedure and resumed in 48 hours in patients without signs of renal failure. In patients at high risk of renal failure due to concomitant mediation such as cyclosporine, volume depletion, or low output, the creatinine should be measured prior to resuming metformin. In patients with an elevated creatinine, metformin should be discontinued 48 hours prior to an elective procedure. In emergent situations, metformin should be discontinued at the time of the procedure, hydration administered, and renal function monitored closely (19).

**Renal Disease**

Chronic kidney disease, diabetes, low cardiac output, hypovolemia, and contrast volume are risk factors for contrast nephropathy. Patients with baseline renal insufficiency that have deterioration in renal function after percutaneous coronary intervention (PCI) have poor outcomes, particularly those requiring hemodialysis (20). Patients at risk for contrast nephropathy should be adequately hydrated with intravenous saline for 12 hours before procedure, if possible (21,22). Alternative pretreatment regimens include oral N-acetylcysteine 600 mg every 12 hours starting 24 to 48 hours before the procedure or sodium bicarbonate infusion 3 mL/kg/hr for 1 hour prior to contrast administration followed by an infusion of 1 mL/kg/hr for 6 hours after the procedure (23,24). Additional measures including holding diuretics and other nephrotoxins such as nonsteroidal anti-inflammatory agents should be considered.
Mortality, and valvular heart disease are additional predictors of Renal insufficiency, postprocedural renal function deterioration. The most common complications of cardiac catheterization are procedures, many of which are immediately life-threatening. The risk of complications from cardiac catheterization has decreased over time and is <1% in the majority of cases (Table 5.4). Even with experienced operators and modern equipment, complications will occur. Many factors including patient demographics, comorbidities, cardiovascular anatomy, procedural type and circumstances, and operator and hospital volume, can influence the risk to an individual patient and these should be weighed in each case (25,26). The risks are lowest in stable patients undergoing elective procedures and diagnostic angiography in this setting has <0.1% risk of a major adverse event such as death, MI, or stroke (27–29). The risk can increase up to eightfold in patients with multivessel disease, congestive heart failure, and renal insufficiency (30). To justify performance of the procedure, the expected benefits, in terms of diagnostic or therapeutic outcomes, should be greater than the potential risks. Physicians performing invasive procedures have to be knowledgeable about potential complications and capable of administering treatment. This way every effort can be made to minimize the incidence and severity of complications, many of which are immediately life-threatening. The most common complications of cardiac catheterization are reviewed below.

Death

Despite an aging population and performance of coronary angiography in higher risk individuals, the procedural mortality reported for 222,553 patients by the Society for Cardiac Angiography and Interventions (SCAI) registry in 1989 was 0.098%, compared with 0.14% reported in 1982 (28,29). Procedure-related mortality in a subsequent multicenter registry of 58,332 patients in 1990 was 0.08% (31). A later single-center study of 11,821 patients undergoing 7953 diagnostic and 3868 therapeutic procedures was congruent. The total mortality rate was 0.2%, with a fivefold higher rate for interventions, compared with diagnostic procedures (32). The cause of in-hospital death after PCI has been evaluated and procedural complications accounted for about half of deaths and the remaining cases were attributed to preexisting cardiac disease, predominantly low output failure (33).

Several subgroups at higher risk of procedural mortality have been identified. In the initial registry, patients with left main disease >50%, ejection fraction <30%; NYHA class III or IV, age >60 years, and three-vessel disease were at increased risk of mortality from diagnostic cardiac catheterization (34). Renal insufficiency, postprocedural renal function deterioration, and valvular heart disease are additional predictors of mortality (20,35).

Myocardial Infarction

Myocardial ischemia may occur during diagnostic angiography as a result of catheter engagement or contrast injection and more commonly during PCI with balloon inflations, but is usually transient and self-limited. Development of anginal symptoms, electrocardiographic, or hemodynamic changes may all indicate ischemia and should prompt an evaluation of the cause. Attention to catheter flushing and monitoring for pressure damping reduces the risk of ischemia due to technical-related factors such as embolization or vessel occlusion. Even with careful technique, removal of the catheter from the coronary ostium or administration of nitroglycerin may be required to reverse ischemia due to obstructive coronary artery disease or vasospasm.

During diagnostic catheterization, progression of ischemia to MI is uncommon. In the first, second, and third SCAT registries, the risk of MI was rare and decreased over time, from 0.09% and 0.06% to 0.05% (28,31,36). Patient-related factors such as the extent of coronary artery disease (0.06% for single-vessel disease, 0.08% for triple-vessel disease) and location (0.17% for left main disease) slightly increase the risk of MI (28). Postprocedural MI is rare following an uncomplicated elective diagnostic catheterization and the majority of patients can be discharged after several hours of observation (37).

Cerebrovascular Events

Stroke is an uncommon but potentially devastating complication of cardiac catheterization and PCI. In several large series involving over 43,000 patients, the rate of clinically diagnosed procedural related stroke ranged from 0.18% to 0.4% (38–42). Several patient and procedural factors are associated with an increased risk of stroke, including diabetes, prior stroke, longer procedure times, intra-aortic balloon pump placement, and treatment with fibrinolytic therapy (40,43). Patients that suffer from a periprocedural stroke have a poor prognosis with persistent neurologic deficits and a high in-hospital mortality rate of up to 32% (38).

Cerebral microembolism is the primary mechanism of periprocedural ischemic stroke occurring with left heart catheterization. Manipulation of guidewires and catheters results in disruption of atherosomatous plaques from the walls of the aorta. In more than 50% of PCIs, guiding catheter placement is associated with scraping debris from the aorta as indicated by retrieval of atheromatous material (44). Transcranial Doppler and serial magnetic resonance imaging studies of patients undergoing cardiac catheterization and PCI support embolization as the main cause of stroke with asymptomatic microemboli detected in about 15% of cases (45–47). Stroke can also result from embolization of air or thrombus, or intracerebral hemorrhage. Stroke risk can be minimized, therefore, by meticulous procedural technique such as withdrawal of blood from and flushing of catheters with heparinized saline and performing catheter exchanges over wires in the descending aorta.

The optimal management of periprocedural stroke is unknown, but favorable results have been shown in small series of patients treated with neurovascular intervention and intraarterial fibrinolytics (48–50). The clinical situation should prompt an emergent response and multidisciplinary management with cardiology, neurology and a neurointerventional specialist (51).
Vascular Complications
Several complications can occur at the arterial site of catheter insertion that cause significant patient discomfort, increased length of stay, and increased health care costs. Vascular access site complications are not uncommon, but only about 0.5% of cases require specific intervention. The majority of these complications, including arterial thrombosis, dissection, uncontrolled or retroperitoneal bleeding, and hematoma formation, commonly occur during or within hours following catheterization. Development of a pseudoaneurysm or arteriovenous fistula, however, may not manifest for several days. In general, arterial thrombosis is more common with radial access, whereas other vascular complications are more frequent with femoral or brachial approaches (6,36). Treatment of vascular complications is often conservative for hematomas but surgical intervention or interventional techniques are required for arterial thrombosis, arteriovenous fistulas, large or expanding pseudoaneurysms, and retroperitoneal bleeds not responsive to supportive care (52).

Hemostasis at the access site can be accomplished either by manual or device compression or with a closure device, of which there are several types (53–55). The approach chosen for hemostasis depends on catheterization laboratory and patient-related factors such as availability of trained staff for sheath removal, anticoagulation status, sheath size and location, presence of peripheral vascular disease, and patient comfort. In patients undergoing diagnostic procedures, collagen and suture type arterial puncture closure devices shorten the time to ambulation and have comparable safety to manual compression (54–56). In two large meta-analyses involving over 37,000 patients undergoing diagnostic and interventional procedures with numerous types of devices in 30 studies, closure devices had an increased risk of local complications (56,57). The risk of complications, however, differed among the various closure devices (56). Overall, the data suggest that closure devices are an acceptable alternative to manual compression in appropriate patients.

Arrhythmias
Although predominantly benign and self-limited, a gamut of arrhythmias can occur during cardiac catheterization, necessitating continuous electrocardiographic monitoring and a staff trained in arrhythmia treatment. The majority of arrhythmias are induced by intracoronary contrast injection or right heart catheter manipulation. Ventricular tachycardia and fibrillation are rare, but occurred in 0.4% of cases in the second SCAI registry (28). Bradycardia and conduction disturbances are also uncommon, with an incidence of approximately 1% in diagnostic catheterization and PCI. Patients are generally responsive to forceful coughing and atropine. Initiation of temporary pacing is rarely required (0.06% diagnostic cases, 0.4% PCI) (58). Vasovagal reactions occur in up to 3% of patients as a result of anxiety or pain. Patients generally respond to removal of painful stimuli, fluid administration, and atropine. These reactions, however, can be life-threatening in patients with severe valvular or ischemic disease and should be rapidly treated to prevent hemodynamic decompensation.

Perforation
The risk of perforation of the heart or blood vessels is exceedingly rare in diagnostic cardiac catheterization, but may occur with transseptal procedures, pacemaker placement, myocardial biopsy, or elective pericardiocentesis. Patients may present with vagal reactions, hypotension, chest pain, or arrhythmia. Echocardiographic guidance can be used if immediately available and anticoagulation should be reversed if possible. In a large single-center series, emergent pericardiocentesis relieved acute tamponade in 99% of patients and was the only therapy required in 82% of patients (59).

Atheroembolism
Atheromatous debris can be dislodged from the arterial wall during catheter manipulation and exchanges and may result in systemic embolization. When systematically evaluated, approximately half of patients undergoing PCI had detectable atheromatous debris in blood removed after placement of the guiding catheter (44). None of the patients, however, had clinical events, suggesting that operator technique is critical to the prevention of embolic events. The incidence of clinically evident atheroembolic events is reported to be 0.6% to 1.9% (60). In a large prospective study, cholesterol embolization syndrome, as defined by peripheral cutaneous involvement or renal dysfunction, occurred in 1.4%; 48% of patients had cutaneous involvement as defined by the presence of livedo reticularis, blue toe syndrome, or digital gangrene; and 64% of patients had renal insufficiency. Eosinophil counts were significantly higher in patients suffering from atheroembolism both before and after catheterization, but the only independent predictor of cholesterol emboli syndrome was baseline C-reactive protein. Unadjusted mortality was 32-fold greater in patients with cholesterol emboli syndrome (16% vs. 0.3%). Unfortunately, no specific therapy exists and care is supportive, with hemodialysis and wound management as required (61).

Infection
As cardiac catheterization is performed using sterile technique, the incidence of bacteremia or infection at the access site is rare and routine use of prophylactic antibiotics is not recommended. SCAI infection control guidelines discuss techniques for minimizing risk to the patient and catheterization laboratory personnel (62). Protection of both the patient and personnel includes the proper use of gowns, caps, gloves, masks, and sterile technique including hand washing. Additional protection to laboratory staff comes from eye wear and proper handling and disposal of contaminated equipment. All personnel should receive vaccination for hepatitis B (63). Immediate cleansing of needlestick injuries and prompt medical attention is required. The use of prophylactic antibiotics is recommended by the manufacturers of certain closure devices.

Radiation Exposure
Although the risk of radiation to patients and staff is an accepted consequence of cardiac catheterization, every effort should be made to manage patient radiation dose (64). All personnel working with fluoroscopy should be trained and competency monitored (65). Radiation exposure is determined by multiple factors (Table 5.5) (66,67). Cardiac catheterization laboratory systems should be equipped with the capability of monitoring cumulative radiation dose. The energy delivered to air by the X-ray beam, or air kerma, is measured at a fixed reference point during a procedure to calculate the reference point dose. The reference point dose is the cumulative dose derived from fluoro, cine, and dosimetric effects of patient size and is typically displayed as milligray (64). Some systems use a
CONCLUSIONS
To provide the highest level of care with the lowest risk, invasive and interventional cardiologists must ensure they have up-to-date, in-depth knowledge of procedural indications and risks and meticulous technical skills. Appropriate patient selection and preparation requires individualized care and attention to high-risk features. Procedural risk and patient stress can be minimized by the process of informed consent, patient preparation, and an experienced, trained catheterization laboratory staff.

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Conscious sedation (local anesthetics, sedatives, and reversing agents)

Steven P. Dunn

INTRODUCTION
Conscious sedation, also known as moderate sedation, is the practice of choice recommended by the American College of Cardiology (ACC) and the Society for Cardiac Angiography and Interventions (SCAI) to relieve pain and anxiety during cardiac catheterization (1). The American Society of Anesthesiologists (ASA) has defined moderate sedation as a drug-induced depression of consciousness that continues to allow the patient to purposefully respond to commands and maintain airway, breathing, and circulation without mechanical or pharmacologic support (Table 6.1) (2). This level of sedation is optimal for cardiac catheterization since patient symptoms can often be the first warning of a procedural complication. In addition, by allowing patients to maintain physiologic respiratory and cardiac function, recovery time is significantly lessened. While there are general recommendations regarding the most appropriate methods to achieve this level of sedation, significant variability in practice exists across different cardiac catheterization laboratories.

FUNDAMENTALS
Preprocedure Assessment
A preprocedure assessment is an important part of ensuring safe and effective sedation therapy is applied to each patient situation, as many metabolic determinants can put the patient at risk for adverse reaction to sedation (Table 6.2) (1). Ideally this would include an assessment of major organ system function, history of drug and alcohol abuse (including tobacco), date and time of last oral intake, and allergic history relative to local anesthesia and sedative drugs.

As sedative agents can affect airway reflexes, patients undergoing cardiac catheterization are at risk for aspiration of gastric contents. Therefore, patients undergoing this procedure should ideally fast for an appropriate amount of time to allow for sufficient gastric emptying, generally four hours after a meal. Clear liquids may be permitted up to two hours prior to the procedure (2). Medications, particularly antihypertensive medications, should be ingested as ordered, unless prescribed by the invasive cardiologist.

A preprocedure assessment will include an evaluation of anatomic variables that may affect sedation or, if necessary, intubation, and allow proactive planning to take place. In planning for potential intubation, examination specific to the airway is recommended, including evaluation of the neck and dentition. The Mallampati Scale (3), an objective anatomical assessment of the oral cavity that predicts ease of intubation, is also a useful examination tool (Table 6.3). In addition, a general physical assessment is also warranted. This should include vital signs and auscultation of the heart and lungs (1). Although many catheterization laboratories achieve adequate preprocedural sedation with the use of oral medications, intravenous access for medication administration is a necessity.

While there are many metabolic determinants to both the choice and the amount of sedation administered to a patient to achieve conscious sedation, a systematic approach to both assessing the patient and selecting the therapeutic modality will ensure optimal outcomes.

Monitoring of Sedation
The ASA focuses on four key areas of monitoring for moderate sedation: level of consciousness, pulmonary ventilation, oxygenation, and hemodynamics (1). Although the methods utilized to achieve moderate sedation may differ, the following should serve as a universal method to assess whether appropriate sedation is achieved. Monitoring will require a combination of direct observation and assessment, along with various medical equipment, as appropriate. Of note, as respiratory depression is the principle concern with the use of moderate sedative modalities, monitoring of both ventilation and oxygenation is recommended.

The level of sedation can also be objectively assessed with the use of the Aldrete score (Table 6.4) (4). This score assigns point values for activity, respiration, circulation, consciousness, and color.

Level of Consciousness
For moderate sedation, a level of consciousness where the patient purposefully responds to commands (physically or verbally) is appropriate. While there is little literature to suggest that monitoring level of consciousness improves clinical outcomes associated with procedural sedation, it is strongly felt that early intervention when the patient’s level of sedation is supertherapeutic (e.g., no response, or response only to painful stimuli) will likely prevent adverse outcomes associated with sedation such as respiratory or cardiac depression.

Pulmonary Ventilation
One of the principle adverse effects from oversedation is drug-induced respiratory depression. Therefore, the ASA strongly recommends monitoring respiratory ventilation via observation or auscultation during moderate sedation, despite little literature to suggest this practice to be of value in preventing drug-induced respiratory effects. While there are some noninvasive techniques to assess ventilation, such as impedance plethysmography, these are considered complementary to observation and auscultation, and not substitutes.
Oxygenation

Pulse oximetry has been shown to effectively monitor and prevent hypoxemia during moderate sedation and should be utilized in all patients undergoing cardiac catheterization. It should also be noted that pulse oximetry is not singularly adequate for assessing respiratory function and should be combined with assessment tools for pulmonary ventilation.

Hemodynamics

Pharmacologic agents used in moderate sedation have the potential to blunt autonomic response to the procedure. Hemodynamic variables such as blood pressure and heart rate may indicate inadequate sedation when elevated. However, sedation agents may also adversely depress these variables. Additionally, some local anesthetics and sedative agents may cause cardiac dysrhythmias which may be more pronounced in patients with extensive cardiovascular disease. The ASA recommends monitoring vital signs at five-minute intervals until adequate sedation is achieved. However, given the higher risk of the cardiovascular patient and the need for general hemodynamic data for procedural effectiveness and/or safety, this monitoring may occur at more frequent intervals (or continuously) during cardiac catheterization. In addition, continuous electrocardiographic monitoring is warranted to monitor sedative adverse effects, although this is also generally part of standard monitoring independent of sedation practices.

Table 6.1  American Society of Anesthesiology Continuum of Sedation

<table>
<thead>
<tr>
<th></th>
<th>Minimal sedation (anxiolysis)</th>
<th>Moderate sedation/analgesia</th>
<th>Deep sedation/analgesia</th>
<th>General anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsiveness</td>
<td>Normal response to verbal stimulation</td>
<td>Purposeful response to verbal or tactile stimulation</td>
<td>Purposeful response following repeated or painful stimulation</td>
<td>Unarousable even with painful stimulus</td>
</tr>
<tr>
<td>Airway</td>
<td>Unaffected</td>
<td>No intervention required</td>
<td>Intervention may be required</td>
<td>Intervention often required</td>
</tr>
<tr>
<td>Spontaneous ventilation</td>
<td>Unaffected</td>
<td>Adequate</td>
<td>May be inadequate</td>
<td>Frequently inadequate</td>
</tr>
<tr>
<td>Cardiovascular function</td>
<td>Unaffected</td>
<td>Usually maintained</td>
<td>Usually maintained</td>
<td>May be impaired</td>
</tr>
</tbody>
</table>

Source: From Ref. 2.

Table 6.2  Preprocedure Evaluation

<table>
<thead>
<tr>
<th>System</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting cardiac or pulmonary disease</td>
<td>Sedative agents can cause cardiovascular or respiratory depression.</td>
</tr>
<tr>
<td>Preexisting renal or hepatic disease</td>
<td>Abnormalities may impair how fast the drug is metabolized and excreted from the system, resulting in longer drug action and increased drug effect.</td>
</tr>
<tr>
<td>Time and type of last oral intake</td>
<td>Reflex suppression could result in aspiration.</td>
</tr>
<tr>
<td>History of drug and alcohol abuse</td>
<td>The dose and action of sedative agents may be affected in patients that abuse drugs and alcohol. In addition, procedural agitation may be higher.</td>
</tr>
<tr>
<td>History of smoking</td>
<td>Patients who smoke are at increased risk of bronchospasm, airway problems, or coughing.</td>
</tr>
<tr>
<td>Previous experience with sedative agents</td>
<td>Any previous adverse reactions to sedation should be noted.</td>
</tr>
</tbody>
</table>

Source: From Ref. 2.

Table 6.3  The Mallampati Scale

<table>
<thead>
<tr>
<th>Class</th>
<th>Anatomic findings</th>
<th>Difficulty of intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Soft palate, uvula, fauces, pillars available</td>
<td>No difficulty</td>
</tr>
<tr>
<td>II</td>
<td>Soft palate, uvula, fauces available</td>
<td>No difficulty</td>
</tr>
<tr>
<td>III</td>
<td>Soft palate, base of uvula available</td>
<td>Moderate difficulty</td>
</tr>
<tr>
<td>IV</td>
<td>Hard palate only visible</td>
<td>Severe difficulty</td>
</tr>
</tbody>
</table>

Source: From Ref. 3.

Oxygenation

Pulse oximetry has been shown to effectively monitor and prevent hypoxemia during moderate sedation and should be utilized in all patients undergoing cardiac catheterization. It should also be noted that pulse oximetry is not singularly adequate for assessing respiratory function and should be combined with assessment tools for pulmonary ventilation.

Table 6.4  The Aldrete Scoring System for Sedation

<table>
<thead>
<tr>
<th>Score</th>
<th>Activity</th>
<th>Respiration</th>
<th>Circulation</th>
<th>Consciousness</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Able to move four extremities</td>
<td>Able to breathe deeply and cough</td>
<td>BP ± 20% of baseline</td>
<td>Fully alert and answers questions</td>
<td>Normal pink</td>
</tr>
<tr>
<td>1</td>
<td>Able to move two extremities</td>
<td>Limited respiratory effort (dyspnea)</td>
<td>BP ± 20-50% of baseline</td>
<td>Arousable</td>
<td>Pale, dusky, blotchy</td>
</tr>
<tr>
<td>0</td>
<td>Not able to control any extremities</td>
<td>No spontaneous respiratory effort</td>
<td>BP &gt;50% of baseline</td>
<td>Failure to elicit response</td>
<td>Frank cyanosis</td>
</tr>
</tbody>
</table>

*aScores of 8 or greater are generally considered acceptable to indicate recovery from sedation.*
Table 6.5 American Society of Anesthesiology–Recommended Emergency Equipment for Moderate Sedation

<table>
<thead>
<tr>
<th>Airway management equipment</th>
<th>Compressed oxygen</th>
<th>Endotracheal tubes</th>
<th>Face masks</th>
<th>Lubricant</th>
<th>Stylets</th>
<th>Suction</th>
<th>Suction catheters</th>
<th>Alcohol wipes</th>
<th>Gloves</th>
<th>Intravenous catheters</th>
<th>Intravenous fluids</th>
<th>Intravenous tubing</th>
<th>Needles for drug administration or intramuscular or intraosseous injection</th>
<th>Sterile gauze pads</th>
<th>Syringes</th>
<th>Tape</th>
<th>Tourniquets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous equipment</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Medications</td>
<td>Amiodarone</td>
<td>Atropine</td>
<td>Dextrose (50%)</td>
<td>Diazepam or midazolam</td>
<td>Diphenhydramine</td>
<td>Epinephrine</td>
<td>Hydrocortisone, methylprednisolone, or dexamethasone</td>
<td>Lidocaine</td>
<td>Nitroglycerin</td>
<td>Vasopressin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: From Ref. 2.

EQUIPMENT

The ASA recommends a minimum level of emergency equipment in the event of pulmonary or cardiac arrest induced by procedural sedation and/or analgesia (Table 6.5). Also, given the high cardiovascular acuity of the patient undergoing cardiac catheterization and the potential for cardiac and/or pulmonary arrest independent of sedation use, the ACC/SCAI recommends a baseline level of emergency resuscitative equipment be immediately available (1). In addition, cardiac catheterization laboratory personnel should possess a minimum level of training (basic life support) and advanced levels of training are highly recommended.

CLINICAL ASPECTS

Local Anesthesia

Local anesthesia continues to be the preferred method to relieve pain and sensation associated with vascular access. Local anesthetics primarily act by competitive antagonism of the \( \alpha \)-subunit of voltage-gated sodium channels in the nerve membrane. In addition, there are effects on G protein–coupled receptors, calcium channels, and potassium channels which complement the classically known effect on sodium channels (5,6). Inhibition of these pathways essentially results in temporary cessation of nerve impulse conduction.

In general, local anesthetics are both safe and effective although some significant pharmacologic differences exist among agents (Table 6.6). Lidocaine (0.5–2% concentration) is the local anesthetic of choice in cardiac catheterization due to its rapid onset, short duration of action, and minimal risk of cardiotoxicity. Cardiotoxicity induced by local anesthetics can be caused by several mechanisms, but classically is described as both direct and indirect (central nervous system mediated) effects on the myocardium with conduction delays leading to a prolonged PR interval or a wide QRS complex (6). In addition, many anesthetic agents can cause ventricular arrhythmias through this same mechanism by unidirectional block and reentry (9,10), the risk of which may be heightened by mechanical disturbance of myocyte electrophysiology during cardiac catheterization. Some agents also possess strong negative inotropic activity which is generally not a desirable pharmacologic property for administration to a patient with significant structural heart disease (11). Bupivacaine is widely regarded as the local anesthetic with the highest potential for cardiotoxicity and should not be considered for use in cardiac catheterization (8).

Since most anesthetics are vasodilators, a vasoconstrictor (typically epinephrine at 1:100,000 or 1:200,000) may be utilized in combination with a local anesthetic to minimize local bleeding and improve anesthetic duration. Use of a vasoconstrictor has not been shown to significantly affect hemodynamic parameters (12,13), although little data exist to establish the safety of local vasoconstrictor use in the patient with high cardiovascular acuity. Of note, the administration of a vasoconstrictor in combination with a local anesthetic will reduce the potency of the anesthetic employed by reducing tissue diffusion, necessitating higher doses for equivalent effect. This also lowers the risk of local anesthetic toxicity by minimizing vascular uptake via vasoconstriction of capillary beds (14,15).

Sedation and Analgesia

Cardiac catheterization is most often performed under the influence of agents with anxiolytic and amnestic properties in combination with an analgesic, if necessary. The most frequently used sedative agent is a benzodiazepine, which may also be combined with a sedating antihistamine. Opioid analgesics may also be utilized in combination with benzodiazepines to achieve adequate sedation. Literature suggests that combining a sedative with an opioid provides adequate moderate sedation (16), but there are few data describing the superiority of the combination versus either agent alone. Furthermore, data suggest that

Table 6.6 Selected Local Anesthetic Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset</th>
<th>Potency</th>
<th>Duration</th>
<th>Cardiotoxicity</th>
<th>Maximum dose (mg/kg)</th>
<th>Maximum dose with vasoconstrictor (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Mepivicaine</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>2.5</td>
<td>4</td>
</tr>
</tbody>
</table>

Note: +, low; ++, intermediate; ++++, high.

Source: From Ref. 7.
50  CARDIOVASCULAR CATHETERIZATION AND INTERVENTION

Table 6.7  Selected Benzodiazepines for Use in Procedural Sedation

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Peak effect</th>
<th>Duration of effect</th>
<th>Metabolic pathway</th>
<th>Active metabolite?</th>
<th>Protein binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>IV: 0.5–2 mg</td>
<td>3–5 min</td>
<td>30–80 min</td>
<td>Oxidation</td>
<td>Yes</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Maximum: 5–10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Oral: IV: 5 mg</td>
<td>2–4 hr</td>
<td>3–4 hr</td>
<td>Oxidation</td>
<td>Yes</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Oral: IV: 5–10 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral: IV: Maximum: 20 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Oral: IV: 4 mg</td>
<td>6–8 hr</td>
<td>Conjugation</td>
<td>No</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral: 2 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum: 4 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: From Ref. 7.

The combination of a sedative agent with an opioid increases the risk of adverse outcomes such as respiratory depression and hypoxemia (17). Therefore, the combination of a benzodiazepine with an opioid may be utilized, but ideally, therapy should be individualized for each specific patient’s needs and administered separately to determine the response of the patient and if the desired level of sedation can be achieved with minimal use of drug stacking. This also underscores the need for continuous monitoring of the patient not only to achieve adequate sedation, but also to prevent adverse outcomes associated with the effort. Repeat dosing may be required with longer procedures.

Antihistamines

Oral antihistamines, especially diphenhydramine, have been described as early as the 1960s as sedative medication for cardiac catheterization (18). They remain a popular preprocedural medication, particularly in combination with an oral benzodiazepine, because of the sedative properties and also to blunt unreported or unknown allergic reactions to contrast media. First-generation antihistamines exert sedative effects largely through a combination of anticholinergic properties and lipophilicity, allowing the drug to easily cross the blood-brain barrier and affect histamine mediated neurologic function (19). While diphenhydramine is most often used as a proactive baseline level of preprocedure sedation, additional reactive methods may be required on the basis of the individual patient.

Of note, in part because of the strong anticholinergic effects of diphenhydramine, elderly individuals appear to have more pronounced and prolonged sedative effects (20). In combination with diazepam, a drug that is also slowly metabolized by elderly patients, this may result in excessive and/or prolonged sedation and may be considered a less preferred method of achieving adequate baseline procedural sedation for all patients.

Benzodiazepines

The most commonly used agents for sedation in cardiac catheterization are the benzodiazepines, which act as the γ-aminobutyric acid (GABA) complex in the central nervous system and produce hypnosis and anxiolysis, in addition to an amnestic effect. Several methods of dosing are commonly utilized in the cardiac catheterization laboratory, including premedication with oral benzodiazepines (such as diazepam) and/or the use of rapid and short acting benzodiazepines (such as midazolam). Drug properties of each benzodiazepine are listed in Table 6.7. Significant differences exist among agents in terms of onset and duration of action and institutional practice will likely be tailored for the specific agent preferred. There are no data sustaining the superiority of any benzodiazepine in terms of efficacy or safety for moderate sedation. Patients with altered clearance or significant drug-drug interactions will require either alternative benzodiazepines or lower doses. For example, patients who are elderly or those with significant liver disease will have prolonged clearance of diazepam due to slower oxidative activity within the liver and may have shorter recovery time with a drug that is conjugated without active metabolite formation (e.g., lorazepam).

Adverse effects of benzodiazepines in moderate sedation generally relate to respiratory depression as a result of oversedation. Hemodynamic effects are minimal, but hypotension can result with rapid administration of intravenous benzodiazepines containing propylene glycol (e.g., diazepam, lorazepam).

Opiates

The opiates, such as morphine, fentanyl, and meperidine, are commonly used for analgesia in moderate sedation practice in combination with local anesthesia. Opiates are preferred not only because of their superior pharmacologic profiles for procedural analgesia (quick onset and quick offset) but also because of their lack of interaction with the renal prostaglandin system (unlike nonsteroidal compounds), resulting in safer interactions with nephrotoxic contrast media. Unfortunately, the opiates carry a greater risk of respiratory depression, particularly in combination with benzodiazepines. Caution and judicious use should be applied to their use, along with careful monitoring. Table 6.8 lists the various opiates that could be considered for use during cardiac catheterization. Of note,

Table 6.8  Selected Opiates for Use in Procedural Sedation

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Peak effect</th>
<th>Duration of effect</th>
<th>Active metabolite?</th>
<th>Cardiovascular effects (%)</th>
<th>Protein binding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>IV: 25–50 mcg</td>
<td>1 min</td>
<td>30–60 min</td>
<td>No</td>
<td>Low</td>
<td>80–86</td>
</tr>
<tr>
<td></td>
<td>Maximum: 3 mcg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>IV: 1–2 mg</td>
<td>1–2 min</td>
<td>3–4 hr</td>
<td>Yes</td>
<td>Moderate</td>
<td>20–30</td>
</tr>
<tr>
<td></td>
<td>Maximum: 0.15 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>IV: 10–20 mg</td>
<td>1–2 min</td>
<td>2–3 hr</td>
<td>Yes</td>
<td>Low</td>
<td>65–80</td>
</tr>
<tr>
<td></td>
<td>Maximum: 1.5 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: From Ref. 7.
meperidine should not be used in patients with severe renal insufficiency as seizures may be provoked via active metabolite accumulation, and should also be considered less preferred in general because of the risk of contrast nephropathy with cardiac catheterization.

SPECIAL ISSUES
Local Anesthetic Allergies
While patients occasionally report a history of an allergic reaction to a local anesthetic, true IgE-mediated hypersensitivity reaction has not been noted in the literature (21). In many cases, such reactions are misclassified adverse effects or allergic responses from preservatives (methylparaben) or other excipients contained within the anesthetic solution, such as bisulfate compounds designed to prevent oxidation of vasoconstrictors. Certain local anesthetics containing ester compounds (procaine, tetracaine, or benzocaine), which are derivatives of para-aminobenzoic acid (PABA), may cause an allergic reaction since their structures contain a potentially immunogenic amine substitution. When confronted with a history consistent with an anesthetic induced allergic reaction, the safest course of action without undergoing allergy testing would be to choose an amide anesthetic (lidocaine, mepivacaine, bupivacaine, or ropivacaine) in a preservative free solution [typically denoted as “methylparaben free” (MPF)] that does not contain a vasoconstrictor.

Reversal of Sedation and Analgesia
Pharmacologic antagonists are available for both opiates and benzodiazepines (Table 6.9) and should be immediately accessible for use. Naloxone is a competitive antagonist for all receptors affected by opiates (μ, δ, σ) and it possesses no agonist effects. Complete antagonism of analgesic response, although sometimes necessary, can result in severe onset of pain and physiologic pain response (hypertension, tachycardia) and may require further intervention. Flumazenil is an antagonist of the benzodiazepine receptor and has been shown to be beneficial in reversing the central nervous system depressant effects of the benzodiazepines. Reversal of benzodiazepine induced respiratory depression is less conceptually clear, although literature does exist supporting its role in this area (22,23). Caution must also be exercised in complete reversal in the patient receiving prior long-term benzodiazepine therapy, as this may provoke withdrawal symptoms, including seizures (24). Of note, many benzodiazepines and opiates have longer elimination half-lives than their pharmacologic antagonists. Successful reversal should be followed up with an appropriate duration of monitoring based on the elimination half-life of the offending agent and particularly close attention should be given to patients with altered drug clearance.

FUTURE DIRECTIONS
While modern day methods to achieve moderate sedation are generally adequate, room remains for improvement in the efficacy and particularly the safety of sedation practice. An ideal agent would be a drug that has rapid onset and offset, minimal effects on respiratory function at maximal efficacy, and is not affected by patients with altered organ function. However, widespread inclusion of a new agent into practice may be cost prohibitive, and benefit to the patient must be demonstrated.

Some literature exists for the use of ketamine as an alternative analgesic agent which also produces a “dissociative” anesthetic effect (25). Although the mechanism of action of ketamine is not entirely clear, it appears to act on a wide variety of central nervous system receptors, including N-methyl-aspartate (NMA), opiate, serotonin, and norepinephrine receptors (25). One clear advantage of ketamine in procedural sedation is that it has only minimal effects on respiratory function. This may make ketamine more desirable in situations where intensive analgesia is required.

Dexmedetomidine has also gained considerable interest as a central σ-2 agonist that achieves adequate sedation without affecting respiratory function (26). Although dexmedetomidine is more selective for σ-2 receptors than its structural relative clonidine (26), significant decreases in blood pressure and heart rate have been noted with its use that may limit widespread applicability to patients with significant cardiovascular disease.

CONCLUSIONS
The preferred level of sedation during cardiac catheterization is defined as moderate sedation. However, sedation level is highly continuous and requires constant monitoring to ensure adequate efficacy without oversedation. Short acting benzodiazepines are the preferred pharmacologic agents to induce sedation in the catheterization laboratory and may be paired with opioid analgesia, however, extreme care must be taken to avoid oversedation with this combination. While tremendous variability in individual sedation practice exists, a systematic approach to using conscious sedation will aid in improving patient comfort during cardiac catheterization while also avoiding potential adverse effects associated with current sedation practices.

REFERENCES

<table>
<thead>
<tr>
<th>Table 6.9 Pharmacologic Reversal of Sedation and Analgesia</th>
<th>Dose</th>
<th>Peak effect</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flumazenil (benzodiazepine antagonist)</td>
<td>0.2 mg initial, Maximum (total): 1 mg</td>
<td>6–10 min</td>
<td>1–4 hr</td>
</tr>
<tr>
<td>Naloxone (opioid antagonist)</td>
<td>0.4 mg initial, Maximum (total): 2 mg</td>
<td>5–10 min</td>
<td>45 min–3 hr</td>
</tr>
</tbody>
</table>

Source: From Ref. 7.
Vasopressors, vasodilators, and antithrombotics in the catheterization laboratory

Tracy E. Macaulay and David J. Moliterno

INTRODUCTION
This chapter provides an overview of medications commonly used during cardiac catheterization and interventional procedures. It will focus on medications that provide hemodynamic optimization during procedures as well as agents used to prevent thrombotic complications. Other chapters addressing specific therapeutic areas (e.g., ST segment elevation myocardial infarction) may address individual treatments in more detail, while this chapter will serve as a broad overview of pharmacology, therapeutic applications, monitoring, and safety of these agents.

VASOACTIVE OVERVIEW
In critically ill patients, hemodynamic stability can be achieved using mechanical support with intra-aortic balloon pumps and assist devices, however an initial pharmacologic approach is typically preferred. The main goal of using vasoactive medications is to maintain tissue perfusion and optimize oxygen delivery. Although the hemodynamic goals vary depending on the situation, the overall goal of meeting metabolic demands and preventing multisystem organ dysfunction and death remains the same (1,2). When considering the use of vasodilators, inotropes, and vasopressors keep in mind that the aim is to provide adequate oxygen delivery while maintaining a minimal effective perfusion pressure. This approach limits the myocardial oxygen demand and ischemia, as well as other deleterious effects of using these agents.

ANATOMIC CONSIDERATIONS WITH VASOACTIVE AGENTS
Vasodilator therapy is most frequently used in the treatment of hypertension. It is also useful in patients with left ventricular systolic dysfunction (LVSD) with or without pulmonary edema, and has demonstrated a mortality reduction in both acute and chronic management (3,4). In the catheterization laboratory these medications can be given systemically to lower peripheral vascular resistance or locally as direct coronary arterial vasodilators. Some vasodilators may also be used in the characterization and treatment of pulmonary arterial hypertension.

Intravenous inotropic therapy is often necessary for the treatment of cardiogenic shock, particularly in patients with LVSD. In cardiogenic shock, a decrease in cardiac output results in a hypoperfusion state, thereby increasing adrenergic drive. The release of endogenous catecholamines is temporarily effective, however it may be necessary to stimulate β1-receptors or administer phosphodiesterase inhibitors to augment cardiac output (5). Use of inotropic agents such as dobutamine and milrinone to achieve an adequate cardiac index of 2.2 L/min/m² may provide necessary support. However these agents have not been shown to provide a mortality benefit (6–8). Temporary increases in cardiac preload and afterload may also be required and can be achieved by increasing volume (blood or intravenous fluids) and/or stimulation of α-receptors in the periphery.

When treating patients with vasopressor therapy, targeting a minimal perfusion pressure or mean arterial pressure of approximately 65 mmHg is widely accepted (9). However, because blood pressure alone is not a determinant of adequate oxygen delivery, advanced hemodynamic monitoring and individualized goals are appropriate. This will allow for selection of the appropriate vasoactive medication based on the clinical situation and limit unnecessary exposure or deleterious side effects.

PHARMACOLOGIC FUNDAMENTALS
Vasodilators
NO
Nitric oxide (NO) is a potent vasodilator (Table 7.1) that is decreased in patients with coronary artery disease. Nitroglycerin provides an exogenous source of NO, which works by increasing vascular cyclic guanosine monophosphate (cGMP) resulting in smooth muscle relaxation. The majority of nitroglycerin’s effect is in preload reduction making it an ideal choice for the patient with hypertension and elevated pulmonary capillary wedge pressure. For the same reason caution should be used in patients that are preload dependent, such as those with right ventricular failure. Nitroglycerin also causes endothelium-independent coronary artery dilation, antagonizes vasoconstriction and vasospasm and increases collateral blood flow. These effects make it useful in treatment of ischemia symptoms, although no mortality reduction has been demonstrated in large clinical trials (11,12). Tachyphylaxis can develop within 24 hours of continuous therapy, but can generally be overcome by increasing the dose or providing a nitrate-free interval if possible (5).

Sodium Nitroprusside
Sodium nitroprusside is an endothelium-independent nitrovasodilator like nitroglycerin, however it has greater arterial vasodilating properties than venous (13). Unlike other vasodilators, nitroprusside causes only mild increases in heart rate and an overall decrease in myocardial oxygen demand. The molecular composition of sodium nitroprusside includes five cyanide ions which can accumulate as either cyanide or thiocyanate in patients with liver or renal failure, respectively. Patients
receiving high doses (10 mcg/kg/min) for a prolonged time (>2 days) are particularly at risk of toxicity. Despite disadvantaged toxicities, nitroprusside is the gold standard intravenous antihypertensive for its remarkable effectiveness and rapid onset of action (Table 7.2).

**Table 7.1 Vasodilator Overview**

<table>
<thead>
<tr>
<th>Generic (brand)</th>
<th>Starting dose</th>
<th>Maintenance and titration</th>
<th>Intracoronary dose</th>
<th>ADR</th>
<th>Precautions and CI</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>5 mcg/min</td>
<td>Increase every 3 min to maximum 200 mcg/min</td>
<td>50–250 mcg</td>
<td>Headache, tachyphylaxis</td>
<td>RV failure (preload dependent patients)</td>
<td>Used to treat symptoms of ischemia at low doses (10), hypertension with or without pulmonary edema at higher doses</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.5 mcg/kg/min</td>
<td>Increase every 5 min to maximum of 5–10 mcg/kg/min (ideally for &lt;48 hr)</td>
<td>25–100 mcg</td>
<td>With prolonged use (or high doses) cyanide toxicity and methemoglobinemia may develop</td>
<td>Severe renal or liver impairment, COPD</td>
<td>Cardiac failure due to increase afterload, ADHF, vasodilatory challenges (pulmonary HTN)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>For arrhythmias 10 mg IVP (0.25 mg/kg)</td>
<td>5–20 mg/hr continuous infusion. Consider rebolus with each uptitration.</td>
<td>AV blockade</td>
<td>LVSD, AV blockade, sick sinus syndrome, WPW</td>
<td>AF/flutter, PSVT</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>For arrhythmias 2.5–5 mg IVP</td>
<td>100–200 mcg (up to 4 times)</td>
<td>AV blockade</td>
<td>LVSD, AV blockade, sick sinus syndrome, WPW</td>
<td>AF/flutter, PSVT</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>3–15 mg/hr</td>
<td></td>
<td>LVSD, AV blockade, sick sinus syndrome, WPW</td>
<td>Severe aortic stenosis, peripheral edema</td>
<td>Stability of more concentrated solution unknown, therefore infusion provides large volume of fluid</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Clevedipine</td>
<td></td>
<td>Hypotension, tachycardia, headache, peripheral edema</td>
<td>Hypotension, tachycardia, headache, peripheral edema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine</td>
<td>12–24 mcg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[Abbreviations: ADR, adverse drug reaction; AV, atrioventricular; LVSD, left ventricular systolic dysfunction.\]

**Table 7.2 Comparison of Intravenous Vasodilators**

<table>
<thead>
<tr>
<th>MOA</th>
<th>NTG</th>
<th>Nitroprusside</th>
<th>Diltiazem</th>
<th>Verapamil</th>
<th>Nicardipine</th>
<th>Clevedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exogenous NO, cyclic guanosine monophosphate</td>
<td>Venovasodilation</td>
<td>Arterial and venous dilator</td>
<td>Decrease heart rate and vasodilation</td>
<td>Decrease heart rate and vasodilation</td>
<td>Decrease blood pressure</td>
<td>Decrease blood pressure</td>
</tr>
<tr>
<td>Overall hemodynamic effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contractility</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0</td>
<td>1 (reflex)</td>
<td>0/1</td>
<td>0/1</td>
<td>1 (reflex)</td>
<td></td>
</tr>
<tr>
<td>SA automaticity</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrioventricular conduction</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vasodilation</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

**Adenosine**

Adenosine is a purine nucleoside in human cells involved in cellular metabolism. High doses of exogenous adenosine slow sinus node conduction interrupting reentry pathways and restoring normal sinus rhythm (14,15). The most common
therapeutic use for adenosine is treatment of atrioventricular (AV) nodal reentrant tachycardia, which is terminated with a near 90% success rate. For this purpose adenosine is given as a 6 mg IV rapid injection. After two minutes 12 mg can be given if needed, and then repeated for a total dose of 30 mg. When administering adenosine, it is important to follow each dose with an intravenous flush to ensure rapid distribution, as the onset is immediate and the duration of effect is mere seconds. When given through a central line these doses should be halved, as there are case reports of adenosine initiating atrial fibrillation. In cardiac catheterization, adenosine can be used to evaluate coronary flow reserve since it causes maximal coronary vasodilation. The greatest benefit of the short duration is that any adverse effects (angina, dyspnea, AV nodal block, and flushing) are quickly self-limiting.

Calcium Channel Blockers
Calcium channel blockers (CCB) are a large and growing class of medications. The unifying mechanism is inhibition of calcium from entering “slow channels” or voltage-sensitive areas of vascular smooth muscle, producing smooth muscle relaxation and vasodilation. CCB are further classified as dihydropyridine and nondihydropyridine on the basis of differences in structure and pharmacologic effects. Diltiazem and verapamil are nondihydropyridines and offer greater negative chronotropic effects than dihydropyridines. Both agents slow AV nodal conduction and exert a negative inotropic effect with less arterial vasodilation. In the catheterization laboratory these agents are most often used for treatment of rapid ventricular heart rate secondary to atrial fibrillation. Nifedipine is the classic dihydropyridine CCB, although newer second-generation agents are more often used in an acute setting. Dihydropyridines have selectivity for peripheral vasculature, resulting in extensive blood pressure lowering with little to no effect on heart rate. In fact, more often compensatory increases in heart rate are seen. Use in the setting of acute coronary syndrome (ACS) and in patients with heart failure is controversial, as they can result in fluid retention in addition to adrenergic activation.

Inotropes
Inotropic agents are indicated for the treatment of low-output failure in patients with elevated left ventricular filling pressures (15). Effects are either directly mediated through β1-receptor agonism or indirectly through an increase in intracellular cAMP, raising heart rate and therefore cardiac output (Table 7.3). All inotropes have arrhythmogenic properties and therefore should be reserved for acutely ill patients and used for the shortest duration necessary.

**Table 7.3 Inotrope Overview**

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Starting dose</th>
<th>Maintenance and titration</th>
<th>PK properties</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>Dobutrex</td>
<td>1 mcg/kg/min</td>
<td>20 mcg/kg/min</td>
<td>Metabolized by methylation and conjugation, inactive metabolites are renally excreted, ( h_{1/2} = 2 \text{ min} )</td>
<td>Angina, hypertension, tachyarrhythmia, headache</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>Isuprel</td>
<td>0.01 mcg/kg/min</td>
<td>Increase every 5 min to maximum 0.3 mcg/kg/min</td>
<td>Hepatic metabolism, ( h_{1/2} = 3-7 \text{ hr} )</td>
<td>Syncope, tachyarrhythmia, confusion, tremor</td>
</tr>
<tr>
<td>Milrinone</td>
<td>Primacor</td>
<td>0.25 mcg/kg/min</td>
<td>0.75 mcg/kg/min</td>
<td>Renally excreted (83% unchanged), ( h_{1/2} = 2.3 \text{ hr} ) (prolonged in renal failure)</td>
<td>Ventricular arrhythmias, hypotension, headache</td>
</tr>
</tbody>
</table>

Abbreviation: PK, pharmacokinetic.
Table 7.4 Vasopressor Overview

<table>
<thead>
<tr>
<th>Drug type and generic name</th>
<th>Brand name</th>
<th>Starting dose</th>
<th>Maintenance and titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Intropin</td>
<td>3–10 mcg/kg/min</td>
<td>Up to 20 mcg/kg/min</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Adrenalin</td>
<td>1 mcg/min</td>
<td>10 mcg/min</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Lovephed</td>
<td>2 mcg/min</td>
<td>30 mcg/min</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Neo-Synephrine</td>
<td>100 mcg/min</td>
<td>Decrease to maintenance of 40–60 mcg/min</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Pitressin</td>
<td>0.01 units/min</td>
<td>0.04 units/min</td>
</tr>
</tbody>
</table>

Norepinephrine and Epinephrine

Norepinephrine and epinephrine are other vasoactive medications with mixed receptor activity. Norepinephrine has β1- and α-receptor activity, with less β2. This translates clinically into more potent blood pressure affecting properties and less inotropic effects at all dosage ranges as compared with dopamine. For this reason norepinephrine remains the initial catecholamine of choice for septic or vasodilatory shock. Epinephrine is the most potent agonist for the β1, β2, and α-receptors. Use of continuous epinephrine infusion is limited by adverse effects, including arrhythmias, ischemia, tachycardia, hyperglycemia, cerebral hemorrhage, pulmonary edema, and diminished splanchnic blood flow. As such, epinephrine should be reserved for patients who are unresponsive to dopamine or norepinephrine (21).

Epinephrine bolus dosing has a role in treatment of pulseless ventricular tachycardia, ventricular fibrillation, asystole, or pulseless electrical activity. Epinephrine at doses of 0.5 to 1 mg intravenously (0.1–0.5 mg intracardiac or 0.1 mg/kg given via endotracheal tube) remains the first-line medication for use in advanced cardiac life saving and the most common reason for its use in catheterization procedures. Another emergent use is in anaphylactoid reactions to medications, or more commonly contrast. In this setting, depending on the degree of compromise, different doses and routes of epinephrine administration may be appropriate. For systemic anaphylactoid reactions (i.e., hypotension), epinephrine should be given emergently as an intravenous bolus dose of 10 mcg. This dose should be repeated in one-minute intervals until an intravenous infusion of epinephrine can be initiated or until the patient’s hemodynamics have been adequately stabilized. To quickly make a 10 mcg/mL syringe of epinephrine, one can use 0.1 mL of 1:1000 epinephrine or (more easily) 1 mL of 1:10,000 epinephrine and dilute this with saline for a total of 10 mL. For less severe reactions, epinephrine 0.3 to 0.5 mg (0.3-0.5 mL of 1:1000 solution) can be given subcutaneously or intramuscularly. Repeated doses are often necessary while steroids and other symptomatic treatments take effect.

Vasopressin can be used as an alternative to epinephrine in acute cardiac arrest. In these situations vasopressin is given as a bolus of 40 units (22). The proposed mechanism of vasopressin activity is maintenance of vascular tone and modulation of cardiovascular homeostasis (21,23). One potential advantage of the noncatecholamine, vasopressin, over epinephrine is in patients with acidosis, as catecholamine response is diminished in patients with low pH. Fixed-dose vasopressin infusions are recommended as add-on therapy to norepinephrine in patients with vasodilatory shock.

Phenylephrine

Phenylephrine is the drug of choice when a clinical situation calls for pure vasoconstriction. Phenylephrine is an α-receptor agonist with no β-receptor activity. It is ideal for treatment of anesthetic-induced hypotension or in the presence of unopposed parasympathetic activity (i.e., spinal cord injuries). Dosing typically begins at 100 to 180 mcg/min until blood pressures are stable and then infusion is decreased to a maintenance dose of 40 to 60 mcg/min. The potent vasoconstrictor activity may cause a reflexive decrease in adrenergic drive. Therefore, caution should be used in patients with myocardial ischemia or heart failure induced shock, where inotropy is needed. Table 7.5 details the hemodynamic effects of vasopressors and inotropes.

ANTITHROMBOTIC OVERVIEW

To prevent the two most frequent complications from percutaneous coronary intervention (PCI), bleeding and thrombosis, it is important to achieve adequate protection from thrombosis without resultant hemorrhage. This balance is reached by using an optimal combination of anticoagulant and antiplatelet medications. The ideal balance would be the lowest possible yet adequately effective regimen. This section examines current evidence for the efficacy and safety of antiplatelet and antithrombotic agents in PCI.

ANTITHROMBOTIC OVERVIEW WITH ANTITHROMBOTIC AGENTS

Under normal circumstances the body’s hemostatic system is finely regulated by opposing mechanisms. Prostacyclin, nitric oxide, tissue plasminogen activator, thrombomodulin, protein C, and protein S protect against coagulation in individuals with
intact endothelium. In cases of vascular damage, life-threatening hemorrhage may be prevented by thrombus formation. However, the same thrombotic mechanisms are seen when coronary endothelial damage occurs, and this can result in deleterious effects. Exposure of circulating blood to a thromogenic surface results in platelet activation and aggregation as well as release of vasoconstrictive substances worsening underlying damage and ischemia. Thrombin converts fibrinogen to fibrin, and it further stimulates platelet activity. Once formed, a thrombus may be degraded by endogenous or therapeutic fibrinolysis or mechanically by opening the coronary artery via PCI; however, these processes may acutely promote further platelet activation and thrombosis.

Two types of agents discussed in this chapter act on different aspects of the thrombotic process. Antiplatelet medications prevent platelet aggregation, while anticoagulants limit further fibrin formation. These different sites of action allow for additive, or potentially synergistic effects, resulting in greater efficacy with combination (antiplatelet and antithrombin) therapy. Combination therapy also increases bleeding risk.

### PHARMACOLOGIC FUNDAMENTALS

#### Antiplatelets

Antiplatelet medications have been a large focus of drug development, and medications are now available to target various aspects of platelet function (Fig. 7.1). Antiplatelet medications can protect against platelet activation, aggregation, adhesion, and platelet-induced vasoconstriction. Pharmacologic targets include inhibition of thromboxane A2 (TXA2) and adenosine diphosphate (ADP) to decrease platelet activation and blockade of the glycoprotein (GP) IIb/IIIa receptor activity, the final common pathway of platelet aggregation.

**Acetylsalicylic Acid**

Acetylsalicylic acid (aspirin) was the first antiplatelet therapy used clinically. Aspirin exerts its antiplatelet effect via irreversible acetylation of cyclooxygenase-1 (COX-1), which prevents arachidonic acid–induced production of TXA2. Thereby, both TXA2-mediated platelet aggregation and vasoconstriction are inhibited for the life of the platelet (25). Aspirin has been shown to reduce cardiovascular events in the acute setting of MI and stroke, and in the secondary prevention of related ischemic events (26). Risk reductions extend to secondary prevention in patients with unstable angina, coronary angioplasty, transient ischemic attack (TIA), atrial fibrillation, and peripheral arterial disease (26).

In addition to the desired therapeutic effects, inhibition of COX-1 can erode protective gastric prostaglandin and cause direct gastric irritation, resulting in gastrointestinal bleeding. Bleeding events requiring hospitalization are rare (2/1000 patients) (27), and are more common with doses exceeding 325 mg daily or in combination with other antiplatelet agents (28). Another worrisome adverse effect that appears to be dose related is intracranial hemorrhage. Therefore, use of the lowest effective aspirin dose is vitally important. Maximal antiplatelet effects of aspirin can be produced with as little as 30 mg once daily (29). And in secondary prevention of TIA, it has been demonstrated that doses as low as 30 mg are as effective as higher doses (282 mg daily) and have fewer adverse effects (30). The disadvantage of low aspirin doses is that it may take up to two days to achieve maximal inhibition. Therefore, when immediate antiplatelet effect is desired, it is recommended that aspirin naïve patients be administered 300 to 325 mg of nonenteric coated aspirin (31). For chronic therapy, 81 mg daily is recommended.

**Thienopyridines**

Thienopyridines are another major pharmacologic oral antiplatelet class. Agents of this class irreversibly inhibit the binding of ADP to the P2Y12 receptor on platelets, thereby preventing the transformation of a platelet to its activated form. Currently, three such medications are approved by the U.S. Food and Drug Administration (FDA): ticlopidine, clopidogrel, and prasugrel. The majority of thienopyridine-treated patients in the United States are currently given clopidogrel because of its favorable adverse effect profile compared with ticlopidine (32,33), the numerous clinical trials supporting its use in a
variety of settings, and the only recent FDA approval and availability of prasugrel.

Monotherapy with a thienopyridine is indicated in patients with intolerance or contraindication to aspirin, or for the secondary prevention of ischemic stroke. However, the majority of thienopyridine use is in conjunction with aspirin (dual antiplatelet therapy) following coronary artery stenting procedures or ACS. Short-term use of dual antiplatelet therapy following placement of bare-metal stents was established in the late 1990s when studies demonstrated that aspirin plus a thienopyridine could decrease the incidence of life-threatening subacute stent thrombosis and major adverse cardiovascular events following PCI (34,35). Superior efficacy and safety of a dual antiplatelet therapy was seen when 257 patients undergoing PCI were randomized to either antiaggregation (heparin bridged to phenprocoumon with a target INR of 3.5-4.5 plus aspirin 100 mg twice daily) or antiplatelet therapy (ticlopidine 250 mg twice daily plus aspirin 100 mg twice daily) in the ISAR trial (36). The primary efficacy end point at 30 days (a composite of death, MI, bypass surgery, or repeat angioplasty) was significantly reduced in the patients randomized to the antiplatelet group (1.6% vs. 6.2%, RR 0.25, 95% CI 0.06-0.77). In addition, the noncardiac composite end point of death from noncardiac causes, stroke, severe hemorrhage, or peripheral vascular events was also significantly lower in the antiplatelet group, driven primarily by a reduction in hemorrhagic events. Later, a clinical trial comparing aspirin alone, aspirin plus anticoagulation, and aspirin plus ticlopidine yielded similar results, with improved efficacy and less bleeding with dual antiplatelet therapy compared with anticoagulation, also at 30 days (37). These trials established a minimum duration of dual antiplatelet therapy of 30 days following PCI with bare-metal stent placement. More recent observations have suggested the value of longer durations of treatment (one year) with drug-eluting stents (DES).

Evidence to support dual antiplatelet therapy, beyond when stent endothelization should be complete, comes from several landmark clinical trials. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial investigators examined the effects of clopidogrel (300 mg, followed by 75 mg daily) in 12,562 patients with ACS without ST segment elevations. The composite end point of cardiovascular death, MI or stroke occurred less frequently in the clopidogrel arm compared with placebo (9.3% and 11.4%, respectively) (34). Also, in the CREDO trial subjects who underwent planned PCI and received clopidogrel for one year had reductions in cardiovascular death,

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Figure 7.1 Platelet activation is an important early step in the pathophysiology of atherothrombosis. Platelet activation involves (i) a shape change in which the platelet membrane surface area is greatly increased; (ii) the secretion of proinflammatory, prothrombotic, adhesive, and chemotactic mediators (release reaction), that propagate, amplify, and sustain the atherothrombotic process; and (iii) the activation of the GP IIb/IIIa receptor from its inactive form. Multiple agonists including thromboxane A2 (TXA2), ADP, thrombin, serotonin, epinephrine, and collagen, can activate the platelet and thus contribute toward establishing the environmental conditions necessary for atherothrombosis to occur. Aspirin inhibits the production of thromboxane A2 by its effect on the enzyme cyclooxygenase (COX)-1. The ADP receptor antagonists ticlopidine, clopidogrel, and prasugrel prevent the binding of ADP to its receptor. The effect of combining aspirin and clopidogrel is synergistic in preventing platelet aggregation. Antithrombins such as unfractionated or low-molecular-weight heparin, hirudin, or bivalirudin are important in interfering with both thrombin-induced platelet activation and coagulation. The GP IIb/IIIa receptor antagonists act at a later step in the process by preventing fibrinogen mediated cross-linking of platelets, which have already become activated. Abbreviations: GP, glycoprotein; ADP, adenosine diphosphate; ATP, adenosine triphosphate; PAI, plasminogen activator inhibitor; PDGF, platelet-derived growth factor; vWF, von Willebrand factor. Source: Adapted from Ref. 24.
Prasugrel LD: 60 mg twice daily 50–70% 4–7 days CYP450 3A and 2C +++ ++ TTP, skin rash, liver toxicity, diarrhea Nonreversible +

Clopidogrel LD: 300–600 mg MD: 75 mg once daily 50–70% 1–8 hr (following load) CYP450 3A and 2C +++ 0/+ Nonreversible +

Prasugrel LD: 60 mg MD: 10 mg once daily 90% 30 min (following load) ++ 0/+ Nonreversible +

MI, and strokes compared with placebo (35). Most recently, 13,608 patients with ACS and planned PCI were randomized to either prasugrel (60 mg, followed by 10 mg/day) or clopidogrel (300 mg, followed by 75 mg/day). Patients receiving prasugrel had a significant reduction in the primary composite end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke throughout the follow-up period of over 14 months. Increased efficacy of prasugrel over clopidogrel must be balanced with increased bleeding, including fatal bleeding, as seen in this trial (38). These studies and evaluations following DES (39–41), have led to the recommended use of aspirin plus a thienopyridine for at least one year following ACS or PCI with stent placement.

In addition to secondary prevention of atherosclerotic vascular disease, clopidogrel has been investigated as a peri-interventional therapy. On the basis of its ability to decrease platelet activation, use as an adjunct to, as well as an alternative to more traditional options, such as GP IIb/IIIa inhibitors has been proposed. A substudy of the CURE trial analyzed the 2658 subjects who underwent PCI (42). All patients received open-label aspirin and thienopyridine for four weeks after PCI. Importantly, clopidogrel or placebo was started for a median of six days prior to PCI. Overall, pretreatment with clopidogrel was associated with a reduction in the composite end point of cardiovascular death, MI, or urgent target vessel revascularization (TVR). Similarly, a substudy of the CREDO trial demonstrated that patients who received 300 mg loading dose greater than 15 hours prior to PCI had a decrease in the 28-day composite end point of death, MI, or urgent TVR (43). Table 7.6 outlines important characteristics of the individual thienopyridines.

Further evidence supporting clopidogrel pretreatment (particularly with a high loading dose) as an alternative to GP IIb/IIIa in low-risk patients comes from the ISAR-REACT 1 (44) and ISAR-REACT 2 trials (45). The former evaluated the use of abciximab versus placebo in 2159 undergoing elective PCI, all of whom had received 600 mg of clopidogrel in advance. No difference was seen in the composite end point of death, MI, or urgent TVR within 30 days after randomization (RR 1.05, 95% CI 0.69–1.59, p = 0.82). ISAR-REACT 2 had a similar trial design applied to 2022 patients with non–ST elevation ACS undergoing PCI. In this higher-risk patient population, abciximab reduced the composite end point of death, MI, or urgent TVR at 30 days when compared with placebo (RR 0.75, 95% CI 0.58–0.97, p = 0.03). These studies demonstrate that clopidogrel pretreatment is sufficient for low-risk PCI, however, in patients in whom adequate pretreatment is not possible, or among high-risk patients (i.e., troponin positive), alternate antiplatelet strategies may be needed.

Intervenability variability in antiplatelet responses to thienopyridine therapy has been described and is of concern (46). One theory that may partially explain the unpredictable response is related to alterations in metabolism of prodrugs to their clinically effective metabolites. This occurs via metabolism by the liver cytochromes, primarily CYP3A4, CYP1A2 and CYP2C19 isoenzymes (47). Several potentially significant drug interactions have been proposed with clopidogrel, all involving this metabolic conversion in the liver. Although the interaction between statins and clopidogrel has been shown to be clinically irrelevant, this was one of the first examined (48–50). Atorvastatin was thought to compete with clopidogrel for CYP3A4 and pharmacodynamic data suggested a decreased antiplatelet effect with coadministration (51). Recently, decreased antiplatelet effects have been observed with coadministration of proton-pump inhibitors (PPI) and clopidogrel, likely due to inhibition of CYP2C19 (52). Studies of platelet assays and observational data from large clinical trials resulted in the FDA issuing a warning of decrease antiplatelet effect when using the combination of PPIs and clopidogrel. In contrast however, the preliminary results of the only randomized placebo-controlled clinical trial show no worsening in outcome among patients receiving omeprazole and clopidogrel. In addition, smoking, a known inducer of the CYP1A2 isoenzyme, may enhance the antiplatelet effects of clopidogrel by enzyme induction (53). The elucidation of clinical implications of these interactions warrants further study. Nonetheless, it appears that fewer drug interactions and less interpatient variability is seen with use of prasugrel, resulting in faster, greater, and more consistent inhibition of ADP-induced platelet aggregation than with clopidogrel (54).

**GP IIb/IIIa Receptor Antagonists**

**GP IIb/IIIa receptor antagonists** block the final common pathway of platelet aggregation by preventing fibrinogen binding and cross-linking of platelets at the αIIbβ3-receptor. Interference with this process results in inhibition of approximately 80% of platelet aggregation function (55). Three such medications are FDA approved for use in conjunction with aspirin and antithrombotic therapy, all are administered intravenously and for a limited period of time, providing potent antiplatelet therapy for the most critical interval following ACS diagnosis and/or stent placement. As previously mentioned, the use of clopidogrel pretreatment and newer antithrombotic regimens has lessened the role of GP IIb/IIIa inhibition, however, they remain important for intermediate- and high-risk ACS and higher-risk PCI cases.

GP IIb/IIIa inhibitors have been widely tested. The majority of benefit is seen among ACS patients who undergo
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early PCI, those with dynamic ST segment changes, and individuals with elevated troponin levels (56). Benefit has also been established among patients with high-risk features such as diabetes or home aspirin therapy (57). Additionally, use of these agents prior to planned PCI has been clearly established (57–59). However, much of the trial data came from studies prior to the routine inclusion of thienopyridines and in lower risk patient populations no benefit has been observed. Mixed outcomes have resulted in the practice of preferentially treating only the highest risk patients with upstream GP IIb/IIIa antagonists, although no study has validated this approach. Individual differences in the GP IIb/IIIa antagonists and supportive clinical trial data can be used to guide which therapy to use depending on the specific patient and clinical scenario.

Several important pharmacologic factors define the use of abciximab. In contrast to other GP IIb/IIIa inhibitors, abciximab is a monoclonal antibody blocking GP IIb/IIIa receptors. Following intravenous bolus, antiplatelet effects occur within minutes and return to normal within 48 hours in most cases (60). The general irreversibility and slower offset compared with small-molecule GP IIb/IIIa inhibitors limits abciximab when there is a high likelihood of bleeding complications or surgical intervention. Since abciximab is an immune fragment, immune mediated thrombocytopenia and other responses, while overall rare, are also more common (61).

Abciximab is only approved for use in patients undergoing or planned to undergo PCI. In the first evaluation of GP IIb/IIIa inhibitors for PCI, abciximab (0.25 mg/kg bolus plus 10 mcg/min infusion for 12 hours) resulted in a significant reduction in the primary composite end point (death, MI, revascularization, stent placement, or IABP insertion). This study enrolled 2099 patients with unstable angina, high-risk features, or undergoing angioplasty or atherectomy for MI (62). Benefit was subsequently observed in a lower risk, elective PCI cohort. This evaluation of 2792 patients was stopped early when abciximab resulted in a 6.5% absolute risk reduction in the primary efficacy end point (death, MI, or urgent TVR) (63). Later, once implementation of PCI with stent placement became widespread, the EPISTENT trial sought to investigate abciximab’s role in stenting procedures (64).

EPISTENT enrolled 2399 patients scheduled to undergo elective or urgent PCI with stent placement to one of three arms: stenting plus placebo, stenting plus abciximab, or balloon angioplasty plus abciximab. All patients received heparin and ASA. Again, thienopyridines were routinely administered before PCI with a loading dose. Both abciximab arms resulted in a statistically significant reductions in the composite of death from any cause, MI, or urgent revascularization relative to placebo plus stenting (64). Abciximab was separately observed to be effective during primary PCI for treatment of ST segment elevation MI. A meta-analysis of three trials (ISAR-2, ADIMIRAL, and ACE) compared 550 patients on abciximab with 551 patients receiving placebo. Abciximab use resulted in a 37% reduction in the composite of death or reinfarction (p = 0.008), with a nonsignificant increase in bleeding (65). More recent studies with high loading doses of clopidogrel have not observed a reduction in ischemic events, though these observations have not been definitive.

Eptifibatide and tirofiban are both small-molecule agents. Although different from abciximab in pharmacology, the end result of preventing fibrinogen and Von Willebrand factor binding to the GP IIb/IIIa receptor is similar. Tirofiban is a highly specific nonpeptide peptidomimetic GP IIb/IIIa inhibi-

tor, and eptifibatide is a synthetic cyclic heptapeptide. Both are inherently less likely to cause hypersensitivity reactions than abciximab (61). Additionally, these agents are preferred in patients at increased risk of bleeding, because of reversible antiplatelet activity, shorter duration of action, and lower incidence of severe thrombocytopenia (66). These agents have been studied with favorable results in PCI-patient populations similar to those in trials of abciximab (67–69), but also have a role in ACS patients managed without PCI.

Several trials have evaluated the adjunctive use of small-molecule GP IIb/IIIa inhibitors as medical therapy for ACS in patients receiving aspirin and heparin. Among the earliest of these was the PURSUIT trial, where treatment with eptifibatide was continued for up to 72 to 96 hours (59). The eptifibatide treated patients experienced a 1.5% absolute risk reduction in the 30-day composite end point of death or nonfatal MI. The effect was pronounced in patients undergoing PCI during drug administration. Trials evaluating the use of tirofiban in a similar non–ST elevation ACS patient population showed similar benefit, reducing early cardiovascular ischemic events (70,71). However, subjects in these trials had limited “upstream” exposure with median time to PCI of < 6 hours, and conflicting results were seen in the recently published EARLY-ACS trial (72).

Evaluations of upstream GP IIb/IIIa inhibitor use in patients experiencing STEMI and undergoing primary PCI have yielded mixed results. Both the ADMIRAL and RELAX-AMI trials demonstrated that early abciximab administration resulted in improved coronary angiographic findings at the time of PCI (73,74). However, clinical outcomes were not improved by the early addition of abciximab in the FINESSE trial (75). In the placebo-controlled second Ongoing Tirofiban in Myocardial Evaluation (ON-TIME 2) trial, the prehospital administration of high-bolus-dose tirofiban significantly improved ST segment resolution both before and after primary PCI in patients with acute STEMI (76).

Overall, meta-analysis including multiple trials, enrolling 31,402 patients with ACS without planned PCI showed a modest benefit of GP IIb/IIIa inhibitors compared with controls (77). Considering a 30-day end point, Boersma and colleagues reported a 9% relative risk reduction (10.8% vs. 11.8%, p = 0.015) in death or myocardial infarction. The authors concluded that upstream IIb/IIIa inhibitors might be started and continued until an invasive approach was made. With mixed trial results, growing emphasis placed on improving the time from symptom onset to reperfusion, rapid-acting thienopyridine strategies, and alternative anticoagulation regimens such as bivalirudin, the upstream use of GP IIb/IIIa inhibitors have most recently lost some appeal.

Contraindications to GP IIb/IIIa therapy are similar among abciximab, eptifibatide, and tirofiban. Given their ability to cause profound thrombocytopenia (abciximab > eptifibatide > tirofiban), history of such reactions should result in a clear contraindication to readministration. Also, patients with baseline platelet counts <100,000 should not receive GP IIb/IIIa therapy. Recent history of ischemic stroke (within three months) and any history of hemorrhagic stroke warrant careful evaluation of risk verses benefits of use. Also, with bleeding a limiting side effect, administration in patients with trauma, recent surgery, and bleeding disorders is questionable. Finally, careful attention should be paid to the dosing of these medications, particularly given the weight-based dosing and renal adjustments recommended with several of the medications. Table 7.7 shows the characteristics of the GP IIb/IIIa inhibitors.
Anticoagulants

Anticoagulation during PCI is of vital importance. The previously mentioned antiplatelet therapies are all given on a background of anticoagulation during PCI and often peri-procedurally. In addition to the thrombogenicity of the acute circumstance, introduction of a foreign body (e.g., coronary guidewires) and mechanical injury caused by the procedure can easily result in thrombus formation or clot progression. Use of anticoagulation can reduce clot progression, acute stent thrombosis, and subsequent ischemic events. Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and bivalirudin are the most commonly used anticoagulants in PCI. Agent selection is based on clinical data, diagnosis, and patient characteristics. However, benefits must be balanced with increases in bleeding. Table 7.8 enumerates currently available antithrombotic agents for PCI.

Heparin

Heparin is a heterogenous mucopolysaccharide with complex effects on the coagulation pathway (83). Heparin is a naturally-occurring anticoagulant produced by human basophils and mast cells (83); however, most of the pharmaceutically available heparin in the United States is derived from porcine mucosal tissue. The primary pharmacologic effect is thought to be driven by the binding of heparin to antithrombin and simultaneous binding of heparin to thrombin. This promotes the effects of antithrombin III, which prevents the binding of fibrinogen to thrombin, and hence is an anticoagulant. Importantly, it also exerts indirect antiplatelet effects by binding to and inhibiting Von Willebrand factor. Additionally, UFH binds to plasma proteins, endothelial cells, and macrophages, which in turn inactivates heparin. These wide-ranging activities result in variable anticoagulant effects, and as such, therapy with UFH requires close monitoring and dosing adjustments during use.

Heparin has been the gold standard for anticoagulants in the catheterization laboratory; however, no prospective trials have clearly defined the optimal level of anticoagulation necessary during PCI, and concomitant antithrombotic regimens continue to evolve. Monitoring and titration of UFH during PCI can be facilitated through point-of-care testing of the activated clotting times (ACT) (84). Historically, the standard heparin regimen has been 100 units/kg bolus with additional weight-based boluses to achieve and maintain an ACT of 250 to 350 seconds, depending on concomitant therapies (85). Although lacking prospective validation, retrospective data
show that this approach is reasonable. One retrospective study showed short-term ischemic events were more likely (6.6% compared with 11.1%) in patients with ACTs of 171 to 195 compared with those with higher ACT ranges of 350 to 375 seconds (86). This is balanced with the knowledge that maximum ACT is predictive of bleeding complications (87). Importantly, sheath removal is safest once ACTs fall below 150 to 180. When UFH is administered with GPIIb/IIIa inhibitors, lower ACT values of ~200 seconds result in similar reductions of ischemic events with less risk bleeding risk (85,88). A different approach is used when UFH is started upstream, and used for the medical management of ACS, or when used for prevention of reocclusion following fibrinolysis. In these scenarios, UFH is traditionally administered as a maximal 5000 unit bolus followed by 1000 units/hr for up to 48 hours (89). Rather than ACT, the activated partial thromboplastin time (aPTT) is utilized for monitoring with a goal of 50 to 70 seconds or 1.5 to 2 times baseline (90). Whether UFH is started before procedure or only utilized during PCI, immediate discontinuation following successful PCI is recommended. Continuation has shown no benefit and results in higher rates of access site bleeding (91,92). Given the many idiosyncrasies with UFH, it is far from ideal as an anticoagulant.

**Low-Molecular-Weight Heparins (LMWH)**

LMWH are heparin salts and are about one-third of the molecular weight of UFH. Mechanistically, these shorter-chain polysaccharides bind to antithrombin and thrombin, but the binding to thrombin is to a lesser extent than UFH. Rather, the majority of anticoagulant effect comes from binding to factor Xa, the catalyst for conversion of prothrombin to thrombin. As a result, LMWH has only a minimal effect on aPTT and ACT, and monitoring requires measurement of anti-Xa activity. Bedside monitoring of anti-Xa levels is not routine; therefore, in patients receiving LMWH during PCI, dosing recommendations should be based on available evidence from clinical trials (93). LMWH have several important pharmacologic differences compared with UFH, including an increased bioavailability, a prolonged route of elimination, and a more consistent anticoagulant effect. Therefore, following IV or SQ administration, they offer a reasonably predictable level of anticoagulation and longer lasting antithrombotic effect than that achieved with UFH. Several LMWH are available though the majority of evaluations in PCI has involved enoxaparin. Like UFH, enoxaparin may be used to treat ACS or without planned PCI and to prevent recurrent vessel occlusion following thrombolytic reperfusion.

Several clinical trials have compared UFH and enoxaparin in the medical treatment of ACS. As examples, the two drugs were compared in patients with NSTE ACS in both the ESSENCE trial and the A to Z trial. Both trials were open-labeled, randomized, noninferiority designs comparing standard dosing regimens of UFH with enoxaparin 1 mg/kg subcutaneously every 12 hours. In ESSENCE enoxaparin was found to be superior to UFH by reducing the combined end point of death, MI, or recurrent angina (94). Later, in the tiotrofiban arm of the A to Z trial, enoxaparin was shown to be noninferior to UFH when given in addition to aspirin and tiotrofiban (95). On the basis of these trial results, either UFH or enoxaparin are viable options for medical management, though guideline preference is given to enoxaparin.

LMWH has also been compared with UFH in the setting of PCI. The Superior Yield of the New Strategy of Enoxaparin, Revascularization and GP IIb/IIIa Inhibitors (SYNERGY) trial randomized 9978 higher-risk ACS patients with planned early invasive treatment to either UFH or enoxaparin. The results showed noninferiority, with no difference in the primary end point (death or MI), subacute stent thrombosis, or unsuccessful procedures (96). These findings are in agreement with results of the subgroup analysis of patients who received PCI in the A to Z trial (95). However, the SYNERGY trial did yield another interesting and important finding. Bleeding was increased in patients who received enoxaparin before PCI and crossed over to receive UFH during PCI. Therefore, “crossover” should be avoided and in patients who present to a catheterization procedure already receiving enoxaparin, subsequent doses should be based on the timing of the previous dose. If the last dose of enoxaparin was <8 hours prior to PCI, no additional anticoagulant is needed. If received 8 to 12 hours prior to PCI, 0.3 mg/kg IV enoxaparin should be given, and finally, if enoxaparin was administered >12 hours prior, a full-dose is needed or conventional therapy is indicated (97).

The safety of enoxaparin in elective PCI was evaluated in the STEEPLE trial (98). Patients undergoing PCI were
Fondaparinux
Fondaparinux is a synthetic pentasaccharide that is an antithrombin-dependent indirect inhibitor of activated factor X (Xa). Its use as an alternative to heparin, in both the medical management of ACS and antithrombotic protection post fibrinolysis has been evaluated. In the Fifth Organization to Assess Strategies in Ischemic Syndromes (OASIS)-5 trial, 20,078 patients experiencing ACS were randomized to enoxaparin or fondaparinux. The primary short-term efficacy end point of death, MI, or stroke occurred at a similar frequency in both groups; with fondaparinux recipients experiencing 50% fewer bleeding events and 17% fewer mortalities at 30 days. In 2007, Mehta et al. published results from the planned analysis of the 6238 patients who underwent PCI (99). Short-term rates of ischemic events were similar, and major bleeding was reduced by one-half; however, patients in the fondaparinux group experienced higher rates of catheter thrombosis (0.9% compared with 0.4%). Because of the risk of this potentially devastating complication, fondaparinux should not be used as the sole anticoagulant to support PCI (85). Furthermore, fondaparinux should be avoided in patients when an early invasive strategy is planned. Several new oral anticoagulants are being developed, with the oral direct factor Xa inhibitor apixaban being evaluated in the treatment of patients with recent ST elevation or non–ST elevation acute coronary syndrome. The phase II trial, APPRAISE-1, showed dose-related increases in bleeding and a decrease in ischemic events (100). Apixaban 5 mg twice daily is being evaluated in a phase III study in a similar patient population.

Direct Thrombin Inhibitors
Direct thrombin inhibitors (DTI) currently available in the United States include bivalirudin, argatroban, and lepirudin. DTI inhibit soluble and clot-bound thrombin without involvement of antithrombin. Another potential advantage over heparin is that DTI do not promote platelet activity, rather the degree of thrombin inhibition at high doses, decreases platelet activation. The earliest experience with DTI in PCI was mostly with argatroban, however the majority of prospective randomized evaluations has utilized bivalirudin. In 1999, patients with known or suspected HIT and requiring PCI were given argatroban rather than heparin. In this small, single-arm study, use of the DTI argatroban resulted in adequate anticoagulation, and bleeding was minimal (101). Later, when GP IIb/IIIa therapy was more common, a retrospective evaluation of argatroban yielded similar results (102). Now clinical trial data (103,104) and extensive experience with bivalirudin in PCI support its use in high-risk patients with HIT requiring PCI. Favorable experiences seen in these patients, and inherent weaknesses of heparin therapy resulted in evaluation of bivalirudin in patients without contraindication to heparinoids.

The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial randomized 6010 patients undergoing urgent or elective PCI to intravenous bivalirudin (0.75 mg/kg bolus plus 1.75 mg/kg/hr for the duration of PCI) or UFH with a GP IIb/IIIa inhibition (105). The authors concluded that bivalirudin was noninferior to heparin and GP IIb/IIIa inhibition with regard to suppression of the primary efficacy end points (death, MI, or TVR) and was associated with less bleeding (2.4% vs. 4.1%; p < .001) (105). Provisional GP IIb/IIIa inhibitor therapy was administered to 7.2% of the patients in the bivalirudin arm. This trial extended bivalirudin use to patients undergoing elective PCI. Bivalirudin would later demonstrate efficacy when initiated upstream from PCI, in the management of NSTEMI, unstable angina, and STEMI (106–108).

In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, bivalirudin (with and without GP IIb/IIIa inhibition) was compared with heparin plus a GP IIb/IIIa inhibitor (106). The trial enrolled 13,819 patients with moderate to high-risk acute coronary syndromes and planned early interventions. Stone et al. reported that a strategy of bivalirudin alone reduced rates of major bleeding (3.0% vs. 5.7%, p < 0.001) with similar efficacy (7.8% and 7.3%, p = 0.32) to heparin plus GP IIb/IIIa inhibition. Later, the HORIZONS-AMI trial addressed the use of bivalirudin in patients with ST segment elevation MI undergoing primary PCI (107). The end points studied were major bleeding and the combination of death, reinfarction, TVR, and stroke. Anticoagulation with bivalirudin alone was compared with heparin plus GP IIb/IIIa inhibitors and resulted in a significant decrease in bleeding and similar efficacy with regard to ischemic end points.

Considering the findings of ACUITY and HORIZONS-AMI, bivalirudin is an attractive approach for patients undergoing elective or urgent PCI, particularly when adequate antiplatelet therapy with a thienopyridine is present. In these settings, with over 10,000 patient experiences in clinical trials, bivalirudin therapy continues to be noninferior to heparin plus GP IIb/IIIa inhibitor therapy with substantial reductions in bleeding.

CONCLUSION
Given there are many antiplatelet, antithrombin, and antifibrin drugs available for PCI, polypharmacy-based procedures are standard of care with literally hundreds of potential drug combinations. The overall pharmacologic management of patients during PCI can be remarkably complex. Hemodynamic management is undertaken with the ultimate goal of patient stabilization to allow potentially life-saving procedures to take place and ultimately to improve outcomes and survival. It is also vitally important to prevent complications using appropriate periprocedural pharmacotherapy. Development of the ideal antithrombotic and antiplatelet regimen continues to be a goal for the cardiology community. New therapies are in development and may help increase efficacy and limit adverse effects in this at-risk patient population.

REFERENCES
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**CARDIOVASCULAR CATHETERIZATION AND INTERVENTION**


**INTRODUCTION**

The familiar percutaneous vascular access approach pioneered by Seldinger in 1953 (1) revolutionized invasive medicine. It provided an alternative to the time-consuming and morbid surgical cutdown techniques that had been part of vascular access since before the time of Werner Forssmann’s self-catheterization by cutdown in 1929. Cardiac catheterization, however, was still primarily via surgical access through the 1960s, with the radial cutdown a ubiquitous feature of the Sones technique (2). Peripheral angiography and intervention were also largely by femoral cutdown, with a high associated access site complication rate (3). The introduction of the Judkins technique in the 1960s (4) was associated with widespread adoption of Seldinger’s method. The radial approach, nearly universally by percutaneous puncture, was introduced for cardiac catheterization in 1989 (5) and by Kiemeneij for cardiac intervention in 1993 (6). Percutaneous brachial access, although occasionally utilized for peripheral angiography starting in the 1950s (7), now has limited overall utilization, and the least appealing overall safety profile (8).

The Seldinger method has been subjected to relatively few investigations and has changed remarkably little over a half century. Two major modifications are noteworthy: first, the original Seldinger technique involved through-and-through puncture of the artery, typically with a stylet in the needle, and pullback with the stylet removed until flashback was noted. Because the back wall puncture facilitates bleeding and hence hematoma formation, and has been implicated as a cause of retroperitoneal hemorrhage (RPH), the “modified Seldinger technique” has now been adopted almost universally. This modification involves puncture of the anterior wall only (Fig. 8.1). The second major innovation was the introduction of sheath introducers in 1979 (9); this eliminated the introduction of multiple catheters directly through the skin, obviated the need for performing exchange procedures every time another catheter was utilized, and resulted in a smoother arteriotomy without the fraying at the edges that was common after multiple catheter introductions. It also prevented accumulation of debris in the tip of the catheter as it passed through skin, muscle and cartilage. Although debris embolization from catheter tips remains a source of morbidity, it is now rarely associated with naked catheter passage through the skin (10).

Vascular access has been subjected to significant clinical investigation in the past decade and an evidence base is accumulating that addresses both access and closure methods. Although incomplete, the literature now has a number of important studies addressing access site selection, radial versus femoral access, puncture location, adjunctive use of fluoroscopy and ultrasound, and manual compression versus device-based vascular closure; all will be covered in this chapter.

**ACCESS SITE**

The choice of access site is influenced by the end organ to be investigated or treated, the size of the catheters to be used, and the success and complication rates associated with each approach. Most diagnostic and therapeutic procedures in the United States utilize femoral access, in contrast to other parts of the world where coronary procedures are now most commonly performed via the radial approach. The brachial approach is a distant third in terms of frequency, followed by a number of relatively uncommon or rare arterial access routes, including retrograde popliteal, axillary, translumbar aortic, direct carotid, direct left ventricular apex, and direct infrapopliteal access.

A number of randomized studies have compared access routes, most commonly transfemoral and transradial access, while one has compared transradial, transfemoral, and transbrachial (8). Meta-analyses in general have convincingly demonstrated the highest success rates with the femoral approach, and the lowest complication rates with radial access (11), with intermediate success rate but the highest complication rate with percutaneous transbrachial procedures (8).

**Access Technique**

Virtually all percutaneous access now involves anterior wall hollow needle puncture of the artery followed by introduction of a guidewire through the needle, after which a catheter (typically a sheath) is introduced over the guidewire (Fig. 8.1). An uncommon variation in cardiac catheterization, but commonly used for intravenous lines, is the insertion of a sleeve over the outside of the needle, a technique that is occasionally used for radial catheterization as well. The use of sheaths, typically with sidearms for pressure monitoring, blood sampling, or angiography requires an approximately 0.7 mm increase in the size of the arteriotomy. A common misconception is that a 6 French (F) sheath is 2 mm in size (one French size is the equivalent of 0.33 mm); although a 6F sheath will accommodate a 2-mm catheter, it has an outer diameter in the range of 2.7 mm. Thus, by convention, catheter size refers to outer diameter, whereas sheath size refers to inner lumen; in fact a catheter equivalent in outer diameter to a 6F sheath would be 8F in size.

**Access Needle Size**

Most cardiologists continue to utilize large bore 18-gauge needles for percutaneous vascular access. These provide considerable “splash-back” of blood on arterial entry. In contrast, most radiologists use micropuncture techniques, as do cardiologists performing radial access, typically with a 21-gauge needle, which is approximately 0.8 mm in diameter. Micropuncture results in only a trickle of blood through the needle at the time of vessel entry, which is a significant potential safety advantage,
although arterial entry is less obvious. In contrast, the 18-gauge needle is approximately 1.3 mm in outer diameter, 56% larger than the 21-gauge needle, and results in nearly six times as much blood flow (Fig. 8.2). Thus, errant vessel puncture has the potential for significantly greater extravasation of blood, leading in turn to higher risk of hemorrhagic complications. Although intuitively appealing, there is as yet no compelling evidence base for the benefits of micropuncture access.

**FEMORAL ACCESS**

**Puncture Location**

The femoral artery continues to dominate access in the United States because of two advantages: first, large devices, 24F or greater, can be accommodated if vessels are both large and compliant, and second, relative ease of access. Three primary landmarks have been utilized for arterial access: the inguinal crease, the point of maximal pulsation, and a line drawn between the anterior superior iliac crest and the symphysis pubis. The most common landmark continues to be the inguinal crease, an unfortunate choice since it tends to lead to puncture outside the common femoral artery. In a study by Grier et al. (13) surveying the practices of 200 interventional radiologists and cardiologists, 40% used the inguinal crease as the sole landmark for initial puncture. Figure 8.3 shows the common femoral artery as traditionally depicted in most textbooks. There are three major misconceptions represented in this cartoon. First, the inguinal ligament is depicted above the femoral head, a relationship that is less common than most operators realize. Second, the inguinal crease is depicted as overlying the center of the femoral head. Finally, the inguinal crease is depicted as being superior to the femoral bifurcation. In fact, the inguinal ligament descends over the upper half of the femoral head in a significant percent of cases, and the crease is an average 6 mm below the femoral bifurcation (13), which in turn is at or below the femoral head in more than three-quarters of patients (14).
Puncture at the inguinal crease tends to predispose to low sticks, especially in obese patients, including entry into one of the femoral bifurcation vessels, either the superficial femoral artery or the profunda femoris. Low puncture (below the femoral head), whether entry into the common femoral or one of its branches, predisposes to several complications, most notably arterial pseudoaneurysm (16). Postprocedure compression of the artery with catheter/sheath removal is impaired by lack of the anvil represented by the femoral head itself; compression against layers of fat, muscle and other soft tissue elements can result in inadequate hemostasis and subsequent pseudoaneurysm formation (Fig. 8.4). Two other consequences of note accompany low puncture: the venous circulation runs closely parallel or overlaps with the femoral bifurcation vessels, increasing the risk of arteriovenous fistulae (17). Femoral nerve branches approximate the artery at and below the femoral bifurcation, increasing the risk of nerve compression with hematoma formation or, if vascular closure devices (VCDs) are used, of injury to the nerve from direct trauma, including rare cases of stitch or clip strangulation.

Of far more concern in terms of overall morbidity and mortality, however, is high puncture, associated with up to an 18:1 odds ratio for RPH (18). Once considered to be a problem primarily with punctures above the femoral head, an increasing evidence base has explored the relative location of femoral punctures with relationship to various bony and vascular landmarks. Figure 8.5 shows the relative position of the inguinal ligament to various anatomical features. The most useful single landmark is the inferior epigastric artery (IEA); this vessel arises from the external iliac artery and initially has a downward course toward the inguinal ligament. It approaches but does not cross the ligament and then ascends cranially toward the epigastrium, where its circulation overlaps with that of the internal mammary arteries. Punctures below the most inferior sweep of the IEA are least likely to be associated with RPH. Typically the IEA does not descend below the femoral head centerline.

The location of the femoral bifurcation, on the basis of a 200-patient study (20), is at or below the bottom of the femoral head in approximately 77% of patients and above the centerline of the femoral head in less than 2% of cases. Because of the greater risk associated with high puncture, and the fact that the exact excursion of the IEA is variable among patients and is unknown in most at the time of access, an optimal location, below the centerline of the femoral head but high enough to minimize the risk of entry into the femoral bifurcation vessels, is shown in Figure 8.5. Puncture 5 mm or more below the centerline of the femoral head results in access below the IEA in 97% of patients (21).

**Fluoroscopy and Ultrasound Guidance**

Fluoroscopy to guide common femoral artery access was widely adopted by radiologists thirty years ago (22) (Fig. 8.6A). Localizing the relatively small target zone can be accomplished by placing a hemostat at the bottom edge of the femoral head as originally described by Kim (16) or over the target area below the femoral head centerline. An important additional element of the technique is iterative fluoroscopy once the needle has entered the tissue track but before the needle is advanced far enough to enter the artery (Fig. 8.6B). Removing his or her hands...
from the field, the operator confirms that the needle tip is close the desired target area, and then advances into the anterior wall of the artery. This additional step shows the needle track to be outside the desired horizontal or vertical plane in a large percentage of cases, and requires repositioning prior to vessel entry. Even so, fluoroscopy without this additional step has been shown to decrease overall complication rates in one retrospective analysis by Fitts and colleagues (23), which demonstrated lower rates of pseudoaneurysm and arterial injury in the practices of operators who used fluoroscopic guidance. A recent randomized prospective comparison of fluoroscopic versus traditional landmark guided femoral access by Abu-Fadel et al. (24) demonstrated fewer punctures below the femoral head with fluoroscopy but was underpowered to assess complication rates. Importantly, this study did not utilize the iterative fluoroscopic technique described above and had nearly half the punctures above the centerline of the femoral head, an undesirable consequence of reliance on hemostat fluoroscopy as the sole source of radiographic guidance. Over all, the potential benefit remains unproven (25).

Figure 8.4 (See color insert) Computed tomographic angiogram showing relationship of the iliac and common femoral arteries to the bony structures of the pelvis and the femoral head. Note that the distance from the artery to a bony support structure (that can serve as an anvil against which compression forces can be applied) is shortest (green arrow) over the common femoral artery. The lower red arrow shows the increased distance between the shaft of the femur and the distal common femoral artery if punctures are below the femoral head; this requires compression through additional soft tissue including muscle, fat and cartilage with associated increased risk of pseudoaneurysm. Puncture into the superficial femoral artery is associated with increased risk of arteriovenous fistulae. The upper red arrow shows the extensive distance between the external iliac artery, which descends toward the retroperitoneum, and the deep pelvis; high puncture has odds ratios up to 18 to 1 for RPH in fully anticoagulated patients (18). Abbreviation: RPH, retroperitoneal hemorrhage.

Figure 8.5 (A) Anatomy for femoral puncture. A, bottom of femoral head; B, centerline of femoral head; C, line drawn from anterior superior iliac crest to symphysis pubis; D, inguinal ligament; E, inferiormost excursion of the inferior epigastric artery; and F, inguinal crease. The oval depicts the ideal location for femoral access. (B) The landmarks depicted in (A) are seen here superimposed on a femoral angiogram. Landmarks A through C can be detected on plain fluoroscopy. The sheath is seen to enter in the ideal target location. Source: From Ref. 19.

An alternative approach is utilized by many interventional radiologists, and involves ultrasound-guided access, typically with visualization of the artery in cross sectional view (26). This technique allows predictable arterial entry and minimizes the risk of inadvertent venous puncture. It does not provide similar guidance as fluoroscopy with regard to avoiding high puncture, and preliminary results of the Femoral Arterial Access with Ultrasound (FAUST) trial (27) included a substantial number of punctures above the inguinal ligament.
The technique requires modest additional preparation in the cath lab, does appear to decrease the number of needle passes required to access the artery, and reduces inadvertent venous access, but has not been adopted by many cardiologists.

Finally, techniques such as percutaneous aortic valve interventions, percutaneous ventricular assist devices, and abdominal aortic aneurysm stent-graft placement have increased the importance of first pass access into the femoral artery. Besides the fluoroscopy and ultrasound methods already described, techniques include contralateral catheterization with contrast media injection, or placement of a pigtail catheter into the common femoral artery to provide a target for the needle on fluoroscopy.

**Femoral Access Technique**

Once the target location is determined, local anesthesia is infiltrated several centimeters below the target zone. Lidocaine is typically used for local anesthesia; because of zero order kinetics, the percentage of lidocaine in the injectate determines duration of anesthesia and not level of anesthesia. Thus for procedures that are relatively short in duration, 1% local anesthetic is adequate. For longer procedures, 2% lidocaine may be preferable; an alternative, utilized for long duration procedures such as ablations, is bupivacaine. Importantly, each percent solution means 10 mg of lidocaine injected subcutaneously; thus, 10 to 20 cc of injectate will result in systemic levels of lidocaine, and in older patients, those with small body mass or those with hepatic failure, lidocaine toxicity should be considered in cases of altered mental status or seizures. Some laboratories use lidocaine with epinephrine to decrease the rate of absorption, thereby increasing duration of anesthesia, and decreasing oozing in the tissue track. Buffering the solution with sodium bicarbonate decreases the pain associated with local anesthesia (28).

The access needle is approximately 7 cm in length; the depth of access will depend on the patient’s body mass. The typical angle of puncture is approximately 45°, and should be aligned in the same plane as the artery. Using the iterative fluoroscopic technique, flashback of blood should indicate passage through the anterior wall of the artery. The typical J-tipped guidewire can be seen to traverse the iliac circulation to the aorta (patient’s left side), and fluoroscopy is usually not necessary when a 0.035" J-tipped guidewire passes freely. However, if a micropuncture technique is used, the micropuncture wire must be visualized prior to sheath introduction, since the wire can easily enter a small caliber branch vessel, and pushing a sheath into small vessels such as the lateral circumflex of the hip can result in arterial rupture.

An adjunctive technology that is occasionally used is the SmartNeedle (Escalon, New Berlin, Wisconsin). This uses Doppler technology through an obturator in the needle to localize venous or arterial pulsations. If the groin is scarred, as is the case after multiple prior catheterizations, a stiff 0.035" J-tipped guidewire should be placed through the needle to provide sufficient support for sheath entry, or, if micropuncture is used, a reinforced micropuncture sheath can be utilized. If there is extensive atherosclerotic disease or tortuosity in the external or common iliac, use of a hydrophilic guidewire can be considered, although care should be taken to avoid advancing into sidebranches or creating an intimal dissection, and withdrawal of a hydrophilic guidewire through an introducer needle can readily lead to severing the guidewire tip. On occasion, femoral access is desirable in a patient with aorto- or iliofemoral bypass grafts. There is no contraindication to access in this setting, but automated compression devices should not be used for hemostasis.

Anticoagulation is rarely used for routine diagnostic angiography via the femoral route. Early in the history of catheterization, prolonged catheter dwell times, thrombogenic materials, and the need for prolonged guidewire placement while catheters were exchanged all predisposed to thrombus
formation. When intervention is planned, we advocate routine femoral angiography prior to anticoagulation as described below.

**Femoral Angiography**

Angiography of the femoral artery after sheath placement allows the operator to assess three parameters important to avoidance of complications: first, location of puncture; second, size of the artery; and third, presence of atherosclerotic disease at the puncture site. Most importantly, if angiography is performed immediately after sheath access, in the presence of anatomy that predefines high risk for postprocedure vascular complications (e.g., puncture above the inguinal ligament), anticoagulation and aggressive antiplatelet therapy can be avoided, since the complication rate is substantially higher in those settings (29). Angiography is typically performed in the ipsilateral view (Fig. 8.7); this optimizes visualization of the femoral bifurcation, although the sheath entry point is frequently obscured. Placing tension on the sheath and moving it side to side during contrast injections can help localization. Alternatively, an ipsilateral caudal or contralateral view can be used.

Although the mean size of the common femoral artery is 6 to 8 mm, the minimal size of the vessel is only 5.0 mm in women and 6.3 mm in men (20). At least one-quarter of women have minimal lumen size of 4 mm or less; in this setting the external diameter of a 6F sheath will occlude three-quarters or more of an otherwise healthy artery. In addition to women, diabetics also have smaller vessel diameters. Various interventions are simply incompatible with common femoral artery size in patients with small arteries, in particular abdominal aortic aneurysm stent-grafts and percutaneous aortic valve replacement that require sheaths that are 8 mm or greater in diameter.

**Complications**

The precise complication rate of femoral artery access is elusive, and predicated on wide variability of definitions, in particular hematoma rates. The definitions for significant hematoma vary from 2 to 15 cm in the literature, and rates range from less than 1% to more than 10%. Using a 10-cm threshold, a 12,000 patient study from the Montreal Heart Institute (30) found a 1.8% vascular complication rate associated with femoral diagnostic catheterization and 4.0% associated with interventions. While the most common complication over all is hematoma formation, the most lethal is RPH, with a mortality in the range of 5% (18,29). The incidence of RPH has increased substantially in the interventional era, and approaches 1% (18,29,31). Pseudoaneurysm occurs in a range from 1% to 5% (the higher values are seen with routine ultrasound that detects clinically insignificant pseudoaneurysms) (32), while arteriovenous fistulae, significant vessel dissection, obstruction, neural damage, and venous obstruction occur in less than 1% of cases. The other clinically important complication, infection at the access site, occurs in less than 0.3% of cases, but has a mortality in the 6% range (33).

There is compelling evidence that bleeding episodes are a strong independent predictor of adverse outcomes (34). In general bleeding complications have decreased substantially in the past two decades. A comparison (35) of three major abciximab trials revealed a greater than 10% rate of major bleeding including transfusions in the EPIC trial (36), decreasing over the subsequent four years to approximately 2% in the EPISTENT study (37). A number of factors appear to have led to the decline, including lower heparin dosage, weight adjusted heparin, elimination of postprocedure anticoagulation, and smaller sheath sizes. A further decline in the bleeding rate, and an overall decline in vascular complications, has continued throughout the past decade (38), reflecting more prudent

![Figure 8.7](image-url) Femoral angiography in (A) contralateral and (B) ipsilateral views. The solid arrow shows the point of sheath entry. The circle overlies the femoral bifurcation. The dashed arrow denotes the inferiormost excursion of the inferior epigastric artery, which descends to, but does not cross the inguinal ligament.
anticoagulation and antiplatelet regimens, and better vascular access and closure techniques.

The relatively high RPH rates, despite an overall decline in hemorrhagic complications, appears related to glycoprotein IIb/IIIa use (39) as well as vascular closure devices (VCDs) (18). In part because manual compression is performed only after the activated clotting time has normalized, the rate of RPH, even after intervention, is relatively low when manual compression is used (39); RPH rarely occurs in unanticoagulated patients. In contrast, VCDs are deployed when patients are fully anticoagulated, and the rate of RPH is dramatically increased (18). The problem is exacerbated by the interposition of soft tissue, especially muscle and other connective tissue, between the skin surface and the external iliac artery as it dives toward the retroperitoneum, resulting in inability to advance the plug/clip/staple/knot or other closure device onto the surface of the artery, even though an anchor is in place inside the artery (Fig. 8.8). Although the evidence base is not conclusive (40), it is generally advisable to avoid VCD use with known high femoral punctures.

Several algorithms for management of high puncture have been suggested. First, in the setting of elective catheterization, anticoagulation and antiplatelet therapy are best avoided if a high stick occurs. Diagnostic catheterization can proceed, but the patient should be brought back for any intervention. Second, if the patient is already anticoagulated, the operator should consider allowing anticoagulation to wear off, and pulling the sheath manually. Although vascular compression may be ineffective, the rate of RPH is substantially reduced in the absence of anticoagulation (39). Finally, if the patient is actively hemorrhaging, contralateral access and balloon occlusion of the puncture site can be life saving, sometimes with the incorporation of a fabric covered stent if balloon tamponade alone is inadequate (41). In general, all hypotension after femoral access should raise the question of RPH, since hypotension is the most sensitive early marker. Although a number of other signs and symptoms are more specific (29), the time course of RPH frequently does not allow for delay in diagnosis. CT scanning is diagnostic, but in the setting of hemodynamic instability, a prompt return to the catheterization laboratory for diagnosis and intervention is preferable, assuming that trained staff and appropriate equipment are available; if not, surgery should not be delayed. Anticoagulation should be reversed in this setting and early blood transfusion can be life saving.

Similar to RPH, vascular access site infection is associated with VCD use. This represents one of the worst complications of femoral access, although relatively rare, occurring in as few as 0.25% of cases (33). It occurs a median of eight days after access (range two days to approximately one month), is typically caused by Staphylococcus aureus, is frequently blood culture positive and occurs primarily in diabetics and the immune deficiency population. Further details on management are available in Ref. 19.
suppressed. A mycotic pseudoaneurysm is present in nearly half of cases, and if so, surgical exploration is required. Aggressive, early and parenteral antibiotics are usually needed. A high index of suspicion is important. In practice, even in the absence of fever or other signs of infection, the occurrence of late bleeding or oozing at the access site should always raise the suspicion of dehiscence secondary to localized infection.

Pseudoaneurysms are now readily diagnosable with ultrasound, and can be treated conservatively in most cases if less than 2 cm in diameter. The primary causes are low puncture as already discussed and inadequate compression time. Although ultrasound-guided compression and occasionally surgery are required, both procedures are associated with significant discomfort, and most pseudoaneurysms are now treated with offlabel ultrasound-guided thrombin injection with a high rate of success and low complication rate (42,43).

Arterial obstruction is rare, and usually occurs in the presence of preexisting atherosclerotic disease; some atherosclerosis at the access site is relatively common (20); occlusion secondary to VCDs is the most common scenario (44). Dissection at the femoral access site is typically retrograde, thus the entry point of the false channel faces opposite to the direction of blood flow. These are usually self-limited and rarely require intervention as long as the operator does not try to advance guidewires or catheters aggressively into the false lumen. Nerve compression typically manifests as dysesthesia radiating to the medial aspect of the knee and occasionally to the ankle. This is typically secondary to compression of a femoral nerve branch by hematoma, and usually resolves within days to weeks. Direct injection of local anesthetic into the nerve or transsection by the needle or sheath along with strangulation of the nerve by a VCD can all theoretically cause long-term sequelae, but these complications are rare.

Vascular Closure Devices

Vascular closure of percutaneous access sites was invariably by manual or mechanical device compression for the first 40 years of the Seldinger technique. A variety of compression devices were introduced as early as the 1950s and vary in design from mechanical clamps to inflatable bladders such as the Femostop (St. Jude Medical, St. Paul, Minnesota, U.S.). Devices designed to facilitate hemostasis can be classified into a number of subcategories (Fig. 8.9). In general, they can be thought of as invasive if they are deployed in the tissue track itself, as opposed to various noninvasive agents, such as topical hemostatic patches, that are applied to the surface only. A second subclassification considers devices that suture (Perclose, Abbott Medical, Santa Clara, California, U.S.), clip (StarClose, Abbott Medical), staple (AngioLink, Medtronic, Minneapolis, Minnesota, U.S.), or sandwich (Angio-Seal, St. Jude Medical, St. Paul, Minnesota) the arteriotomy between an internal anchor and an external plug; these are active approximators. Passive approximators place a device on top of the arteriotomy without an anchor left in place (Mynx, Access Closure, Mountain View, California). A third subclassification relates to the use of hemostatic agents such as collagen or thrombin (Angio-Seal; Duett, Vascular Solutions, Minneapolis, Minnesota) or sealing agents such as polyethylene glycol (Mynx) or polyglycolic acid (Exoseal, Ethicon, Warren, New Jersey, U.S., not FDA approved), typically as a plug in the tissue track. Finally, devices can be subclassified by whether they leave behind a permanent foreign body (Perclose; StarClose), temporary foreign body (Angio-Seal, Duett, Mynx), or no foreign body at all (Catalyst, Cardiva Medical, Sunnyvale, California).

In general, VCDs facilitate closure by decreasing time to hemostasis and time to ambulation. This is potentially offset by cost and complications. Failure to obtain hemostasis is the primary manifestation of device failure, typically a minor problem after diagnostic catheterization, but potentially a cause of major morbidity if deployment is attempted while patients are still fully anticoagulated after interventional procedures. Passive closure devices, typically unanchored plugs, have what appears to be the highest failure rate (45). There is a significant learning curve incorporated in the use of VCDs (46,47).

An important application of VCDs has been preclosure, a technique that involves deploying sutures around the arteriotomy without tying a knot until sheath withdrawal, and is performed prior to placing a large lumen sheath. This technique has been used with a high degree of success to close arterial fenestration after withdrawal of large sheaths up to 28F used for a variety of arterial and to a lesser degree venous interventions, avoiding the need for surgical access or closure (48).

The cost-to-benefit ratio is the subject of some controversy; the most compelling study demonstrating reduced costs with VCDs was predicated on a lower complication rate than with manual compression along with earlier discharge that resulted in decreased resource utilization (49). Two meta-analyses concluded that complication rates associated with VCDs were higher than those associated with manual compression (50,51), but the quality of the underlying studies in these meta-analyses was poor, and significant study design issues, including incorporation of learning curves and variable device platforms, have made broad conclusions unreliable. Two large propensity analyses have been promising, and suggest that with proper patient selection, meticulous access technique, and experienced operators, VCDs can in fact demonstrate equivalent or lower complication rates than manual compression (52,53) (Fig. 8.10). Nevertheless, a review of the FDA database confirms that some complications of VCDs are additive to those seen with manual compression, in particular RPH, infections, and occasional vascular occlusion. The ultimate decision regarding risk-to-benefit ratios remains with individual operators, without a consensus from the evidence base.

RADIAL ACCESS

Anatomy

The circulation to the hand is redundant in over 95% of patients, with a loop between the ulnar and radial arteries providing crossover filling. Because the radial artery is smaller in size than the common femoral, there is some limitation in the range of interventional procedures that can be performed via radial access. The learning curve is significant, procedure times and radiation to the patient and operator are potential issues, and spasms of the arm vessels is occasionally painful and limits applicability of the procedure. Nevertheless, radial catheterization is now the dominant access route in some parts of the world, and its use is increasing steadily in the United States as well (54).

The technique requires confirming the redundancy of radial and ulnar circulation. The standard approach is the Allen test (55), with occlusive pressure applied to both the
Figure 8.9  A gallery of vascular closure devices. The top row (A–C) features devices that provide for approximation of the puncture site in the arterial wall by creating a “sandwich” of anchor and collagen (Angio-Seal), suturing (Perclose), or clipping (StarClose) the fenestration closed. The second row (D–F) features passive closure devices that seal the arteriotomy by placing sealing plugs (Mynx, ExoSeal) in the tissue track on top of the hole in the artery created by the puncture. The Catalyst (F) uses compression from inside the artery to achieve hemostasis, after which the nitinol disk is collapsed and withdrawn. The final two rows feature two devices that start the closure process at the time of access: Arstasis (Arstasis, San Carlos, California, U.S.) (G) is inserted by placing a small device using micropuncture to establish access to the vessel (small access track—arrow); the device in turn deploys a needle that establishes a diagonal track across the arterial wall (double arrow) through which the procedure sheath is placed. After withdrawal (H), hydrostatic pressure of blood against the arterial wall (solid arrows) contributes to sealing the arteriotomy. The Femoral Introducer Sheath and Hemostasis (FISH) device (Morris Innovative Research, Bloomington, Indiana, U.S.) introduces a biodegradable material (small intestinal submucosa) wrapped around the sheath at the time of access (I), which forms a plug (J) at the time of sheath withdrawal. The ExoSeal device is not FDA approved. See text for manufacturers of devices in panels (A) to (F).
radial and ulnar arteries. The patient then makes a fist with his hands several times and then extends the palm demonstrating blanching due to lack of adequate inflow. With release of the pressure over the ulnar artery, rapid resolution of the blanching is a sign of an intact and widely patent palmar arch. By convention, normal dual circulation is referred to as a “positive” Allen test (56). The mean time for the vascular blush to normalize is relatively short, typically less than five seconds (57). The Allen test has been criticized both for lack of specificity and sensitivity (58), but an analysis of the literature suggests that it remains a useful guide over all (59). Most cath labs use a modification of the Allen test, placing a pulse oximeter on the thumb and monitoring oximetry (60), or oximetry and plethysmography combined (61), while compressing the radial artery. The Allen test alone has somewhat reduced specificity: in over 1000 patients (57) a normal palmar flush in at least one hand could be detected within nine seconds in 93.6%. Using plethysmography combined with oximetry, an oximeter placed on the thumb demonstrated preserved saturation of 90% or greater and an arterialized waveform immediately after radial occlusion in 96.4% of the same patient cohort. An additional 2.1% had no arterial waveform immediately after occlusion, but within two minutes of continuous radial occlusion sufficient flow through the palmar arch occurred to achieve an arterialized waveform in an additional 2.1%. Thus, only 1.5% of patients had no discernable waveform at 120 seconds. The suitability of patients for radial procedures based on oximetry alone remains the subject of some debate (62), in part because oximetry may suggest adequate collateralization even when flow is reduced by more than 90% (63). The use of plethysmography combined with oximetry has led to the Barbeau classification, based on the data cited above (Fig. 8.11) (57).

Access Technique
After placement of the oximeter on the ipsilateral thumb, the entire hand and forearm are prepped and care is taken to have a sterile environment under and around the forearm. Some operators use a sterile sock placed over the hand to the wrist through which a hole is cut at the radial access point. Although some laboratories abduct the arm, this is usually not necessary, and placement of the patient’s straight arm against the thigh makes the distance to the radiation source similar to femoral access. It also eliminates a gap between the wrist and the cath table that otherwise results in blood, saline, contrast and various devices falling to the floor. Specialized drapes are available, although many labs simply position the two “doughnut holes” so that one is over the right wrist and the other over the prepped right femoral, allowing easy conversion to femoral access if necessary. The artery is most accessible without overlying connective tissue if the wrist is not extended. Left arm access is preferred by some operators, in particular when the distance to the target vessel is long (such as for renal or lower extremity interventions), the left internal mammary artery is to be entered, or the right radial is inadequate. Catheter manipulation into the coronary arteries is simpler via the left radial approach (64), and the success rates are equivalent to right radial catheterization (65), although slightly longer procedure times have been reported (66). If the patient’s body habitus allows flexing the left hand over his or her abdomen, the procedure can be performed from the right side of the table.

Local anesthesia is injected intradermally approximately 2 cm proximal to the styloid process, using a 25-gauge or smaller needle, and minimizing the subdermal volume of anesthetic to minimize distortion of the anatomy, inadvertent arterial entry, and potential induction of radial spasm. Radial
No waveform is detected immediately after occlusion, but some source frequently exhibit a type B response if the test is repeated early. Type C response, presumably after recruitment of collaterals, will occur in 90% or greater with a waveform present. Note that patients with a arterial occlusion. Oximetry is expected to demonstrate saturation of diminished, and returns to a full excursion within two minutes. (A) The initial postocclusion waveform is present but diminished, and returns to a full excursion within two minutes. (B) No waveform is detected immediately after occlusion, but some phasic waveform is seen within two minutes. (D) There is no flow detected by plethysmography with temporary occlusion of radial artery. (C) There is no flow detected by plethysmography with temporary occlusion of radial artery. The Barbeau classification. Four patterns of the Allen test, as detected by plethysmography with temporary occlusion of the radial artery. (A) A normal “positive” Allen test, showing no significant diminution of the waveform immediately after radial occlusion. (B) The initial postocclusion waveform is present but diminished, and returns to a full excursion within two minutes. (C) No waveform is detected immediately after occlusion, but some phasic waveform is seen within two minutes. (D) There is no flow detected by plethysmography with temporary occlusion of radial artery. Oximetry is expected to demonstrate saturation of 90% or greater with a waveform present. Note that patients with a type C response, presumably after recruitment of collaterals, will frequently exhibit a type B response if the test is repeated early. Source: From Ref. 57.

access uses a micropuncture technique in most laboratories, typically a 4 cm long 21-gauge needle (rather than the typical 7-cm needle used for femoral access). Bleed through the needle, typically a trickle of blood, is followed by introduction of a micropuncture wire, ranging from 0.018” to 0.025” diameter. On occasion, tortuosity of the radial artery does not allow conventional micropuncture wire access, and a 0.014” coronary guidewire will successfully traverse the forearm. A number of sheaths have been utilized for radial access, and because of the smaller caliber of the radial artery as well as the potential for spasm, most operators prefer hydrophilic-coated sheaths (67). These are 4F to 8F in diameter (typically 5-6F), with step-up dilators, and range in length from 4 to 30 cm, the latter used by some operators to reduce the potential for spasm in the forearm caused by torqueing of catheters as they traverse the radial and brachial vessels.

After sheath introduction, most operators inject a “cocktail” of one or more medications. These typically include vasodilators to minimize spasm and anticoagulants to prevent thrombosis. Although the evidence base is incomplete, the most studied have been intra-arterial nitroglycerin and verapamil (68,69), with doses in the range of 100 to 250 µg for the former, and 1 to 5 mg for the latter. Heparin has been given at doses typically in the range of 1000 to 5000 units (70,71), with some evidence that patency is related to heparin dosage (72). Weight-based dosing, an important factor in decreasing bleeding complications by the femoral route (35), has also been implemented for radial procedures (73). Given that there is substantial discomfort reported by some patients after intra-arterial heparin administration, intravenous administration should be considered. A randomized comparison of 500 patients failed to demonstrate any difference in radial artery occlusion between direct intra-arterial versus intravenous heparin application (74). Systemic enoxaprin also appears to have similar rates of radial artery patency (75), and transition from the initial heparin injected for arterial patency to systemic bivalirudin for coronary intervention has not been shown to impact bleeding complication rates (71); a 30-minute interval between heparin and bivalirudin administration has been recommended (76). Most operators inject the spasmolytic and anticoagulant cocktail in a solution diluted with saline. Consideration should be given to filling the remainder of the syringe with blood rather than saline (77), injecting small amounts of the mixture, and diluting repeatedly by drawing back on the syringe, since blood is a more effective buffer and may result in less patient discomfort.

Once access is obtained, and appropriate medication infused, consideration should be given to assessing systemic pressure through the sheath sidearm. Pressures lower than the contralateral arm cuff pressure will provide an early clue to stenosis or occlusion of the ipsilateral radial or more proximal arm circulation, or may imply spasm or hypoplasia of the arm vessels. Higher pressures may suggest a subclavian or axillary stenosis in the contralateral arm.

Three distinct anatomic segments need to be traversed: from the radial to the axillary artery, the axillary to the innominate, and from the transverse arc to the coronary cusps. The first segment requires dealing with vessel caliber, tortuosity and anatomical variance issues; the second with tortuosity, sidebranches and occasionally occlusion; the third with steering away from the descending aorta and into the cusps, since blood is a more effective buffer and may result in less patient discomfort.

A variety of anatomical variations may require extensive manipulation, use of smaller, sometimes coronary wires, and occasionally a buddy wire system (78); regardless, considerable care is required to avoid arterial perforation or dissection, or catheter entrapment. The most common variations are high radial bifurcation (usually not an impediment to catheterization), radiolunar loops, severe tortuosity, and hypoplasia, and occur in up to 10% to 15% of patients (80), although the majority of these can be traversed safely (81). In a small percentage of cases, catheter passage to the shoulder is impossible or best avoided; a significant learning curve exists (11) (Fig. 8.12). Once the guidewire is in the axillary and subclavian arteries, the operator needs to avoid major head and neck vessels. Entry into the vertebral and carotid circulations is particular common, especially with hydrophilic wires. Tortuosity of the right subclavian and innominate is particularly common in the elderly, and care should be taken to minimize
guidewire manipulation to avoid dislodging plaque. Once the subclavian has been fully negotiated, there is a tendency to enter the descending aorta. Moving to a left anterior oblique view helps identify catheter passage into the ascending aorta.

Because traversing the arm circulation requires more effort than the typical iliac circulation, most operators attempt to use a single catheter for diagnostic coronary angiography. Although a number of catheter curves are made for this purpose, an ideal catheter shape has been elusive. Exchange length guidewires should be used to switch catheters when this is necessary; prolonged dwell time of guidewires in the subclavian and innominate circulation is a risk for cranial embolization, and multiple catheter passages through the arm circulation tend to provoke spasm. Manipulation of catheters in the coronary cusps requires different technique than femoral access, and as a rule, left coronary catheter curves need to be a half size smaller when approaching from the right arm.

Because of the smaller caliber of radial arteries [typically in the 3–4 mm range, compared with 6–8 mm for the average femoral (20,82)], diagnostic catheterization is typically performed with 5F catheters, although some operators use 4F. These require higher pressure to obtain adequate contrast flow into the coronary arteries for optimal visualization. Catheter manipulation sometimes requires guidewires to be left in place until the coronary is intubated to prevent catheter kinking and to facilitate torque control.

An occasional variant to radial access is ulnar access; the ulnar artery is typically smaller and more likely to be associated with spasm (82). Finally, both right and left heart catheterization are done from the arm by an increasing number of operators, using the right radial artery and right antecubital vein in most cases, a technique that is particularly appealing in fully anticoagulated patients where there is contraindication to discontinuation of anticoagulation (83).

**Closure**

Because of the relatively long compression times required for hemostasis, various mechanical compression devices are used (84–86). The compression time is variable, and ranges from as little as 30 minutes (or less) to as long as four hours, with the longer intervals typically recommended for fully anticoagulated patients. Hand ischemia occurs if mechanical compression devices occlude both the radial and ulnar arteries. Excessive pressure can result in vascular soft tissue and nerve injury. Of particular importance is evidence (see below) that compression of the artery with only partial occlusion of blood flow is important for maintaining long-term patency.

**Complications**

Although one of the main advantages of the radial approach is the lower complication rate, some adverse events are associated with this approach. These include occlusion of the radial artery, spasm, bleeding, compartment syndrome, hand ischemia, dissection and other trauma to the head and neck vessels, embolization, and a myriad of rare complications including arteriovenous fistula, major hematoma, transfusion, stroke and pseudoaneurysm.

Occlusion of the radial artery as a consequence of catheter placement has been reported to range from 1% to 38%, the higher range being associated with prolonged dwell times of...
Catheter entrapment and simultaneous hand ischemia, likely as an allergic response. Friction, have potential associated toxicity (93,94), in particular trial (92). Some coatings, although they reduce the coefficient of withdrawal (91). Lower force required to withdraw the sheath as result in a reduction of spasm, with less resistance to withdrawal being recorded (Fig. 8.13). Hydrophilic sheaths have catheter trapping, with occasional cases of radial artery evulsion require conversion to femoral access. It can result in occlusion of the radial artery, and number of arterial accesses. There is some evidence that prolonged interruption of radial artery flow for hemostasis exacerbates the problem of chronic radial artery occlusion (89). In a study using plethysmography (73), patients were randomized to two hours of total occlusion versus two hours of compression with preserved radial artery flow; the latter was associated with a decrease in long-term radial occlusion by an odds ratio of nearly 4 to 1. Similarly, a randomized trial compared inflation of a compression device over the radial artery to mean arterial pressure (102.5 mmHg) compared with injection of a fixed volume of air (device pressure 185 mmHg). The study was stopped prematurely because the radial artery occlusion rate was only 1.1% with the former, compared with 12% for the latter (90).

Spasm can cause pain, limit torque control, and on occasion require conversion to femoral access. It can result in catheter tramping, with occasional cases of radial artery evulsion being recorded (Fig. 8.13). Hydrophilic sheaths have resulted in a reduction of spasm, with less resistance to withdrawal (91). Lower force required to withdraw the sheath as well as less pain have also been demonstrated in a randomized trial (92). Some coatings, although they reduce the coefficient of friction, have potential associated toxicity (93,94), in particular sterile abscess formation, likely as an allergic response.

Figure 8.13 Catheter entrapment and simultaneous hand ischemia. Contrast injection demonstrates no flow around the catheter tip (white arrow). The patient’s hand became ischemic [note severe stenosis in the ulnar artery (black arrow)]. The catheter was extracted surgically.

Compartment syndrome is a rare but dreaded complication of radial access (95), occurring in substantially less than 1% of patients. Any apparent perforation, particularly in the forearm, should be a cause for concern, and if possible should result in reversal of anticoagulation. A suggested algorithm has been to promptly apply pressure at a level 10 to 15 mmHg below systemic systolic so as to allow distal flow, and maintain compression for 15-minute periods (95). Vigilance, a high index of suspicion, and prompt intervention are required to prevent permanent injury.

A persistent concern has been the need to preserve the radial artery for future catheterization and potentially for harvesting for coronary bypass grafting. The artery does develop intimal hyperplasia and decreased vasomotor tone after use for catheter access (96), with inconsistent findings regarding the apparent long-term affect of catheterization on radial artery physiologic function (97,98).

Radial Compared with Femoral Access

A large evidence base, including randomized comparisons, has addressed the issue of radial versus femoral access (11,99). A meta-analysis by Agostini (11) of 12 randomized trials enrolling over 3000 patients demonstrated superiority of the radial approach in access-related complication rates (0.3% vs. 2.8%), but higher failure rates (7.2% vs. 2.4%). The latter is due to failed cannulation of the radial artery, failure to gain access to the ascending aorta through complex arm or shoulder anatomy, or failure to intubate the coronary arteries.

The largest nonrandomized comparison, using the ACC-NCDR database, compared nearly 600,000 coronary interventions via the femoral approach with close to 8000 via the radial approach and found evidence of a greater than 2:1 odds ratio for hemorrhagic complications with femoral access. Moreover, this relationship was consistent, statistically or with a strong trend, across age groups and in settings such as ST-elevation myocardial infarction. The benefits of radial access in acute ST-elevation myocardial infarction have been confirmed in several studies (100,101), with a modest percentage of patients crossing over to femoral access to prevent significant delay in door-to-balloon time when radial access was not immediate. The radial approach has particular appeal in rescue angioplasty after failed thrombolytic therapy (102). In patients over age 80, the advantages of the radial approach remain striking (103).

The learning curve has played a substantial role, and the more recent trials included in the meta-analyses did not show a difference in success rates between femoral and radial access (11). In a review of radial access success rates, the failure rate was greatest in an operator’s first 20 cases (14%), but decreased to 4% when experience exceeded 100 cases; concomitant fluoroscopy time decreased from a mean of 9.6 to 6.8 minutes (104).

Figure 8.14 shows the influence of the learning curve on fluoroscopy times and success rates in the hands of a single operator.

There is evidence of strong patient preference for the radial technique (87,106), in large part because it avoids the immobilization associated with femoral closure, as well as the discomfort associated with manual compression of the femoral artery (66) and with many VCDs. Costs associated with radial catheterization are lower, in part because of earlier ambulation, lower complication rates (106,107), and the lower cost of radial compression devices than most femoral VCDs (108). The lower cost of the radial approach holds true for diagnostic
Figure 8.14 Relationship between operator experience, procedure time and technical failure for radial artery access. Source: From Ref. 105.
simplicity. Contraindications include thrombosis of the ipsilateral iliac vein, the inferior vena cava, or infection at the inguinal access site. The presence of a vena caval filter does not preclude the passage of catheters or sheaths, although some operators will inject contrast in this setting to assure absence of obvious thrombus that might result in embolization. Femoral venous access uses similar landmarks as those discussed for the femoral artery, with the vein located one-half to one cm medial to the artery. We use fluoroscopy, but the evidence base is most compelling for ultrasound-guided access (124). Although some operators choose a lower puncture site for venous than for arterial access, we believe the same considerations apply, namely, avoidance of low puncture because of increased risk of arteriovenous fistula and more difficult compression, and avoidance of high puncture because of the risk of RPH. Valsalva maneuver and pressure on the patient’s abdomen can distend the femoral vein and make access easier; hydration, especially for a patient who has taken nothing by mouth for a prolonged period, can increase the diameter of the vein as well.

Most operators use 18-gauge needle access for the femoral vein, with similar methodology as for the modified Seldinger technique, using a hollow needle and puncture of the anterior wall of the vein. Because of low pressure in the venous system, continuous aspiration through the hollow needle helps identify vessel entry. We use a micropuncture technique in venous access as well. Inadvertent entry into the femoral vein is relatively common during planned arterial access (occurring in up to 30% of cases in one study (27)); in this event, we leave a wire in place in the vein during arterial access as a fluoroscopic marker to guide entry into the artery.

Internal jugular access avoids the problems associated with the femoral triangle, facilitates early ambulation, provides a superior angle of entry into the right ventricle for right heart catheterization, and provides for superior control during right ventricular endomyocardial biopsy. Ultrasound guidance substantially improves the time to access, success rate, avoidance of inadvertent entry into adjacent structures, and lowers the overall complication profile of the procedure (124). The internal jugular vein courses in close proximity to the carotid artery and inadvertent carotid intubation is relatively common (in the range of 3–4%) in the absence of two dimensional ultrasound guidance (125). Carotid puncture, especially with a large needle, has a wide range of associated risk, including cerebrovascular events. Associated hematoma can be difficult to control with rare cases of tracheal compression. An additional important complication is pneumothorax, associated with inadvertent puncture of the lung, sometimes associated with a high pulmonary bleb in patients with chronic lung disease. While subclavian access is relatively safe, the general consensus is that internal jugular access is safer, although the evidence base is not compelling (126).

Venous closure is almost always by compression, although in various settings adjunctive noninvasive closure methods, such as topical patches, have been utilized (127). Care should be taken to avoid excessive compression time, since venous thrombosis remains a potential complication (128), likely related to duration of compression with total occlusion of the femoral vein. Various VCDs have been used for femoral venous closure (offlabel) (129), but the risk-to-benefit ratio is not established, and given the low pressure in the venous circulation there is no compelling case for routine use. For some structural heart disease interventions, where large sheaths are required (14F or greater), a “preclosure” technique can be used to facilitate hemostasis (130). The femoral vein is relatively fragile, and care needs to be taken to avoid excessive traction on the vein during suture closure to prevent severing the vessel, a potentially serious adverse event, since virtually all venous efflux from the leg is through the common femoral vein. A novel “figure-of-eight” alternative has been described that places a deep suture around a large femoral vein catheter (without entering or passing deep to the femoral vein itself), capturing substantial tissue and compressing the puncture site when the sheath is pulled and tension is applied to the suture (131).

CONCLUSIONS

Vascular access has evolved over a half century with the development of a substantial evidence base, in particular in the past 15 years. Use of adjunctive technologies for access, in particular ultrasound and fluoroscopy, micropuncture, and modifications in anticoagulation and antiplatelet therapy has combined to improve access success and reduce overall complication rates. Awareness of anatomy, and routine use of femoral angiography can avoid or potentially help address a number of complications. A transition from primarily femoral to primarily radial access is taking place worldwide, although the femoral route remains dominant in the United States. VCDs, without a compelling evidence base to justify routine use, improve patient comfort and convenience after femoral access. The expanding role of structural heart disease interventions will place further emphasis on safe access for large diameter catheters, and should lead to development of additional novel techniques for percutaneous closure.

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6. Kiemeneij F, Laarman GJ. Percutaneous transluminal arterial access is taking place worldwide, although the femoral route remains dominant in the United States. VCDs, without a compelling evidence base to justify routine use, improve patient comfort and convenience after femoral access. The expanding role of structural heart disease interventions will place further emphasis on safe access for large diameter catheters, and should lead to development of additional novel techniques for percutaneous closure.

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CARDIOVASCULAR CATHETERIZATION AND INTERVENTION


84 CARDIOVASCULAR CATHETERIZATION AND INTERVENTION


Right heart catheterization
Franz R. Eberli

INTRODUCTION
In addition to Doppler echocardiography and cardiac magnetic resonance imaging right heart catheterization is a complementary, but indispensable investigation for hemodynamic assessment and diagnosis of many cardiac diseases. Right heart catheterization provides data on the pressures and oxygen saturations in the right heart chambers and the pulmonary artery (PA), including PA occlusion pressure or “wedge” pressure. Combined with the data obtained during simultaneous left heart catheterization cardiac output, pulmonary and systemic vascular resistances and ejection fractions are calculated, and shunt detection and quantification in structural heart disease can be performed. From these measurements information about preload, afterload, and contractility are derived. Hemodynamic responses to changes in loading conditions and/or to pharmacologic interventions are often performed for accurate evaluation of the physiology of a specific condition and are part and parcel of right heart catheterizations in the cardiac catheterization laboratory. This information is particularly valuable in the assessment of adult congenital heart disease and pulmonary hypertension prior to any therapeutic intervention or operation (1,2).

In contrast to its undisputed value as diagnostic investigation in the cardiac catheterization laboratory, the value of bedside use of a PA catheter in critically ill patients is more controversial. Reports that its use leads to increased mortality and morbidity (3) have resulted in a careful evaluation of the use of bedside right heart catheters in patients with cardiac disease (4). Recently, two randomized trials (PAC-MAN and ESCAPE) have found no increased mortality with the use of PA catheters in critically ill patients and have concluded that PA catheters are safe for use in an appropriate patient populations (5,6).

ANATOMIC CONSIDERATIONS AND FUNDAMENTALS
Access to the right heart can be gained via the inferior or superior vena cava. In the cardiac catheterization laboratory the inferior vena cava is the preferred approach, for bedside right heart catheterization the superior approach is used. The superior vena cava is assessed either from the (right) internal jugular vein or the (left) subclavian vein. Although in the catheterization laboratory most right heart catheters are performed via femoral access, certain conditions make a superior caval vein approach preferable. Such conditions are: Suspected femoral vein/iliac vein thrombosis, renal vein thrombus, inferior vena cava filter, anomalous inferior vena cava. Other conditions, such as massive dilation of the right sided chambers, severe tricuspid or pulmonary regurgitation, and pulmonary hypertension are technically easier to assess by a superior vena cava approach.

The PA catheter (Fig. 9.1) is advanced through the right atrium, the right ventricle (RV), and the PA until a PA occlusion pressure is reached (Fig. 9.2). The static column of blood between the tip of the PA catheter and the pulmonary vein will transmit the pressure from the left atrium (LA). During diastole, when the mitral valve is open, the measured pressure also corresponds to the left ventricular diastolic pressure (Fig. 9.2). A prerequisite of a correct measurement is that the pulmonary venous pressure exceeds pulmonary alveolar pressure. This is more likely the case, when the catheter tip is directed into the lower lobe (8). The lung tissue between the tip of the catheter and the left heart results in a damping (2-4 mmHg) and delaying (100-150 milliseconds) of the pressure wave in the pulmonary capillary wedge pressure (PCWP) as compared with left ventricular or left atrial pressure (LAP) (Fig. 9.3).

Cardiac output measurements are usually performed by thermodilution, preferable in a normal and high output states, or by the Fick method, which is preferable in low output states, valvular regurgitation or intracardiac shunts. Shunt detection and quantification is nowadays complementary to echocardiography results. Echocardiographic findings should be reviewed before performing right heart catheterization, so that the invasive procedure can be tailored toward the unresolved and specific questions. This will allow the investigator to shorten the oxymetry run and help to plan a potentially valuable pharmacologic intervention or volume load.

INDICATION
Right heart catheterization is no longer part of every diagnostic heart catheterization. Echocardiography, other imaging modalities and noninvasive hemodynamic measurements have reduced the need for right heart catheterization. Nevertheless, direct measurements of pressure, flow and oxygen saturations are often necessary to correctly diagnose or quantify cardiac diseases. For example, despite the undisputable achievements, Doppler echocardiography has its limitations for correct assessment of pressures (9). The indications for right heart catheterization can be divided into two main categories: (A) diagnostic catheterization for establishing a diagnosis and for planning and guiding a therapeutic intervention and (B) monitoring and guiding of intensive medical care or perioperative hemodynamics (Table 9.1) (10).

CONTRAINDICATION
Absolute contraindications to right heart catheterizations are mechanical tricuspid or pulmonic valve prosthesis and terminal illness. Relative contraindications are endocarditis, tumor or thrombus in the right heart chambers, and newly implanted pacemaker or defibrillator electrodes. A profound coagulopathy
Figure 9.1  Diagram depicting the PA catheter. A PA catheter with two pressure monitor lumens is depicted. The distal lumen goes to the tip of the catheter to measure PA pressure and, if the balloon is inflated and the PA occluded, the pulmonary capillary wedge pressure is measured. A thermistor near the catheter tip measures PA blood temperature and is used for thermodilution cardiac output measurements. The proximal lumen is located 30 cm from the tip of the catheter and usually lies within the right atrium. This lumen is also used for injection of cold saline for thermodilution cardiac output measurements. In the cross section the distribution of the four lumens within the catheter are depicted. Source: From Ref. 7, with permission. Abbreviation: PA, pulmonary artery.

Figure 9.2  Principles of right heart catheterization. The balloon-tipped right heart catheter is inserted from an inferior vena cava approach into the right atrium (RA), through the tricuspid valve into the right ventricle (RV) and up into the PA and “wedged” into the distal PA. Distal to the inflated balloon a blood column is present between the PV and the catheter. The PV is connected to the LA and, importantly, if the MV is open, to the LV. According to the law of pressures in communicating vessels the left ventricular end diastolic pressure corresponds to left atrial pressure, which in turn corresponds to PV pressure and pulmonary capillary wedge pressure. Abbreviations: PA, pulmonary artery; PV, pulmonary vein; LA, left atrium; LV, left ventricle; MV, mitral valve.

Figure 9.3  Simultaneous left ventricular and PCWP. This figure depicts the simultaneous pressure measurement with a tip manometer catheter (Millar catheter) in the left ventricle and in pulmonary capillary wedge position. The left atrial contraction results in an a-wave that is transmitted into the LV and retrogradely into the PCWP [the time delay (Δt) is usually 80–140 milliseconds]. Similarly the v-wave is delayed and dampened (2–4 mmHg). After mitral valve opening (MVO) the v-wave should decrease simultaneously with the LV pressure. The recorded delayed pressure decay is the result of the dampening of the pressure transmission through the lung tissue. Abbreviations: PCG_LV, phonocardiogram left ventricle; PCG_PA, phonocardiogram pulmonary artery; LVP, left ventricular pressure; PCWP, pulmonary capillary wedge pressure; ECG, electrocardiogram; LV, left ventricle.
### Table 9.1 Indications for Right Heart Catheterization

<table>
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<tr>
<th>A. Diagnosis and planning of therapeutic interventions</th>
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<tbody>
<tr>
<td>1. Valvular heart disease</td>
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<tr>
<td>- Assessment of severity of valve disease and concomitant pulmonary hypertension.</td>
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<td>- Planning of surgical or interventional valve interventions.</td>
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<td>2. Intracardiac shunts</td>
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<tr>
<td>- Shunt detection and quantification. Assessment of concomitant pulmonary hypertension. Exploratory balloon occlusion of the defect.</td>
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<tr>
<td>- Vasoreactivity test in case of pulmonary hypertension.</td>
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<tr>
<td>3. Left heart failure</td>
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<tr>
<td>- To differentiate between cardiogenic or noncardiogenic pulmonary edema. Guide therapy in acute and chronic heart failure.</td>
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<tr>
<td>- Differentiate between diastolic and systolic dysfunction. Test for reversible pulmonary hypertension in transplant candidates.</td>
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<tr>
<td>4. Shock states</td>
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<tr>
<td>- Differentiate shock states. Cardiogenic vs. noncardiogenic, hypovolemic, septic shock.</td>
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<tr>
<td>5. Acute myocardial infarction</td>
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<tr>
<td>- Complicated by hypotension, unclear volume status (acute MI and bleeding, acute MI and renal insufficiency). Right ventricular infarction.</td>
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<tr>
<td>- Mechanical complications (ventricular septal defect, papillary muscle rupture).</td>
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<td>6. Pulmonary hypertension</td>
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<tr>
<td>- Diagnostic gold standard. Assessment of etiology of pulmonary hypertension.</td>
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<td>- Determination of severity. Testing for vasoreactivity.</td>
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<td>7. Pericardial diseases</td>
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<tr>
<td>- Differentiation between constrictive and restrictive physiology. Cardiac tamponade (only when echocardiography is unavailable or nondiagnostic).</td>
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<th>B. Monitoring of intensive medical therapy</th>
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<tr>
<td>1. Heart failure</td>
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<tr>
<td>- Guidance of vasodilator, positive inotrope and diuretic therapy, perioperative management of patients with decompensated heart failure.</td>
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<tr>
<td>2. Myocardial infarction</td>
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<tr>
<td>- Guidance of pharmacologic and mechanical support. Management of pulmonary edema that does not respond to usual medical treatment.</td>
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<td>3. Perioperative use in cardiac surgery</td>
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<tr>
<td>- To determine etiology of low cardiac output, differentiate between left and right heart failure, management of pulmonary hypertension.</td>
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<td>4. Severe acute respiratory distress syndrome</td>
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<tr>
<td>- Assess cardiac output during positive end-expiratory pressure trials.</td>
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</tbody>
</table>

with an INR >2 or low platelet count (<20,000/mm³) increases the bleeding risk, particularly when a jugular vein or subclavian vein approach is chosen. Periprocedural administration of fresh frozen plasma or platelets might be considered under certain circumstances.

### TECHNIQUE

**Equipment**

The most widely used and safest catheter for right heart catheterization is a multilumen, balloon-tipped flotation catheter, the so-called Swan-Ganz catheter (Fig. 9.1). When used from a superior caval vein approach the catheter floats easily through the right heart chambers and the balloon wedges into the distal PA. The distal and proximal lumen of the catheter allow measurement of pressures in the PA and in the right atrium, the built-in thermistors allow measurements of cardiac output by thermodilution. The inflated balloon stabilizes the catheter and the large lumen has no end-holes but several side-holes proximal to the balloon. The inflated balloon stabilizes the catheter and the large lumen allows flows similar to that in pigtail catheters. The flow and injection rate on the right side should be somewhat lower than on the left side and the maximal pressure of injection should be reduced to 600 psi.

The soft Swan-Ganz catheter has a low risk of injury. However, when floated from a femoral vein it is not easily guided by torquing. Maneuverability is improved by guide-wires (usually 0.021–0.032 in). Unfortunately, the soft catheter with a small diameter has a poor frequency response which might impede pressure measurements (11). Instead of Swan-Ganz catheters multipurpose catheters or stiffer (woven Dacron) Goodale-Lubin or Courand catheters might be used in the cardiac catheterization laboratory. If a PA or pulmonary vein angiography is to be performed, a regular pigtail catheter or an angled (Grolman) pigtail catheter is the preferred catheter. A Berman catheter can also be used. This is a balloon-tipped catheter specifically designed for right-sided angiography. It has no end-holes but several side-holes proximal to the balloon. The inflated balloon stabilizes the catheter and the large lumen allows flows similar to that in pigtail catheters. The flow and injection rate on the right side should be somewhat lower than on the left side and the maximal pressure of injection should be reduced to 600 psi.

**Access Site and Venous Introducer Insertion**

**The Femoral Vein**

The femoral vein is the preferred access when the right heart catheterization is part of a diagnostic or interventional procedure in the catheterization laboratory. For a description of gaining access and inserting the sheath see chapter 8. The advantages of the femoral access are the ease of cannulation...
and the ease of compression, as well as the absence of the risk of a pneumothorax. Disadvantages are the increased technical difficulties of guiding and advancing the Swan-Ganz catheters as well as the risk of a femoral artery puncture. For longer term monitoring there are additional disadvantages to the femoral vein access, particularly patient immobility, the higher risk of thrombosis and infection.

**Internal Jugular Vein**

If the internal jugular vein access is used, the right side is the preferred side, since it provides a direct access to the right atrium. Furthermore, the left internal jugular vein sometimes has a venous valve at the entrance into the subclavian vein. The advantages of a jugular vein approach are the easy compressibility of the access site and the low risk of a pneumothorax. The disadvantage is the risk of puncture of the carotid artery. The internal jugular vein is the preferred access for hemodynamic monitoring in the ICU or CCU and peripherally. In the cardiac catheterization laboratory it is often preferred when simultaneously a myocardial biopsy (e.g., in posttransplant patients) is performed or when inferior access is impossible.

**Subclavian Access**

The great advantage of subclavian access is the patient comfort and the ease of insertion of the catheter. The disadvantages are the danger of puncture of the subclavian artery and the risk of a pneumothorax. Subclavian access is seldom used in the catheterization laboratory, it is mainly reserved for long-term hemodynamic monitoring in the CCU and ICU.

**Pulmonary Artery Catheter Insertion**

After flushing, the Swan-Ganz catheter is introduced into the sheath and brought up into the common iliac vein, where the balloon is inflated under fluoroscopy. An inflation of the balloon in a small vein should be avoided. When the balloon is not inflated without fluoroscopic control, it has to be attached to the pressure manifold, so that the balloon may be deflated immediately if a pressure increase, that is an over-inflation is detected. During advancement deviation from the straight path along the spine usually suggests entry into a renal or hepatic vein. The catheter is then withdrawn, rotated and advanced further. When the right heart catheter is performed to detect or quantify a left-to-right shunt, the catheter should first be advanced into the vena cava superior. To do this the balloon is best deflated and the catheter rotated to the lateral wall and then advanced by further counterclockwise rotation movement. It is advisable to transverse the straight path from the vena cava inferior to superior by using a guidewire within the Swan-Ganz catheter. Once the catheter is advanced into the vena cava, a blood sample is drawn from the vena cava superior and at the entrance of the vena cava superior into the right atrium (for detection or exclusion of anomalous pulmonary venous return).

The advancement of the PA catheter from the right atrium into the RV and PA is usually done by passing directly, that is medially across the tricuspid valve into the RV. This directs the tip of the catheter toward the apex of the RV. Therefore, the catheter has to be pulled back slightly and then rotated further clockwise. To transmit the torque, it is important to maintain pressure on the catheter and use slight forward and backward movements. When the balloon tip is pointing upward toward the right ventricular outflow tract, the catheter is advanced quickly into the PA. Deep inspiration might help to advance the catheter up into the PA and to advance the tip of the catheter into a wedge position in the distal PA.

In case of an enlarged right atrium direct advancement of the PA catheter via the tricuspid valve might not be easily achieved. It is sometimes necessary to increase the bend on the catheter. To do that one can loop the catheter by bending it against the lateral wall of the right atrium or by engaging it into the ostium of the hepatic vein. The catheter is then advanced and rotated clockwise. This will help to advance the catheter into the right atrium. Another helpful technique is to loop the catheter toward the lateral wall of the right atrium with the balloon deflated. Subsequently, the operator can advance the catheter such that a loop in the right atrium is formed. When the tip of the loop is directed toward the tricuspid valve the balloon is reinflated and the catheter floats across the tricuspid valve, similar to floating the balloon catheter from the superior vena cava approach. If the tip of the catheter reaches the right ventricular outflow tract, it can usually be advanced easily into the PA and the wedge position. Occasionally, the balloon is so soft that it will not advance despite a nice loop in the RA across the tricuspid valve and into the RV. Introducing a guidewire into the loop, but not to the tip of the catheter might help to advance it further into the PA.

Catheters advanced from the vena cava inferior tend to advance into the left PA, whereas catheters advance from the vena cava superior tend to advance into the right PA. If both pulmonary arteries need to be engaged for a procedure, a guidewire can be introduced into the PA catheter with an appropriate bend so that the catheter can be advanced into both pulmonary arteries. It is often necessary to use the stiff end of the guidewire to assure an appropriate bend. In such a case, the guidewire is never to be advanced to the tip of the PA catheter. The stiff end of a guidewire has a very high risk of a perforation and should never be exposed into the right heart or in the PA. Even the soft end of the guidewire carries a certain risk of perforation in the PA and should not be routinely used.

After recording the pulmonary wedge pressure, the balloon is deflated under slight tension, such that no abrupt forward movement of the catheter tip occurs. Then the PA pressure is measured and blood oxygen saturation samples are taken simultaneously from the PA and from a systemic artery (femoral or radial) to measure cardiac output according to the Fick formula. Pressure measurements (and if needed oxygen saturations) are recorded during withdrawal of the catheter from the PA to the RV and right atrium by counterclockwise rotation and pulling.

Advancing a multipurpose catheter from the femoral vein to the PA is done by the same technique. In the right atrium the guidewire is withdrawn and the tip of the multipurpose catheter is directed medially toward the tricuspid valve and advanced into the RV. Under clockwise rotation it is advanced into the RV and up to the PA. The guidewire is then advanced into the PA and the catheter gently brought forward into a wedge position.

When advancing the catheters into the right heart anatomic variants and anomalies, such as patent foramen ovale, a persistent left superior vena cava, and anomalous returning pulmonary veins, might direct the catheter into an unwanted cavity. Fluoroscopy and oxymetry help to correctly locate the position of the catheter. Erroneous catheter placement into the LA and pulmonary vein is recognized by a path through the heart and deviation into a posterior position on a lateral view and can be confirmed by oxygen saturation measurements. A
catheter position in the coronary sinus is suspected by fluoroscopy and confirmed by oxygen saturation measurements between 20% and 30%.

Right heart catheterization from a superior caval vein approach is usually done with an inflated balloon and the balloon connected to the pressure transducer. The distance marker on the catheter (every 10 cm) is helpful for orientation. After 15 to 20 cm, the right atrial tracing is seen and with the inflated balloon the catheter is advanced across the tricuspid valve. The catheter is then advanced into the PA and into wedge position. This position should be reached after about 50 to 55 cm. If no wedge position is reached after this distance, the catheter might be coiled in the RV. It is advisable to deflate the balloon, withdraw the catheter into the right atrium, and start the process all over.

Complications
The complications of PA catheters can be divided into complications related to vascular access, to catheter insertion, and to catheter residence (Table 9.2) (12). Additional complications are related to vasoreactivity testing, volume loading, and pulmonary or right ventricular angiography (see chapters 10 and 22) (13). The risk of catheter related complications seems to have declined over time. In earlier reports an approximately 5% rate of serious complications was reported (14–16). In recent studies serious complications were encountered in less than 1%, even in patients with pulmonary hypertension (5,13). Hemodynamic monitoring in critically ill patients carries additional risks related to medium to long-term indwelling of the PA catheter. Thromboembolic complications and infections are the most frequent complications encountered in these patients (17). In the ESCAPE trial 4.2% of patients suffered PA catheter related complications, of which two thirds were attributed to long-term catheter residence. These complications were infections and pulmonary infarction/haemorrhage (6).

Table 9.2 Complications of PA Catheter

<table>
<thead>
<tr>
<th>Vascular access complications</th>
<th>Arterial puncture</th>
<th>Arteriovenous fistula</th>
<th>Bleeding from insertion site</th>
<th>Nerv injury</th>
<th>Air embolism</th>
<th>Pneumothorax, hemothorax (subclavian, internal jugular vein approach)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related to catheter insertion</td>
<td>Arhythmias (supraventricular tachycardia, ventricular premature beats, VT, VF)</td>
<td>Right bundle branch block or complete heart block</td>
<td>Injury to chordae in right ventricle</td>
<td>Tricuspid regurgitation</td>
<td>Dislodgement of pacemaker leads</td>
<td>PA rupture/right ventricular perforation</td>
</tr>
<tr>
<td>Related to catheter residence</td>
<td>PA rupture</td>
<td>Pulmonary infarction</td>
<td>Thrombosis</td>
<td>Infection/endocarditis/thrombophlebitis</td>
<td>Balloon rupture / embolization</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PA, pulmonary artery; VT, ventricular tachycardia; VF, ventricular fibrillation.

The most serious complication of the PA catheter is PA rupture. In a prospective study the rate of PA rupture was 0.2%, in retrospective studies it varied between 0.001% to 0.47% (14,18). Elderly patients and patients on chronic steroid therapy are at increased risk, whereas pulmonary hypertension does not constitute a higher risk for this complication (19,20). The rupture may cause an asymptomatic pseudoaneurysm, hemothysis, that stops spontaneously, or hemothysis and hemothorax (18). In case of hemothysis and hemothorax the mortality rate is reportedly between 45% and 70%. Diagnosis should be suspected upon the onset of chest pain related to catheter advancement or balloon inflation, frank hemothysis and dyspnea. If frank hemothysis is present, immediate selective intubation of the uninjured lung should be performed. If no hemothorax is present, techniques such as balloon tamponade of the ruptured artery, tamponade of the bleeding lung by bronchoscopy, and embolization of the ruptured artery have all been used to control the bleeding (21). In case of hemothorax the treatment is mostly surgical and a lobectomy or pneumectomy is sometimes the only option to stop the bleeding (22). To avoid this most serious complication the balloon should only be inflated in the large proximal PA, the time of the balloon in wedge position should be minimized and traction on the catheter when deflating the balloon should be maintained to prevent a rapid forward movement of the catheter tip (18).

Insertion of PA catheters in patients with preexisting left bundle branch block is complicated in approximately 3% to 5% by the occurrence of additional right bundle branch block that can lead to complete heart block (15,16). Therefore, when performing a PA catheter in a patient with a left bundle branch block a temporary pacemaker should be available for emergency pacing if needed.

PRESSURE MEASUREMENTS AND PRESSURE WAVE FORMS
A prerequisite for accurate pressure measurements is a pressure recording with a satisfactory frequency response and few artefacts. The most common problem in pressure recording on the right side is related to the quality of the soft catheters. The long soft tubing results in over-damping of the pressure wave forms similar to air bubbles or to kinking in the catheter. Stiffer catheters and hyperdynamic states result in under-damping. Whipping the catheter against the septum results in pressure artefacts. Therefore, it is important to carefully examine the position of the pressure transducer, the quality of the wave form and the simultaneously recorded electrocardiogram. A crisp dicrotic notch on the PA pressure usually indicates a properly responsive pressure system.

The intracardiac and transmural pressures are greatly influenced by intrathoracic pressures. Intrathoracic pressure is transmitted to the intracardiac pressures and thus pressures will vary with respiration. In normal physiology insulation will decrease intrathoracic pressure and increase venous return. The right atrium and ventricle being rather elastic will accommodate this increased volume without greatly increasing intracardiac pressure. Thus in normal hearts the net effect of inspiration is a decrease in right-sided pressures and an increase during expiration (23). At end-expiration the intrathoracic pressure is almost zero and closest to atmospheric pressure. Therefore, all pressures should be recorded at
end-expiration. For a nice steady recording ask the patient to stop breathing at the end of a nonlabored expiration. Intra-thoracic pressures are reversed in a mechanically ventilated patient. On a mechanical ventilator intrathoracic pressures are increased and venous return impaired during inspiration, and conversely intrathoracic pressures are decreased and venous return increased during expiration. However, as is the case in normal respiration, the intrathoracic pressures are closest to atmospheric pressure at the end of expiration and should be measured at this point, too (23).

The normal pressure wave forms are depicted in Figures 9.3 to 9.6. If there is an impairment to filling (e.g., restrictive physiology) or a great increase in right heart filling (e.g., in decompensated heart failure) the pressures will not vary with respiration. Right atrial pressures may remain flat (and elevated) throughout the respiratory cycle or even increase during inspiration (Kussmaul’s sign) (Fig. 9.7).

The PCWP is particularly sensitive to pathologic intrathoracic pressures. Since PCWP is an indirect measurement of LAP, transmitted by a blood column from the LA to the tip of the catheter, any changes in intrathoracic pressures that influence this fluid column will change PCWP. An increase in intraalveolar pressure (e.g., in chronic obstructive lung disease, positive end-expiratory pressure) will lead to an overestimation of left atrial filling pressures.

**Figure 9.4** Right atrial pressure. The right atrial systole follows the p-wave on the electrocardiogram. The a-wave indicates atrial contraction and is followed by the x descent that corresponds to atrial relaxation. The closure of the tricuspid valve produces a slight upward deflection of the x descent and is called the c-wave. The x‘ descent represents the descent of the atrioventricular ring during ventricular systole and atrial relaxation. The c-wave is not always present and the wave form is than reduced to the a-wave and the x descent. Following the t-wave on the ECG a v-wave is present. The v-wave represents the atrial filling during diastole. The v-wave is followed by the y descent that marks the opening of the tricuspid valve and the emptying of the atrium during the rapid diastolic ventricular filling. **Abbreviation:** RA, right atrium. Figures 9.4 to 9.6 kindly provided by H. Hirzel, MD.

**Figure 9.5** RVP and PAP. The RVP and PAP are simultaneously recorded by a tip manometer (Millar catheter). Also recorded are the phonocardiogram (PCG) and the ECG. The patient has a minimal pulmonic stenosis and a mild pulmonary regurgitation. The atrial contraction results in an a-wave that occurs after the p-wave of the ECG. The end of the a-wave marks closure of the tricuspid valve as evidence by the first heart sound and represents right ventricular end diastolic pressure. This is followed by ventricular systole. Ventricular relaxation results in closure of the pulmonary valve = second heart sound (2. HS) and isovolumic relaxation of the RV until tricuspid valve opens and rapid diastolic filling of the RV occurs. Usually right ventricular end diastolic pressure and peak systolic pressure are measured. The PAP contains a v-wave, which corresponds to the right ventricular systolic pressure and relaxation. The pulmonic valve closure produces a dicrotic notch. The decline of the pressure tracing continues throughout diastole until PAP starts to increase again with ventricular contraction. **Abbreviations:** ECG, electrocardiogram; RV, right ventricle; RVP, right ventricular pressure; PAP, pulmonary artery pressure.
CARDIAC OUTPUT MEASUREMENTS

The delivery of the blood to the body per minute is termed cardiac output. Cardiac output is dependent on metabolic state, body size, age, and a number of other factors such as posture, anxiety, and body temperature (24). Baseline cardiac output is mainly determined by the metabolic rate. The baseline metabolic rate is closely correlated to body surface area (BSA). It has therefore become common practice to normalize cardiac output to BSA as the so-called cardiac index (L/min/m² BSA). In the cardiac catheterization laboratory cardiac output is most often determined by the Fick oxygen consumption method or the thermodilution technique. In addition, angiographic cardiac output measurements (stroke volume × heart rate) might be used.

Figure 9.6 Simultaneous LV and LAP. Depicted are the pressure wave forms recorded by fluid-filled catheters in the LV and the LA. The LAP is initially recorded as mean pressure and then in a phasic condition. The a-wave of the LA contraction is followed by the x descent that marks the descent of the atrioventricular ring during ventricular systole and atrial relaxation. The filling of the LA produces the y-wave and the rapid emptying of the LA after mitral valve opening (MVO) results in the y descent. Atrial and left ventricular pressures are overlapping during diastasis of diastole. The a-wave of atrial contraction is transmitted into the LV and results in the a-wave of the LV pressure tracing. The trough after the a-wave marks left ventricular end diastolic pressure. Uncharacteristically, in this example the a-wave is larger than the y-wave. Normally in LAP the y-wave is larger than the a-wave. Abbreviations: LA, left atrium; LV, left ventricle; ECG, electrocardiogram; LVP, left ventricular pressure; LAP, left atrial pressure.

Figure 9.7 Kussmaul sign. The right atrial pressure tracing of a patient with restrictive cardiomyopathy is depicted. Right atrial pressure is elevated. The prominent x and y descents give the wave form the characteristic M or W shaped appearance. During inspiration right atrial pressure increases and the y descent is further augmented. This paradoxical increase in right atrial pressure during inspiration is called the Kussmaul sign.
Fick Principle
The Fick principle states that the total uptake or release of a substance by any organ is the product of the arteriovenous concentration difference of the substance and the blood flow to that organ (24). In the lungs the released substance is oxygen and the pulmonary blood flow can be calculated from the measured differences in arterial and venous oxygen saturations and the oxygen uptake by the lungs per minute. In the absence of intracardiac shunts pulmonary flow equals systemic flow.

The arteriovenous oxygen gradient is calculated from the difference in oxygen saturation between arterial and mixed venous blood. Mixed venous blood is best obtained from the PA or alternatively from an RV blood sample. For correct measurement of blood oxygenation in the lungs a pulmonary venous sample should be measured. For practical reasons a sample from the LV or the femoral artery is taken. The small decrease in saturation due to bronchial and thebesian vein drainage is negligible. In the arterial and venous samples oxygen saturation is measured. The calculation of the oxygen content assumes that red cells with 100% oxygen saturation carry 1.36 mL O2/g hemoglobin. Oxygen content (mL O2/L blood) = % oxygen saturation × 1.36 (mL of O2/g hemoglobin) × hemoglobin (g/dL) ÷ 10 (converts from dL to L).

Oxygen consumption can be measured by a metabolic rate meter (polarographic cell method) where the patient breathes ambient room air in a steady state for several minutes and the metabolic rate meter gives a readout of oxygen consumption in liters per minute. Alternatively, basal oxygen consumption can be assumed from BSA, age, and sex. In young patients a basal oxygen consumption of 3 mL/kg body weight or 125 mL/m² BSA is used in many laboratories. For elderly patients an oxygen consumption of 110 mL/m² is normal. It is important, however, to understand the limitations of this assumption. Baseline oxygen consumption can vary by as much as 25% between patients (25). If the patient is not in a steady state because of anxiety, dyspnea, tachycardia, or is over sedated and breathes shallowly oxygen consumption is either increased or decreased to an unpredicted level. The error is greatest in tachycardic patients. Caution is therefore warranted when cardiac output is calculated using an assumed oxygen consumption, and consequently also when this value is used to calculate valve areas or vascular resistances.

Another important source of error in calculating cardiac output by the Fick method is the administration of supplemental oxygen to the patient. This makes it almost impossible to calculate oxygen content (dissolved oxygen in plasma) and hence cardiac output. Therefore, supplemental oxygen should be discontinued at least 15 minutes before determination of cardiac output by the Fick oxygen consumption technique.

Thermodilution Technique
The thermodilution technique to measure cardiac output is an indicator dilution technique, with a cold fluid as the indicator. It is based on the Stewart-Hamilton-Principle: a known quantity of an indicator is injected as bolus into the circulating system and after thorough mixing a concentration-time curve is sampled downstream (26). Practically, cold saline is injected via the hands of the operator. However, warming of the cold solution caused by prolonged stay of the injectate in the right atrium secondary to severe tricuspid regurgitation or low cardiac output makes the thermodilution method unreliable (27). Similarly, heavy respiration might induce PA temperature changes and may result in inaccuracies of thermodilution cardiac output measurements (23).

VASCULAR RESISTANCE
Ohm’s law defines hydraulic resistance as the ratio of mean pressure drop (ΔP) across the hydraulic system to laminar flow through it. In such a system the resistance to flow depends solely on the diameter of the tubing and the viscosity of the fluid. The concept of vascular resistance was established in analogy to Ohm’s law. However, the cardiovascular system differs in a number of ways from a hydraulic system: for example, it is a pulsatile system; the blood is an inhomogeneous fluid, the vessels are elastic; and pressure waves are reflected. Therefore, the concept of vascular resistance is questionable. Vascular impedance, defined as the ratio of pulsatile pressure to pulsatile flow, would be a more accurate concept to describe the resistance and elasticity of the cardiovascular system (24). Nevertheless, the concept of systemic and pulmonary vascular resistance has gained wide acceptance. Its usefulness to assess pathophysiologic conditions has been established by many empiric data. Calculation of vascular resistances is now widely used for clinical decision making.

Systemic or pulmonary vascular resistance might also be termed systemic or pulmonary arterial resistance. However, only about 60% of the pressure drop across the system occurs at the arteriolar level, the other 40% at other sites in the vascular bed (24). Therefore, systemic and pulmonary vascular resistance is the preferred term.

The systemic vascular resistance is calculated as the ratio of the pressure drop from aorta to right atrium (mean aortic pressure—mean right atrial pressure) to systemic flow (Qs). The result of this ratio is expressed either in an arbitrary resistance unit (mmHg/L/min), also called hybrid resistance unit or Wood unit (according to its first introduction by Dr Paul Wood). This hybrid resistance unit is used in pediatric cardiology. In adult cardiology it is usually converted into metric resistance unit, expressed in dynes × sec × cm⁻² by use of the conversion factor 80 (Table 9.3). In pediatric cardiology the resistance is also usually normalized for BSA, thus resulting in a vascular resistance index. The resistance index is obtained by dividing the mean pressure drop by the cardiac index (not obtained by dividing the resistance by BSA).

Pulmonary vascular resistance is calculated as the ratio of the pressure drop from the PA to the LA to pulmonary flow (Qp).
O2 consumption
CO
mean aortic pressure
SV
CO
mean PAP
Wt

\[ \text{CO}_\text{Fick} = \frac{\text{AVO}_2\text{difference (mLO}_2/100\text{mL blood)} \times 10}{\text{Wt} \times 3\text{mLO}_2/kg\text{BW}} = \text{L/min} \]

Cardiac index (CI) = \frac{\text{CO}}{\text{BSA}} = \text{L/min/m}^2

Stroke volume (SV) = \frac{\text{CO} (\text{mL/min})}{\text{Heart rate (beats/min)}} = \text{mL/beat}

Stroke index (SI) = \frac{\text{SV} (\text{mL/beat})}{\text{BSA (m}^2)} = \text{mL/beat/m}^2

Transpulmonary pressure gradient = mean PAP – mean PCWP = mmHg

Pulmonary vascular resistance (PVR) = \frac{\text{CO} \times 80}{\text{mean PAP} – \text{mean PCWP}} = \text{dynes \times sec \times cm}^{-5}

System vascular resistance (SVR) = \frac{\text{mean aortic pressure} – \text{mean RAP}}{80 \times \text{mean aortic pressure} – \text{mean RAP}} = \text{dynes \times sec \times cm}^{-5}

System vascular resistance index (SVRI) = \frac{\text{mean aortic pressure} – \text{mean RAP}}{80 \times \text{mean aortic pressure} – \text{mean RAP}}

Abbreviations: Wt, weight (kg); AO2%, arterial oxygen saturation; VO2%, venous oxygen saturation; Hgb, hemoglobin concentration (g/dL); BSA, body surface area (m^2); PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

LAP is in most cases substituted by PCWP. The mean pressure drop from the PA to the LA or the pulmonary capillaries is termed transpulmonary pressure gradient (Fig. 9.8). In a normal pulmonary vascular bed the transpulmonary pressure gradient is no larger than 12 mmHg (2). In case of increased PA pressures a normal or near normal transpulmonary pressure gradient indicates that this increase is due to increased pulmonary venous filling pressure and not to changes in the pulmonary vascular bed. If the transpulmonary pressure gradient exceeds the normal range it is an indication of pathologic changes in the vascular bed across the lungs (Fig. 9.8) (28). For hemodynamic evaluation and testing of pulmonary vascular reactivity in case of pulmonary hypertension see chapter 10.

SHUNT DETECTION

Patients with clinically suspected intracardiac shunts nowadays undergo echocardiographic examination that usually reveals the location of cardiac shunts and allows their quantification. Even small, hemodynamically insignificant shunts like small atrial defects (ASD) or minimal shunts through a patent foramen ovale (PFO) are visualized by contrast echocardiography or color Doppler echocardiography. Accordingly, the main purposes of right heart catheterization in patients with known intracardiac shunts are their quantification, the assessment of relative shunt volumes in bidirectional shunts, or the evaluation of concomitant pulmonary hypertension. Nevertheless, unsuspected intracardiac shunts are occasionally found during routine right heart catheterization. A left-to-right shunt should be suspected, when PA oxygen saturation is \( \geq 80\% \), a right-to-left shunt, when arterial oxygen saturation is below 90% or approaches 80%, without apparent underlying heart failure, pulmonic disorder or alveolar hypventilation. In case of suspected right-to-left shunt, alveolar hypventilation should be excluded by making the patient cough and taking deep breathes. If arterial desaturation persists, oxygen should be given by face mask to achieve full arterial oxygenation. If full arterial oxygenation can not be achieved by providing oxygen, right-to-left shunt is presumed to be present.
Oxygen consumption

**Table 9.4** Detection of Left-to-Right Shunt by Oxygen Saturation Step-Up

<table>
<thead>
<tr>
<th>Level of shunt (chambers)</th>
<th>O₂ % saturation step-up</th>
<th>Possible causes of step-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial (superior vena cava/ inferior vena cava to RA)</td>
<td>≥7%</td>
<td>ASD, sinus venosus defects, partial anomalous pulmonary venous drainage, coronary or other arteriovenous fistula to the RA, ruptured sinus venalsae, VSD with tricuspid regurgitation</td>
</tr>
<tr>
<td>Ventricular (RA to RV)</td>
<td>≥5%</td>
<td>VSD, primum ASD, fistula to RV, patent ductus arteriosus with pulmonary regurgitation</td>
</tr>
<tr>
<td>Great vessel (RV to pulmonary artery)</td>
<td>≥5%</td>
<td>Patent ductus arteriosus, aorto-pulmonic window, aberrant coronary artery origin</td>
</tr>
</tbody>
</table>

Abbreviations: RA, right atrium; ASD, atrial septal defect; RV, right ventricle; VSD, ventricular septal defect.

Source: Adapted from Ref. 29.

**Table 9.5** Sample Sites for Oxygen Saturation During Diagnostic Oxymetry Run

1. Left and/or right PA
2. Main PA
3. Right ventricular outflow tract
4. Right ventricular, mid
5. Right ventricular, apex
6. Right atrium, low or near tricuspid valve
7. Right atrium, mid
8. Right atrium, high (near junction with superior vena cava)
9. Superior vena cava, low (near junction with right atrium)
10. Superior vena cava, high
11. Inferior vena cava, high (just beneath heart, above hepatic vein)
12. Inferior vena cava, low (above renal vein, below hepatic vein)
13. Pulmonary vein
14. Left atrium
15. Left ventricle
16. Aorta (distal to insertion of ductus)

Abbreviation: PA, pulmonary artery.

**Oxymetry Run**

If a left-to-right shunt or a right-to-left shunt is suspected, it should be localized and quantified. In the case of a left-to-right shunt the receiving heart chamber gets an admixture of arterial blood that will increase its oxygen saturation as compared with the upstream chamber (Table 9.4). The simplest way to screen for a left-to-right shunt is to search for an oxygen saturation step-up over the entire right-sided heart by sampling the superior vena cava and the PA. If an oxygenation step-up of more than 8% from the superior vena cava to the PA is detected, a left-to-right shunt may be present. For exact localization (atrial, ventricular, great vessels) of the oxygen saturation step-up an oximetry run is performed. On the atrial level an oxygen saturation step-up of ≥7% and on the PA and samples should be obtained in the various locations after verification of the position of the catheter by fluoroscopy. The possible sample sites are listed in Table 9.5. It is advisable to obtain two samples of the most important sites (e.g., PA) and to sample the receiving chambers several times and average the values. The oxymetry run is performed during steady state conditions within a few minutes. In equivocal cases increasing systemic flow by exercise will increase the likelihood of detection of a small left-to-right shunt (29). Importantly, supplemental oxygen should be withheld. If a significant oxygen step-up and thus a left-to-right shunt is detected, the blood oxygen saturation may be used to calculate the shunt magnitude.

However, it is important to understand, that the step-up indicates a net left-to-right shunt. A concomitant right-to-left shunt may be present. For example, in large atrial septal defects a right-to-left shunt of varying magnitude is almost always present. In analogy to the step-up of the oxygen saturation of the left-to-right shunt, a right-to-left shunt is detected by a step-down of oxygen saturation in the chambers of the left heart. To detect and to calculate the magnitude of a right-to-left shunt an oxygen saturation sample of the pulmonary vein, LA, left ventricle (LV), and aorta (below the insertion of the ductus) is obtained.

**Calculation of Shunt Size**

If an intracardiac shunt is present pulmonary flow (Qp) no longer equals systemic flow (Qs). In the presence of a left-to-right shunt pulmonary flow is increased by the shunt volume and conversely in the presence of a right-to-left shunt pulmonary flow relative to systemic flow is decreased by the shunt volume. The shunt fraction is then the ratio of the pulmonary flow to the systemic flow (Qp/Qs).

**Calculation of Pulmonary Flow (Qp)**

The pulmonary flow is calculated according to the Fick formula.

\[
\text{Pulmonary flow (Qp)} = \frac{\text{oxygen consumption}}{\text{pulmonary vein oxygen saturation} - \text{pulmonary artery oxygen saturation}} \times 1.36 \times \text{Hgb} \times 10 = \frac{\text{L/min}}{}
\]

If no pulmonary vein sample has been obtained arterial oxygen saturation may be used. A prerequisite for the use of an arterial oxygen saturation as substitute for pulmonary vein saturation is the exclusion of a right-to-left shunt and an arterial oxygen saturation of ≥95%. If a right-to-left shunt is present, an assumed oxygen saturation of 98% should be used for the calculation of pulmonary blood flow (30).
Calculation of Systemic Flow ($Q_s$)
The systemic flow is calculated according to the following formula:

$$Q_s = \text{oxygen consumption} / \text{(systemic arterial – mixed venous oxygen saturation}) \times 1.36 \times \text{Hgb} \times 10 \text{ L/min}$$

The mixed venous oxygen saturation refers to the oxygen saturation of the heart chamber upstream to the chamber receiving the shunt. For shunts on the atrial level the mixed venous oxygen saturation is therefore the oxygen saturation of the superior and inferior vena cava. For shunts on the ventricular level and for shunts on the great vessel level the mixed venous saturation used for flow calculation is the oxygen saturation of the right atrium, respectively, the RV.

In adults the mixed venous oxygen saturation is calculated as the sum of three times the superior vena cava oxygen saturation plus one time the oxygen saturation of the inferior vena cava divided by four (31). (In pediatric cardiology, the saturation difference between superior and inferior vena cava is ignored and the saturation of the superior vena cava is usually used as venous oxygen saturation.) The increased weighting of the more desaturated blood of the superior vena cava is due to the fact that the admixture of the heavily desaturated blood from the coronary sinus is not measured. The empiric formula has proven to approximate best the mixed venous saturation in adults at rest (31). During exercise however, oxygen saturation of the inferior vena cava weighs more prominently on mixed venous oxygen saturation. During exercise mixed venous oxygen saturation therefore is computed as the sum of the oxygen saturation of the vena cava superior plus two times the oxygen saturation of the inferior vena cava divided by three (31).

Effective blood flow ($Q_{eff}$) =

$$\text{(pulmonic vein saturation – mixed venous saturation) \times 1.36 \times \text{Hgb} \times 10}$$

Quantification of Left-to-Right and Right-to-Left Shunts
In absence of a right-to-left shunt the left-to-right shunt is calculated as pulmonic flow ($Q_p$) minus systemic flow ($Q_s$).

The magnitude of the left-to-right shunt can be expressed as the ratio of pulmonic to systemic flow ($Q_p/Q_s$). The ratio $Q_p/Q_s$ can be calculated by knowing the oxygen saturations alone (Table 9.6). The $Q_p/Q_s$ ratio derived from the oxymetry data is routinely compared with the $Q_p/Q_s$ ratio obtained from echocardiographic shunt quantification. Shunt ratios between 1.0 and 1.5 indicate a small left-to-right shunt. A $Q_p/Q_s$ ratio between 1.5 and 2.0 an intermediate and a ratio greater than 2.0 a large left-to-right shunt. Surgical or percutaneous defect closure is recommended in large and most of the intermediate shunts. Of note, shunt size is not equal to defect size. In the case of increased right heart pressures left-to-right shunt might be small despite a large atrial septal defect.

In the presence of a right-to-left shunt or a bidirectional shunt (simultaneous left-to-right and right-to-left shunts) the magnitude of each shunt can be calculated by the additional quantification of the hypothetic effective pulmonic and systemic blood flow. The effective blood flow is the blood flow that would exist in a pulmonic or systemic vascular system in absence of any left-to-right or right-to-left shunt. The effective blood flow ($Q_{eff}$) is calculated according to the formula:

$$\text{effective blood flow} = \text{oxygen consumption} / \text{(pulmonic vein saturation – mixed venous saturation) \times 1.36 \times \text{Hgb} \times 10}$$

The left-to-right shunt then equals $Q_p - Q_{eff}$ and conversely the right-to-left shunt equals $Q_s - Q_{eff}$.

Knowing the effective blood flow allows the calculation of the percentage of shunt volumes. The percentage left-to-right shunt equals $(1 - Q_p/Q_{eff})$ and the percentage

### Table 9.6  Formulas for Shunt Calculation

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_s$</td>
<td>Systemic flow</td>
</tr>
<tr>
<td>$Q_p$</td>
<td>Pulmonary flow</td>
</tr>
<tr>
<td>$Q_{eff}$</td>
<td>Effective blood flow</td>
</tr>
<tr>
<td>$Q_p/Q_s$</td>
<td>Ratio of pulmonic to systemic flow</td>
</tr>
<tr>
<td>$Q_p$ effective</td>
<td>Pulmonic flow minus effective flow</td>
</tr>
<tr>
<td>$Q_{right-left}$</td>
<td>Left-to-right shunt</td>
</tr>
<tr>
<td>$Q_{left-right}$</td>
<td>Right-to-left shunt</td>
</tr>
<tr>
<td>% left-to-right shunt</td>
<td>Percentage of left-to-right shunt</td>
</tr>
<tr>
<td>% right-to-left shunt</td>
<td>Percentage of right-to-left shunt</td>
</tr>
</tbody>
</table>

**Abbreviations:** SVC$_{sat}$, blood oxygen saturation of the superior vena cava; IVC, inferior vena cava; PV, pulmonary vein; PA, pulmonary artery; Art, arterial; Hgb, hemoglobin.
### Table 9.7 Anticipated Normal Values

<table>
<thead>
<tr>
<th>Source</th>
<th>Note: Normal values are expected values in average sized adults at rest.</th>
<th>Source: From Refs. 26 and 32.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right atrium</strong></td>
<td>A-wave 2–10 mmHg</td>
<td>A-wave 2–10 mmHg</td>
</tr>
<tr>
<td></td>
<td>V-wave 2–10 mmHg</td>
<td>V-wave 2–10 mmHg</td>
</tr>
<tr>
<td></td>
<td>Mean 0–8 mmHg</td>
<td>Mean 0–8 mmHg</td>
</tr>
<tr>
<td><strong>Right ventricle</strong></td>
<td>Systolic 15–30 mmHg</td>
<td>Systolic 15–30 mmHg</td>
</tr>
<tr>
<td></td>
<td>End diastolic 0–8 mmHg</td>
<td>End diastolic 0–8 mmHg</td>
</tr>
<tr>
<td><strong>Pulmonary artery</strong></td>
<td>Systolic 15–30 mmHg</td>
<td>Systolic 15–30 mmHg</td>
</tr>
<tr>
<td></td>
<td>End diastolic 3–12 mmHg</td>
<td>End diastolic 3–12 mmHg</td>
</tr>
<tr>
<td></td>
<td>Mean 10–21 mmHg</td>
<td>Mean 10–21 mmHg</td>
</tr>
<tr>
<td><strong>Left atrium or Pulmonary capillary wedge pressure</strong></td>
<td>A-wave 4–15 mmHg</td>
<td>A-wave 4–15 mmHg</td>
</tr>
<tr>
<td></td>
<td>V-wave 4–15 mmHg</td>
<td>V-wave 4–15 mmHg</td>
</tr>
<tr>
<td></td>
<td>Mean 4–12 mmHg</td>
<td>Mean 4–12 mmHg</td>
</tr>
<tr>
<td><strong>Transpulmonary pressure gradient</strong></td>
<td>Mean 4–12 mmHg</td>
<td>Mean 4–12 mmHg</td>
</tr>
<tr>
<td><strong>Cardiac output</strong></td>
<td>Stroke volume 80–160 mL</td>
<td>Stroke volume 80–160 mL</td>
</tr>
<tr>
<td><strong>Cardiac index</strong></td>
<td>Stroke volume index 40–160 mL/m²</td>
<td>Stroke volume index 40–160 mL/m²</td>
</tr>
<tr>
<td><strong>Systemic vascular resistance</strong></td>
<td>Mixed venous oxygen saturation 65–75%</td>
<td>Mixed venous oxygen saturation 65–75%</td>
</tr>
<tr>
<td><strong>Pulmonary vascular resistance</strong></td>
<td>Stroke volume index 770–1500 dynes cm⁻⁵</td>
<td>Stroke volume index 770–1500 dynes cm⁻⁵</td>
</tr>
<tr>
<td><strong>Cardiac index</strong></td>
<td>Cardiac output 5–10 L/min</td>
<td>Cardiac output 5–10 L/min</td>
</tr>
<tr>
<td><strong>Ventricular performance</strong></td>
<td>End diastolic pressure 2–10 mmHg</td>
<td>End diastolic pressure 2–10 mmHg</td>
</tr>
<tr>
<td><strong>Right atrium</strong></td>
<td>Mean pressure 0–8 mmHg</td>
<td>Mean pressure 0–8 mmHg</td>
</tr>
<tr>
<td><strong>Right ventricle</strong></td>
<td>V-wave 2–10 mmHg</td>
<td>V-wave 2–10 mmHg</td>
</tr>
<tr>
<td><strong>Pulmonary artery</strong></td>
<td>End diastolic pressure 6–12 mmHg</td>
<td>End diastolic pressure 6–12 mmHg</td>
</tr>
<tr>
<td><strong>Left atrium</strong></td>
<td>End diastolic pressure 0–8 mmHg</td>
<td>End diastolic pressure 0–8 mmHg</td>
</tr>
<tr>
<td><strong>Initial pressure</strong></td>
<td>Mean pressure 0–8 mmHg</td>
<td>Mean pressure 0–8 mmHg</td>
</tr>
<tr>
<td><strong>Systemic vascular resistance</strong></td>
<td>V-wave 2–10 mmHg</td>
<td>V-wave 2–10 mmHg</td>
</tr>
<tr>
<td><strong>Pulmonary vascular resistance</strong></td>
<td>End diastolic pressure 0–8 mmHg</td>
<td>End diastolic pressure 0–8 mmHg</td>
</tr>
<tr>
<td><strong>Right atrium</strong></td>
<td>V-wave 2–10 mmHg</td>
<td>V-wave 2–10 mmHg</td>
</tr>
<tr>
<td><strong>Right ventricle</strong></td>
<td>Mean pressure 0–8 mmHg</td>
<td>Mean pressure 0–8 mmHg</td>
</tr>
<tr>
<td><strong>Pulmonary artery</strong></td>
<td>Mean pressure 0–8 mmHg</td>
<td>Mean pressure 0–8 mmHg</td>
</tr>
<tr>
<td><strong>Left atrium</strong></td>
<td>Mean pressure 0–8 mmHg</td>
<td>Mean pressure 0–8 mmHg</td>
</tr>
</tbody>
</table>

### REFERENCES


Pulmonary hypertension—hemodynamic assessment and response to vasodilators

Myung H. Park and Vallerie V. McLaughlin

INTRODUCTION
The first observation of patients with pulmonary hypertension was described by a German physician Dr. Ernst von Romberg as “sclerosis of the pulmonary arteries” from autopsy findings (1). The term primary pulmonary hypertension (PPH) was used by Dresdale and colleagues in 1951, describing a hypertensive vasculopathy of pulmonary vessels of unknown cause (2). Paul Wood contributed to understanding of possible etiology of this disease by observing that a reduction in pulmonary artery pressure was seen in response to intravenous (IV) administration of acetylcholine in patients with pulmonary hypertension secondary to mitral stenosis, eliciting a proposal that a “vasoconstrictive factor” may be a cause (3).

However, it was not until an outbreak of aminorex-induced pulmonary hypertension in 1960s in Europe which prompted the World Health Organization (WHO) in assembling a group of experts to determine the current state of knowledge of PPH (4). The National Heart, Lung and Blood Institute (NHLBI) created a National Registry of Patients with PPH from 1981 to 1987, enrolling 187 patients from 32 clinical centers. This registry has had a monumental impact in elucidating clinical, epidemiological, and pathophysiological information, which has paved the way for subsequent research. The data from the registry has revealed that PPH occurs more frequently in women than men (1.7:1) with a mean age of diagnosis of 36 years and when left untreated, is a progressive disease with high mortality with a median survival of 2.8 years (5,6). In addition, this study brought to attention that a significant delay was reported in making the diagnosis from onset of symptoms (2.5 years), a factor which has prompted efforts in increasing awareness of pulmonary hypertension.

The 2nd WHO meeting was held in Evian, France in 1998, commemorating the 25th anniversary of the first meeting in Geneva. The experts developed a classification categorizing pulmonary hypertension into five groups based on different etiologies. However, the most comprehensive changes were made during the 3rd World Symposium in Venice, Italy, held in 2003. This meeting was heralded by tremendous advances in the field of molecular and genetics sciences, as well as development of effective therapies, which changed the understanding and practice of pulmonary hypertension. The 2003 Venice Classification of Pulmonary Hypertension replaced the term PPH with idiopathic pulmonary arterial hypertension (IPAH) along with modifications of the five categories previously established (7). In 2008, the 4th World PH Symposium took place in Dana Point, California, where current research and clinical trials were evaluated resulting in an updated classification system and treatment guideline (see “Clinical Aspects”) (8,9).

FUNDAMENTALS
Pathobiology of Pulmonary Arterial Hypertension
The pulmonary vasculature is a low-pressure system with normal systolic pulmonary artery pressure (SAP) range of 15 to 30 mmHg and mean pulmonary artery pressure (mPAP) of 9 to 18 mmHg, essentially functioning at less than one tenth the resistance to flow observed in the systemic vascular bed, in part because of the large cross-sectional area of the pulmonary circulation (10).

The current definition of pulmonary arterial hypertension (PAH) from the 4th World Symposium is mPAP > 25 mmHg and pulmonary capillary wedge pressure (PCWP) < 15 mmHg (11). PAH is characterized by structural changes in the pulmonary vascular bed resulting in pulmonary arterial obstruction due to vascular proliferation and remodeling. This leads to progressive increase in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) resulting in right ventricular failure and death. The predominant cause of increased PVR is the loss of vascular luminal cross-sectional area due to pulmonary vascular remodeling. This process involves all layers of the vessel wall and is characterized by intimal hyperplasia, medial hypertrophy, adventitial proliferation, and in situ thrombosis.

The process by which pulmonary vasculopathy is initiated results from interaction of a predisposing state and one or more inciting stimuli, a concept known as “multiple-hit hypothesis” (12,13). Two or more “hits” is thought to consist of a genetic abnormality or substrate that renders an individual susceptible. The second hit may be either a systemic disorder (i.e., connective tissue disease (CTD), human immunodeficiency virus (HIV)), an environmental trigger (i.e., hypoxic state, ingestion of an anorexigen), or additional genetic conditions (i.e., mutation, polymorphism). Once a combination of factors affect a susceptible individual, various mechanisms are activated which result in vasoconstriction, cellular proliferation and prothrombotic state leading to PAH.

Molecular and Cellular Mechanisms
Prostacyclin and Thromboxane A2
The two prostanoids, prostacyclin (PGI2) and thromboxane A2, are main metabolites of arachidonic acid. PGI2 produced by the action of PGI2 synthase, is a potent vasodilator and a strong inhibitor of platelet aggregation and smooth muscle cell proliferation. Thromboxane A2 is a potent vasoconstrictor and promotes platelet activation. In PAH, PGI2 synthase activity and PGI2 levels are reduced whereas thromboxane level is increased, thereby resulting in vasoconstriction, cellular proliferation and thrombosis (Fig. 10.1) (14-16).
Endothelin-1
Endothelin (ET)-1 is a 21-amino peptide that is produced by endothelium-converting enzymes from big endothelin. ET-1 is a potent vasoconstrictor and smooth muscle mitogen and it exerts its effects through two receptors, $\text{ET}_A$ (located on smooth muscle cells) and $\text{ET}_B$ receptors (located on vascular endothelial cells and smooth muscle cells) (17,18). Activation of the $\text{ET}_A$ and $\text{ET}_B$ receptors on smooth muscle cells induces vasoconstriction and cellular proliferation and hypertrophy, whereas stimulation of $\text{ET}_B$ receptors on endothelial cells results in production of vasodilator [nitric oxide (NO) and prostacyclin (PGI$_2$)]. $\text{ET}_B$ receptors are also involved in the clearance of ET-1 from the circulatory system (18). In PAH patients, plasma levels of ET-1 is increased and its level has been shown to be inversely proportional to the magnitude of the pulmonary blood flow and cardiac output (Fig. 10.1) (19,20).

Nitric Oxide Pathway
NO, produced from arginine by NO synthase in endothelial cells, is a potent selective pulmonary vasodilator. It exerts its effects through its second messenger, cyclic guanosine monophosphate (cGMP), which is degraded by phosphodiesterase-5 (PDE-5). Patients with PAH have decreased NO synthase activity, thus promoting vasoconstriction and cellular proliferation (21). PDE-5 inhibitors (PDE5-Inhs) act by selectively blocking this enzyme, thus promoting the accumulation of intracellular cGMP and enhancing NO mediated effects (Fig. 10.1).

Serotonin
Serotonin (5-hydroxytryptamine) is a vasoconstrictor that promotes smooth muscle cell hypertrophy and hyperplasia (22). Elevated plasma serotonin and reduced content of serotonin in platelets have been reported in IAPH and PAH associated with...
ingestion of dexfenfluramine, which increases the release of serotonin from platelets and inhibits its reuptake (23,24). Furthermore, mutations in the serotonin transporter (5-HTT) and its receptor 5-HT2B have been described in PAH patients (25). However, it is not certain if elevated serotonin levels are implicated in PAH since selective serotonin reuptake inhibitors (SSRIs) are not associated with an increased incidence of pulmonary hypertension and may be even protective against hypoxic PH (26).

Additional Mechanisms
Inhibition of voltage-dependent potassium channels (Kv) have been linked to factors which promote PAH, such as hypoxia and fenfluramine derivatives (27,28). Abnormalities of the coagulant cascade including increased levels of von Willebrand factor, plasminogen activator inhibitor-1, and plasma fibrinopeptide have been reported in PAH patients (29). Furthermore, inflammatory factors such as proinflammatory cytokines and autoantibodies have been implicated in PAH (30).

Genetic Substrates
Molecular genetic studies have identified mutations in a receptor in the transforming growth factor β (TGFβ) receptor pathway, named bone morphogenetic protein receptor 2 (BMPR2), in certain patients identified with heritable pulmonary arterial hypertension (HPAH) (31,32). The mutation in the BMPR2 receptor protein results in aberrations of signal transduction with a BMI

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The Right Ventricle in Pulmonary Hypertension
Although it is the pulmonary arterial vasculature where the pathological processes take place in PAH, the factor which determines symptom and survival rests on the ability of right ventricle (RV) to function under the increased pressure and resistance. The RV is a thin walled, compliant, crescent-shaped structure, formed by the RV free wall [connected to the left ventricle (LV) by the anterior and posterior septum] and the interventricular septum. Because of the low resistance of the pulmonary vasculature, the compliant RV is able to pump the same stroke volume as the LV with much less work (34,35).

The RV must be able to adapt to the increased afterload for survival in PAH. The initial adaptive response is usually RV hypertrophy, which has been seen within 96 hours of inducing pulmonary hypertension in animal models (36). RV hypertrophy can be followed by contractile dysfunction and/or RV dilatation for further compensatory maneuver to maintain cardiac output by increase in preload to offset decrease in fractional shortening. Continued remodeling of the RV soon causes alterations in RV shape from crescent to concentric and in flattening out the septum. Because of interventricular dependence, these changes cause LV diastolic dysfunction and decrease in LV end diastolic volume, resulting in further decline in stroke volume and deterioration of end organ function (37).

However, the development of RV failure due to PAH is quite variable and the reasons why some RV can compensate maintaining adequate cardiac output for prolonged periods of time while others immediately decompensate remains unclear. Several mechanisms have been proposed including retention of the “fatal” genotype believed to be contributory factor for favorable survival of PAH associated with congenital heart disease (CHD), polymorphisms in genes related to rennin-angiotensin-aldosterone system, and differences in the degree of ischemia and apoptosis (35,38,39). Resurgence of interest in determining mechanisms of RV failure and more effective method of imaging the RV are currently underway. As for now, one fact remains clear which is that RV function is the single most important determinant of survival in patients with PAH.

INDICATIONS FOR RIGHT HEART CATHETERIZATION IN PULMONARY ARTERIAL HYPERTENSION
Right heart catheterization is necessary to establish diagnosis, perform acute vasodilator testing, assess prognosis and guide therapy in PAH. While echocardiography is the single most important screening tool in PH, it lacks the accuracy to make the diagnosis in PAH. Furthermore, the definition of PAH is based on hemodynamically derived set of parameters: mPAP > 25 mmHg and PCWP ≤ 15 mmHg (11).

Establishing Diagnosis in Pulmonary Arterial Hypertension
Measuring Pulmonary Artery Pressure: Limitations of Echocardiography
The method most widely used to screen for PH is measuring the peak systolic velocity of the tricuspid regurgitation (TR) jet with continuous-wave spectral Doppler. An estimation of right ventricular systolic pressure (RVSP) is generated by adding an assessment of right atrial pressure (RAP) to the gradient using the modified Bernoulli equation: $RVSP = 4v^2 + RAP$, in which $v$ is the velocity of the tricuspid jet in meters per second (10,11,40). Several factors influence the accuracy of this measurement as estimation of SPAP. First, this pressure estimation is the RVSP rather than PASP, which is a valid assumption in the absence of obstruction to right ventricular outflow (pulmonary valve stenosis or outflow tract obstruction). Second factor is the accuracy of RAP estimation, which can greatly influence the RVSP value. Some centers use an arbitrarily fixed value for RAP, while others employ a clinically estimated value derived from the jugular venous pulse (40,41). Another commonly used method is to make an estimation on the basis of the degree of inferior vena cava collapse during spontaneous respiration. One study suggested that ≥50% or <50% collapse reflect RAP values of <10 mmHg or ≥10 mmHg, respectively (42).

Inability to obtain TR jets is another factor and studies have demonstrated that the Doppler profile was insufficient to measure RV to right atrium (RA) pressure gradients in 10% to 70% of patients referred for PH evaluation, mainly because of poor acoustic windows (43–45). Patients with advanced lung disease are particularly challenging in this regard. Furthermore, age and weight also affect SPAP in normal individuals. In a large-scale study of 3790 subjects from 1 to 89 years of age, a SPAP > 40 mmHg was found in 6% of those ≥50 years old and 5% of those with a BMI ≥ 30 kg/m² (46). The level of physical training has also been shown to affect SPAP. Comparing a group of highly trained athletes versus normal males, SPAP was higher among the trained individuals both at rest and with exercise, largely because of increases in stroke volume affecting pulmonary artery pressures (47).

While some studies comparing Doppler-derived SPAP with catheterization have reported good correlation, others have demonstrated substantial discrepancy between the
techniques (44,48–54). In patients with severe PH, Doppler-derived SPAP has been shown to commonly underestimate pressures (50). With advanced lung disease and PH, SPAP measurements frequently overestimated true PAPs leading to over diagnosis (51–53). A similar lack of adequate correlation was reported in patients with PH associated with systemic sclerosis (54).

**Essential Components of a Complete Hemodynamic Assessment in Pulmonary Arterial Hypertension**

Although the basic principles of right heart catheterization were discussed in chapter 9, some comments specific to PAH are appropriate. The most common abnormality in RAP in PAH is due to TR, which can produce attenuated x descent, prominent c-v wave and a deep and rapid y descent (Fig. 10.2) (55,56). In severe TR, ventricularization of RAP may occur where RAP is nearly indistinguishable from the RV pressure contour (Fig. 10.2). In PAH with RV hypertrophy and volume overload, a prominent a wave may appear on the ventricular waveform at end-diastole indicative of RA contracting against a noncompliant RV. A careful assessment of RAP is imperative since RAP carries a significant prognostic importance in PAH. In advanced PAH, the PAPs can be elevated to various degrees and can reach systemic levels (Fig. 10.3). The PA diastolic pressure does not correlate well with the mean PCWP in the presence of pulmonary vascular disease.

Accurate measurement of left heart filling pressure is critical for correct diagnosis of PAH. Definition of PAH requires both elevation of mPAP (>25 mmHg) and normal PCWP (or LVEDP of ≤15 mmHg). The difference between these two measurements calculates the transpulmonary gradient (TPG = mPAP – PCWP). Elevated PCWP is characteristic of PH in the setting of chronically elevated left-sided cardiac filling pressure, termed pulmonary venous hypertension (PVH), and is classified as WHO group 2 PH (8). PVH usually results from systolic and/or diastolic cardiac dysfunction or valvular disease. Thus therapeutic decisions can be significantly different on the basis of the left-sided filling pressure measurement. PAH is characterized by elevated PAPs, normal PCWP and elevated TPG whereas in PVH, PAPs are elevated but TPG is normal because of elevated PCWP.

Careful attention to wave forms and timing of measurement is essential for accuracy. The most common mistake is “underwedging,” which occurs with incomplete advancement of the PA catheter resulting in a hybrid tracing of PAP and PCWP. This usually results in a falsely elevated PCWP, leading to misdiagnosing a patient as PVH (Fig. 10.4). If an operator is suspicious that the PCWP being measured is greater than expected on the basis of clinical assessment, an oxygen saturation measurement can be done from the distal port with the catheter in the wedge position. Its measurement should be equal or close to the systemic arterial oxygen saturation (usually >90%) done by pulse oximetry. If it is markedly lower, the catheter is most

---

**Figure 10.2** (A) Right atrial waveform from a patient with secondary tricuspid regurgitation from associated severe left-sided heart failure and right-sided heart failure. Attenuation of the x descent is present, leading to prominent c-v wave. (B) These tracings are from a patient with severe tricuspid regurgitation. The right atrial waveform shows ventricularization (left). Compare with the right ventricle (RV) waveform from same patient (right). **Abbreviation:** RA, right atrium. **Source:** From Ref. 56.
likely underwedged. In patients with significant elevation of PAP and/or PA that is dilated, placing the catheter in the correct anatomic position for optimal PCWP measurement can be challenging. One helpful maneuver is deflating the balloon, allowing the catheter to migrate distally, and carefully reinflating the balloon following the pressure tracings closely. Usually with this approach, optimal placement is obtained with balloon partially inflated. An intraluminal guide wire can also aid in advancing the catheter to a more distal position. All these maneuvers should be performed very cautiously and under direct fluoroscopic visualization since patients with PAH are at increased risk of PA rupture, a potentially fatal event.

Characteristics of a physiologically reliable PCWP and steps that can aid in obtaining the measurement include the following (55–57): (i) A distinct a and v waves should be present. Exception noted in atrial fibrillation where a wave will be absent. (ii) Waiting for steady state in PCWP tracing to occur (not immediately after the balloon is inflated) and record at end-expiratory phase. (iii) A distinct immediate rise in pressure when balloon is deflated out of the wedge position. (iv) Catheter tip should be stable in PA when viewed under fluoroscopy with the balloon inflated (not moving back and forth). (v) An oxygen saturation measured in PCWP > 90%. (vi) Multiple measurements of PCWP with similar results. If these maneuvers fail to obtain a reliable PCWP, a left heart catheterization should be performed to measure LVEDP.

Although less common, the catheter can also be “over-wedged” with excessive inflation of the balloon relative to the size of the vessel. This should be avoided not only because of inaccurate pressure measurement but also because of increase in risk of vessel rupture. In bedside catheter measurements, the potential for PA catheter migration also need to be kept in mind. The balloon should be slowly inflated at every measurement with close monitoring of the pressure tracings, with inflation stopped when a PCWP tracing is obtained.

The presence of a “large” v wave can also lead to inaccurate reading of PCWP. The v wave is a normal finding on the wedge tracing and normally higher than the a wave so as to what measurement constitutes a large v wave is subjective. Common causes of a large v wave include mitral regurgitation (MR), though the height of the v wave is neither sensitive nor specific indicator of the degree of MR (58,59). Other causes include any situations which increase volume or flow into a

![Figure 10.3](image1.png)  
**Figure 10.3** Pulmonary artery pressure and pulmonary capillary wedge tracing from a patient with severe pulmonary arterial hypertension. PA pressure 102/34 mmHg with mean of 63 mmHg and PCWP 7 mmHg. Each line represents 10 mmHg.

![Figure 10.4](image2.png)  
**Figure 10.4** Differences between correct pulmonary capillary wedge pressure and underwedged tracings.
PULMONARY HYPERTENSION—HEMODYNAMIC ASSESSMENT AND RESPONSE TO VASODILATORS

noncompliant left atrium, such as ventricular septal defect, mitral stenosis, cardiomyopathy of any etiology, or postoperative surgical conditions.

Accurate cardiac output measurement is critical in calculating PVR and assessing prognosis in PAH. The total pulmonary resistance (TPR) calculates the relationship between the mPAP and CO: TPR = mPAP × 80/CO; the normal TPR is 100 to 300 dynes-sec/cm². The PVR measures the resistance to flow imposed by pulmonary vasculature without the influence of the left-sided filling pressure: PVR = (mPAP – PCWP) × 80/CO or PVR = TPG × 80/CO; the normal PVR is 20 to 130 dynes-sec/cm². Cardiac output assessment is a critical measure of RV performance in the presence of elevated PAPs and low cardiac output is a marker of poor prognosis (see Assessment of Prognosis) (6).

Chronic left-to-right intracardiac shunting can result in PAH. Echocardiogram with agitated saline contrast can detect right-to-left shunt but can fail to detect left-to-right shunts. Multiple measurements of oxygen saturations from superior and inferior vena cava, RA and PA can detect and quantify shunts (see chap. 9). If the shunt has reversed, the typical “step-up” may not be present. A detailed oxygen saturation study is a crucial part of right heart catheterization in a patient with clinical or echocardiographic suspicion of intracardiac shunting.

Assessment of Prognosis
Since PAH is a disease manifested by an increase in afterload of pulmonary arteries leading to progressive right ventricular dysfunction and failure, hemodynamic markers are considered to be the gold standard for indicating prognosis. This was first demonstrated in the NIH Registry where the investigators concluded, “Mortality was most closely associated with right ventricular hemodynamic function and can be characterized by means of an equation using three variables: mean pulmonary artery pressure, mean right atrial pressure, and cardiac index” (6). Specifically, RAP ≥ 20 mmHg, mPAP ≥ 85 mmHg, and cardiac index (CI) < 2 L/min/m² were associated with an increased risk of death. The data obtained were the basis of formulating the regression equation to calculate survival on the basis of hemodynamics, which was validated in a prospective study (60). Subsequent studies have corroborated the importance of elevated RAP and low CO as determinants of poor outcome (61). The relevance of mPAP on prognosis has been variable. In the retrospective study among patients treated with epoprostenol, patients with lower mPAP correlated with poor outcome which may indicate that mPAP per se is not a reliable surrogate for RV function but needs to be assessed as part of PVR (mPAP/CO) (62).

Acute Vasodilator Testing
The purpose of evaluating PAH patients with a short-acting vasodilator is to determine the degree in which the pulmonary vasoconstriction is contributing to the elevated PAPs. Vasodilator responsiveness identifies patients with a better prognosis and those who are more likely to have a sustained beneficial response to oral calcium channel blockers (CCBs).

IV epoprostenol and IV adenosine have both been studied as acute vasodilators. Both are short-acting, potent vasodilators and investigators have reported different degrees of responsiveness depending on the criteria used (63–65). However, because both agents have the potential to cause systemic hypotension and side effects, using inhaled NO emerged as the vasodilator of choice because of its pulmonary selectivity, short half-life, and lack of systemic side effects (Table 10.1) (66). However, it is expensive and requires trained respiratory personnel to administer.

The definition of what constitutes acute vasodilator “responder” has undergone changes over the years. The current consensus definition is a fall in mPAP of at least 10 mmHg to ≤40 mmHg, with an increased or unchanged cardiac output (67,68). If a patient meets this acute criteria, they should be treated with oral CCBs, however, need to be followed closely for a clinical response. Those who improve to functional class (FC) I or II without the need for additional therapy are likely to do well. However, this response is rare, approximately 6.8% of IPAH patients in a large French series (67). Patients who do not meet the definition of an acute response should not be treated with CCBs.

Acute vasodilator response is very rare in patients with associated forms of PAH. Patients with advanced disease such as FC IV symptoms, overt right heart failure, or hemodynamic markers of advanced process (high RAP and/or reduced CO, systemic hypotension) should not undergo acute vasodilator testing since these patients need prompt treatment with PAH-approved therapies and are not appropriate candidates for CCBs. The development of acute pulmonary edema during vasodilator testing should raise the suspicion of veno-occlusive disease or pulmonary capillary hemangiomatosis, in which therapy with pulmonary vasodilator is contraindicated (69).

Risks Associated with RHC in PAH Patients
Although RHC is necessary for correct diagnosis of PAH, concerns regarding risks in this population have been raised. A recent multicenter study, which included 15 PAH centers over five-year period with >7000 procedures, evaluated the safety and risks of this procedure (70). The overall incidence of serious adverse events was 1.1%. The most frequent complications were related to venous access; others included arrhythmia and hypotension due to vagal reactions or pulmonary

### Table 10.1  Agents Used in Acute Vasodilator Testing in Patients with Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Nitric oxide</th>
<th>Epoprostenol</th>
<th>Adenosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Inhaled</td>
<td>IV</td>
</tr>
<tr>
<td>Dose range</td>
<td>10–80 ppm</td>
<td>2–10 ng/kg/min</td>
</tr>
<tr>
<td>Dosing increments</td>
<td>None to variable titration (10–80 ppm for 5–10 min)</td>
<td>1–2 ng/kg/min every 10–15 min</td>
</tr>
<tr>
<td>Side effects</td>
<td>Increased left-sided filling pressure in susceptible patients</td>
<td>Hypotension, headache, flushing, nausea, lightheadedness</td>
</tr>
</tbody>
</table>

*Abbreviation: IV, intravenous.*

*Source: From Ref. 68.*
vasoreactivity testing. Thus the authors concluded that when performed in experienced centers, RHC in PAH patients are safe and associated with low morbidity rates.

The following maneuvers can enhance safety of the procedure. When accessing from an internal jugular approach, use of an ultrasound device to visualize the size and depth of the vein greatly assists in gaining access safely. Since PAH patients often have dilated right-sided chambers which can make maneuvering the catheter difficult, especially under high pressure systems and under significant tricuspid valvular regurgitation, performing the procedure under fluoroscopy reduces the risks of catheter “coiling” and inducing arrhythmia. Direct visualization also assists in placing the catheter in the safe and optimal “wedge” position to avoid PA rupture, “overwedgeing” and migration of the catheter. Fluoroscopy is also necessary in patients with intracardiac devices. Furthermore, having peripheral IV access in patients prior to starting the procedure is recommended to promptly deliver treatment in the event of vago episodes, which can lead to significant clinical deterioration in PAH patients.

**Evaluating PH with Left-Sided Heart Disease**

**Diastolic Dysfunction and Pulmonary Hypertension**

Diastolic heart failure (DHF) refers to clinical syndrome in which patients present with heart failure symptoms with preserved left ventricular systolic function. Epidemiological studies have shown high prevalence of DHF (~40-70%) among symptomatic patients and the risk factors have been well elucidated (age >65, hypertension, elevated pulse pressure, obesity, coronary artery disease, diabetes mellitus, atrial fibrillation) (71,72). The predominant underlying structural abnormalities in DHF are concentric remodeling and hypertrophy of the LV caused by chronic pressure overload, usually due to systemic hypertension. These alterations produce abnormalities in both relaxation and filling, which can be a precursor to LV systolic dysfunction or be the main structural abnormality producing symptoms and signs of heart failure (73,74).

Patients presenting with diastolic dysfunction and PH is a common clinical dilemma and can be very challenging to distinguish from PAH. Up to 70% of patients with LV diastolic dysfunction may develop PH, the presence of which is associated with a poor prognosis (75). The presentations are similar to PAH and include dyspnea and/or signs and symptoms of heart failure. Echocardiographic findings suggestive of LV diastolic dysfunction include left atrial enlargement, LV hypertrophy and elevated LV filling pressure (grade II to IV diastolic dysfunction) (Table 10.2) (68,76).

At this juncture, it is critical to perform RHC to measure the left-sided filling pressure and calculate the TPG and PVR. It needs to be emphasized that attention must be paid to the quality of the PCWP tracing for correct diagnosis to be made. Misinterpretation of either “underwedged” or hybrid tracing as true PCWP (thereby misdiagnosing as diastolic dysfunction because of falsely elevated PCWP) or recorded measurements from improper placement of the catheter can lead to wrong diagnosis. The possible results obtained fall into one of three categories.

1. PCWP is normal (<15 mmHg) and TPG and PVR is elevated [≥3 Wood units (WU)], the patient has PAH and treatment need to be considered after full evaluation. If the patient has clinical risk factors and/or echo findings suggestive of diastolic dysfunction, PCWP or LVEDP can be normal after treatment with diuretics. Some investigators have advocated fluid challenge or exercise to assess response as a measure of the LV compliance. Although there are no definite standardizations, the recently published ACCF/AHA Expert Consensus Document on Pulmonary Hypertension and reports from the 4th World Symposium on Pulmonary Hypertension outline consensus-based recommendations for evaluation of patients presenting with both syndromes (Fig. 10.5) (68,76).

2. PCWP is elevated (>15 mmHg) and PVR is <3 WU and TPG is normal, the patient has diastolic dysfunction and therapy should be aimed at optimizing volume status, heart rate and systemic blood pressure.

3. If the PCWP and the PVR are both elevated (the TPG can be normal or elevated), careful evaluation and intervention need to be made to determine if the elevated PVR is passive (because of elevated filling pressure and thus responsive to diuretics and/or systemic vasodilator) or fixed (remain elevated despite normalizing PCWP and systemic blood pressure). If the PCWP and PVR both decrease (TPG normal) with optimal heart failure therapy, then patients need to be treated aggressively with these regimen. If the PCWP normalizes but PVR remains elevated (elevated TPG), this may be indicative of pulmonary arteriopathy being the dominant disorder with structural changes in pulmonary vasculature along with diastolic dysfunction.

No PAH-specific therapies have been systematically studied for PH associated with diastolic dysfunction. In patients with chronic heart failure, treatment with epoprostenol and endothelin receptor antagonists (ERAs) have failed to show beneficial effects, though these trials did not specifically target patients with heart failure and PH (77-79). The PDE5-Inh sildenafil has shown improvement in LV systolic and diastolic function as well as systemic vasoreactivity in animal models of heart failure (80,81). Recent small, short-term studies evaluating patients with chronic systolic heart failure and PH using sildenafil have demonstrated improvement in exercise capacity and quality of life (82,83). However, data from a well-designed trial studying long-term benefits is necessary before any recommendations can be made in regards to use of sildenafil in patients with heart failure and PH.

**Table 10.2 Risk Factors Favoring Diagnosis of Diastolic Heart Failure**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 yr</td>
<td></td>
</tr>
<tr>
<td>Elevated systolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>Elevated pulse pressure</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
</tbody>
</table>

**Echocardiography**

- **Left atrial enlargement**
- **Concentric remodeling (relative wall thickness > 0.45)**
- **Left ventricular hypertrophy**
- **Elevated left ventricular filling pressures (grade II to IV diastolic dysfunction)**

**Interim evaluation (after echocardiography)**

- **Symptomatic response to diuretic drugs**
- **Exaggerated increase in systolic blood pressure with exercise**
- **Rereview of chest radiograph consistent with heart failure**

**Source:** From Ref. 76.
Systolic Heart Failure and Pulmonary Hypertension: Evaluation for Cardiac Transplantation

PH secondary to LV systolic dysfunction is a common complication in patients presenting with advanced HF and RV dysfunction (75,84). This process is mainly due to chronic increase in left-sided filling pressure resulting in perturbations in vascular mediators resulting in increase in vascular tone and structural remodeling. Typically the duration and severity of heart failure is an important determinant that governs the degree of these changes, with abnormalities in vascular tone being the early phase that is manageable with vasodilator agents (reversible PH), and structural changes appearing at more advanced stage usually not amenable to pharmacological maneuvers (fixed PH) (85,86).

Preoperative assessment of PH is a critical part of heart transplant (HTx) evaluation since preoperative PVR is an independent risk factor for early mortality after HTx (87). The degree of pulmonary vascular changes in the recipient is a major factor that determines the RV function post transplant and RV dysfunction accounts for both early deaths and postoperative complications (88). It is imperative to determine if the elevation in PVR is reversible and manageable with pharmacological therapies to avoid donor heart RV failure from subjecting to acute rise in pulmonary vascular tone of the recipient.

There is no absolute or reliable hemodynamic threshold below which RV failure is avoidable or beyond which it is certain to occur. The relationship between PH and mortality after HTx is a continuous positive one with the risk of death rising with increase in PASP and PVR for early and late transplant outcomes (88). In determining hemodynamics, the values reported to define “reversible” from “fixed” PH are variable and is center dependent.

1. PASP > 50 mmHg despite optimal vasodilation has been reported to be a relative contraindication to HTx (89).
2. Different PVR values have been reported to be associated with adverse outcome. PVR > 4 WU has been reported to be an independent predictor of early post transplant mortality (90). PVR < 5 WU at rest or < 3 WU with maximal vasodilatation is considered favorable.
3. TPG is viewed by some centers to be a more reliable marker for pulmonary vascular tone since it does not rely on CO. TPG /C21 > 16 mmHg has been shown to have an increased risk of postoperative RV failure (84).

Agents used to test vasoreactivity differ widely ranging from systemic vasodilators to more selective pulmonary vasodilators. One needs to consider various factors which include systemic blood pressure, severity of PH, CO, and clinical stability in determining the optimal agent (91,92). Some investigators have also advocated combining more than one agent to target multiple hemodynamic abnormalities to determine degree of reversibility. For patients who are determined to have severe PH despite maximal medical therapy, consideration for mechanical unloading with left ventricular assist

**Figure 10.5** Diagnostic approach to distinguish between PAH and PH caused by diastolic left heart disease. **Abbreviations:** DHF, diastolic heart failure; Dx, diagnosis; EF, ejection fraction; HF, heart failure; NTG, nitroglycerine; OMT, optimal medical therapy; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; RHC, right heart catheterization; WU, Wood units. **Source:** From Ref. 76.
devices (LVAD) is the next step. Mechanical unloading of the LV has been shown to decrease PVR by inducing reverse remodeling of pulmonary vascular through alleviating chronic elevation of left-sided filling pressures and by improving oxygenation and CO. These effects are not immediate and optimal changes reported to occur between two and six months of support. Successful orthotopic HTx after LVAD placement in patients with fixed PH have been reported (93–95). Both pulsatile and continuous flow VAD systems have been used.

CLINICAL ASPECTS

Classification of Pulmonary Hypertension

The clinical classification of PH from the 4th World Symposium at Dana Point has several modifications to the Venice Classification (Table 10.3) (8). Some key changes include subclassification of heritable PH and addition of chronic hemolytic anemia and schistosomiasis to the associated PAH category under WHO Group 1.

**Pulmonary Arterial Hypertension**

IPAH is PAH of unknown cause, a diagnosis of exclusion determined after a thorough evaluation. IPAH is more common among young females as reported from the NIH registry (F:M 1.7:1, mean age 37 years), though the age of affected individuals appear to be increasing likely reflecting increased awareness of the disease and improved survival with therapy (5,8,9). Heritable PAH has been reported in 6% to 10% of patients with PAH (5). It is characterized by autosomal dominant transmission, incomplete penetrance and genetic anticipation, in which family members of successive generation who develop PAH manifest at an earlier age with more aggressive disease course. The mutation in BMPR2 loci is the most widely studied and has been identified not only in patients with familial PAH (50–90%) but also among 25% of IPAH patients, raising the possibility of spontaneous mutations in some individuals or familial transmission among members without clinically evidence disease (13,96,97).

Although the incidence of IPAH is rare, PAH has been identified to occur with increased frequency in the presence of CTD, HIV, portal hypertension and CHD. Patients with CTD, especially the scleroderma spectrum, comprise the largest subgroup of population affected. Patients with PAH associated with CTD have poorer survival than IPAH patients; median survival of 12 months have been reported compared with 2.6 years in IPAH patients (5,98). Furthermore, current therapies are less effective in CTD patients compared with IPAH patients (99).

PAH associated with CHD occurs as a result of high pulmonary blood flow from systemic-to-pulmonary shunts and from smaller lesions such as atrial septal defect. Portopulmonary hypertension is PAH that occurs in association with liver disease and portal hypertension and is reported in 4% to 15% of patient being evaluated for liver transplantation (100,101). Portal hypertension results in a high cardiac output state, so in

### Table 10.3 Clinical Classification of PH from Dana Point Meeting, 2009

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Idiopathic PAH</td>
</tr>
<tr>
<td>1.2 Heritable</td>
</tr>
<tr>
<td>1.2.1 BMPR2</td>
</tr>
<tr>
<td>1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic Telangiectasia)</td>
</tr>
<tr>
<td>1.2.3 Unknown</td>
</tr>
<tr>
<td>1.3 Drug- and toxin-induced</td>
</tr>
<tr>
<td>1.4 Associated with</td>
</tr>
<tr>
<td>1.4.1 Connective tissue diseases</td>
</tr>
<tr>
<td>1.4.2 HIV infection</td>
</tr>
<tr>
<td>1.4.3 Portal hypertension</td>
</tr>
<tr>
<td>1.4.4 Congenital heart diseases</td>
</tr>
<tr>
<td>1.4.5 Schistosomiasis</td>
</tr>
<tr>
<td>1.4.6 Chronic hemolytic anemia</td>
</tr>
<tr>
<td>1.5 Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td>1.5.1 Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)</td>
</tr>
<tr>
<td>2. Pulmonary hypertension due to left heart disease</td>
</tr>
<tr>
<td>2.1 Systolic dysfunction</td>
</tr>
<tr>
<td>2.2 Diastolic dysfunction</td>
</tr>
<tr>
<td>2.3 Valvular disease</td>
</tr>
<tr>
<td>3. Pulmonary hypertension due to lung diseases and/or hypoxia</td>
</tr>
<tr>
<td>3.1 Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>3.2 Interstitial lung disease</td>
</tr>
<tr>
<td>3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
</tr>
<tr>
<td>3.4 Sleep-disordered breathing</td>
</tr>
<tr>
<td>3.5 Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td>3.6 Chronic exposure to high altitude</td>
</tr>
<tr>
<td>3.7 Developmental abnormalities</td>
</tr>
<tr>
<td>4. Chronic thromboembolic pulmonary hypertension (CTEPH)</td>
</tr>
<tr>
<td>5. PH with unclear multifactorial mechanisms</td>
</tr>
<tr>
<td>5.1 Hematological disorders: myeloproliferative disorders splenectomy.</td>
</tr>
<tr>
<td>5.2 Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis</td>
</tr>
<tr>
<td>5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders</td>
</tr>
<tr>
<td>5.4 Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure on dialysis.</td>
</tr>
</tbody>
</table>

**Abbreviation:** PH, pulmonary hypertension.

**Source:** From Ref. 8.
general, the cardiac outputs of portopulmonary hypertension patients tend to be higher than other types of PAH. A normal cardiac output in a portopulmonary hypertension patient suggests right ventricular dysfunction. The degree of PAP elevation (mPAP > 35 mmHg) has significant impact on peri-transplant morbidity and survival (102). Regarding toxic agents, a definite association between ingestion of amphetamine-derived drugs and PAH has been established, the most notable ones being appetite suppressants aminorex, fenfluramine, and dexfenfluramine (24). All of these agents have been removed from the market after studies demonstrated linkage between these drugs and PAH. An association between methamphetamine use and PAH has been reported recently as well (8,103). HIV infection is a risk for PAH with approximately 1 of 200 patients being affected (104). Among patients with PAH, survival is the worst for patients with CTD and HIV (61).

**Evaluation of PAH**

Evaluating patients with suspected PH encompasses recognizing at risk population, screening for PH, identifying the underlying cause or associated disease, and confirming diagnosis and assessing prognosis. A diagnostic approach including pivotal and contingent tests and rationale is shown in Figure 10.6. The right heart catheterization is required to make the diagnosis of PAH.

**Prognostic Indicators in PAH**

Prognosis in PAH is related to RV function and indicators utilized to assess include WHO FC, exercise capacity, and hemodynamics (16). The importance of RAP, mPAP, and CO as critical determinants of outcome as initially shown in the NIH registry has been discussed in prior section (“Assessment of Prognosis”). The NIH registry also demonstrated that survival correlated directly with FC: for patients who were in FC I or II at presentation, the median survival was almost 6 years versus 2.5 years for patients in FC III and six months for patients presenting in FC IV (6). Even on therapy, FC was shown to be an important determinant in two large retrospective studies among IPAH patients receiving epoprostenol in that prognosis was worse for patients who were initiated on therapy with more advanced symptoms (62,105). Furthermore, patients who improved to FC I or II after the initial period (3–17 months) had a significantly better long-term prognosis than those who remained in FC III or IV on IV epoprostenol.

The six-minute walk distance (6MWD) is the most commonly used test to evaluate exercise capacity in PAH. In the first PAH trial evaluating treatment with epoprostenol, baseline 6MWD was a powerful predictor of survival (106). Sitbon and colleagues report among patients treated with epoprostenol, the 6MWD performed after three months of therapy correlated with long-term survival; specifically, patients who walked >380 m demonstrated a significantly better outcome than the cohorts who did not (62). Used less commonly mainly because of patient limitations, cardiopulmonary exercise testing has also been studied and one study demonstrated that maximum oxygen consumption of >10.4 mL/kg/min and peak systolic BP > 120 mmHg to be favorable indicators (107).

Echocardiographic findings correlating with prognosis include measurements reflecting right-sided cardiac function (right atrial and right ventricular size, Doppler parameters and indices of RV function, eccentricity index) and presence of pericardial effusion (108,109). Biomarkers, specifically brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) have been shown to correlate with outcome, though the specifics of how to utilize this marker is still under investigation (110–112). It is recommended that a composite of subjective and objective data be used to determine risk of the patient which can be used to choose appropriate therapy and as a guide to determine response to treatment (Table 10.4) (16,68).

**Treatment of PAH**

**Prostanoids**

**Epoprostenol**

IV epoprostenol improves FC, exercise capacity, hemodynamics, and survival in IPAH, which was demonstrated in an open-label, randomized trial of 81 FC III and IV IPAH patients comparing IV epoprostenol with conventional treatment (106). All eight deaths during the 12-week trial period occurred among patients who were randomized to conventional therapy, which resulted in a survival benefit (P = 0.003). IV epoprostenol has also been studied in PAH associated with CTD demonstrating marked improvements in 6MWD and hemodynamics but no effect on mortality in a 12-week, open-label randomized trial (113). Observational studies have also reported beneficial effects of IV epoprostenol in patients with PAH related to HIV, CHD, and portopulmonary hypertension (114–116). Two longer-term observational studies have confirmed the chronic benefits of IV epoprostenol in IPAH patients, specifically improvements in survival compared with historical controls, FC, 6MWD, and hemodynamics (62,105).

IV epoprostenol is a challenging therapy to implement because of its short half-life (<6 minutes) and the need for continuous IV infusion via a tunneled catheter. Each patient must learn the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump, and care of the central venous catheter. Incidences of sepsis and catheter related infections are not negligible (0.1–0.6 case per patient year) and can cause significant morbidity (105). Any interruption of the drug infusion can be potentially life threatening because of short half-life of epoprostenol and potential for rebound pulmonary hypertension. IV epoprostenol is commonly started in the hospital at a dose of 2 ng/kg/min and titrated on the basis of PAH symptoms and side effects. Most experts consider optimal dose of chronic therapy to be between 25 and 40 ng/kg/min. Chronic overdose can lead to high cardiac output failure and lead to recurrent symptoms (117). Common side effects include headache, jaw pain, diarrhea, nausea, flushing, rash, and musculoskeletal pain. Because of the complexity of administering this therapy, epoprostenol use should be limited to experienced centers (Table 10.5) (118).

**Treprostinil**

Treprostinil is a PGI2 analogue with a half-life of four hours which was studied as a continuous subcutaneous infusion in a 12-week, placebo-controlled, randomized trial of 470 patients with FC II, III, or IV PAH (119). There was a modest but statistically significant median increase of 16 m in 6MWD; the improvement was dose related and patients in the highest dose quartile reported close to 40 m improvement. However, the major hindrance of using subcutaneous treprostinil is the pain and erythema at the infusion site, which was reported by 85% of the patients and limited the dose increases. It is now recognized that site pain is not dose related, and that some patients feel better after proper dose escalation which helps them to improve their PAH symptoms.

Because of limitation of subcutaneous delivery system, IV treprostinil was studied in a 12-week open-label trial of
16 patients (120). It demonstrated improvements in 6MWD (82 m) and hemodynamics. In another open-label trial, 31 FC II and III PAH patients on IV epoprostenol were transitioned to IV treprostinil (121). Twenty-seven patients completed the transition, and four were transitioned back to epoprostenol. 6MWD measurements were maintained among patients who completed the transition; however, there was a modest increase in mPAP and decrease in CI. Noteworthy is that the dose of IV treprostinil at the end of the study period was more than twice the dose of epoprostenol at the start of the study. Inhaled treprostinil was recently approved by the FDA and oral treprostinil is currently undergoing active clinical investigation (Table 10.5).

**Inhaled Illoprost** Illoprost is a stable PGI2 analogue that is delivered via an aerosolized device six to nine times per day. Illoprost was studied in a 12-week, multicenter, placebo-controlled,
randomized trial of 207 FC III and IV patients with either IPAH, PAH associated with CTD or appetite suppressants, or PH related to inoperable chronic thromboembolic disease (122). Treatment with iloprost resulted in meeting a novel composite end point of improvement in FC by at least one level and increase in 6MWD by at least 10% in the absence of clinical deterioration (16.8% vs. 4.9%, treated vs. placebo, P = 0.007). It was generally well tolerated with coughing, headache and flushing occurring as most common side effects (Table 10.5).

**Table 10.4 Risk Assessment for PAH**

<table>
<thead>
<tr>
<th>Determinates of risk</th>
<th>Lower risk (good prognosis)</th>
<th>Higher risk (poor prognosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evidence of RV failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>Gradual</td>
<td>Rapid</td>
</tr>
<tr>
<td>WHO class&lt;sup&gt;a&lt;/sup&gt;</td>
<td>II, III</td>
<td>IV</td>
</tr>
<tr>
<td>6MW distance&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Longer (greater than 400 m)</td>
<td>Shorter (less than 300 m)</td>
</tr>
<tr>
<td>CPET</td>
<td>Peak VO&lt;sub&gt;2&lt;/sub&gt; greater than 10.4 mL/kg/min</td>
<td>Peak VO&lt;sub&gt;2&lt;/sub&gt; less than 10.4 mL/kg/min</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Minimal RV dysfunction</td>
<td>Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP less than 10 mmHg, CI greater than 2.5 L/min/m²</td>
<td>RAP greater than 20 mmHg, CI less than 2.0 L/min/m²</td>
</tr>
<tr>
<td>BNP&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Minimally elevated</td>
<td>Significantly elevated</td>
</tr>
</tbody>
</table>

Note: Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions.

<sup>a</sup>WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class.

<sup>b</sup>6MW distance is also influenced by age, gender, and height.

<sup>c</sup>As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.

**Abbreviations:** 6MW, six-minute walk; BNP, brain natriuretic peptide; CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO<sub>2</sub>, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; WHO, World Health Organization; PAH, pulmonary arterial hypertension.

**Source:** Reprinted from Refs. 16 and 68.

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**Endothelin Receptor Antagonists**

**Bosentan**

Bosentan, a nonselective endothelin receptor blocker, was the first orally available therapy approved for PAH. It was studied in two placebo-controlled, randomized trials of FC III or IV patients with either PAH or PAH related to CTD (123,124). In the pivotal BREATHE-1 trial, bosentan improved the primary end point of 6MWD by 36 m, whereas placebo patients deteriorated by 8 m (P = 0.0082). Bosentan also improved the composite end point of time to clinical worsening, which was defined as death, initiation of IV epoprostenol, hospitalization for worsening PAH, lung transplantation or atrial septostomy. Long-term observational findings in survival of patients treated with bosentan as first line therapy have shown improved survival compared with expected outcome based on the NIH registry equation (125). Bosentan was shown to be effective in mildly symptomatic patients in EARLY study, a six-month, multicenter, placebo-controlled trial, which enrolled 168 FC II PAH patients (126). The results demonstrated a significant decrease in PVR, which was the primary end point to evaluate treatment effects on vascular remodeling, and a significant delay in clinical worsening.

Bosentan is mainly metabolized through the hepatic P450 enzymes and increase in hepatic transaminases >3 times the upper limit of normal has been reported in 10% to 12% (124). Bosentan is teratogenic and may decrease the efficacy of hormonal contraception so women of child-bearing age must be counseled to use dual contraception for birth control. Other side effects include headache, flushing, lower-extremity edema, and anemia. Treatment with bosentan requires monitoring of liver function tests on a monthly basis, and pregnancy tests on women of child-bearing potential on a monthly basis, and hemoglobin/hematocrit on a quarterly basis. Patients should be counseled regarding potential for lower-extremity edema, especially in the initial weeks of therapy, and possible need for diuretic adjustments. Glyburide and cyclosporine A are contraindicated with bosentan because of significant drug-drug interactions (Table 10.5).

**Ambrisentan**

Ambrisentan is a selective ET<sub>A</sub> receptor antagonist studied in two placebo-controlled, randomized, 12-week study of WHO Group I patients (ARIES-1 and ARIES-2), which were conducted in the United States and Europe/South America, respectively (127). The treatment resulted in a significant improvement in 6MWD and delay in time to clinical worsening in all treatment groups. Ambrisentan is available in 5-mg and 10-mg oral tablets taken once a day.

The incidence of hepatic transaminase elevation >3 times the upper limit of normal was 0.8% for patients receiving ambrisentan (127). This was further investigated in a recently published study of 36 patients, who did not tolerate bosentan or sitaxsantan because of hepatic transaminase increases and were placed on ambrosentan therapy (128). Ambrisentan therapy was tolerated well in this group. Peripheral edema is another side effect of the ERA class and was reported in mild to moderate severity in the clinical trials (127). An increase report of incidences of peripheral edema during post marketing use has prompted the FDA to issue a labeled warning for elderly patients (129). The mechanisms behind this observed edema is currently undergoing evaluation. No drug interaction was found with sildenafil (129). Ambrisentan is teratogenic. Monthly blood test for liver function tests and pregnancy tests for women of child-bearing age is required (Table 10.5).
Phosphodiesterase-5 Inhibitor

Sildenafil
Sildenafil was studied in a 12-week randomized placebo-controlled study of 278 symptomatic PAH patients (130). The primary end point of 6MWD improved by 45, 46, and 50 m in the 20-, 40-, and 80-mg groups, respectively ($P < 0.001$). There was no change in the time to clinical worsening at week 12. The result of 222 patients who completed one year of treatment demonstrated that the 6MWD improvement was maintained; however, nearly all patients were titrated up to a dose of 80 mg three times a day. Side effects include headache, flushing, dyspepsia and epistaxis (Table 10.5).

Tadalafil
Tadalafil, a PDE5-Inh with a longer half-life than sildenafil, was recently studied in a 16-week, double-blind, placebo-controlled trial among 405 PAH patients using 2.5-, 10-, 20-, and 40-mg tablets once a day (131). The highest dose of tadalafil

### Table 10.5  Approved Treatments for PAH and Commonly Reported Side Effects

<table>
<thead>
<tr>
<th>Drug, class</th>
<th>Dose/route of administration</th>
<th>Common side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol (Flolan), prostanoid</td>
<td>Start 2 ng/kg/min intravenously and titrate following side effect and PAH symptoms</td>
<td>Prostanoid side effectsa Leg pain (more common than with epoprostenol)</td>
<td>Central tunneled catheter needed. Long-term data available. Effective in advanced PAH. Because of therapy being complicated, it is recommended that patients be referred to specialist PAH centers. Injection site pain affects majority of patients. Experienced centers have reported successful outcome in managing patients with injection site pain. Long-term survival data available. More convenient for chronic infusion than epoprostenol. Revised recommendations for central tunneled catheter care (see text). Rapid inhalation time.</td>
</tr>
<tr>
<td>Treprostinil (Remodulin), prostanoid</td>
<td>Start 2 ng/kg/min intravenously and titrate following side effect and PAH symptoms</td>
<td>Prostanoid side effectsa (generally less severe) and cough</td>
<td>Well tolerated with oral PAH therapies. Compliance can be an issue with need for frequent treatments. Recent approval of 20 mcg/mL concentration to decrease treatment duration.</td>
</tr>
<tr>
<td>Treprostinil (Tyvaso), prostanoid</td>
<td>6 mcg per inhalation; titrate to target maintenance dosage of nine inhalations</td>
<td>Prostanoid side effectsa (generally less severe) and cough</td>
<td>Well tolerated with oral PAH therapies. Compliance can be an issue with need for frequent treatments. Recent approval of 20 mcg/mL concentration to decrease treatment duration.</td>
</tr>
<tr>
<td>Illoprost (Ventavis), prostanoid</td>
<td>5 mcg per inhalation 6–9 inhaled treatments daily</td>
<td>Prostanoid side effectsa (generally less severe) and cough</td>
<td>Well tolerated with oral PAH therapies. Compliance can be an issue with need for frequent treatments. Recent approval of 20 mcg/mL concentration to decrease treatment duration.</td>
</tr>
<tr>
<td>Bosentan (Tracleer), ERA</td>
<td>62.5 mg twice daily oral x 4 wk, then 125 mg twice daily if LFT normal</td>
<td>Headache, dizziness, edema</td>
<td>Monthly LFTs required. Contraindicated with cyclosporine and glyburide. Decreases effectiveness of oral hormonal contraceptives. Longer-term observational survival data available. Decrease in pulmonary vascular resistance in FC II patients.</td>
</tr>
<tr>
<td>Ambrisentan (Letairis), ERA</td>
<td>5 or 10 mg once daily oral</td>
<td>Peripheral edema, nasal congestion, sinusitis</td>
<td>Monthly LFTs required, but lower incidence of LFT abnormalities compared with other ERAs. Higher incidence of edema in elderly patients compared with other ERAs. May decreases effectiveness of oral hormonal contraceptives. Longer-term observational survival data available. No drug interaction observed in combined treatment with sildenafil.</td>
</tr>
<tr>
<td>Sildenafil (Revatio), PDE5-Inh</td>
<td>20 mg thrice daily oral</td>
<td>Epistaxis, headache, flushing, diarrhea</td>
<td>Contraindicated with nitrates. Some patients may need up titration of dose.</td>
</tr>
<tr>
<td>Tadalafil (Adcirca), PDE5-Inh</td>
<td>40 mg once daily oral</td>
<td>Headache, myalgia, flushing</td>
<td>Contraindicated with nitrates.</td>
</tr>
</tbody>
</table>

aSide effects related to prostacyclin: jaw pain, diarrhea, flushing, headache, nausea. 

Abbreviations: ERA, endothelin receptor antagonists; LFT, liver function test; PAH, pulmonary arterial hypertension; PDE5-Inh, phosphodiesterase-5 inhibitor. 

Source: From Ref. 118.
demonstrated a 41 m increase in 6MWD compared with 9 m for placebo ($P < 0.001$). There was also a delay in the time to clinical worsening (defined as death, hospitalization, initiation of new PAH therapy, worsening WHO FC). Side effects include headache, diarrhea, nausea, back pain, dizziness, dyspepsia and flushing (Table 10.5).

**Conventional Treatment**

CCBs are recommended for patients who demonstrate responsiveness during an acute vasodilator testing (see Acute Vasodilator Test). Patients with IPAH who meet the criteria may be considered treatment with CCBs. Long acting nifedipine, diltiazem, or amlodipine is suggested. Verapamil should be avoided because of its potential negative inotropic effects. Patients need to be followed closely for efficacy and safety on CCBs. If a patient does not improve to FC I or II with CCBs, the patient should not be considered a chronic responder and PAH-directed treatment should be initiated.

Anticoagulation has been studied in two small uncontrolled trials in IPAH patients. On the basis of these studies, most experts recommend warfarin anticoagulation (68,132). The recommended targeted to international normalized ratio varies from 2.0 to 2.5 and 2.0 to 3.0 to 1.5 to 2.0 in some centers. In patients with APAH, anticoagulation is controversial with few data to support its use. In CTD and portopulmonary patients, the risk of gastrointestinal bleeding may be increased. Most experts recommend warfarin anticoagulation in APAH patients being treated with IV prostanoids in the absence of contraindicating factors.

Hypoxemia is a potent pulmonary vasoconstrictor and thus can contribute to progression of PAH. It is recommended that patients with PAH to maintain oxygen saturation $>90\%$ at all times though the use of supplemental oxygen in patients with Eisenmenger physiology is controversial. Diuretics are used to treat volume overload because of right heart failure. For diuretic naïve patients, slow initiation and monitoring of renal function are recommended with goal of attaining near-normal intravascular volume. In acute decompensated right heart failure and/or in presence of diuretic resistance, IV diuretics are needed. Although digoxin has not been well studied in patients with PAH, it is used with careful monitoring in low doses in the setting of refractory right heart failure and/or atrial arrhythmia.

**Figure 10.7** PAH evidence-based treatment algorithm. Drugs within the same grade of evidence are listed in alphabetical order and not order of preference. Not all agents listed are approved or available for use in all countries. *To maintain oxygen at 92%, +Investigational, under regulatory review. Abbreviations: APAH, associated pulmonary arterial hypertension; ERA, endothelin receptor antagonist; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; PAH, pulmonary arterial hypertension; PDE-5, phosphodiesterase type 5; SC, subcutaneous; WHO, World Health Organization. Source: From Ref. 9.
Combination Therapy in PAH

With the approval of therapies targeting different pathways, utilizing combination approach in the hope of improving outcome has attracted marked interest. The potential to increase efficacy by utilizing combination therapy must be measured against possible toxicity and drug-drug interactions. Several small, open-label observational studies reported potential benefit of combination treatment (133,134). Initial study, evaluating combining bosentan or placebo to FC III or IV patients receiving IV epoprostenol, failed to show benefit thought this study was underpowered (135). Two studies evaluated adding inhaled iloprost to bosentan therapy in a randomized, double-blind, placebo-controlled design. The STEP study enrolled 67 patients in a 12-week study which demonstrated safety as well as improvement in 6MWD (26 m, placebo corrected, \( P = 0.051 \)). The COMBI study which evaluated 40 patients failed to demonstrate benefit and the study was terminated (136,137). The largest completed combination trial in PAH to date is PACES study, which added adding sildenafil as add-on therapy to IV epoprostenol (138). This 16-week, multinational, double-blind, placebo-controlled study enrolled 267 patients who were on stable epoprostenol therapy. Patients were randomized to receive 20 mg three times a day titrated to 40- and 80-mg TID, at four week intervals, or corresponding placebo. At the end of 16 weeks, more than 80% of patients had reached the 80-mg TID dosing level. The primary end point was change in 6MWD and there was placebo-adjusted increase of 26 m in the subjects who received sildenafil. There were seven deaths in the placebo group and none among patients receiving sildenafil. Clinical worsening events defined as death, transplant, hospitalization, or an increase in epoprostenol dose, were significantly different in favor of the treated group. Several large studies are currently underway evaluating the effect of combining different classes of oral regimen including the COMPASS-2 trial (Effects of combination of bosentan and sildenafil versus sildenafil monotherapy on morbidity and mortality in symptomatic patients with PAH), which is the first morbidity/mortality driven trial focusing on combination therapy in PAH.

Treatment Algorithm and Assessing Response to Therapy

The most recent treatment guideline from the Dana Point meeting is shown in Figure 10.7 (9). Incorporating risk-based approach by combining known factors that determine prognosis in PAH in selecting therapy has been recommended and is widely utilized by clinicians (Fig. 10.8) (16). The ACCF/AHA...
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Table 10.6 Longitudinal Evaluation of Pulmonary Arterial Hypertension Patients on Therapy

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>Stable</th>
<th>Unstable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No increase in symptoms and/or decompensation</td>
<td>Increase in symptoms and/or decompensation</td>
</tr>
<tr>
<td></td>
<td>No evidence of right heart failure</td>
<td>Signs of right heart failure</td>
</tr>
<tr>
<td></td>
<td>FC II</td>
<td>FC IV(^a)</td>
</tr>
<tr>
<td></td>
<td>6MWD &gt; 400 m</td>
<td>6MWD &lt; 300 m(^b)</td>
</tr>
<tr>
<td></td>
<td>RV size/function normal</td>
<td>RV enlargement/dysfunction</td>
</tr>
<tr>
<td></td>
<td>RAP normal; CI normal</td>
<td>RAP high; CI low</td>
</tr>
<tr>
<td></td>
<td>BNP normal/stable or decreasing</td>
<td>BNP elevated/increasing</td>
</tr>
<tr>
<td></td>
<td>Oral therapy</td>
<td>IV prostacyclin and/or combination treatment</td>
</tr>
</tbody>
</table>

Frequency of evaluation
- Q 3–6 mo\(^a\)
- Every clinic visit
- Q 1–3 mo
- Every clinic visit
- Q 12 mo or center dependent
- Center dependent
- Q 6–12 mo or center dependent
- Center dependent
- Q 6–12 mo or clinical deterioration

Note: For patient in the high-risk category, consider referral to a PH specially center for consideration for advanced therapies, clinical trials, and/or lung transplantation.

\(^a\)The frequency of follow-up evaluation for patient in FC II and/or 6MWD between 300 and 400 m would depend on composite of detailed assessments on other clinical and objective characteristics listed.

\(^b\)For patient who remain stable on established therapy, follow-up assessments can be performed by referring physician(s) or PH specialty centers.

\(^c\)Echocardiographic measurement of PASP is estimation only and it is strongly advised not to rely on its evaluation as the sole parameter to make therapeutics decisions.

\(^d\)The utility of serial BNP levels to guide management in individual patients has not established.

Abbreviations: BNP, brain natriuretic peptide; CI, cardiac index; FC, functional class; 6MWD, six-minute walk distance; Q, every; RAP, right atrial pressure; PH, pulmonary hypertension; RV, right ventricle; IV, intravenous; mo, months.

Source: From Ref. 68.

2009 Expert Consensus Document recently published a guideline outlining recommendations in assessing response and following patients on therapy (Table 10.6) (68).

CONCLUSION

The field of PAH has advanced from a disease of little knowledge and treatment to improved understanding of the pathobiology with seven approved drugs targeting known identified pathways. As recognition and screening of PH increases, accurate diagnosis of PAH utilizing the proper techniques of RHC takes greater significance. Continued efforts are being pursued in several directions: to study other affected pathways in PAH and novel therapies to targeting the specific pathways; to update current epidemiology and treatment patterns; ongoing studies evaluating the efficacy and safety of using combination therapies in this complex disease. The study of patients being affected with disproportionate PH in association with underlying hypoxic lung disease, left-sided heart disease and chronic thromboembolic disease need to be further elucidated.

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INTRODUCTION

In 1929, Werner Forssmann published a radiograph of the successful right heart catheterization of himself (1). Subsequently Dickinson Richards and Andre Cournand used the heart catheter to make a series of seminal hemodynamic measurements in man resulting in the three men winning the Nobel Prize in Medicine in 1956 for their accomplishments. In 1951, the Gorlin Formula (2) for calculating cardiac valve area was published, and for the next three decades invasive hemodynamics held sway as the gold standard for assessing cardiac physiology and pathophysiology.

In the 1980s, the use of Doppler interrogation of the heart made assessment of cardiac physiology easily applied noninvasively. While at first there was serious debate about whether noninvasive measurements could be reliably substituted for invasive hemodynamics, the echocardiogram was eventually accepted then largely supplanted invasive hemodynamics. In fact, the 2006 AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease (3) gives invasive assessment of valve disease a class III recommendation (not indicated and possibly harmful) when there is no doubt about the diagnosis following clinical and noninvasive evaluations. On the other hand, it is a class I recommendation (indicated and beneficial) to obtain invasive hemodynamic data when the diagnosis is unclear. Thus, we currently rely on a progressively less practiced modality to help us solve our most important diagnostic dilemmas. The problem is compounded by a relative lack of teaching of hemodynamic principles in our cardiovascular medicine fellowships and by computers that allow calculations to be made without the operator understanding the pitfalls of such calculations. Thus, the gold standard of cardiac diagnosis is threatened with a good deal of tarnish. In this light, the following is a summary of the modern use of invasive hemodynamics in the assessment of valvular heart disease.

ASSESSMENT OF STENOTIC VALVES

Normal cardiac valves permit unidirectional circulatory flow at low resistance with equal pressure on both sides of an open valve. Even when these valves are narrowed to 50% of their normal aperture, only a small pressure gradient exists during flow. However, further narrowing results in progressively greater obstruction to flow and persistently higher and higher transvalvular pressure gradients. Because pressure gradient varies with flow, a gradient by itself may be an unreliable indicator of stenosis severity. Knowledge of this concept led to the use of valve area to help quantify stenosis severity.

Both invasive and noninvasive assessments of stenosis severity use the same hemodynamic principle to calculate valve area: Flow ($F$) = valve area ($A$) $\times$ flow velocity ($V$). Thus $A = F/V$. In the echo laboratory, $V$ is measured directly by Doppler ultrasonography. When using invasive hemodynamics, the pressure gradient across the valve is measured and converted to velocity where $V = 2\sqrt{P_1 - P_2}$. Here, $P_1 - P_2$ is the mean pressure gradient and $g$ is the acceleration due to gravity. This last term is incorporated because pressure is expressed in mmHg, which depends on the specific weight of mercury—mass $\times$ acceleration. Thus, in the catheterization laboratory, accurate calculation of valve area relies on an accurately determined pressure gradient, an accurate determination of flow [cardiac output (CO)], and an accurate formula that relates the two together.

AORTIC STENOSIS

Accurate Pressure Gradient Assessment

To record an accurate transaortic valvular pressure gradient, two properly placed catheters must be connected to two properly calibrated transducers, reporting to an accurate recording device. Alternatively, a pressure gradient may be recorded in patients in sinus rhythm during pullback of the catheter from the left ventricle (LV) to the aorta recognizing that a pullback determination is a “one-time” opportunity. If premature beats or any technical problems arise during the pullback the data are lost, necessitating recrossing the valve or abandoning the procedure.

Proper Catheter Placement

Figure 11.1 depicts the potential positions that might be used in recording a transvalvular pressure gradient, and most of them create erroneous data (4). Of the two potential positions for the LV catheter, the proper one is with the lumen placed in the body of the LV. As shown in Figure 11.2, in most patients with aortic stenosis (AS), a subvalvular gradient usually exists between the body of the LV and the LV outflow tract (5). This gradient does not represent subvalvular AS but rather occurs as blood normally accelerates into the outflow tract which is narrower than the body of the LV. If the LV catheter is placed in the outflow tract, or if the natural ejection of blood pushes the catheter there, the true LV-aortic (Ao) gradient can be underestimated by as much as 20 to 40 mmHg. The distal catheter should be placed in the proximal ascending aorta just distal to the valve. For convenience, some operators have used the side port on the femoral sheath to record the distal pressure. This practice is fraught with difficulty and should be avoided (6). By the time the pulse reaches the femoral artery (FA) the turbulent flow present above the valve has become relaminarized causing pressure recovery and a reduced pressure...
gradient. Because it takes a finite period of time for the pulse to reach the FA, it is impossible for LV and FA pressures to be simultaneous. This requisite misalignment overestimates the true pressure gradient. Unfortunately, manual realignment causes substantial underestimation of the gradient. Because invasive hemodynamics are only recorded when the diagnosis is in doubt, it is crucial to obtain the best data possible. This is done by obtaining pressures from two properly placed lumens (or transducers if micromanometer catheters are used). To place the lumens properly, either two separate catheters can be employed or a double lumen catheter is used. In either case, scrupulous attention to proper damping and catheter flushing are requisite to obtaining an accurate gradient.

**Accurate Transducer Calibration**

The most effective way to ensure accurate transducer calibration is to connect the transducer to a mercury manometer because pressure is defined as mmHg. The pressure displayed from the transducer must be identical to the reading from the mercury manometer, or if not, adjusted to be so. Frankly, this procedure is ignored in many laboratories, relying instead on the pressure recorder’s internal calibration device. If internal calibration is used, two absolute tenets must be observed. First, after the catheters (or double lumen catheter) are placed in the circulation, the closely approximated lumens must record identical pressures because in that position there can be no gradient. If the pressures are not identical, (i) ensure that the lines connecting the catheters to the transducers are properly flushed and free of kinks, (ii) be sure the zero references of the two transducers are accurate and identical, and (iii) recalibrate both transducers. If these steps do not mitigate the errors in the pressure being recorded, mercury calibration is then necessary. Second, the above process only proves that the catheters are recording identical pressures, but not necessarily that the pressures are accurate. To be certain that the pressures recorded invasively are at least in the “ballpark” of accuracy, their pressure should be similar to cuff pressure measured by sphygmomanometry.

It should be recognized that some recording devices falsely “assume” that the operator is going to use the FA as the distal recording site despite its inaccuracies. The recorder then offsets the distal pressure to compensate for the expected delay in registering it. The result will be that the upstroke of the Ao pressure will actually precede that of the LV pressure, an obviously physiologic impossibility leading to inaccurate pressure recording.

**Accurate Cardiac Output Determination**

The second datum crucial to the accurate assessment of stenosis severity is the CO. The gold standard for this determination is use of the Fick principle, which states that the oxygen consumed by the body is the product of O₂ delivery (CO) and O₂ extraction by the tissues. Thus, O₂ consumption = CO × (arterial O₂ – venous O₂ content, i.e., AO₂ – VO₂Δ). Rearranging the terms, CO = O₂ consumption/AO₂ – VO₂Δ. Expanding the latter term, AO₂ – VO₂Δ = (arterial O₂ saturation – venous O₂ saturation) × hemoglobin (Hb) concentration (g/dL) × 1.36 cc O₂/g Hb × 10 dL/L. The principles for the use of the Fick principle are (i)
accurate measurement of \(O_2\) consumption, (ii) accurate measurements of \(O_2\) saturations in arterial and venous blood (the latter best taken from the pulmonary artery where mixing is ideal), and (iii) an accurate measurement of hemoglobin concentration. Unfortunately, \(O_2\) consumption is rarely measured today but rather is assumed from standard tables usually estimated as function of body size and habitus in normal subjects. However, the patient with severe valve disease is hardly normal and significant error in \(CO\) determination and hence valve area determination arise when \(O_2\) consumption is estimated rather than measured by actual analysis of expired air (7). This error can be as much as 50%.

By far, the most commonly used method to determine \(CO\) is thermodilution.

\[
\text{CO}_{TD} = \frac{V_i(T_B - T_i)(S_1 \cdot C_t/S_B \cdot C_B)60(\text{sec}/\text{min})}{\int_0^{t_f} \Delta T_B/\Delta t \, dt}
\]

where \(T_B\) is the temperature of blood before injection, \(T_i\) is the temperature of the injected saline, \(S_1\) and \(S_B\) are the specific gravities of the injectate and blood, respectively, \(C_t\) and \(C_B\) are the specific heats of the injectate and blood, respectively, and \(\int_0^{t_f} \Delta T_B/\Delta t \, dt\) is the area under the time-temperature curve recorded by the thermister at the end of the thermodilution catheter. When cold saline is injected into the pulmonary artery the saline mixes with the blood and cools it. The larger the blood pool and the faster the blood flow is, the smaller will be the change in downstream blood temperature, thus the area under the time-temperature curve will be smaller causing the calculated \(CO\) to be larger than when the blood volume and rate of flow are less. In general, thermodilution is accurate, but pitfalls exist. The tacit assumption is that all of the coldness of the injectate is transferred to the blood stream. However, when \(CO\) is low (an obvious consequence of severe AS), the right atrium and ventricle absorb some of the cold, warming up the blood so that the time-temperature curve area will be factiously small. Other causes of inaccuracy include faulty thermisters, tricuspid regurgitation, and intracardiac shunts.

The Gorlin Formula

In 1951, the Gorlins published their formula for calculating valve area (4).

\[
A = \frac{F}{C_v \sqrt{2gh \cdot C_s}} = \frac{F}{C_v \sqrt{2 \cdot 980 \cdot h}} = \frac{F}{(C(44.3))^{1/2}}
\]

where \(F\), flow; \(C_v\) the constant of velocity dissipation; \(C_s\), constant of orifice contraction; \(g\), acceleration due to gravity, and \(h\), transvalvular pressure gradient (2). \(C_s\) accounts for the loss of energy as blood flows through the valve since not all of the driving gradient is converted to flow. \(C_v\) accounts for the fact that as blood flows through an orifice it tends to stream through the middle so that the physiologic aperture is less than the anatomic one. Because flow only occurs when the valve is open during each beat, flow = \(CO\)/heart rate \times flow duration. Aortic valve area (AVA) =

\[
A = \frac{CO}{(\text{SEP})(HR)} \quad \text{AVA} \quad \text{(3)}
\]

where SEP is systolic ejection period.

When the Gorlins devised their formula it was considered malpractice to cross the Ao valve retrogradely as it is done today and other methods for entering the LV had not yet been perfected. Their formula was vetted against data from patients with mitral stenosis (MS) where they assumed a left ventricular end diastolic pressure of 10 mmHg and substituted wedge pressure for left atrial pressure (LAP) to obtain the transmitral gradient. The actual mitral valve area (MVA) was measured from autopsy or surgical specimens and the data compared with their calculations. They then substituted an empirical constant (\(C\)) for \(C_v\) and \(C_s\). The empirical constant simply reduced the calculated valve area to a value closer to the actual measured valve area. However, the Gorlins had no data for developing a similar empiric constant for the Ao valve so they simply assumed a constant of 1.0 warning that when data became available the constant should be calculated, but to this day it never has been.

Flow Dependence of Calculated Aortic Valve Area

It has been well demonstrated that calculated Ao valve area may be quite flow dependent at C0s of <5.0 L/min, with AVA varying directly with flow (8). Increased AVA with increasing flow may be real or factitious. It could be that low CO produced by a weakened LV is unable to fully open a moderately but not severely stenotic Ao valve. As output is increased by exercise or infusion of positive inotropic drugs, the valve is opened more widely and output increases more than gradient causing an increase in calculated AVA that truly reflects increased orifice area. Conversely, it may be that problems with the Gorlin Formula cause calculated AVA to be flow dependent, either because it assumes constant flow or because the discharge coefficients were never calculated. Existing data supports both viewpoints. One recommended method for circumventing this problem is to calculate AVA at increasing outputs, constructing a relationship to project what the AVA would be at an output of 5.0 L/min, where AVA becomes less flow dependent (8). Flow dependence of calculated AVA is rarely a problem when mean gradient exceeds 40 mmHg since in such cases AVA almost always falls in the severe range of AS irrespective of CO.

Assessment of Inotropic Reserve

The outcome of aortic valve replacement (AVR) for patients with AS is usually excellent, resulting in substantial prolongation of life, a dramatic improvement in symptoms, and an improvement in LV function (9). Even when preoperative ejection is markedly reduced, ejection fraction (EF) may return to normal following removal of a large transvalvular gradient and the afterload that accompanies such a gradient (10). However, this is not the case in patients with a low gradient (<30 mmHg mean gradient) and low EF (<0.30) (11,12). Such patients have severe myocardial dysfunction and a poor prognosis. However, some such patients may improve substantially following AVR. Many are patients that have inotropic reserve (Fig. 11.3) (13). If stroke volume increases by 20% or more during the infusion of dobutamine and gradient increases concomitantly, prognosis following AVR is acceptable. For patients lacking inotropic reserve, operative risk is as high as 30% although even then some patients still improve if they survive AVR. A third group of patients exists where stroke volume increases but gradient does not, resulting in a large increase in calculated AVA (14). It is thought that such patients have moderate but not severe AS and primary muscle disease. When increased output is pushed through such a valve it opens more widely (see above). In such
cases (termed pseudo-AS) (15), it is believed, but not certain, that AVR would not be of benefit since it is myocardial disease rather than valve disease which lies at the crux of the problem.

While inotropic reserve is often tested for in the echocardiography laboratory, the catheterization laboratory is also ideal for making such determinations since careful hemodynamic measurements can be made before and during the inotropic challenge. Further, one cause of failed inotropic reserve can be the presence of obstructive coronary artery disease where increasing intropy can induce ischemia leading to misinterpretation of the test results. In the catheterization laboratory, coronary arteriography can be performed to establish the presence or absence of coronary disease allowing for better understanding of the results of the inotropic challenge.

MITRAL STENOSIS
The hemodynamic determination of MVA in MS employs the same principles as the hemodynamic determination of AS severity. It requires an accurate transmirtal valvular gradient, an accurate CO, and an accurate formula relating the two.

Accurate Pressure Gradient
In common practice, the transmirtal gradient is obtained using direct measurement of LV pressure, while pulmonary capillary wedge pressure (PCWP) is used as a surrogate for LAP. While PCWP may overestimate LAP and therefore overestimate the gradient and the severity of MS, overestimation is minimized to a few millimeters of mercury when careful technique is followed (16). In most labs, PCWP is obtained using a Swan-Ganz balloon-tipped catheter. Once the balloon is inflated, the catheter is advanced to the wedge position at which time the pressure wave form changes from that of a pulmonary artery tracing to that of the PCWP. However, the change in wave form does not by itself guarantee that the catheter is fully wedged and that an accurate LAP is being measured. To ensure that the catheter is truly wedged, it is necessary to confirm the wedge position by withdrawing highly oxygen-saturated left atrial blood from the catheter while it is wedged. When comparison of PCWP with direct measurement of LAP is made using this technique the difference is usually less than 3 mmHg, while comparisons made in the absence of oxymetric confirmation show larger overestimation of LAP by PCWP (16).

Exact calibration and zeroing of the transducers is crucial in establishing the transmirtal gradient. Whereas an error of 3 to 4 mmHg would only rarely affect clinical decisions in AS, this magnitude of gradient could be one-third of the total in MS and lead to serious misdiagnosis.

The Gorlin Formula in MS
The Gorlin formula applied to the mitral valve is

$$\Delta P = \frac{CO/\sqrt{HR}\times DFP}{[MVA\times(44.3\times0.85)]}$$

where DFP is the diastolic filling period and 0.85 is the empiric constant derived by the Gorlins. MVA calculated by the Gorlin formula is generally less flow dependent than calculated AVA, and calculated MVA usually compares well to actual planimetered measurements of MVA (17). Why there is better agreement with invasive data used to calculate MVA and noninvasive techniques than for AVA is uncertain. Perhaps it is due to employment of the empiric constant or perhaps the MVA changes less than does AVA with flow or perhaps it is a combination of both phenomena.

Shortcut for Calculating AVA and MVA: the Hakki Formula
Because the heart rate, filling time, and square root of the acceleration due to gravity typically equal a similar constant in most patients, a rough approximation of valve area can be made simply by dividing the CO (in liters) by the square root of the gradient (18). This shortcut is useful in making a quick ballpark estimation of valve stenosis severity in the catheterization laboratory before off-line calculations can be employed.

TRICUSPID STENOSIS
Tricuspid stenosis (TS) is rare today in developed nations because its major cause, rheumatic heart disease, is also rare. TS may also result from carcinoid syndrome. The diagnosis is usually made echocardiographically and its clinical significance is usually well defined at the bedside by examination of the neck veins from which central venous pressure can be estimated. If the diagnosis is uncertain, invasive hemodynamics may be helpful. A double lumen catheter (or separate right atrial and right ventricular catheters) is advanced across the tricuspid valve so that one lumen is positioned on either side of the valve and the gradient is recorded. Since there is no agreed on valve area that constitutes severe TS, severity is estimated from the gradient alone. A mean gradient of >5 mmHg is clinically important as it will yield a systemic venous pressure >10 mmHg at rest, usually enough venous hypertension to cause symptoms.

PULMONARY STENOSIS
The severity of pulmonary stenosis is inferred from the magnitude of the transvalvular gradient. Mean gradients of less than 25 mmHg are considered hemodynamically insignificant.
while gradients in excess of 75 mmHg indicate severe disease requiring intervention. Mean gradients between 25 and 75 mmHg are intermediate with a decision to intervene based on symptomatology (19).

VALVULAR REGURGITATION

Both the invasive and noninvasive assessment of lesion severity for regurgitant lesions tends to be less accurate than is the assessment of valvular stenosis. While relatively precise methods for regurgitation severity are available, they are more difficult to apply than are the quantitative approaches to stenosis severity. Thus, uncertainty about lesion severity following noninvasive evaluation is not uncommon for Ao and mitral regurgitation (MR), in turn necessitating invasive evaluation. In the catheterization laboratory, evaluation of pressures and wave forms at rest and with exercise, quantification of regurgitant flow and regurgitant fraction (RF), and visualization of the regurgitant flow contribute to the assessment of regurgitant severity.

Wave Forms

Aortic Regurgitation

Figure 11.4 shows some of the classic features of the hemodynamics of aortic regurgitation (AR) (15). FA systolic pressure is about 50 mmHg greater than LV systolic pressure (Hill’s sign). The mechanism of this phenomenon is not entirely clear. It is postulated that standing waves along the Ao periphery sum with the systolic pressure wave produced by the increased total stroke volume of AR to augment Ao systolic pressure as it moves down the aorta to the FA.

Ao diastolic pressure and LV diastolic pressure equalize (diastasis) because the physical barrier between the aorta and LV is largely removed. In turn there is a rapid rise in LV diastolic pressure because the LV is filling from both the LA and from the aorta. In chronic AR there is usually a very wide pulse pressure indicative of the large total stroke volume ejected into the aorta.

Mitral Regurgitation

Much has been written about the implications of a large v wave in the LA (or PCWP) pressure tracing with regard to the severity of MR (20). In fact, the presence of a large v wave is neither sensitive nor specific for the presence of severe MR. The v wave height is related to LA systolic volume and compliance. A large regurgitant volume (RV) and normal or low LA compliance will yield a large v wave. However, when severe MR coexists with a large compliant LA, the v wave may be of normal amplitude. On the other hand, large v waves may occur in acute heart failure without MR and also with ventricular septal defects.

Angiography

Aortic Regurgitation

Aortography has the potential to add significant data in the evaluation of the patient with AR. Whereas Doppler interrogation of the valve images only the velocity of the regurgitant jet, injection of contrast medium into the aorta during aortography visualizes actual flow of opacified blood from the aorta across the leaking valve into the LV. The severity of AR is classified on the basis of the density of this opacification. Mild AR (1+) is diagnosed when the regurgitant dye fails to opacify the whole LV. Moderate AR (2+) is thought present when contrast faintly opacifies the entire LV cavity. Moderately severe AR (3+) is present when opacification of the LV is equal to that of the aorta, and severe AR (4+) is present when opacification of the LV exceeds that of the aorta. In performing aortography, it is important to inject enough contrast to fully opacify the aorta and the enlarged LV, usually 60 cc of contrast injected over three seconds.

Mitral Regurgitation

Ventriculography has a similar advantage in visualizing MR as aortography does in AR; it images actual flow instead of flow velocity. Severity is judged by the level of LA opacification during injection of contrast into the LV. The scale used for MR is similar to that for AR, grading the density of dye in the LA instead of in the LV. However, the tendency of ventriculography to cause ventricular ectopy (which by itself causes MR) has made the use of ventriculography uncommon in assessing MR severity. However, a diagnostic ventriculogram may be obtained by placing the injection catheter just underneath the mitral valve and using a test injection to evaluate the potential for ectopy. If the test is unsatisfactory the catheter is repositioned and the injection repeated. As with AR, enough contrast must be injected to opacify the two enlarged chambers of interest.

Volumetric Quantification

More precise assessment of the amount of AR or MR can be made by measuring the RV, which is the difference between total and forward stroke volume. Total stroke volume (SVt) is all that is ejected from the LV and can be calculated as end diastolic minus end systolic volume, where the volumes are determined angiographically (see chap. 21). Forward stroke volume (SVf) is determined as CO from the Fick or thermodilution methods divided by the heart rate. The volume regurgitated back into the receiving chamber (the LV in AR and the LA in MR), RV, is the difference between total and forward stroke volume (SVt – SVf). RF = RV/SVf. A RF > 0.50 or regurgitant flow >60 cc is considered to be severe AR or MR (3).

Exercise Testing

In most cases, symptoms develop during exercise, yet hemodynamics are measured at rest. Therefore, exercise testing during hemodynamic recording can be very illuminating. Either
supine bicycle exercise or isometric handgrip exercise can be employed. Handgrip exercise is well suited for evaluation of valvular regurgitation because it increases afterload by raising mean arterial blood pressure by 10 to 20 mmHg (21). Normal subjects and patients with well-compensated AR or MR maintain normal LV filling pressure and increase CO with handgrip. On the other hand, in poorly compensated patients filling pressure may increase dramatically giving insight into the mechanism of the patient’s symptoms and supporting the need for intervention.

Indications for Surgery

Surgery is recommended either when symptoms referable to severe valve disease or when there is evidence of LV dysfunction (3) in the case of the AR and MR. Symptomatology is based on obtaining a good history. However, if the source of the dyspnea, the commonest symptom of VHD, is unclear, invasive hemodynamics can be helpful in establishing cause. If the filling pressures are normal both at rest and during exercise it is likely that the dyspnea is coming from a noncardiac source. If the patient has both lung and heart disease, examining PCWP and pulmonary artery pressure (PAP) at rest and exercise can be diagnostic. A normal PCWP and high PAP suggests severe lung disease with increased pulmonary vascular resistance, a condition unlikely to be improved by valve surgery. On the other hand, a high PCWP indicates LV failure as the culprit.

LV dysfunction is inferred from the LVEF at ventriculography. An EF of <0.50 for AR and <0.60 for MR is considered evidence of LV dysfunction and an indication for valve replacement or repair (3).

SUMMARY

The diagnosis of valvular heart disease is usually made at the bedside and is confirmed by echocardiography. However, in some cases the severity or disease is still in doubt following noninvasive testing. In such cases careful hemodynamic evaluation at rest and/or with exercise can be diagnostic. Further, invasively based angiography can contribute diagnostic information especially for the regurgitant lesions.

Our modern understanding of cardiac function is based on hemodynamic information obtained invasively from pressure and flow measurement. These principles still have an important diagnostic role to play even in the 21st century, but for them to be useful, the careful techniques of 60 years ago must still be employed.

REFERENCES

Hemodynamic assessment for restriction, constriction, hypertrophic cardiomyopathy, and cardiac tamponade

Paul Sorajja

INTRODUCTION

Historically, cardiac catheterization has been the principal diagnostic modality for the evaluation of the patient with constrictive pericarditis, cardiac tamponade, and the different forms of cardiomyopathy. The advent of newer cardiac imaging modalities, such as echocardiography, magnetic resonance imaging, and computed tomography, has led to a shift in the evaluation of patients with these disorders, with the initial diagnostic approach consisting of comprehensive noninvasive imaging following the history and physical examination. The hemodynamic consequences of these disorders may be accurately delineated in most instances by Doppler echocardiography. Therefore, in most cases, the diagnosis and hemodynamic assessment of these entities can be made without the need for cardiac catheterization.

When clinical and noninvasive findings are discrepant, however, an invasive hemodynamic catheterization should be considered. Although noninvasive modalities can diagnose the presence and severity of these entities, their accuracy is limited. Assessment of absolute intracardiac pressures, for example, cannot be assessed noninvasively, and cardiac catheterization needs to be performed when this information is needed. Patients with complex disorders are increasingly evaluated in the catheterization laboratory, whereas patients with straightforward conditions are assessed primarily with noninvasive methods. Thus, obtaining accurate and clinically relevant data from invasive cardiac catheterization has become increasingly important.

ANATOMIC CONSIDERATIONS

The approach to hemodynamic assessment of patients with constrictive pericarditis, cardiac tamponade, and the different forms of cardiomyopathy should be individualized. Proper planning of the procedure requires full knowledge of what data are known, what clinically relevant information is required, and a comprehensive differential diagnosis of the patient’s problems. The vascular access sites and approach to gathering data should be delineated fully before proceeding.

Where both right and left heart catheterization is needed, a standard approach begins with obtaining arterial and venous access. The femoral sites can be utilized in most situations; however, the internal jugular approach will facilitate the performance of the right heart catheterization in cases involving severe tricuspid regurgitation with enlarged right-sided chambers. The internal jugular approach should also be favored when an endomyocardial biopsy is required (e.g., suspicion of infiltrative cardiomyopathy), and if hemodynamic information during supine bicycle exercise is desired.

The following sequence of catheter placement and advancement allows prospective examination of the relation of the pressures between the left ventricle and right-sided chambers, which is needed in patients undergoing evaluation for pericardial disease, restrictive cardiomyopathy, or diastolic dysfunction:

- Following vascular access, the right heart catheter is used to acquire oxygen saturations from the inferior and superior vena cavae to calculate mixed venous oxygen content and to screen for intracardiac shunts.
- The right atrial pressure is measured with the catheter in the mid-portion of the right atrium and turned to the lateral wall to avoid prolapse across the tricuspid valve.
- Ascending aortic pressure is then measured by placement of a left heart catheter, followed by advancement of the catheter into the left ventricle to measure simultaneous left ventricular and right atrial pressures.
- The right heart catheter is then advanced into the right ventricle to measure simultaneous right ventricular and left ventricular pressures.
- The right heart catheter then is placed into the pulmonary artery (PA). Simultaneous saturations from the PA and left ventricle are obtained for calculation of cardiac output by the Fick method.
- Finally, the PA wedge pressure is obtained with position confirmation by oxygen saturation. Pulmonary arteriolar resistance (PAR) may be calculated from these measurements.

For patients with hypertrophic cardiomyopathy (HCM), transseptal catheterization should be considered in the evaluation of left ventricular outflow tract (LVOT) obstruction. The advantages of transseptal catheterization over a retroaortic approach are discussed separately in the section on HCM.

While all patients should be fasting before the catheterization procedure, intravenous fluids should be administered to patients who have a long waiting period between their last oral intake and the procedure. This prevents the hemodynamic measurements from being taken during a low-output, low-volume state. Patients can be lightly sedated, but should be awake to simulate the hemodynamic milieu of their outpatient state with close approximation of the heart rate and blood pressure that occurs in their usual daily activities. No parenteral oxygen should be administered prior to the procedure to allow measurements of oxygen saturations.

FUNDAMENTALS

Key fundamentals of hemodynamic assessment include the following:

- A comprehensive differential diagnosis of the patient’s clinical problems aids in the planning of the invasive hemodynamic evaluation.
LVOT obstruction in HCM is dynamic and highly dependent on ventricular load and the contractile state. Physical or pharmacological provocation should be performed to determine the presence of latent obstruction in symptomatic patients with no evidence of a significant LVOT gradient at rest.

In patients with obstructive HCM, the typical response on the post-premature ventricular contraction (PVC) beat is a decrease in the pulse pressure and an increase in the LVOT gradient (Brockenbrough sign). In patients with fixed aortic stenosis, the pulse pressure increases on the post-PVC beat.

Transseptal catheterization provides the most complete and accurate hemodynamic information in patients with HCM. A retroaortic approach can also be used with understanding of the potential pitfalls.

Invasive assessment of restrictive cardiomyopathy and constrictive pericarditis should entail the use of high-fidelity, micromanometer tip catheters to avoid artifacts due to overdamping.

Early rapid ventricular filling (i.e., dip and plateau pattern) can be seen in patients with restrictive cardiomyopathy, constrictive pericarditis, or any volume overload state that results in a decrease in effective myocardial or pericardial compliance.

Both traditional and respiratory criteria should be utilized to distinguish restrictive cardiomyopathy from constrictive pericarditis. Respiratory criteria are (i) dissociation of intrathoracic and intracavitary pressures and (ii) discordance of the right and left ventricular systolic pressures.

The hemodynamic hallmarks of cardiac tamponade are pulsus paradoxus and loss of the y descent in the atrial waveform.

Endomyocardial biopsy has low clinical yield and does not significantly impact therapy in most cardiac disease states. However, endomyocardial biopsy should be considered in patients with possible acute fulminant giant cell myocarditis, where immunosuppressive therapy may be beneficial.

Accurate determination of PAR and its reversibility is an essential component of the comprehensive invasive hemodynamic evaluation.

With few exceptions, pericardiocentesis is best performed under echocardiographic guidance.

INDICATIONS
Table 12.1 lists indications for use of hemodynamic assessment for specific patient conditions. Indications for patients with suspected HCM, restrictive cardiomyopathy, and constrictive pericarditis are discussed below.

Hypertrophic Cardiomyopathy: Indications
For the majority of patients with HCM, two-dimensional and Doppler echocardiography reliably assesses the presence and severity of LVOT obstruction (1). However, in some circumstances echocardiography may be inaccurate. Mitral regurgitation frequently accompanies LVOT obstruction in HCM. The presence of mitral regurgitation may contaminate the LVOT signal, resulting in erroneous or inaccurate estimates of the LVOT gradient (Fig. 12.1). The velocity jet of mitral regurgitation that occurs secondary to LVOT obstruction also is eccentric, and thus is difficult to quantify with current noninvasive methods. In some patients, a high intracavitary velocity can be mistaken on Doppler echocardiography for an LVOT gradient.

Table 12.1 Indications for Use of Hemodynamic Assessment for Specific Patient Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Assess LVOT obstruction; assess severity of mitral regurgitation; evaluate diastolic function; perform alcohol septal ablation.</td>
</tr>
<tr>
<td>Restrictive cardiomyopathy</td>
<td>Confirm diagnosis and rule out other potential causes of heart failure (e.g., constrictive pericarditis, cor pulmonale); measure pulmonary arteriolar resistance for potential transplant candidates; perform endomyocardial biopsy.</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
<td>Establish the diagnosis and examine for other potential causes of heart failure.</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>Invasive assessment is not necessary for the diagnosis of tamponade, but the typical hemodynamic findings of tamponade during cardiac catheterization need to be understood.</td>
</tr>
</tbody>
</table>

Figure 12.1 Contamination of the Doppler left ventricular outflow tract signal with mitral regurgitation in a patient with obstructive hypertrophic cardiomyopathy. Contamination from mitral regurgitation leads to an erroneous calculation of the left ventricular outflow tract gradient (left). The correct Doppler left ventricular outflow tract gradient (right). Cardiac catheterization is indicated when it is difficult to separate the velocities and the severity of left ventricular outflow tract obstruction is unclear. Abbreviations: Ao, ascending aortic pressure; LV, left ventricular pressure.
(2). For patients with combined valvular stenosis and subaortic obstruction, cardiac catheterization may be necessary to assess the relative contributions of these different levels of obstruction. For patients with cardiovascular symptoms and no evidence of significant LVOT obstruction at rest, cardiac catheterization with provocative maneuvers is utilized to delineate the presence of latent LVOT obstruction (3).

Restrictive Cardiomyopathy and Constrictive Pericarditis: Indications

The diagnosis of restrictive cardiomyopathy is made by the presence of diastolic dysfunction, dilated atria, and the absence of ventricular hypertrophy or dilatation on noninvasive imaging (Fig. 12.2) (4). In these patients, systolic function is preserved or out of proportion to the degree of diastolic dysfunction. For patients presenting with restrictive cardiomyopathy, the major differential diagnosis that must be considered is constrictive pericarditis. If constrictive pericarditis is present, complete pericardiectomy can result in relief of symptoms and improvement of longevity (6). However, for patients with idiopathic restrictive cardiomyopathy, there is no curative treatment apart from cardiac transplantation (7). During cardiac catheterization, it is also important to examine for other potential causes of heart failure. The presence of severe intrinsic pulmonary hypertension, tricuspid regurgitation, and left ventricular or right ventricular failure will lead to symptoms and signs similar to those of constrictive pericarditis and restrictive cardiomyopathy.

EQUIPMENT

Accurate measurement of intracardiac pressures with fluid-filled catheters requires the use of rigid, large-bore catheters with minimization of the tubing length between the catheter and pressure transducer. Awareness of potential errors of measurement due to catheter whip, entrapment, damping, and other artifacts is always necessary during an invasive hemodynamic study. The use of coronary catheters with single end holes and potential for entrapment (e.g., right Judkins catheter) should be avoided. In patients with intracavitary gradients (e.g., HCM and known or suspected LVOT obstruction), multiple shaft side holes on a left ventriculography catheter (i.e., pigtail) also will lead to errors in the measurement of the subaortic pressure and thus should not be used in these patients.

Fluid-filled catheters can reliably measure mean and absolute intracardiac pressures. For analysis of pressure waveforms, however, instantaneous recordings with high-fidelity micromanometer tip catheters should be utilized (Millar Instruments, Houston, Texas, U.S.). These catheters should be calibrated to fluid-filled pressures at baseline, and calibration needs to be repeated following any catheter repositioning. For right heart pressure measurements, a 6 or 7 French (Fr) single lumen balloon wedge catheter (Arrow International, Teleflex Medical, Research Triangle Park, North Carolina, U.S.) is relatively rigid with a large bore that will accommodate a 2-Fr high-fidelity micromanometer tip catheter.

For patients with irregular heart rates (e.g., atrial fibrillation), temporary pacing should be considered to maintain consistent R-R intervals to improve the diagnostic interpretation of the hemodynamic findings. If possible, continuous recording of all hemodynamic pressures should be made to allow retrospective review of these pressures throughout the entire study.

CLINICAL ASPECTS

Hypertrophic Cardiomyopathy

HCM is a heritable cardiac disorder with a prevalence of 1 in 500 persons in the general population. It is defined, according to the World Health Organization, by the presence of severe myocardial hypertrophy in the absence of a local or systemic etiology (8). In the late 1980s, molecular studies demonstrated that HCM is due to genetic mutations in sarcomeric contractile proteins (9). Several hundred mutations in 10 different genes have since been identified. The diagnosis of HCM typically is made by two-dimensional echocardiography. In most instances, Doppler echocardiography can accurately diagnose and quantify LVOT obstruction. The late peaking systolic velocity can be converted to a pressure gradient using the modified Bernoulli equation (gradient = 4velocity²).

Pathophysiology

Diastolic abnormalities are the major pathophysiological mechanisms contributing to signs and symptoms for patients with HCM. These abnormalities arise from impaired myocardial relaxation and poor compliance in the presence of altered...
loading conditions, ventricular nonuniformity, myocardial ischemia, and severe hypertrophy. The cumulative result of diastolic dysfunction is an increase in left ventricular filling pressures, which leads to typical symptoms of dyspnea and angina. In patients with HCM, there may be a significant discrepancy between the left atrial pressure and left ventricular end-diastolic pressure. Therefore, measurements of both of these pressures should be made if possible.

Dynamic LVOT obstruction may be present in up to two-thirds of patients with HCM (3). Because the presence of LVOT obstruction serves as the basis for therapy, it is important to document the presence and severity of the LVOT gradient. Two mechanisms lead to the development of dynamic LVOT obstruction: (i) septal hypertrophy and narrowing of the LVOT promote the generation of Venturi forces that accelerate during ventricular emptying and pull the mitral apparatus anteriorly; and (ii) anterior papillary muscle displacement subjects the mitral leaflets to systolic intraventricular currents that drag the apparatus anteriorly (3). Decreased mitral leaflet coaptation occurs because of systolic anterior motion of the mitral valve, leading to mitral regurgitation in patients with LVOT obstruction (10). It is important to note the dynamic nature of LVOT obstruction and secondary mitral regurgitation, and the marked sensitivity of these abnormalities to changes in preload, afterload, and the contractile state of the left ventricle. Mitral regurgitation may be related to intrinsic valve abnormalities in a subset of patients, and such abnormalities have implications for septal reduction therapy.

During catheterization, HCM should be suspected when there is a small, hypertrophied left ventricle with hyperdynamic systolic function on left ventriculography. Left ventriculography may demonstrate regional hypertrophy, such as basal septal hypertrophy (Fig. 12.3). In patients with the apical form of HCM, a typical “spade-shaped” configuration is on ventriculography (Fig. 12.4). A dynamic LVOT obstruction can also be suspected if there is a gradient between the left ventricular apex and base or if a “spike and dome” pattern is on the aortic pressure trace.

Catheterization Techniques
Measurement of the LVOT gradient should be made with simultaneous ascending aortic and left ventricular pressures. Because of peripheral amplification, femoral tracings should not be used. In patients with significant LVOT obstruction, a typical spike and dome pattern appears in the ascending aortic pressure (Fig. 12.5). The optimal method for measurement of LVOT obstruction is to measure the left ventricular pressure via a transseptal approach to avoid catheter entrapment. The
catheter can be placed in the left ventricular inflow region immediately distal to the opening of the mitral valve leaflets (Fig. 12.6). Using a transseptal sheath with a side-arm, simultaneous left atrial pressure also can be obtained (Fig. 12.5).

If transseptal catheterization cannot be performed, left ventricular pressure is obtained by a retrograde approach across the aortic valve. In these instances, a pigtail catheter with shaft side holes should not be used. Importantly, catheter entrapment may occur with left ventricular pressure measured from a retrograde approach and may falsely elevate the LVOT gradient. If catheter entrapment is present, there will be a lack of systolic pulsation when the catheter is disconnected and the left ventricular pressure contour will be dampened. In the retrograde approach, it is also important to confirm that the catheter position is beneath the level of LVOT obstruction (Fig. 12.7). A hand contrast injection should be performed to ensure that the end of the catheter is floating freely within the left ventricular cavity.

The dynamic nature of LVOT obstruction due to HCM will lead to a Brockenborough response. On the beat following a premature contraction, the LVOT gradient increases and the pulse pressure decreases (Fig. 12.8). Because of its high sensitivity to loading conditions, variation of the LVOT gradient may also be seen in different phases of respiration (Fig. 12.9). If the resting LVOT gradient is <50 mmHg in a patient with HCM, provocative maneuvers should be performed in the catheterization laboratory. These maneuvers include the Valsalva maneuver, amyl nitrate inhalation, and drug provocation. The optimal drug to use for provoking LVOT obstruction is isoproterenol because of its β1 and β2 agonist activity (12,14). Simultaneous echocardiography should be performed during isoproterenol infusion to determine the location of obstruction (e.g., systolic anterior motion of the mitral valve, mid-cavity obstruction) when a gradient is detected during these maneuvers. It is the subset of patients who have both systolic anterior motion and LVOT gradient >50 mmHg (either at rest or during provocation) who will benefit from septal reduction therapy (1).

**Restrictive Cardiomyopathy**

Restrictive cardiomyopathy is characterized by a nondilated, rigid ventricle, resulting in severe diastolic dysfunction and restrictive filling. Desmin and troponin I mutations have been described in patients with restrictive cardiomyopathy (15–17). Infiltrative cardiomyopathies, such as amyloidosis, hemochromatosis, and sarcoidosis, can present with an appearance of a restrictive cardiomyopathy. Endomyocardial biopsy can be performed for patients in whom restrictive cardiomyopathy due to infiltrative disorders is suspected (see section “Endomyocardial Biopsy” below). Restrictive cardiomyopathy also may result from radiation therapy and eosinophilic syndromes.

**Figure 12.5** Dynamic left ventricular outflow obstruction in hypertrophic cardiomyopathy. Arrow indicates typical “spike and dome” configuration, indicating dynamic systolic obstruction. Abbreviations: Ao, ascending aorta; LA, left atrium; LV, left ventricle.

**Figure 12.6** Transseptal versus retrograde approach for assessment of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. In the retrograde approach, the catheter becomes easily entrapped and lead to erroneous left ventricular pressure measurements (left). In the transseptal approach, the left ventricular catheter can be easily positioned in near the mitral inflow (right). This catheter position leads to the most accurate measurements of left ventricular pressure in patients with subaortic obstruction. Source: From Ref. 12.
**Figure 12.7** Importance of catheter position in the retroaortic approach in hypertrophic cardiomyopathy. When a retroaortic approach is utilized for assessment of LVOT obstruction in hypertrophic cardiomyopathy, it is important confirm that the catheter position is beneath the level of LVOT obstruction. A catheter in the ascending aorta and a catheter in the left ventricle (A). With the catheter in this position, the LVOT gradient is either not detected (C) or measured to be approximately 80 mmHg (D). However, the true gradient is obtained by advancing the left ventricular catheter further into chamber (B), leading to the correct LVOT gradient of 120 mmHg (E). **Abbreviations:** LVOT, left ventricular outflow tract; Ao, ascending aorta; LV, left ventricle.

**Figure 12.8** Dynamic left ventricular outflow obstruction (Brockenbrough sign) in hypertrophic cardiomyopathy (left) versus a patient with aortic stenosis (right). On the beat after a PVC, the increased inotropy leads to dynamic outflow tract obstruction. The left ventricular outflow tract gradient increases and the pulse pressure decreases. Conversely, in a patient with aortic stenosis, the increase in contractility leads to an increase in stroke volume and pulse pressure. **Abbreviations:** Ao, ascending aorta; LA, left atrium; LV, left ventricle; RA, right atrium. **Source:** From Ref. 13.
Cardiac Catheterization

The major abnormality in restrictive cardiomyopathy is the presence of significantly elevated filling pressures in all four cardiac chambers. Early rapid ventricular filling leads to a “dip and plateau” pattern or “square root sign” in the ventricular pressure curves during early diastole, and rapid x and y descents on the atrial pressure curves (Fig. 12.10). Because underdamping from fluid-filled catheters can mimic early rapid ventricular filling, high-fidelity micromanometer catheters should be used if early rapid ventricular filling is suspected.

Both restrictive cardiomyopathy and constrictive pericarditis present with evidence of early rapid diastolic filling and elevation of diastolic pressures that are out of proportion to systolic dysfunction. Traditional criteria for differentiation of restrictive cardiomyopathy from constrictive pericarditis have included the following:

- Left ventricular end-diastolic pressure exceeds right ventricular end-diastolic pressure by \( \geq 5 \) mmHg.
- PA systolic pressure is \( >50 \) mmHg.
- In the right ventricle, end-diastolic pressure is \( <0.3 \) of systolic pressure.

Nonetheless, these traditional criteria have been found to have poor specificity, and they cannot be used in isolation to differentiate restrictive cardiomyopathy from constrictive pericarditis. On the other hand, changes in the hemodynamic pressure relationships during respiration have been shown to be useful in distinguishing between these two disorders (see section “Constrictive Pericarditis” below).

Constrictive Pericarditis

Constrictive pericarditis results from pericardial inflammation, fibrosis, and possibly calcification, with subsequent loss of elasticity. Radiation therapy, cardiac surgery, trauma, and systemic diseases that affect the pericardium (e.g., connective tissue disease, tuberculosis, malignancy) can lead to constrictive pericarditis.

In patients with constrictive pericarditis, the noncompliant pericardium is rigid, impairs diastolic filling, and prevents the complete transmission of intrathoracic pressure to the intracardiac cavities. Ventricular filling rapidly occurs in early diastole and terminates abruptly because of pericardial restraint. The diastolic pressures become equalized or nearly equalized in all four cardiac chambers. The total intracardiac volume is fixed by the noncompliant pericardium. Because the ventricular septum is not affected in constrictive pericarditis, bulging of the septum toward the left ventricle occurs during inspiration and returns toward the right ventricle during expiration, leading to marked enhancement of ventricular interaction. This ventricular interaction leads to reciprocal changes in the filling and emptying of the right and left ventricles (18).

Invasive Hemodynamic Criteria

Invasive evaluation of the patient with suspected constrictive pericarditis is accomplished with comprehensive, simultaneous right and left heart catheterization. High-fidelity micromanometer catheters should be utilized to avoid artifacts from
underdamping. For patients with atrial fibrillation, temporary pacing should be performed for constant heart rate intervals during the study.

Criteria for the diagnosis of constrictive pericarditis include both traditional hemodynamic criteria and dynamic respiratory criteria (18–21). Respiration affects ventricular filling in constrictive pericarditis in a manner that is distinct from restrictive cardiomyopathy.

- In patients with constriction, the inspiratory fall in thoracic pressure affects the pulmonary wedge pressure, but ventricular pressure is shielded from respiratory pressure changes by the pericardial scar. By lowering pulmonary wedge pressure and presumably left atrial pressure, inspiration leads to a decrease in pressure gradient for ventricular filling. Reciprocal changes occur in right ventricular filling that are mediated by the ventricular septum (not by increased systemic venous return). These findings are described as dissociation of the intrathoracic and intracavitary pressures (Fig. 12.11).

- In patients with constriction, the enhancement of ventricular interaction leads to discordant right and left ventricular pressures. This discordance typically manifests as reciprocal changes in stroke volume, pulse pressure, or peak systolic pressure during respiration (Fig. 12.12).

Both dissociation of intrathoracic and intracavitary pressures and enhancement of ventricular interaction are not present in patients with restrictive cardiomyopathy. In these patients, inspiration lowers the pulmonary wedge and left ventricular diastolic pressures equally. Thus, the pressure gradient for ventricular filling is virtually unchanged during respiration. Because ventricular interaction is not enhanced, the left ventricular and right ventricular pressures are concordant throughout the respiratory cycle in patients with restrictive cardiomyopathy.

Equalization of pressures in all cardiac chambers is commonly said to be a major criterion for constrictive pericarditis but is nonspecific. This equalization also may be present in patients with restrictive cardiomyopathy or other disease states, when acute volume overload leads to pericardial restraint. Examples of this phenomenon include right ventricular dilatation after right ventricular infarction, severe decompensated left heart failure, severe tricuspid insufficiency, and in acute mitral regurgitation secondary to chordal rupture. In addition, equalization of diastolic pressures may not be present in a patient with constrictive pericarditis who has been diuresed and has low to normal right atrial pressure. In these patients, the cardiac output will be low, and fluid challenge will be necessary to unveil the hemodynamic findings of constrictive pericarditis (22).

Figure 12.11 Dissociation of intracavitary and intrathoracic pressures in constrictive pericarditis. In patients with constrictive pericarditis, inspiration leads to a decrease in ventricular filling by decreasing intrathoracic pressure relative to ventricular diastolic pressure. Conversely, during expiration, positive intrathoracic pressure leads to an increase in ventricular filling. These respiratory effects can be seen by examining the changes in the pressure gradient between the PCWP and ventricular early diastolic pressure (gray). Abbreviations: PCWP, pulmonary capillary wedge pressure; LV, left ventricle. Source: From Ref. 5.

Figure 12.12 Enhancement of ventricular interdependence. In patients with constrictive pericarditis, the total ventricular volume is fixed by the noncompliant pericardium. Thus, reciprocal respiratory changes in the filling of each ventricle occur. These changes are described as discordance in pulse pressure, systolic pressure, or stroke volume between the right and left ventricles during respiration. Abbreviations: RV, right ventricle; LV, left ventricle. Source: From Ref. 5.
Cardiac Tamponade

Cardiac tamponade may result from any disorder that causes a pericardial effusion. The pericardium normally contains 15 to 50 mL of fluid between its parietal and visceral layers, and the intrapericardial pressure approximates intrapleural pressure (~5 to +5 cm H2O). Tamponade occurs when intrapericardial pressure exceeds the intracardiac pressure. The progression in the effect of a pericardial effusion may be acute or gradual, depending on the amount and rate of fluid accumulation. The most common etiology of tamponade is malignancy, of which breast and lung are the most frequent. Other important etiologies are idiopathic or viral pericarditis, aortic dissection with complications, and pericarditis or myocardial rupture from myocardial infarction. Unusual manifestations of cardiac tamponade include the following:

- **Low-pressure tamponade**, which is tamponade without elevated jugular venous pressure because of the intracardiac filling pressures are low (23,24). Examples of this manifestation are patients with malignancy or tuberculosis that is complicated by severe dehydration.

- **Localized tamponade**, which occurs when a loculated pericardial effusion is tactically located to cause impairment of ventricular filling. An example of this manifestation is in the postoperative setting, where a loculated effusion is present in the posterior pericardial space adjacent to the atria. A posterior effusion may not be seen with transesophageal echocardiography and must be carefully sought in a postoperative patient with hemodynamic instability.

- **Pneumopericardium**, which may be caused by gas-forming bacterial pericarditis following penetrating chest trauma.

Cardiac tamponade should be considered when there is a compatible history, hypotension, and an elevated jugular venous pressure or pulsus paradoxus. The chest x-ray (e.g., “water bottle heart”) and electrocardiography (e.g., electrical alternans, sinus tachycardia) may be helpful. However, echocardiography is the primary test for the diagnosis. Specific signs include collapse of the right atrium and right ventricle, ventricular septal shifting with respiration, and enlargement of the inferior vena cava (25). Respiratory variation in Doppler mitral inflow velocities occurs early in the evolution of tamponade.

The changes in mitral inflow are highly sensitive, and can precede changes in cardiac output, blood pressure, and other echocardiographic evidence of tamponade (26).

**Invasive Hemodynamics**

Although cardiac catheterization is usually not needed to make the diagnosis of cardiac tamponade, recognition of the typical hemodynamic findings has gained renewed importance in the era of increasingly complex cardiac interventions. When performed, the right atrial pressure tracing in tamponade will demonstrate prominent x descents and blunted or obliterated y descents (Fig. 12.13). Preservation of the x descent occurs because systolic ejection decreases the intracardiac volume and leads to a transient reduction in intrapericardial and right atrial pressures. During the remainder of the cardiac cycle, elevated intrapericardial pressure impairs ventricular filling and leads to blunting or obliteration of the y descent. Intrapерicardial pressure rises with fluid accumulation and pericardial restraint. Venous return becomes impaired once the intrapericardial pressure exceeds the filling pressure of the heart. This impairment leads to a reduction in cardiac output, followed by increases in pulmonary venous and jugular venous pressures. During inspiration, there is a fall in the driving pressure to fill the left ventricle, followed by a reduction in ventricular filling, stroke volume, and consequently the pulse pressure. These events during inspiration cause the hallmark finding of pulsus paradoxus in patients with tamponade (27,28).

**SPECIAL ISSUES**

**Endomyocardial Biopsy**

Endomyocardial biopsy provides myocardial tissue for microscopic analysis and can be safely performed using either an internal jugular or femoral venous access. Particular care must be taken to target the apical septum, and to avoid sampling from the right ventricular free wall and the tricuspid valve (Fig. 12.14). Biplane fluoroscopy and/or simultaneous echocardiography are helpful in preventing this from occurring. Complications are infrequent (<1%), but include tricuspid valve injury and tamponade from cardiac perforation (29).

Before proceeding with endomyocardial biopsy, it is important to consider both the expected yield of the biopsy...
procedure and its therapeutic implications. Endomyocardial biopsy can diagnose myocarditis and infiltrative disorders causing cardiomyopathy. However, its sensitivity is limited in disorders with patchy myocardial involvement (e.g., sarcoidosis, lymphocytic myocarditis). Moreover, the histological findings, even if positive, may not alter therapy in other disorders. Thus, few indications for endomyocardial biopsy exist in patients with left ventricular systolic dysfunction. For infiltrative cardiomyopathies, there are usually clinical clues in the history, electrocardiography, and laboratory testing, such as iron studies, protein electrophoresis, and peripheral eosinophilia. In patients presenting with acute fulminant myocarditis, endomyocardial biopsy may identify giant cell myocarditis, which may respond favorably to immunosuppressive therapy (30–32).

Pulmonary Arteriolar Resistance

Patients being considered for cardiac transplantation require cardiac catheterization to ensure suitability for cardiac transplantation. In these patients, an accurate measurement of PAR is critically important in their evaluation. In other patients, measurement of PAR also can be helpful to determine appropriate medical therapy (e.g., vasodilators). Thus, determination of PAR should be a routine component of a comprehensive invasive hemodynamic evaluation.

Calculation of the PAR is made with measurements of the PA pressure, left atrial pressure, and cardiac output. The pulmonary capillary wedge pressure (PCWP) approximates left atrial pressure except in rare circumstances (e.g., cor triatratium, pulmonary veno-occlusive disease).

\[
\text{PAR (Wood units)} = \frac{\text{mean PA pressure} - \text{mean LA pressure (or PCWP)}}{\text{cardiac output}} \times \text{where LA is left atrium.}
\]

For patients with elevated PAR, cardiac transplantation has a poor outcome due to the high afterload imposed on the right ventricle. When the PAR is elevated, vasodilators or inhaled nitric oxide should be used to determine the degree of its reversibility. For patients with normal to mildly elevated filling pressures (left atrial pressure < 20 mmHg), nitric oxide, epoprostenol, or nitroprusside may be administered. For patients with elevated filling pressures, nitroprusside primarily is used. Repeat measurements of PA pressure, left atrial pressure or PCWP, and cardiac output should be made after each increase in infusion rate. The endpoint of the infusion should be either a PAR of < 4.0 Wood units or a systolic blood pressure < 75 mmHg.

Several technical considerations when measuring PAR include the following:

- The measurements of PA pressure and left atrial pressure (or PCWP) should be near simultaneous and at held end expiration.
- If PCWP is used in place of direct left atrial pressure measurement, its accuracy must be confirmed. Phasic respiratory changes in the pressure and oximetric confirmation by > 95% saturation should be evident.
- Cardiac output is a critical measurement, and should be confirmed by at least two methods. The Fick method requires steady state conditions and measurement of myocardial oxygen consumption. Thermodilution is better for acute changes in cardiac output.

Pericardiocentesis

Historically, pericardiocentesis was performed in a blinded or electrocardiographic-guided fashion, usually from a subxyphoid approach. Although these techniques are still used in
The pericardial effusion is removed using either manual
catheterization or percutaneous catheterization. Once the intrapericardial position of the Polytef sheath is
obtained, the needle is advanced slightly further (~2 mm). The Polytef sheath then is advanced over the needle, followed by withdrawal of the needle. The needle should not be readvanced forward into the sheath once it has been removed.

Agitated saline is injected into the Polytef sheath via a three-way stopcock under echocardiographic monitoring. If contrast does not opacify the pericardial space, then the catheter should be repositioned by withdrawal or another needle passage. As previously noted, the needle should not be removed. Once the intrapericardial position of the Polytef sheath is confirmed, it is exchanged over a guidewire for a 5- to 6-Fr introducer sheath followed by placement of a pigtail catheter into the pericardial space. The introducer sheath is subsequently removed to leave only the smooth walled pigtail catheter in place. If needed, reconfirmation of the catheter location and measurement of intrapericardial pressure can be performed with saline injection.

The pericardial effusion is removed using either manual techniques and/or vacuum bottle. Fluid removal is monitored with echocardiography. If drainage stops despite residual effusion on echocardiography, the pigtail is repositioned.

The pigtail catheter is aspirated and flushed with heparinized saline every four to six hours. Reopposition of the parietal and visceral pericardial surfaces in this manner promotes adhesions that prevent fluid recurrence. The catheter is removed when the drainage is minimal (<25 cc/24 hr) and repeat echocardiography reveals no significant residual effusion.

Infrequently, the tense pericardium will discharge its fluid into the pleural space during attempts at needle passage and relieve tamponade. This effect is recognized on echocardiography, and may obviate further attempts at pericardiocentesis. While the majority of pericardial effusions can be treated percutaneously, some still require subxyphoid surgical drainage, especially if they are viscous or loculated. Bacterial infections in the pericardium also usually require large drainage. Recent hemorrhage into the pericardium may result in clot formation that can be difficult to remove percutaneously. A true posterior effusion may be difficult to approach from any thoracic window and may require surgery.

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Endomyocardial biopsy—indications and procedures
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INTRODUCTION
Disorders of the heart muscle remain among the most poorly understood disease processes in all of cardiovascular medicine. Endomyocardial biopsy techniques have now been available for over 50 years to evaluate underlying primary myocardial pathology. Cardiac biopsy has been particularly useful in establishing the diagnosis and prognosis for patients with recent onset or rapidly deteriorating cardiomyopathy and in monitoring patients for rejection after cardiac transplantation. The role of endomyocardial biopsy continues to evolve as novel molecular and genetic analyses are being performed on biopsy specimens. This chapter will review the history of endomyocardial biopsy, define the anatomic considerations and basic biopsy technique, and discuss the indications, complications and future directions of this important procedure.

History of Endomyocardial Biopsy
Techniques for biopsying cardiac tissue outside the operating room have been available now for 50 years. In 1958, Weinberg, Fell and Lynfield first performed heart biopsies through a small incision in the left intercostal space. After dissection, samples of pericardium, epicardium, and myocardium were obtained, revealing inflammatory and restrictive cardiac disorders, and tubercular and traumatic causes of pericardial constriction (1). Because of the need for open incision and surgical extraction, the technique was not widely adopted. The first closed percutaneous biopsy was performed by Sutton and Sutton in 1960 using a needle introduced through the chest wall at the point of maximal impulse to sample myocardial tissue at the left ventricular apex (2). This method and other early percutaneous techniques had only modest diagnostic yield and were plagued with concerns about protecting patients from infection and pyrogen reaction. Richardson in 1974 and Kawai in 1977 added special features to the biopsy forceps for right or left ventricular sampling by increasing sheath flexibility, electrocardiographic monitoring, and intracardiac maneuverability (9,10).

Modern bioptomes in use since the mid-1990s are disposable, single-use devices eliminating concerns about disease transmission, pyrogen reactions, or cutting edge sharpening (Fig. 13.1). Bioptomes are made in standard lengths of 50 cm for use from the neck and chest central venous system, or over 100 cm for use from the femoral vein or artery. The 50-cm bioptomes may be preshaped to facilitate transit across the tricuspid valve or unshaped to be inserted through a preformed sheath. The preformed sheath is generally guided into the ventricular cavity over an angled pigtail or balloon flotation catheter. This sheath remains in the ventricular cavity through the biopsy procedure, increasing risk of arrhythmia or perforation and reducing operator control of the bioptome’s path and biopsy site. In contrast, preshaped bioptomes are introduced through a short venous sheath and give operators greater control of biopsy site selection. The degree of bioptome curvature may be modified to facilitate entry into either the right or left ventricles. Disposable bioptomes and sheaths are available for use from the right or left jugular, subclavian and femoral veins as well as femoral arteries, and vary in length, degree of angulation, diameter and jaw size.

ANATOMIC CONSIDERATIONS
Vascular Access
Right Internal Jugular Vein
The right internal jugular vein is the most common site for performance of right ventricular endomyocardial biopsy procedures (11). With the patient’s head turned to the left 30° to 45°, the internal jugular vein is located lateral to the carotid artery within the anterior triangle of the neck formed by the sternal and clavicular heads of the sternocleidomastoid muscle and the clavicle (Fig. 13.2). This triangle may be clearly outlined by having the patient raise their head off the table briefly to

1Deceased.
tense the muscular boundaries. Entry into the jugular vein in the upper third of this triangle, well above the clavicle, will lessen the risk of pneumothorax and allow for easier compression of accidental carotid punctures as well as the venous access site after the procedure. Routine use of ultrasonography is encouraged to identify the location and size of the jugular vein prior to access attempt, particularly in patients with challenging surface anatomy (Fig. 13.3). The jugular vein is lateral to the carotid artery, is easily compressible when pressure is applied to the ultrasound transducer, and lacks the pulsatility of the artery, which may be confirmed by color or pulse wave Doppler (13). Use of sonography during venous access has been shown to improve access time and decrease complication rates (14).

Once anatomic landmarks have been identified, the patient’s neck is prepared with standard antibacterial solutions and the region is isolated with sterile towels or drapes with the patient’s head resting in a comfortable position. In patients with low venous pressure or a small jugular vein, the legs may be elevated or the patient placed in Trendelenberg position to increase jugular venous filling and augment the puncture target. A 22- or 25-gauge needle is used to introduce local
anesthetic (2% lidocaine) intradermally and subcutaneously along the planned route of access needle entry. After successful local anesthesia is applied, a small 1- to 2-mm superficial incision is made at the anticipated entry site using a surgical blade and may be expanded using a mosquito clamp. This incision prevents the venous sheath from meeting resistance when passing through the skin.

In the classic approach, the 22-gauge needle is directed in small increments toward the venous entry site at an angle of 30° to 40° from vertical and 20° right of the sagittal plane. This aims the finder needle away from the more medially located carotid artery. After each advancement step, the needle should be aspirated before infusing small amounts of lidocaine. Excess anesthetic infiltration is discouraged as it may compress the jugular vein, obscure landmarks, or infiltrate into the carotid sheath or vocal cords resulting in transient Horner syndrome or hoarseness. Once venous blood is aspirated, the operator notes the position and an 18-gauge single wall puncture needle with syringe attached is advanced along the prior pathway of the finder needle. Continuous aspiration should be applied as the 18-gauge needle is advanced in small increments until there is a “give” of the vein wall and blood return is evident. A J-tipped guidewire is introduced followed by the appropriate sheath.

Alternatively, we now frequently use a 22-gauge micropuncture needle as the probe and entry device for jugular venous access. This needle is veryatraumatic and accepts a 0.021-in mandril guidewire over which a coaxial 5-French double dilator guide sheath is advanced. Once this has entered the jugular vein and superior vena cava, the inner cannula and guidewire are withdrawn and a conventional guidewire (0.038 in) is inserted through the outer cannula. This remaining cannula is then removed and a 7- or 8-French self-sealing sheath is introduced over the guidewire. This sheath may be preformed for right ventricular biopsy, or standard length to allow for preshaped bioptome use. Once the sheath is appropriately positioned, the guidewire may be removed and the sheath may be aspirated, flushed and then is available for endomyocardial biopsy.

If initial attempts at venous access are unsuccessful, the probing or micropuncture needle should be retracted to just beneath the skin and redirected more laterally. If there is still no venous return, medial redirection toward the carotid may be attempted. Should arterial puncture occur at any point, the probing needle or micropuncture needle syringe will fill with well-oxygenated blood. The needle must be removed immediately and the area compressed for five minutes or until hemostasis is achieved. This problem may be avoided by using simultaneous ultrasonographic guidance during puncture attempt.

**Right Subclavian Vein**

The right subclavian vein may be used in those rare cases where anatomic abnormalities preclude use of the internal jugular or femoral vein approaches. The entry point should be more lateral than for routine subclavian venous access and should be from an infracavicular approach past the bend of the clavicle. This more lateral approach is required so that the subclavian to vena caval angle will not be too acute, preventing the relatively stiff bioptome from being positioned into the right heart. Application of local anesthetic and needle entry are similar to internal jugular vein access. A standard single wall needle or micropuncture kit may be used. If cannulation is unsuccessful, a more inferior approach with a steeper angle may be required. In both the internal jugular and subclavian techniques, fluoroscopy should be used to ensure that the guidewire is directed down the vena cava toward the right atrium rather than superiorly to the head.

**Femoral Vein and Artery**

Despite relatively easy cannulation, biopsy from the femoral vein can be challenging (15). The femoral vein is located medial to the femoral artery and the entry site should be below the inguinal ligament. The Amplatz, Seldinger, or micropuncture techniques may be used for venous access. A guide sheath is introduced into the inferior vena cava via the femoral vein. The femoral artery may be accessed in a similar fashion and is the site of entry for most left ventricular biopsy attempts. Left ventricular biopsies, though rare, may be indicated in patients with specific intraventricular masses or isolated left ventricular pathology, such as myocarditis or infiltrative disease (16). After femoral arterial sheath insertion, a constant infusion of heparinized saline should be maintained through the sheath to prevent thrombus formation within these long catheters.

**FUNDAMENTALS**

**Biopsy Techniques**

**Guidance Methodology**

Endomyocardial biopsies are most easily performed under fluoroscopic guidance to define the heart borders and easily visualize the course of the sheath and/or bioptome into the heart. Some investigators advocate the use of two-dimensional echocardiography to guide biopsy to reduce radiation exposure and risk of perforation (17). Echocardiographic guidance may be particularly useful in biopsying intracardiac masses in either the left or right heart (18). It is often technically challenging to obtain adequate windows and visualize the biopsy forceps with echocardiography. Compared with two-dimensional echocardiography, fluoroscopy provides the operator with superior information about the course of the bioptome and biopsy site. Widespread use of newer technologies such as cardiac magnetic resonance imaging may allow the detection of a focal disease process in the right or left ventricle. This information can then be used to direct endomyocardial biopsy to a location most likely to demonstrate underlying pathology (19). Advances in three-dimensional echocardiography may improve visualization of myocardium during biopsy, thereby reducing the reliance of fluoroscopic imaging (20).

**Right Internal Jugular Vein Approach: Preshaped Bioptome**

The preshaped 50-cm bioptome is introduced through the venous sheath with the bioptome tip directed toward the lateral wall of the right atrium. The bioptome is slowly advanced, and in the mid right atrium it is rotated counterclockwise to facilitate passage across the tricuspid valve, avoiding the coronary sinus and tricuspid apparatus. The bioptome tip and handle have concordant motion and angulation, but positioning should always be confirmed fluoroscopically. Continued advancement and counterclockwise rotation allow passage into the mid right ventricle with the bioptome forceps directed toward the septum (Fig. 13.4). Extreme care should be taken to avoid perforation of the relatively thin right atrium, vena cava, or right ventricle with the stiff bioptome. If there is any resistance to bioptome passage, it should be withdrawn slightly and a different angle of entry attempted. Bioptome forceps must
never be forced or prolapsed into the ventricle. If passage into the right ventricle remains difficult, the path across the tricuspid valve may be defined by the passage of a balloon-tipped pulmonary artery catheter.

Once the bioptome is in the right ventricle, the tip should lie against the interventricular septum. On anterior-posterior fluoroscopy the bioptome should lie across the vertebral bodies and is usually directed inferiorly below and to the left of the tricuspid valve plane. Bioptome position may be confirmed by fluoroscopy in the 30° right anterior oblique and the 60° left anterior oblique projection. These views will confirm that the bioptome is on the ventricular side of the atrioventricular groove and pointed toward the septum. The absence of ectopy or fluoroscopy showing a position within the atrioventricular groove suggests the bioptome has entered the coronary sinus and must be withdrawn and repositioned before any biopsy is attempted. Even within the right ventricle, the thin right ventricular free wall must be avoided by directing the bioptome toward the septum (Fig. 13.5). The interventricular septum lies on a plane 45° from the chest wall, corresponding to a bioptome handle orientation posteriorly and to the left. In patients with right ventricular enlargement the handle may be straight posterior.

Contact with the interventricular septum is confirmed by premature ventricular beats. The biopsy forceps should be withdrawn 1 to 2 cm, opened, and advanced slowly to engage the septum. The forceps head is then closed slowly to collect the endomyocardial specimen. Given the trabeculations within the ventricle, gentle forward pressure should be applied during jaw closure to maintain contact with myocardium. Septal engagement may be marked by transmission of ventricular pulsations in posttransplant patients or in those with restrictive cardiomyopathy. Patients with idiopathic dilated cardiomyopathies may have no engagement sensation and contact with the septum can be confirmed only by the presence of premature ventricular beats.

The bioptome jaws must be closed to perform the biopsy and pressure must be maintained on the forceps closure device after the sample has been obtained and during withdrawal from the right ventricle, atrium, vena cava, and sheath to prevent the jaws from opening (Fig. 13.6). There may be a slight release of traction once the specimen is removed from the septum. Excessive resistance in bioptome withdrawal suggests entrapment on the tricuspid valve apparatus or an area of scar tissue. When this occurs, the forceps jaws should be opened, the bioptome withdrawn, and the bioptome repositioned to secure another biopsy site. During routine biopsy it is not uncommon for patients to experience a tugging sensation during specimen acquisition. Sharp chest pain, however, implies cardiac perforation. Other evidence that perforation may have
Figure 13.5  Right ventricular free wall. Abbreviations: PA, pulmonary artery; RA, right atrium; RV, right ventricle. Source: Courtesy of Leon Schlossberg, Ref. 12.

Figure 13.6  Bioprome position and tissue sample acquisition from the internal jugular approach. Source: Courtesy of Leon Schlossberg, Ref. 12.
occurred includes persistence of premature beats, excessive retraction of the ventricular septum during biopsy, and a sample that floats in fixative, implying epicardial fat content. Any of these clues should prompt close hemodynamic monitoring and fluoroscopy of the heart borders to detect tamponade. Perforation is less likely in patients with prior cardiac surgery and advanced cardiomyopathy, and more so in nonsurgical patients with normal chamber size and systolic function. At the end of every biopsy procedure, the heart borders should be examined with fluoroscopy to exclude tamponade prior to removal of venous access.

Right Internal Jugular Vein: Preformed Sheath

In this method, the preformed sheath rather than the biopsy probe itself is advanced into the right ventricle. The sheath directs a flexible straight biopsy probe to the desired biopsy site. A 7-French 45-cm preformed sheath may be inserted into the internal jugular vein. The performed sheath is positioned into the right ventricle with the aid of a guidewire or balloon-tipped catheter. Once in the right ventricle, the guidewire or catheter is removed and the sheath flushed with heparinized saline and connected to an infusion port to maintain patency. The sheath should be free-floating and not abutting ventricular myocardium. The distal segment of a flexible biopsy probe should be angulated or curved before insertion to avoid straightening the preformed sheath. Precurved biopsy probes may also be used through the preshaped sheath. The biopsy jaws should be opened immediately upon exiting the sheath to reduce risk of perforation. The biopsy probe is directed posteriorly, perpendicular to the interventricular septum. Gentle pressure is applied as the jaws are closed, then the sample may be removed as described above. The sheath should be flushed with saline and repeat biopsy performed as indicated.

Femoral Vein Approach: Preformed Sheath

From the femoral vein, a 7-French preformed guiding sheath can be introduced into the right ventricle using a balloon-tipped catheter, pigtail catheter, or guidewire. Rarely, in children, the femoral venous approach may be used to facilitate left ventricular biopsy by transseptal puncture (21). The standard preformed femoral sheath has a 130° angle from the right atrium into the right ventricle to facilitate positioning. The preshaped sheath may increase the risk of perforation because the operator may have less control of the direction of the biopsy probe to the cardiac septum. The femoral sheath must be evaluated before insertion to ensure that the sheath length after the angulation does not exceed the anatomic distance from the right atrium to ventricle for a given patient because of risk of perforation. This may be confirmed by placing the patient on a sterile field and imaging under fluoroscopy. Once the sheath is inserted it should be flushed to avoid clot formation. If there is any question about the position of the sheath tip, hand injection of contrast dye and hemodynamic monitoring may be helpful. After sheath insertion, the unshaped biopsy probe should be curved, similar to the jugular approach, to avoid straightening the preformed sheath when inserted. Posterior angulation of the biopsy probe tip out of the plane relative to the broad proximal curvature of the sheath can help direct the biopsy probe toward the interventricular septum upon exiting the sheath (Fig. 13.7).

Fluoroscopy can be used to track biopsy probe passage through the sheath and confirm interventricular septal position. Biopsy probe jaws should be opened just as the biopsy probe exits the preformed sheath to avoid perforation. After slow advancement to the septum, the jaws are slowly closed while forward pressure is maintained. If the sheath tip is resting against the septum, the biopsy probe can be exposed by retracting the sheath while maintaining the forceps in a stable position. After the forceps are withdrawn, the sheath can be repositioned within the ventricle for another biopsy attempt.

Left Ventricular Biopsy: Femoral Artery Preformed Sheath

The femoral artery approach usually requires insertion of a 9-French self-sealing sheath through which a preformed 7-French biopsy sheath is inserted to allow biopsy sheath manipulation. All femoral artery sheaths must be maintained with continuous infusion of heparinized saline to avoid embolic phenomenon. The preformed sheath is gently inserted into the left ventricle across the aortic valve using a guidewire and pigtail catheter. Once in the left ventricle, areas of prior myocardial infarction and inferior-posterior positions should be avoided to reduce the perforation risk in these relatively thin-walled sites. After the sheath is cleared of debris by aspiration and flushing, a 104-cm biopsy probe is inserted into the left ventricular cavity. The biopsy forceps should be directed away from the mitral valve apparatus. The jaws are opened upon exiting the sheath, directed toward the ventricular wall, the specimen is encapsulated, and the jaws are closed firmly while extracting the sample. The sheath is maintained within the left ventricle and repositioned to ensure sampling from several different sites. Since most myocardial disease processes affect both ventricles, right ventricular biopsy is preferred because of greater ease, short procedure time, and reduced likelihood of morbidity. In diseases with confirmed selective left ventricular involvement or in patients in whom right ventricular biopsy has been unsuccessful, left ventricular biopsy may be attempted. In general, left ventricular biopsy is reserved for cases with selective left ventricular involvement such as in endomyocardial fibrosis, scleroderma, left heart radiation, and cardiac fibroelastosis of infants and newborns.

Postprocedure Care

After biopsy sheath removal, pressure must be applied to prevent local bleeding complications. After uncomplicated biopsy, patients with biopsies from the jugular vein may be discharged home after one hour of observation. Patients who had femoral venous entry require two to three hours of supine bed rest before safely attempting ambulation. Patients with femoral arterial access require several hours of bed rest with or without use of a vascular closure device before ambulation. All patients must be monitored for bleeding and hemodynamic changes. The bandage applied to the vascular access site may be removed in 24 hours and oral intake may resume once patients can sit up.

INDICATIONS

Transplant Rejection

Endomyocardial biopsy has been the cornerstone of monitoring patients for rejection after heart or heart-lung transplantation (22,23). Early rejection may be detected on endomyocardial biopsy before clinical manifestations. Regular posttransplantation biopsies monitor antirejection therapy and can confirm the adequacy of pulsed immunosuppressive therapy for episodes of acute rejection. Despite promising research, no single methodology has had the predictive accuracy to replace endomyocardial
biopsy in the assessment of cellular and humoral rejection (24–26). Because rejection is a diffuse immune-mediated phenomenon, sampling errors are rare. The severity of rejection on biopsy has been divided into four grades as established by the International Society of Heart and Lung Transplantation (27). Grade 0R represents no rejection, grade 1R mild rejection, and grade 2R moderate rejection. Severe rejection (grade 3R) is marked by multifocal aggressive infiltrates and/or myocyte damage or diffuse polymorphous infiltrate with necrosis and a variable degree of edema, hemorrhage, or vasculitis. More severe rejection requires aggressive immunosuppression even in asymptomatic patients.

**Biopsy in the Management of Cardiovascular Disease**

Routine use of endomyocardial biopsy to inform management of a variety of cardiovascular diseases in patients without a heart transplant remains controversial. Decisions to proceed with endomyocardial biopsy are most often made on the basis of clinical presentation, not the underlying pathologic diagnosis, which is known only after biopsy. Few randomized, controlled treatment trials have evaluated the utility of heart biopsy in disease management, and recommendations are made on the basis of case-control series and expert opinion. A recent comprehensive Scientific Statement from the American Heart Association, American College of Cardiology, and European Society of Cardiology outlines the appropriate role of endomyocardial biopsy outside the posttransplant setting (28) (Table 13.1). Biopsy does have an important role in the evaluation of unexplained heart failure (29–31). Heart failure is considered to be unexplained when comprehensive testing including ECG, chest radiography, echocardiography, and coronary angiography fails to reveal a diagnosis. Standard evaluations of patients with new-onset cardiomyopathy are informative, but as many as half of this population has no diagnosis after routine testing (32). The potential value of direct assessment of heart muscle tissue in patients with new-onset heart failure may be more valuable in this population.

Patients most appropriate for biopsy are those with new-onset heart failure of less than two weeks duration...
Unexplained atrial fibrillation

Unexplained ventricular arrhythmias

Suspected arrhythmogenic right ventricular dysplasia/cardiomyopathy

New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle, without new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk

Unexplained cardiomyopathy in children

Suspected cardiac tumors

Heart failure associated with unexplained restrictive cardiomyopathy

Heart failure associated with suspected anthracycline cardiomyopathy

Heart failure associated with suspected allergic reaction and/or eosinophilia

Heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk

Class I: Conditions for which there is evidence or general agreement that biopsy is beneficial, useful and effective

- New-onset heart failure of <2 wk duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise.
- New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk

Class IIa: Conditions for which the weight of evidence/opinion is in favor of usefulness/efficacy

- Heart failure of >3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, that responds to usual care within 1–2 wk
- Heart failure associated with a dilated cardiomyopathy of any duration association with suspected allergic reaction and/or eosinophilia
- Heart failure with suspected anthracycline cardiomyopathy
- Heart failure associated with unexplained restrictive cardiomyopathy
- Suspected cardiac tumors
- Unexplained cardiomyopathy in children

Class IIb: Conditions for which usefulness/efficacy of biopsy is less well established by evidence/opinion

- New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle, without new ventricular arrhythmias, second- or third-degree heart block, that responds to usual care within 1–2 wk
- Heart failure of >3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, that responds to usual care within 1–2 wk
- Heart failure associated with unexplained hypertrophic cardiomyopathy
- Suspected arrhythmogenic right ventricular dysplasia/cardiomyopathy
- Unexplained ventricular arrhythmias

Class III: Conditions for which there is evidence and/or general agreement that biopsy is not useful

- Unexplained atrial fibrillation

accompagned by hemodynamic compromise or those with heart failure of two weeks to three months duration who have heart failure or dysrhythmias that fail to respond to standard therapies. Patients with severe cardiac compromise and duration of less than two weeks often have fulminant lymphocytic myocarditis and a good prognosis (33–35). These cases must be distinguished from similarly aggressive disorders such as giant cell myocarditis and necrotizing eosinophilic myocarditis, which have a similarly fulminant course, often requiring permanent mechanical support or consideration of cardiac transplantation (36,37). Giant cell myocarditis in particular may be associated with both ventricular tachycardia and atrioventricular block (38). Confirmation of histologic diagnosis of either giant cell or necrotizing eosinophilic myocarditis would lead to immunosuppressive treatment, while fulminant lymphocytic myocarditis resolves without such agents. Studies are ongoing to define the appropriate diagnostic criteria for myocarditis and guide appropriate immune modulating therapies (39,40).

Patients with long-term and established dilated cardiomyopathy responding to usual heart failure treatments have less to gain from endomyocardial biopsy. In these subjects, biopsy generally displays nonspecific findings of myocyte hypertrophy, interstitial and replacement fibrosis, and endocardial thickening (41,42). Such findings do not establish etiology, long-term prognosis, or guide specific therapies. Nevertheless, there is a subset of patients with dilated cardiomyopathy who may have specific disease processes identified on biopsy, particularly those who fail to respond to standard heart failure therapies and have refractory symptoms (Table 13.2). Patients with suspected cardiac sarcoidosis or myocarditis should be considered for heart biopsy.

Endomyocardial biopsy is also recommended for patients with cardiomyopathy from suspected anthracycline toxicity, cardiomyopathy associated with allergic or eosinophilic reaction, patients with unexplained ventricular tachycardia or conduction disease, or children with unexplained cardiomyopathy (28). Endomyocardial biopsy may also help establish a diagnosis in patients with underlying restrictive physiology, a common entity seen in patients with heart failure and a preserved ejection fraction. By helping distinguish between restrictive cardiomyopathy and constrictive pericarditis, biopsy can help spare patients inappropriate medical or surgical therapies (43). Disorders causing a restrictive cardiomyopathy include primary amyloidosis, Loeffer endomyocardial fibrosis, carcinoid-related heart disease, Fabry disease, and glycogen storage diseases (Table 13.3) (44,45).

<table>
<thead>
<tr>
<th>Table 13.1 Recommendations for Endomyocardial Biopsy</th>
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<tbody>
<tr>
<td><strong>Class I: Conditions for which there is evidence or general agreement that biopsy is beneficial, useful and effective</strong></td>
</tr>
<tr>
<td>- New-onset heart failure of &lt;2 wk duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise.</td>
</tr>
<tr>
<td>- New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Table 13.2 Cardiac Disorders with Specific Findings on Biopsy</th>
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</thead>
<tbody>
<tr>
<td><strong>Immune or inflammatory disease states</strong></td>
</tr>
<tr>
<td>- Myocarditis</td>
</tr>
<tr>
<td>- Cardiac allograft rejection</td>
</tr>
<tr>
<td>- Sarcoidosis</td>
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<tr>
<td>- Cytomegalovirus infection</td>
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<tr>
<td>- Toxoplasmosis</td>
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<tr>
<td>- Rheumatic carditis</td>
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<tr>
<td>- Chagas disease</td>
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<tr>
<td>- Kawasaki disease</td>
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<tr>
<td><strong>Degenerative</strong></td>
</tr>
<tr>
<td>- Idiopathic cardiomyopathy</td>
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<tr>
<td>- Anthracycline cardiomyopathy</td>
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<tr>
<td>- Radiation cardiomyopathy</td>
</tr>
<tr>
<td><strong>Infiltrative</strong></td>
</tr>
<tr>
<td>- Amyloidosis</td>
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<tr>
<td>- Gaucher’s disease</td>
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<tr>
<td>- Hemochromatosis</td>
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<tr>
<td>- Fabry’s disease</td>
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<tr>
<td>- Glycogen storage disease</td>
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<tr>
<td>- Ischemic</td>
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<tr>
<td>- Acute myocardial infarction</td>
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<tr>
<td>- Chronic ischemic cardiomyopathy</td>
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<tr>
<td>- Schonlein-Henoch purpura</td>
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<tr>
<td><strong>Cancer</strong></td>
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<tr>
<td>- Primary cardiac cancer</td>
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<tr>
<td>- Metastatic cardiac cancer</td>
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</tbody>
</table>

Source: Adapted from Ref. 28.
Table 13.3  Restrictive Cardiomyopathies

<table>
<thead>
<tr>
<th>Myocardial</th>
<th>Endocardial</th>
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</thead>
<tbody>
<tr>
<td>Noninfiltrative</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Familial</td>
<td>Carcinoid</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Radiation</td>
</tr>
<tr>
<td>Diabetic</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Drugs</td>
</tr>
<tr>
<td>Amyloid</td>
<td></td>
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<tr>
<td>Sarcoid</td>
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<tr>
<td>Gaucher’s</td>
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<tr>
<td>Hurler’s</td>
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<td>Fatty</td>
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<tr>
<td>Storage</td>
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<tr>
<td>Hemochromatosis</td>
<td></td>
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<tr>
<td>Fabry’s</td>
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<tr>
<td>Glycogen</td>
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</tbody>
</table>

CLINICAL ASPECTS

Equipment needed for endomyocardial biopsy is listed in Table 13.4.

Biopsy Complications

Complications associated with endomyocardial biopsy are considered either acute (while the patient is still in the catheterization laboratory) and delayed. The vast majority of complications fall into the acute category. Potential acute complications include ventricular perforation and pericardial tamponade, malignant ventricular or supraventricular arrhythmias, transient complete heart block, pneumothorax, central artery puncture, nerve paresis, thromboembolism, systemic platelet embolization associated with left ventricular biopsy, venous or arterial hematoma, damage of the tricuspid or mitral valve, and creation of arterial venous fistula within the heart.

Table 13.4  Equipment

- 18-gauge Amplatz needle or 22-gauge micropuncture needle
- 250 mL of flush solution (with heparin unless allergic)
- 4- or 5-French micropuncture sheath
- 7-, 8-, or 9-French self-sealing introducer with 0.038 guidewire
- Assorted syringes (1, 5, 10, 20 mL)
- Automatic intermittent cutaneous or invasive blood pressure monitor
- Continuous electrocardiographic monitor
- Continuous oxygen saturation monitor
- Defibrillator
- Dry ice
- Emergency equipment
- Other screen or drape support (optional)
- Formalin
- Glutaraldehyde
- Lidocaine 1% or 2%, 15 mL
- Micropuncture wire, 0.021
- Mosquito clamp or small-tipped instrument
- Number 11 surgical blade and handle
- 1 25-, 1 22-, and 3-4 18-gauge needles
- Pacemaker and pacing leads
- Pericardiocentesis set
- Plastic or cloth drape set
- Povidone-iodine, alcohol, or both
- Resuscitation drugs and equipment
- Tissue preservative
- Vascular ultrasound machine (i.e., SonoSite M-turbo)

Delayed complications include access site bleeding and damage to the tricuspid valve from repeated trauma associated with transplant rejection surveillance.

Factors associated with endomyocardial biopsy complication risk include operator experience, patient clinical status, indication for biopsy, access site, underlying cardiac conduction disease (presence of a left bundle branch block), and possibly biopsy site, since allergic reactions to reusable biopsies have been reported. Fowles and Mason reported a complication rate of <1% in over 4000 transplant and cardiomyopathy patients biopsied at Stanford University (46). They reported no deaths in their series. Cardiac tamponade occurred in four patients (<0.14%), none of whom needed thoracotomy. Other complications included atrial fibrillation in three patients, and sustained ventricular arrhythmia in one patient. Complications related to the internal jugular vein approach included pneumothorax in three patients, uncomplicated air embolism in six patients, transient right recurrent laryngeal nerve paresis in two patients, and Horner’s syndrome in one patient. Similarly, Sekiguchi and Take reported, by questionnaire, an overall complication rate of 1.17% in 6739 worldwide patients, including perforation in 28 patients (0.42%) and death in two patients (0.03%) (47).

Deckers et al. prospectively recorded complications of right heart biopsy from 546 procedures in 464 consecutive patients with new-onset idiopathic cardiomyopathy (48). The internal jugular vein was the primary site of access in 96% of cases. An overall complication rate of 6% occurred in this series. Of these complications, 15 (2.7%) occurred during catheter insertion including 12 arterial punctures (2%), 2 vasovagal reactions (0.4%), and 1 episode of prolonged bleeding (0.2%), all without sequelae. There were 18 (3.3%) complications during the actual biopsy, including six arrhythmias (1.1%), five conduction abnormalities (1%), four possible perforations (0.7%), and three definite perforations (0.5%) (pericardial fluid). Two (0.4%) of the three patients with definite perforation died.

Biopsy complications occur at a similar rate when echocardiography rather than fluoroscopy is used to guide the procedure. Han et al. prospectively recorded complications of right heart biopsy in 90 consecutive nontransplant patients who underwent two-dimensional echocardiography-guided transseptal biopsy (49). The overall complication rate was 5.6% and no deaths occurred in this cohort. Myocardial perforation occurred in three patients but did not progress to cardiac tamponade requiring pericardiocentesis in any patient. Unstable ventricular tachycardia occurred in one patient, and a new and persistent right bundle branch block occurred in one patient.

Baraldi-Junkins et al. reviewed 2454 endomyocardial biopsies performed in 133 cardiac transplant patients (50). An overall complication rate of 3.0% occurred, however, no perforations or deaths were observed in this cohort. Of these, 56 (2.3%) complications were associated with catheter insertion, including carotid puncture (1.8%), vasovagal reaction (0.1%), and prolonged bleeding (0.4%). Complications during biopsy included arrhythmias (0.25%) and conduction abnormalities (0.2%). Additional complications included five episodes (three patients) of allergic reaction to a reusable bioprobe and one case of pacemaker dislodgement.

Recently, Holzmann and colleagues reported results of a retrospective and prospective study examining the incidence of major and minor complications of right ventricular endomyocardial biopsies via the right femoral vein approach at a single
center in Germany (51). In their study, 1919 patients underwent 2505 endomyocardial biopsy procedures retrospectively evaluated between January 1995 and December 2003, and 496 patients underwent 543 endomyocardial biopsy procedures prospectively assessed between January 2004 and December 2005. Major complications (pericardial tamponade requiring pericardiocentesis, pneumothorax or hemothorax, permanent pacemaker support, cases requiring emergency cardiac surgery, or death) were extremely rare in both the retrospective study (0.12%) and the prospective study (0%). No deaths were reported during either study (total of 3048 endomyocardial biopsies). Major complications reported during the retrospective study included: cardiac perforation in two cases (0.08%) and permanent pacemaker in one patient (0.04%). No major complications occurred during the prospective study. A difference was reported in the incidence of minor complications (hemodynamically insignificant pericardial effusion, conduction abnormality not requiring permanent pacemaker, or arrhythmias not requiring ACLS) between the retrospective and prospective studies. Minor complications occurred in 0.20% of the endomyocardial procedures in the retrospective study and 5.5% in the prospective study. Five patients (0.20%) developed complete heart block requiring temporary pacing during the retrospective study. Minor complications seen during the prospective study included four cases (0.74%) of hemodynamically insignificant pericardial effusion, conduction abnormality not requiring temporary pacing in 12 patients (1.84%), temporary pacing requirement in eight cases (1.47%), and atrial fibrillation in 6 patients (1.1%). The authors believed the most likely reason for the increased minor complication rate observed during the prospective study compared with the retrospective study was a more detailed documentation sheet initiated during the prospective study.

The risk of endomyocardial biopsy in children was studied by Pophal et al. in a retrospective review of 1000 consecutive heart biopsies in 194 children (52). The mean age at the time of biopsy was 8.6 years (8 days–18 years), mean weight was 30 kg (2.8–127 kg), mean height was 121 cm (48–187 cm) and mean body surface area was 0.98 m² (0.18–2.05 m²). Indications for heart biopsy included heart transplant rejection surveillance (84.6%) and the evaluation of cardiomyopathy or arrhythmia for possible myocarditis (15.4%). The overall incidence of a serious complication from endomyocardial biopsy was 1.9%. There were nine perforations (0.9%) and one death (0.1%) secondary to perforation. In the evaluation of cardiomyopathy or myocarditis, the incidence of complication was 9.1%, perforation was 5.2% and mortality was 0.6%. In patients undergoing biopsy for transplant rejection surveillance, the incidence of complication was 0.6%, perforation was 0.1%, and no deaths occurred.

No reported series has estimated complication rates from left ventricular biopsies. In addition to the risk of arterial versus venous access, these patients require antplatelet therapy and heparinized sheaths, which may increase the risk of bleeding. Platelet emboli into the systemic arterial bed place patients at increased risk for central nervous system complications. The risk of perforation from left ventricular biopsy is probably not decreased compared with the right ventricular approach.

On the basis of these studies the estimated risk of complication related to endomyocardial biopsy for the evaluation of cardiomyopathy or for possible myocarditis is 1% to 6%. The risk of fatal complication is 0% to 0.4%. Of note, there appears to be a lower risk of morbidity and mortality related to endomyocardial biopsy for the purpose of heart transplant rejection surveillance.

Perforation
The greatest risk to patients undergoing endomyocardial biopsy is ventricular perforation. If hemodynamically significant and left uncorrected, such perforation can lead to pericardial tamponade and death (53). Factors associated with an increased likelihood of perforation include bleeding diathesis, recent receipt of heparin, pulmonary hypertension, and increased right ventricular systolic pressures or right ventricular enlargement. Patients with a prothrombin time >18 seconds or who have received heparin without reversal within the prior two hours should probably not undergo endomyocardial biopsy. Perforation is usually a complication of injury to the right ventricular free wall, which is only 1 to 2 mm thick. Interestingly, performance of left ventricular biopsy shares similar perforation complication rates despite significantly thicker ventricular walls.

It is critical that clinicians who perform endomyocardial biopsy have a high index of suspicion for cardiac perforation. To this end, any patient complaining of pain during the performance of the endomyocardial biopsy should be considered to have experienced cardiac perforation. Typically, patients with perforation immediately complain of a visceral pain and within one to two minutes may develop vagal symptoms including bradycardia and hypotension. Despite the excess parasympathetic tone thought to underlie these symptoms, limited benefit is achieved by atropine administration. Further biopsy attempts are contra-indicated until a thorough investigation into the patient’s complaints has been completed. If cardiac perforation is suspected, continuous evaluation of right atrial pressure and the pulsatility of the right and left heart borders by fluoroscopy should be performed. Increased right atrial pressure and loss of pulsation of heart borders are strong indicators for pericardial tamponade. Emergent trans-thoracic echocardiography should be obtained to determine the presence and severity of pericardial blood accumulation.

Cardiovascular collapse or electrical mechanical disassociation (PEA arrest) in the setting of a biopsy should be considered to be presumptive evidence of pericardial tamponade, and mandates immediate pericardiocentesis, even in the absence of echocardiographic confirmation of tamponade. Occasionally acute bleeding into the pericardial space will clot and prevent adequate draining by pericardiocentesis. Should this situation arise in a hemodynamically unstable patient, it may be necessary that the pericardial space be surgically evacuated, occasionally in the catheterization laboratory. Because of the risk of tamponade, a pericardiocentesis tray should always be available in the procedure room where endomyocardial biopsies are performed.

**Malignant Ventricular Arrhythmias**

Ventricular ectopy is an expected consequence of cannulation and mechanical stimulation of the cardiac chambers by the sheath or bioptome. In fact, premature ventricular contractions are utilized as an indication of appropriate placement of the bioptome or biopsy sheath within the ventricular cavity. Rarely, sustained malignant ventricular arrhythmias may develop during the biopsy procedure. Risk factors for this complication include cardiomyopathy and preexistent ventricular arrhythmias. Treatment begins with immediate withdrawal of the bioptome or biopsy sheath from the ventricular cavity. Should
this fail to stop the arrhythmia, medical therapy with antiarhythmic agents or cardioversion may be necessary.

Supraventricular Arrhythmias
During instrumentation of the right atrium, the atrial wall may be stimulated leading to supraventricular arrhythmias. Risk factors for this complication include prior history of supraventricular arrhythmia or elevated right sided filling pressures. Operators should try to avoid right atrial wall contact, particularly in patients identified at risk. In the event that a supraventricular tachycardia develops, mechanical interruption of the circus rhythm may be attempted by touching the right atrial wall with the bioptome. However, this may lead to an increased risk of cardiac perforation.

Heart Block
Occasionally patients with preexistent left bundle branch block may develop complete heart block during manipulation of instruments within the right heart. Pressure against the septum near the tricuspid apparatus may “stun” the right bundle resulting in a new right bundle branch block. In patients with a preexistent left bundle branch block, the addition of a new right bundle branch block results in progression to complete heart block. Removal of the offending bioptome or catheter often resolves the complete heart block; however, should complete heart block persist, a temporary pacing catheter can be inserted into the right ventricular cavity. For this reason, a temporary pacemaker and pacing wire should be immediately available in the catheterization laboratory for emergent use if needed, particularly in patients with a preexistent left bundle branch block.

Pneumothorax and Hemotorax
Puncture of the lung pleura during performance of internal jugular or subclavian venous access may result in a pneumothorax or hemotorax. On the basis of a large meta-analysis of 17 prospective comparative trials including data on 2085 jugular and 2428 subclavian catheters, the risk of one of these complications has been estimated at 1.5% for subclavian venous access and 1.3% for internal jugular venous access (54). Several strategies can be utilized to minimize this risk. A growing body of literature supports the use of real time two-dimensional ultrasound guidance for internal jugular venous access (55,56). Secondly, strict attention to detail should be maintained during insertion. This includes performing a “higher” internal jugular stick with avoidance of the immediate supraclavicular region, continuous aspiration of the needle plunger during every attempt at venous entry, and also during subclavian venous access the operator should never let the needle drop below the horizontal plane. Immediate investigation with fluoroscopy of the lung margins should be performed in any patient undergoing endomyocardial biopsy who complains of spontaneous shortness of breath. Urgent pneumothorax or hemotorax evacuation should be performed as needed.

Puncture of the Carotid, Subclavian, or Femoral Artery
Central veins lie adjacent to their corresponding arteries. The risk of carotid, subclavian, and femoral artery puncture has been estimated to be approximately 3%, 0.5% to 5%, and 9%, respectively (54,57). Under most circumstances, the operator can easily distinguish an arterial puncture from a venous puncture by the red color and pulsatile flow of arterial blood. In patients with significant hypoxemia and/or reduced cardiac output (i.e., cardiomyopathy), this distinction can sometimes be difficult. To help distinguish between arterial and venous blood, the operator may send a sample of blood for blood gas analysis. Alternatively, the operator can insert a small 18-gauge catheter over the guidewire and then determine the pressure waveform of the vessel cannulated. Puncture of an artery utilizing the finder or micropuncture needle should be addressed by withdrawal of the needle and compression of the vessel until homeostasis is obtained. This does not preclude performance of a safe venous approach. Cannulation of an artery with a large (7–9 French) sheath is a more serious complication that requires urgent vascular surgery consultation. In this situation the sheath should not be removed before surgical consultation because of the risk of hemorrhage.

Thromboembolic Phenomenon
Patients with preformed sheaths which are not continuously flushed may develop a clot within the sheath during the performance of the endomyocardial biopsy (58). As the bioptome is advanced through the clot-containing sheath, this can lead to expulsion of the clot into the patient’s circulation. When this occurs during right ventricular biopsy it can lead to pulmonary embolization. Should this occur during a left ventricular biopsy or during a right ventricular biopsy in a patient with a right-to-left shunt, systemic embolization can occur. A risk unique to left ventricular biopsy is systemic platelet embolization. The incidence of platelet emboli during left heart biopsy has not been reported. Some operators suggest use of antplatelet therapy such as aspirin prior to biopsying the left heart.

Nerve Paresis
Infiltration of local anesthesia into the jugular venous or carotid sheath may result in a Horner’s syndrome, vocal cord paresis, or rarely diaphragmatic weakness (59,60). These complications typically last a few hours (on the basis of the half-life of the local anesthetic used) unless direct nerve trauma has occurred from the needle itself.

Tricuspid Valve Damage
Tricuspid regurgitation is a well recognized complication of endomyocardial biopsy (61). In fact, tricuspid regurgitation is the most common valvular lesion after orthotropic heart transplantation. The most common etiology of significant tricuspid regurgitation in the posttransplant patient is endomyocardial biopsy performed to detect allograft rejection. Endomyocardial biopsy can lead to direct anatomic disruption of the valve apparatus, such as ruptured chordae tendinae or torn leaflet (62). In their study of 98 posttransplant patients, Mielniczuk et al. found histologic evidence of chordal tissue in 9% of endomyocardial biopsy specimens, which accounted for 47% of patients with significant tricuspid regurgitation in their cohort (63). Nguyen et al. examined whether there was a correlation between the number of endomyocardial biopsies and the risk of severe tricuspid valvular regurgitation (64). In their study of 101 posttransplant patients they found 60% of patients with more than 31 endomyocardial biopsies had developed severe tricuspid regurgitation, whereas none of the patients with fewer than 18 endomyocardial biopsies had severe tricuspid regurgitation.

Hematoma
A venous or arterial hematoma may form as a result of excessive movement of the sheath during the biopsy procedure, inadequate compression of the vascular access site after
removal of the sheath, or late bleeding due to a transient or sustained increase in right atrial or mean arterial pressure. Patients with coagulopathy or who are on anticoagulant therapy as well as aspirin are at increased risk for hematoma formation and should be monitored more closely.

**Arterial-Ventricular Fistula**

Occasionally arterial-ventricular fistulas develop between small branches of a coronary artery and the right ventricle in post cardiac transplant patients (65). These are caused by inadvertent biopsy of septal branches of a coronary artery and subsequent arterial communication into the right ventricle. Several studies have shown that these fistulae are of no clinical consequence and can be followed conservatively.

**LIMITATIONS**

**Sampling Error**

One limitation of endomyocardial biopsy as a diagnostic tool for myocarditis or transplant rejection is that it is prone to sampling error. Since myocarditis, and to a lesser extent transplant rejection, tend to be focal processes, accurate diagnosis depends on adequate sampling of the myocardium. Standard biotomes sample approximately 1 to 2 mm³ (30 mg) of endomyocardium with each biopsy. Researchers have demonstrated on ex-vivo hearts with histologically proven myocarditis (either postmortem or explanted) that sampling error contributes appreciably to false negative results (66). Chow et al. demonstrated that from a single endomyocardial biopsy, histologic myocarditis could be demonstrated in only 25% of samples (67). With more than five random samples, Dallas criteria myocarditis could be diagnosed in approximately two-thirds of subjects. Most recently, Mahrholdt et al. demonstrated by cardiovascular magnetic resonance imaging that the earliest myocardial inflammatory abnormalities in myocarditis are located in the lateral wall of the left ventricle, a site that is not available to biopsy with the standard approach (19). For transplant rejection surveillance, the sensitivity of detecting transplant rejection approaches 98% when five adequate biopsy samples are obtained (68).

**Limitations of the Dallas Criteria**

Originally proposed in 1986, the Dallas criteria established a histopathologic categorization by which the diagnosis of myocarditis could be made (69). According to the Dallas criteria, active myocarditis requires an inflammatory infiltrate and associated myocyte necrosis or damage uncharacteristic of an ischemic event. Borderline myocarditis requires a less intense inflammatory infiltrate and no light microscopic evidence of myocyte destruction. Data from the Myocarditis Treatment Trial reveal that approximately 10% of patients (214 out of 2233) with clinically suspected myocarditis (new-onset unexplained heart failure during the two years preceding enrollment) who underwent endomyocardial biopsy were diagnosed by the current histopathologic Dallas criteria (40).

To compound this further, the Dallas criteria require that biopsy specimens be examined by qualified cardiac pathologists. Additionally, even when specimens are examined by expert cardiac pathologists there are variations in the interpretation of histologic samples. In the Myocarditis Treatment Trial, only 64% of the 111 patients diagnosed with myocarditis by endomyocardial biopsy had their diagnosis confirmed by the expert pathology panel during review of the same biopsy samples at a later date. In a separate analysis of interobserver variability, Shane et al. submitted endomyocardial biopsy specimens from 16 patients with dilated cardiomyopathy to seven expert cardiac pathologists. Their assessments varied remarkably with respect to significant fibrosis (25–69%), hyper trophy (19–88%), nuclear changes (31–94%), lymphocyte count per high-power field (0–38%), and the diagnosis of myocarditis. Definite or probable myocarditis was diagnosed in 11 of 16 patients by at least one pathologist. However, of the 11 patients, three of seven pathologists agreed on the diagnosis in 3 patients and two of seven pathologists agreed on the diagnosis in 5 patients.

Several researchers have demonstrated the presence of cardiotoxic virus in myocardium in the absence of Dallas criteria myocarditis. Martin et al. utilized polymerase chain reaction (PCR) to analyze myocardial tissue samples from 34 patients with suspected acute viral myocarditis. They demonstrated that 26 heart biopsy samples were positive for viral pathogens, and 13 of the 26 positive samples had no evidence of Dallas criteria myocarditis (70). Pauschinger et al. found either adenoviral or enteroviral PCR positivity in 24 myocardial tissue samples (none of which showed histopathologic evidence of myocarditis) from 94 patients with “idiopathic” dilated cardiomyopathy (71). In a separate study of 45 patients with left ventricular dysfunction and suspected myocarditis, Pauschinger et al., demonstrated nonreplicative enterovirus in 40% of patients. Of the 18 patients with nonreplicative virus, 56% were found to have active viral replication as well (72). In this study 13% of the biopsy samples were diagnosed as having Dallas criteria borderline myocarditis, however, histopathology did not help to distinguish between patients with and those without entero viral positivity. Why et al. showed in their cohort of 120 patients with idiopathic dilated cardiomyopathy that the 34% who were enteroviral positive had a significantly worse outcome over two years compared with those who were enteroviral negative (73). Taken together, virus can exist in the myocardium (even in a replicative form) in the absence of histopathologic findings adequate to meet Dallas criteria and may adversely affect outcome.

Another limitation in the usefulness of the Dallas criteria is the dissociation between histopathology findings and response to immune modulation therapy. For instance, in the Myocarditis Treatment Trial, there was no difference in one- or five-year survival or improvement of left ventricular ejection fraction at 28 weeks in patients with Dallas criteria myocarditis treated with immunosuppressive therapy or placebo. Other authors have used alternative criteria to diagnose immune-related heart disease such as HLA upregulation on endomyocardial biopsy. Wojnicz et al. found HLA upregulation in cardiac biopsy samples from 84 of 202 patients (41.6%) with new-onset cardiomyopathy, while only 27% were positive by Dallas criteria for myocarditis (74). HLA-identified patients were randomized to receive treatment with either immunosuppressive therapy or placebo. After two years of follow-up, there was no significant difference in the primary endpoint (a composite of death, heart transplantation, and hospital readmission) between the study groups (22.8% for the immunosuppression group and 20.5% for the placebo group); however, the ejection fraction in the immunosuppressive group increased from 24% to 36%, whereas it remained unchanged in the placebo group (25–27%).

Despite the presence of Dallas criteria myocarditis, response to treatment may be influenced by the presence of...
virus or immunologic response to infection. This was most clearly demonstrated by Frustaci et al. in their study of immunosuppressive therapy in patients with Dallas criteria myocarditis who failed to respond to conventional therapy (75). Out of 652 patients who underwent endomyocardial biopsy, 112 were identified with Dallas criteria myocarditis. Of these 112 patients, 41 had progressive congestive heart failure despite standard medical therapy and were treated with prednisone and azathioprine for six months. Twenty-one patients responded to treatment with improvement of left ventricular ejection fraction from 25.7% to 47.1%, and showed evidence of healed myocarditis on follow-up biopsy. Twenty patients failed to respond to treatment and showed a histologic evolution toward dilated cardiomyopathy. Viral genomes were present in endomyocardial biopsy specimens in 85% of nonresponders versus 13% of responders. Circulating cardiac antibodies were present in 90% of responders versus 0% of nonresponders. Given that the Dallas criteria are prone to sampling error, interobserver variability, variance with other markers of viral infection and immune activation in the heart, and variance with treatment outcomes, we suggest that the Dallas criteria should no longer be used to diagnose myocarditis in isolation. Instead, myocarditis should be diagnosed on the basis of a combination of clinical presentation, histopathology, immunohistochemistry, viral PCR, cardiac antibody assessment, and imaging results.

SPECIAL ISSUES

Tissue Processing

The clinician performing the endomyocardial biopsy is responsible for obtaining adequate tissue for analysis and ensuring the tissue is placed in the appropriate preservative. The number of specimens obtained depends on the clinical situation and studies to be performed. Adequate diagnostic yield from repeated biopsy must be balanced against the risk of the biopsy procedure. It is generally recommended that at least five separate specimens, each 1 to 2 mm³ in size, be obtained from more than one region to minimize sampling error. For transplant rejection surveillance, the International Society of Heart and Lung Transplantation requires a minimum of four biopsy specimens, each with less than 50% of the sample being fibrous tissue, thrombus, or other noninterpretable tissues, such as those with crush artifact. The sensitivity of detecting transplant rejection approaches 98% when the pathologist reviews five adequate biopsy samples (76).

To avoid contamination of the biopsy specimen, once the bioprobe forceps have been removed from the venous sheath and the jaws are opened, the sample should be gently extracted with a sterile needle and placed immediately into preservative solution (10% neutral buffered formalin) (77,78). Fixative should be at room temperature to prevent contraction band artifacts (79). Excessive traction or crushing of the sample, as well as cutting a single larger sample into many, should be avoided because it may disrupt histologic architecture. Additional samples may be submitted for transmission electron microscopy to evaluate infiltrative diseases or anthracycline toxicity (80). For transmission electron microscopy, pieces are fixed in 4% glutaraldehyde at room temperature. One or more samples may be frozen for molecular analysis, immunofluorescence, immunohistochemistry, or viral genome analysis. To prepare frozen specimens in the catheterization laboratory, samples should be placed in embedding solution then snap-frozen in OCT-embedding medium or alternatively placed in RNAlater solution and stored at −80° F. These study samples may be required for suspected myocarditis, amyloid classification, tumor typing, or viral genome analysis. Additional sample preparation may be individualized for evaluation of specific disease states (e.g., amyloid, iron staining). It is the operator’s responsibility to ensure timely delivery of biopsy samples to the appropriate pathologic laboratory.

Cardiac Pathologist

Experienced cardiac pathologists are central to any biopsy program. The safest and most pristine biopsy specimen is useless without an experienced cardiac pathologist who is fully trained in the evaluation of biopsy-obtained tissue and conversant with the latest classification schemes. Crush artifacts or contraction bands are frequently present in biopsy specimens and may be incorrectly interpreted by an inexperienced or noncardiac pathologist. The operator may assist the pathologist through careful handling of the biopsy specimen in the catheterization laboratory, by ensuring that the heart biopsy specimens obtained are delivered to the appropriate laboratory for analysis, and by reviewing the slide material obtained with the pathologist to provide clinical details and to ensure that special studies are obtained as needed.

Light Microscopic Examination and Stains

Endomyocardial biopsy tissue that is going to be examined by routine light microscopy is embedded in paraffin and serially sectioned into 4 µm thick layers mounted on sequentially numbered glass slides. In cases of suspected myocarditis, most laboratories stain every third slide with hematoxylin and eosin for histomorphologic characterization. Two slides are typically stained with Movat or elastic trichrome stain to visualize collagen and elastic tissue. In addition, many laboratories will stain one slide for iron on specimens from men and all postmenopausal women. Congo red staining is performed on a 10- to 15-µm section in all patients over the age of 50 to identify cardiac amyloidosis. Table 13.5 summarizes the stains that are occasionally used in the evaluation of heart biopsy samples depending on the clinical situation.

Molecular Studies

Increasingly, molecular techniques are available which improve the clinical utility of endomyocardial biopsy, above
and beyond the simple histopathologic and biochemical analysis that has been available to this point. Advances in PCR techniques allow pathologists or investigators to determine whether or not the patient’s cardiomyopathy or myocarditis is associated with a preexistent or ongoing viral infection (72). Current PCR techniques can detect fewer than 10 gene copies of viral pathogens in an endomyocardial biopsy sample. For PCR analysis to be considered reliable the biopsy sample must be rapidly and properly transported to the laboratory for analysis. Proper handling of the sample includes the use of pathogen-free biopsy devices and storage vials and the transportation of biopsy specimens in RNA later solution on dry ice at room temperature.

Over the past 20 years, the use of PCR has increased our understanding about possible cardiotropic viruses in patients with unexplained cardiomyopathy. Numerous studies of patients with myocarditis or dilated cardiomyopathy have reported a wide range of viruses including enteroviruses (most commonly Coxsackie B virus), adenoviruses, Parvovirus B19, cytomegalovirus, influenza and respiratory syncytial virus, EBstein-Barr virus, HIV, Hepatitis C virus, and human herpes virus 6 (81–87). There are several limitations to the widespread use of PCR in screening endomyocardial biopsy samples for cardiotropic viruses. Currently available PCR-based viral isolation techniques remain labor intensive, costly, and lack standardization. Existing PCR screening methods are also restricted to a limited number of predetermined candidate viruses. Because the number of biopsy samples needed to attain a clinically acceptable sensitivity for cardiotropic viruses is not known, a positive PCR is diagnostic of viral infection, however, a negative PCR does not exclude viral infection. Lastly, and most importantly, presence of viral genomic material in biopsy specimens does not prove causality of cardiomyopathy and currently does not change management strategy.

Molecular studies can also be utilized to look for immune markers, such as HLA upregulation and immune deposition to identify those patients who have an autoimmune process that may be perpetuating ventricular dysfunction (74). Molecular studies are not limited to diagnostic evaluation but have also been shown to have prognostic implications in patients with new-onset idiopathic cardiomyopathy. Heidecker et al. demonstrated that microarray technology could be utilized to generate a transcriptomic signature (45 genes) from a single endomyocardial biopsy, which could predict prognosis in patients with new-onset heart failure of unclear etiology with very high specificity (90%) (88).

**CONCLUSIONS**

Endomyocardial biopsy remains an integral mode of investigation for diagnosing many primary and secondary myocardial conditions. The modern approach to endomyocardial biopsy was introduced by Sakakibara and Konno in the early 1960s and then modified and popularized by the Stanford group in the early 1970s as a means to monitor graft rejection following cardiac transplantation. Since then, the right ventricular heart biopsy procedure has gained acceptance as a useful investigative tool for nontransplant cardiac pathology. The indications for endomyocardial biopsy have been outlined in a consensus statement published in 2007 by the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Indications for endomyocardial biopsy include post-transplant rejection surveillance, investigation of infiltrative disorders of the myocardium, primary cardiomyopathies, myocarditis, endocardial fibrosis (as a way to help distinguish between constrictive and restrictive pathology), drug toxicity, ventricular arrhythmias, unexplained heart failure in children, and suspected cardiac neoplasia. Cardiac biopsy is extremely safe when performed by an experienced operator. Complication rates are reduced by appropriate patient selection, careful biopsy technique guided by fluoroscopy and ultrasound, as well as close patient monitoring. The role of endomyocardial biopsy continues to evolve as novel molecular and genetic analyses shed new light on heart muscle disorders.

**REFERENCES**


**Future Directions**

The clinical utility of endomyocardial biopsy will no doubt be strengthened by the application of highly specific molecular probes and microarray DNA technology used to look for viral genomic material and autoimmunity in heart biopsy specimens. Our current understanding of idiopathic cardiomyopathies is that they are the consequence of a complex interplay between inflammatory, infectious, autoimmune, and genetic factors ultimately resulting in myocardial injury and remodeling. With the improvement and increased availability of techniques to define immune upregulation and viral persistence it is likely that endomyocardial biopsies will redefine myocarditis and its appropriate treatment. Only through a detailed understanding of the pathobiology of idiopathic cardiomyopathies will we be able to develop novel therapies targeted at these important disorders.
Pericardiocentesis

Carl L. Tommaso

INTRODUCTION
Pericardiocentesis is the transcutaneous drainage of fluid from the pericardium. It may be performed for diagnostic or therapeutic indications. Pericardiocentesis may be performed on an elective or emergent basis and when done emergently may be life saving. It may be done to withdraw fluid from the pericardial space for diagnostic testing or may involve insertion of a drain for relieving the pericardial effusion over hours to days.

ANATOMIC CONSIDERATIONS
The pericardium consists of two layers: the visceral pericardium is adherent to the epicardium, and the parietal pericardium has attachments to the diaphragm, the sternum, and the anterior mediastinum. The parietal pericardium is normally about 1 to 2 mm thick and holds the heart in a relatively fixed position during respiration and changes in body position. The two layers are continuous and form a “sac” surrounding most of the heart except for the left atrium that is mostly extrapericardial. The pericardial reflection includes the origins of the vena cava and the origins of the great vessels. The phrenic nerves are the only nonvascular structures included within the pericardium.

The vena cava and right ventricle are the most anterior cardiac structures and attempted pericardiocentesis may risk perforating or entering either of these structures. The left anterior descending coronary artery is the most anterior of the coronary arteries, and while unlikely, can be punctured during pericardiocentesis. The internal thoracic arteries are located on the posterior surface of the chest wall in the midclavicular line. Although not usually in the path of a pericardiocentesis needle, during attempts at a lateral loculated effusion they could be in the pathway.

Within the normal pericardial sac is approximately 50 mL of serous fluid. The normal pericardium is relatively inelastic and small amounts of additional fluid (<100 mL) may compromise filling of cardiac chambers (cardiac tamponade). With chronic fluid accumulation, however, the pericardium may progressively stretch, become elastic, and accommodate large amounts of fluid without hemodynamic alteration.

When pericardial effusions occur the fluid may be distributed throughout the pericardial space or may be loculated, depending on the etiology of the effusion (Table 14.1) and prior pericardial disease or surgery.

INDICATIONS
Pericardiocentesis may be performed for diagnostic or therapeutic reasons. The most common diagnostic indication is to discern the etiology of accumulated pericardial fluid, usually in a patient with a chronic effusion of uncertain etiology.

Pericardial effusions can be inflammatory, uremic, infectious, or oncologic in nature or due to congestive heart failure (1). Therapeutic pericardiocentesis is performed for the relief of cardiac tamponade. Tamponade may be due to any of the above etiologies, but is most commonly due to trauma such as perforation of a cardiac structure during an intervention (2) or closed chest trauma.

APPRAOCH
There are several approaches to the performance of a pericardiocentesis regarding guidance, technique, and location. The most common approach is echocardiographically guided (3). Prior to the procedure an echocardiogram is obtained to ascertain the size and location of the effusion. A small or noncompressive effusion may not be necessary to drain under most circumstances.

The preechocardiogram technique of pericardiocentesis used the electrocardiogram (EKG) as the marker (4). An alligator clip was connected from the needle to a unipolar EKG lead and monitoring of the EKG was done as the needle was inserted. If the needle touched the myocardium, an injury current (ST segment elevation) would be present on the EKG indicating the needle had been placed too far.

Most effusions are free flowing within the pericardial space and may be accessed from an anterior approach, but the few loculated effusions that occur will need to be approached by a different technique (described below) (5). Some institutions have substituted computed tomography (CT) scans (6) for the echocardiogram, and while this may be as effective, the portability and ease of use make the echocardiogram the imaging modality of choice.

Once the size and location of the effusion has been determined, echocardiogram may be used to visualize the needle to ascertain its location in the pericardial space.

In an elective procedure, a right heart catheterization with simultaneous measurement of pulmonary capillary wedge (PCW) pressure, right atrial (RA) pressure, and intra-pericardial pressure is an elegant method of diagnosis of pericardial tamponade, but it is usually not necessary.

In an emergency, such as a vascular or chamber perforation during a cardiac intervention with free-flowing blood (contrast) into the pericardium and resultant hemodynamic deterioration, no imaging is necessary and pericardiocentesis should be performed as quickly as possible.

To bring the effusion inferior and closer to the chest wall, especially in free-flowing effusions, the elective procedure is best done with the patient sitting up at a 30° to 45° angle (Fig. 14.1). In loculated effusions the patient should be positioned to bring the effusion closest to the chest wall and may require the patient being placed into an extreme lateral decubitus position (7).
Local anesthesia is administered as a skin wheal with a 21-gauge needle and then deeper anesthesia is infused with a 1.5-in 18-gauge needle. On occasion this needle will enter the pericardium as signaled by straw-colored fluid return. This needle can be used as a guide and the pericardiocentesis needle inserted alongside it.

The typical location for skin entry is at the left xiphoid notch aiming toward the left midclavicle (Figs. 14.2–14.5). The needle is initially advanced horizontally and once under the notch it is angled upward toward the clavicle. The position of entry, patient positioning, and puncture site may be altered depending on the location of the effusion.

Other sites of entry include the fifth or sixth intercostal space at the left or right of the sternum. Using this approach, the patient should be in the 30° to 45° upright position and the needle angled to the mid clavicle. The potential advantage to this approach is that the puncture site is already above the diaphragm, so abdominal contents/organs are avoided.

The apical approach is also occasionally used. Since the point of maximal impact will not be present in the setting of a
pericardial effusion, the apex is identified by echocardiogram, and the needle inserted toward the largest accumulation of fluid identified by the echocardiogram. The approach to lateral loculated pericardial effusions is also through puncture at the midclavicular line. The key to puncturing a loculated lateral effusion, whether right or left sided, is to position the patient to bring the effusion as close as possible to the chest wall as determined by the echocardiogram (8). Since the internal thoracic arteries lie in the midclavicular line they may be punctured during a midclavicular line approach. Upon insertion of the needle, pulsatile red blood may signal puncture of the internal thoracic artery.

Since the pericardium is thick, resistance may be felt and a “pop” noted upon entering the pericardial space. Depending on the etiology of the pericardial fluid it may be serous or frankly bloody. The old adage, “blood in the pericardium will not clot,” can no longer be trusted to distinguish pericardial blood from intracardiac blood because patients may be on potent antiplatelet and/or anticoagulant medications. Pressure measurement can be helpful, but the pressures in the right atrium and vena cava may be identical to pericardial pressure, although a right ventricular pressure will be obvious (9).

If in doubt of the needle location injection of nonionic contrast with x-ray visualization or saline administration with echocardiographic visualization will be helpful in ensuring the presence in the pericardium (Fig. 14.6). Once the needle position has been ascertained measurement of pressure to compare with the RA pressure can be made to confirm the presence of tamponade. Withdrawal of as little as 50 to 100 mL of fluid may be adequate to relieve the pressure within the pericardium and restore hemodynamics in the presence of cardiac tamponade.

Figure 14.4 Direction of the needle, the broad arrow is the initial insertion, “walking above the diaphragm” and the narrow arrow indicates aiming toward the left midclavicle.

Figure 14.5 Bony structures of the thorax with the location of the cardiac structure behind to demonstrate the cardiac structures that can be punctured or lacerated during pericardiocentesis.

Figure 14.6 Depiction by echocardiogram (A) when needle is placed properly in pericardium and saline is injected and (B) when needle is placed in the right ventricle and saline is injected. The marked area in frame A represents pericardial space and in frame B represents right ventricular cavity.
If the pericardiocentesis is being performed only for diagnostic purposes in a large effusion, adequate specimens may be withdrawn through the needle, however, it is probably best to exchange the needle for a soft tip catheter or introducer sheath. When a drain is to be placed a 0.035-in guidewire is inserted through the needle and confirmed in the pericardium by fluoroscopy. A 6- or 7-Fr tapered dilator is then placed for ease of inserting the drain. This dilator can be used to withdraw further fluid in a diagnostic-only tap. A drain, usually a pig tail-shaped or straight catheter with multiple side holes is then inserted. The optimum location for this catheter is inferior or posterior to the heart. To ascertain position, nonionic contrast may be injected.

The drainage catheter is then connected to a drainage bag via a plastic tube (10). Hand withdrawal of fluid may be necessary to remove enough fluid to decompress the tamponade. Once the drainage catheter is in place and hemodynamics have been restored, the catheter is sutured in place and gravity drainage begins. The pericardial fluid is usually sent for cell count, differential, chemistries (total protein, pH, LDH, glucose, etc.), serologies, culture, and cytology. Depending on the situation the pericardial drain is left in place for 12 hours or longer, and once the pericardial effusion has been drained as confirmed by echocardiography it can be removed.

**Equipment**

In an elective pericardiocentesis, an echocardiogram at the bedside is necessary for quantitating and localizing the effusion as well as determining needle placement. As noted above the best position for most pericardiocentesis procedures is sitting up at approximately 30° to 45° and this is best accomplished by a wedge placed behind the patient, or if done in bed, elevating the back rest to 45° or greater as such a radio-transparent wedge is necessary. To monitor needle position an EKG or cardiac monitor with a unipolar lead is necessary. Other equipment is usually provided in a commercially available prepackaged pericardiocentesis kit and the contents are outlined in Table 14.2.

**Clinical Aspects**

No specific symptoms are associated with pericardial effusions. Chest pain, dyspnea at rest or with exertion, pleuritic pain, or palpitations alone or together may be present.

<table>
<thead>
<tr>
<th>Table 14.2 Equipment (Much of This Is Packaged Together in Disposable Pericardiocentesis Tray)</th>
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<tbody>
<tr>
<td>• 0.038-in guidewire</td>
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<tr>
<td>• 18-gauge 1.5-in needle</td>
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<tr>
<td>• 21-gauge skin needle</td>
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<tr>
<td>• 30–45° wedge</td>
</tr>
<tr>
<td>• 4–5-in long 18-gauge needle</td>
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<tr>
<td>• 6-Fr dilator</td>
</tr>
<tr>
<td>• 6-Fr pig tail or specialized pericardial drain</td>
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<tr>
<td>• Alligator clip</td>
</tr>
<tr>
<td>• Echocardiogram machine</td>
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<tr>
<td>• Electrocardiogram machine or monitor</td>
</tr>
<tr>
<td>• Lidocaine</td>
</tr>
<tr>
<td>• Skin cleansing agent</td>
</tr>
<tr>
<td>• Sterile drapes(s)</td>
</tr>
<tr>
<td>• Stopcock, tubing and drainage bag</td>
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<td>• Tubes for chemistry and culture</td>
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Cardiac tamponade has nonspecific physical findings, including paradoxical pulse and inspiratory decrease in systemic venous pressure. Distant heart sounds, when noted with the other physical findings, are a further clue; however, this constellation of findings may be present in other disease states including severe obstructive lung disease. Hemodynamic compromise includes hypotension (or a relative decrease from baseline pressure) and tachycardia (which may be masked by the presence of β-blockers). As right-sided cardiac chamber filling decreases, stroke volume also decreases. The heart rate increases in an effort to maintain cardiac output. The most common noninvasive method of determining the presence of tamponade is by echocardiography. Right heart chamber collapse in the presence of pericardial effusion during diastole is sensitive for the presence of tamponade (11,12). Asymptomatic pericardial effusions can be suspected by an abnormal chest x-ray with a typical water-bottle configuration of the cardiac silhouette. The chest x-ray findings can be confirmed by echocardiography or chest CT or MR scans, or the pericardial effusion may be first noted on these modalities.

The most accurate test for the presence of cardiac tamponade is the hemodynamic assessment of intracardiac pressures simultaneous with the measurement of intrapericardial pressure. In the presence of tamponade there will be diastolic equilibration of the pressures equal to the intrapericardial pressure.

The amount of fluid necessary to cause tamponade is variable and depends on the elasticity/stiffness of the parietal pericardium. When pericardial fluid accumulates rapidly in a stiff pericardium, the amount of fluid to cause tamponade will be relatively small. In contrast, when accumulation of fluid is slow (i.e., over weeks to months) and the pericardium has time to stretch, even very large amounts of fluid will not cause hemodynamic compromise.

Given the mechanical nature of tamponade, the only treatment options are pericardiocentesis or surgical drainage. Advantages of pericardiocentesis over surgical drainage are the ability to perform it quickly and at bedside if necessary. Diuretics may worsen the situation by reducing the intracardiac pressures and hastening filling of the heart.

In cardiac tamponade stroke volume is reduced and maintenance of blood pressure and cardiac output may be achieved by an increase in heart rate. A delay in performing pericardiocentesis may necessitate increasing fluid volume and heart rate with isoproterenol or dopamine for the short-term support of blood pressure.

Typically, once a pericardial drain has been placed, the amount of pericardial fluid is monitored in the collection system. In addition, serial echocardiograms may be performed. If fluid continues to drain but no reduction in the size of the effusion is noted, continued accumulation of fluid (bleeding) may make surgical intervention necessary.

**Contraindications**

The contraindications to pericardiocentesis include the following:

1. An inadequate amount of pericardial fluid, particularly in situations of acute/chronic pericarditis, may result in rapid resolution of the effusion, and the performance of an echocardiogram immediately prior to the pericardiocentesis is necessary.
2. Coagulopathy should be corrected prior to performing an elective diagnostic pericardiocentesis to reduce iatrogenic bleeding. However, in the presence of tamponade, pericardiocentesis even in the presence of coagulopathy may be life saving.

3. Loculated lateral or posterior effusions may be difficult or impossible to reach with a needle, and surgical drainage should be considered.

COMPLICATIONS

One complication of pericardiocentesis is laceration of cardiac or noncardiac structures. Because the right ventricle and vena cava lie anterior they are the most common cardiac structures to be inadvertently punctured; however, coronary arteries, coronary veins, and the internal thoracic artery may also be lacerated. Serous colored fluid that quickly turns bloody may be an indication of laceration of a cardiac structure. While rare, noncardiac structures including the liver, spleen, and stomach can be lacerated. The easiest way to avoid inadvertent puncture of these structures is to carefully select the path of the pericardiocentesis needle. Inject iodinated contrast or saline with x-ray or echocardiographic imaging to demonstrate the location of a puncture (13).

Occasionally, congestive heart failure or pulmonary edema may result after drainage of a large pericardial effusion. Echocardiography may be necessary to differentiate these symptoms from reaccumulation of pericardial fluid. A rare phenomenon after relief of a pericardial effusion is biventricular decompensation. The etiology of this is uncertain. It is usually transient, but may require pressors of mechanical support for a short period of time.

Dysrhythmias can occur during pericardiocentesis, and may be due to irritation from the needle or catheter on the epicardium.

REFERENCES

Catheterization of the cardiac venous system

John C. Gurley

INTRODUCTION
For decades, the cardiac venous system was overlooked. Most clinicians considered the coronary sinus (CS) an obscure and inaccessible structure with little purpose other than passive venous drainage. But in recent years the CS has emerged as a vital pathway to the left heart that enables mainstream therapies such as cardiac resynchronization and emerging therapies such as mitral valve repair, myocardial perfusion and gene therapy. Interventional cardiologists and electrophysiologists are now expected to have a good working knowledge of cardiac venous anatomy, as well as the skill to safely catheterize the CS and its branches. This chapter will provide a practical review of the anatomy and physiology of the CS, the techniques of catheterization, and the potential applications of CS catheterization.

After studying this chapter, the reader will understand the following:
1. Why catheterization of the CS and cardiac veins is important
2. How to use accurate terminology to describe the cardiac venous system
3. What is the significance of Thebesian veins
4. Why the CS should be considered the fifth chamber of the heart rather than a vein
5. How to identify the major epicardial veins by name and location
6. How to recognize the major vein-to-vein collateral loops
7. How to localize the CS ostium during catheterization
8. How to catheterize the cardiac venous system safely and efficiently
9. How to avoid complications of CS catheterization
10. How to perform and interpret balloon-occlusion venography
11. How to recognize abnormalities of the CS
12. Why emerging therapies will require knowledge of cardiac venous anatomy and skill at catheterization

Why Catheterize the CS?
Cardiac resynchronization therapy (CRT) has revolutionized the management of patients with heart failure. The dramatic improvements in ventricular function, quality of life and mortality have provided most of the incentive to understand the CS and to develop the tools and techniques that facilitate catheterization (1). But even with the best tools, cardiac resynchronization is operator-dependent, requiring the safe delivery of a left ventricular pacing lead to a location that is anatomically desirable, stable, and free from phrenic nerve stimulation. Effective CRT demands a thorough understanding of cardiac venous anatomy as well as some specific catheter techniques. Other reasons to catheterize the CS are listed in Table 15.1.
The Thebesian network is essential to retrograde myocardial perfusion, drug delivery and gene therapy.

**CS: the Fifth Chamber**

It is a common misconception that the CS is a simply a large vein formed by the confluence of epicardial veins. In fact, the CS is not a vein at all. It is a small, contractile chamber complete with myocardium, two valves, and an electrical conduction system (Fig. 15.3). The CS is very consistent in its structure and position relative to the rest of the heart (6,7).

Externally, the CS lies in the atrioventricular groove behind the left atrium (LA), just above the usual location of the circumflex artery. Note how the GCV crosses marginal branches of the circumflex artery. Abbreviations: AIV, anterior interventricular vein; PIV, posterior interventricular vein; GCV, great cardiac vein; SCV, superior vena cava; CS, coronary sinus; MCV, middle cardiac vein; PCV, posterior cardiac vein; OVM, vein of Marshall. Source: From Netter collection (annotations added).

The Thebesian network is essential to retrograde myocardial perfusion, drug delivery and gene therapy.

### Table 15.1 Reasons to Catheterize the Coronary Sinus

- Cardiac resynchronization
- Percutaneous mitral annuloplasty
- Arrhythmia management
- Myocardial drug delivery
- Gene and cell therapy
- Retrograde myocardial perfusion

### Table 15.2 The Cardiac Venous System

- **Thebesian**
  - Coronary sinus
  - Branch veins
  - Consistent veins
  - Variable veins

- **Epicardial**

### Table 15.3 Epicardial Veins

<table>
<thead>
<tr>
<th>Consistent veins</th>
<th>Variable veins</th>
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<tbody>
<tr>
<td>Anterior interventricular vein</td>
<td>Posterior LV veins</td>
</tr>
<tr>
<td>Posterior interventricular vein (middle cardiac vein)</td>
<td>Lateral LV veins</td>
</tr>
<tr>
<td>Vein of Marshall</td>
<td>Anterolateral LV veins</td>
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*Abbreviation: LV, left ventricle.*
Contractions of the CS can be forceful enough to eject balloon occlusion catheters during venography.

Rhythmic contractions of the CS are absent in atrial fibrillation, indicating that activation of the CS myocardium is dependent on atrial inputs. These inputs consist of electrically conductive muscle bands that connect the CS to both the right atrium (RA) and the LA (14). These connections “bridge” the atria and may help synchronize normal atrial contractions. They can also allow the CS to participate in reentrant atrial arrhythmias by forming left posterior or posterior paraseptal accessory pathways that are difficult to map and ablate. The CS receives additional inputs from the vein of Marshall (OVM), which has been shown to be an autonomically innervated, electrically active trigger for atrial fibrillation. Finally, cells within the CS muscle cells may be capable of intrinsic automaticity, as with other chambers (15).

The CS has two valves. The valve of Vieussens lies at the junction of the GCV and the CS (Fig. 15.5). It is present in 90% of adult hearts, has one or two cusps, and is variably competent (16,17). It is important to recognize the valve of Vieussens because it can be mistaken for a stenosis or occlusion. The valve of Vieussens marks the dividing line between the contractile CS and the noncontractile GCV, which is an important landmark during balloon-occlusion venography. The valve of Vieussens is often associated with a mild, ring-like, less-distensible narrowing—essentially the annulus of the valve of Vieussens—which can be exploited during balloon-occlusion venography.

The Thebesian valve is a flap-like structure that covers the CS ostium to a variable degree (18). It is present in at least two thirds or adults, and can range from a scant remnant to a complete covering (19,20). It can also exist as a mesh-like, multifenestrated membrane. Regardless of its appearance, the Thebesian valve is always attached posteriorly (open anteriorly), a feature that helps direct CS flow toward the tricuspid valve.

Each of the major veins that empty into the CS can also contain valves near their openings. These valves can impede the passage of catheters and pacing leads.

**Figure 15.3** Schematic diagram of the CS. The CS is located between the Thebesian valve at the ostium (T) and the valve of Vieussens (V). It is defined by its muscular, contractile wall. The GCV (G) is a thin-walled venous structure that is separated from the CS by the valve of Vieussens. The GCV is the continuation of the anterior interventricular vein; it is invariably present in this location. The vein of Marshall (M) enters the CS just downstream from the valve of Vieussens. Branch veins can enter the CS or the GCV, and they may contain venous valves. The middle cardiac vein (1) is also known as the posterior interventricular vein; it consistently enters the CS near its ostium. Other cardiac veins that are variably present include a posterior vein (2) and a lateral vein (3). Abbreviations: GCV, great cardiac vein; CS, coronary sinus.

**Figure 15.4** Normal contractility of the CS observed during coronary arteriography. (A) Arterial phase. (B) Venous phase in atrial diastole. The junction of the CS and GCV is indicated by a subtle annular narrowing (arrow). (C) Venous phase during atrial systole. The distinction between contractile CS and noncontractile GCV is apparent (arrow). A large posterolateral vein draining to the GCV provides a position reference. Abbreviations: GCV, great cardiac vein; CS, coronary sinus.
In summary, it is helpful to think of the CS as the fifth chamber of the heart. An appreciation of its structure and function provides the foundation for safe and efficient catheterization.

Epicardial Veins
The epicardial veins carry most of the venous return from the LV to the CS, which empties into the RA. They provide a transvenous path to the LV that can be utilized for cardiac resynchronization, myocardial perfusion, drug delivery and gene therapy. A good working knowledge of cardiac venous anatomy is essential to all of these procedures (21,22).

Unlike the CS, which is consistent in structure and position, the epicardial veins vary considerably in size, number and location. The surface veins of the heart resemble the superficial veins of the forearm: there are many individual variations and a few consistent features. While this has caused a lack of consistency in nomenclature, uncertainty in the interpretation of venograms can be avoided by recognizing the few consistent features and then describing remaining veins according to their location (Table 15.2).

Recognizing Veins with Consistent Features
Two large veins are invariably present. They should be identified in every case because they provide reliable landmarks that orient the rest of the venous anatomy. The anterior interventricular vein (AIV) lies in the anterior interventricular groove, parallel to the left anterior descending (LAD) coronary artery. As it flows from the apex to the base of the heart, the AIV receives branches from the anterolateral left ventricular free wall and the interventricular septum. At the base of the heart, near the origin of the LAD, the AIV turns sharply to the left and follows the circumflex artery around the atrioventricular groove to the back of the heart, where it empties into the CS. The segment in the atrioventricular groove is called the GCV. The GCV then usually receives tributaries from the lateral LV free wall before emptying into the CS. The GCV ends at the valve of Vieuussens (where the CS begins). The posterior interventricular vein (PIV) is the venous equivalent of the posterior descending artery (PDA). It follows the posterior interventricular groove from apex to base, emptying directly into the CS near its ostium. The PIV is also known as the middle cardiac vein (MCV).

The AIV and PIV connect at the apex, forming a semicircle that establishes the plane of the interventricular septum. The GCV and the CS form another semicircle that establishes the plane of the mitral annulus. The intersection of these two semicircles establishes the outline of the LV and provides a frame of reference for orienting all remaining veins (Fig. 15.6).

The remaining left ventricular veins are so variable that they are best described by location (see the next section). Descriptive phrases such as “posterior vein” and “anterolateral vein draining to the AIV” are clinically useful and avoid confusion. These veins may drain into the CS and/or the GCV.

There are several other named cardiac veins that may be visualized during contrast venography. The small cardiac vein lies in the groove between the RA and right ventricle, parallel to the right coronary artery (RCA). It drains the posterior RA and the right ventricle, entering the RA directly or joining the CS near its ostium. Several anterior cardiac veins drain from the front of the right ventricle directly into the RA.

The oblique vein of marshall (OVM) is also known as the oblique vein of the left atrium. It is a short, distinctive vessel that lies diagonally across the posterior wall of the LA. The OVM enters the CS immediately downstream from the valve of Vieuussens. It extends superiorly as the ligament of Marshall (a bundle of fibrous tissue, muscle fibers, nerve tissue and fat) to the left subclavian vein. The CS, the OVM and the ligament of Marshall are all remnants or the left horn of the embryonic sinus venosus. Incomplete regression is the basis for persistent left superior vena cava (PLSVC).

Recognizing the Variable Veins
Variable veins of the LV fall into three general groups. Posterior veins drain to the CS just upstream from the MCV. Lateral veins usually drain into the GCV. Lateral veins are located near the marginal branches of the circumflex artery. Anterolateral veins usually drain to the AIV; their location is similar to diagonal branches of the LAD.
Surface Collateral Patterns
The surface veins of the LV are connected by a network of collateral channels, most of which are too small to be visualized by venography (Fig. 15.7). Four of these channels make collateral loops that are large enough and consistent enough to be clinically useful. By understanding these loops, the angiographer can accurately localize any vein, regardless of imaging projection. The collateral loops can also be exploited for guide-wire and lead placement. Loop 1 connects the AIV and PIV at the apex. Loop 2 connects the apical-lateral branch of the PIV to posterior and lateral veins. Loop 3 connects posterior to lateral veins. Loop 4 connects lateral to anterolateral veins.

The PIV forms two of the basic collateral loops. The first, the AIV-PIV loop, is almost always present. It is important because it establishes the position of the apex and the plane of the interventricular septum. Identifying the AIV-to-PIV loop prevents mistakes in localization. The second loop that includes the PIV is the apical-lateral loop. Most patients have a large apical-lateral branch that connects the PIV to posterior and lateral veins. This loop is important because it helps to distinguish apical from lateral locations. The apical-lateral loop also provides a “back door” to the lateral left ventricular free wall that can be utilized for cardiac resynchronization.

The posterior-to-lateral loop often involves large branches can be useful for left ventricular lead placement.

The anterolateral-to-lateral loop connects the AIV to lateral veins. These branches are less desirable for cardiac resynchronization because they tend to be small and located near the phrenic nerve.

The ability to recognize four basic collateral loops is the key to rapid identification of the epicardial veins and accurate, three-dimensional localization of venous structures (Fig. 15.8).

The Pericardiophrenic Vein
Collateral filling of the left pericardiophrenic vein is sometimes seen during venography in patients with a history of heart surgery. This is not a natural collateral loop, but the result of postoperative inflammation, adhesions and neovascularization. The pericardiophrenic vein is easily recognized by its characteristic trajectory. It is a useful landmark because it identifies the course of the phrenic nerve.

The phrenic nerve, along with the pericardiophrenic artery and vein, form a bundle that courses over the lateral wall of the LV to the left hemidiaphragm (Fig. 15.9). While filling of the pericardiophrenic vein along the cardiac border is usually faint, the straight-line course is easily extrapolated. The pericardiophrenic vein can be catheterized intentionally to mark the phrenic nerve during left ventricular lead placement (23). It can also be catheterized unintentionally (24–26).
The pericardiophrenic vein connects superiorly to the left subclavian vein and inferiorly to the left gastric vein or the inferior vena cava (IVC). Since it forms a collateral connection between abdomen and thorax, it can become dilated when the superior vena cava (SVC) is occluded. Pacing leads and central venous catheters have been inadvertently placed in dilated pericardiophrenic veins, sometimes resulting in tamponade (27–29).

TECHNIQUE OF CS CATHETERIZATION

Experienced operators can catheterize the CS in a matter of seconds using almost any catheter, with few exceptions. Novice operators can struggle for hours. The difference lies not in manual skill, but in a clear understanding of the anatomy. Experienced operators make gentle and purposeful movements toward a clearly defined mental target, utilizing known landmarks as navigation aids. Novice operators tend to probe the RA repeatedly in hopes that the catheter will eventually enter the CS.

This section reviews a simplified approach right atrial anatomy that allows rapid catheterization of the CS. We will discuss general principles rather than specific catheters because the choice of catheters is much less important than the knowledge of where they need to go.

Two Key Steps

Successful catheterization of the CS is a two step process. First, the operator must locate the ostium. This step requires specific maneuvers to align the catheter with the axis of the CS ostium. Second, the operator must negotiate the body of the CS and enter the GCV. This step requires a different set of maneuvers because the CS ostium is not aligned with the CS body or the GCV.

CS interventions, including cardiac resynchronization, are almost always performed with subclavian or internal jugular access. Therefore, we will discuss catheter manipulations appropriate for an upper body approach (catheters entering via the SVC). The manipulations are the same for left-sided and right-sided approaches. The direction of rotation—clockwise or counterclockwise—is from the operator’s perspective, looking down the shaft of the catheter.

Finding the CS Ostium

Difficulties finding the CS usually arise from a lack of familiarity with the orientation of the CS and great veins within the RA. Fortunately, these relationships are very consistent.

The right atrial anatomy in the vicinity of the CS can be simplified. The SVC enters the posterior aspect of the RA and is
oriented anteriorly, toward the tricuspid valve. The IVC, on the other hand, is directed toward the fossa ovalis of the atrial septum. The CS enters the RA between the IVC and the tricuspid valve, with its opening is directed anteriorly toward the tricuspid valve. These angles provide two distinct flow streams during fetal life; oxygenated blood from the IVC flows preferentially toward the LA, while deoxygenated blood from the SVC and CS flow to the right ventricle.

Two valve-like structures help to maintain the divided flow streams within the RA. The Eustachian valve (and its continuation as Chiari tissue) is present to varying degrees in the adult. It arises along the anterior margin of the IVC and continues superiorly as the Eustachian ridge. The Eustachian valve and ridge help to funnel IVC flow toward the fossa ovalis. The Thebesian valve covers the ostium of the CS to varying degrees. It always arises from the posterior margin of the CS ostium and directs flow toward the right ventricle.

Between the IVC and the tricuspid annulus lies a recess of right atrial free wall known as the Eustachian fossa. The Eustachian fossa, the tricuspid annulus, and the Eustachian ridge are easily identifiable landmarks that aid in localizing the CS.

**Catheter Manipulations to Engage the CS Ostium**

Catheters inserted via the SVC will not be aligned with the ostium of the CS, so reorientation is always necessary (Fig. 15.10). It is important to remember that the SVC does not enter the RA vertically, as it appears on two-dimensional fluoroscopy.

To enter the CS ostium, the first step is to advance the catheter to the vicinity of the tricuspid valve. At the tricuspid annulus, the catheter is rotated counterclockwise (from the perspective of the operator, looking down the shaft of the catheter) until the tip contacts the heart. The catheter is then slowly withdrawn while maintaining gentle counterclockwise torque. The catheter tip will ride over the ridge of the tricuspid annulus and drop into a shallow recess between the tricuspid annulus and the Eustachian ridge. At that point, small injections of contrast media should indicate the position of the CS. Forward advancement should engage the ostium.

Counterclockwise rotation is essential. Clockwise rotation causes the catheter tip to engage the Eustachian ridge and valve, deflecting away from the CS and into the IVC. Even if the catheter approaches the CS, clockwise rotations will cause the tip to be deflected by the Thebesian valve, away from the CS and into the right ventricle. The CS cannot be entered with clockwise rotation.

If the CS is not entered immediately, test injections of contrast will indicate one of two likely catheter locations. If the tip is in the Eustachian fossa, it is too inferior but a useful landmark has been identified. The operator knows to repeat the counterclockwise maneuver from a slightly more superior starting point. If the catheter tip is in the body of the RA, it is too superior or too short to reach the tricuspid annulus. The operator knows to advance the catheter and repeat the counterclockwise maneuver from a more inferior starting point.

Telescoping catheter systems are very helpful, especially in patients with chamber dilatation. A typical telescoping system includes an outer guide catheter and an inner angiographic catheter. Each catheter can be advanced and/or rotated independently, with the combination of movements providing a nearly complete range of tip trajectories. In most cases, the outer guide catheter provides the anterior and superior starting position for the angiographic catheter. The outer guide catheter can be directed toward the anterior RA using clockwise rotation while the inner angiographic catheter is directed toward the CS using counterclockwise rotation. The addition of a guidewire creates a triple telescoping system that is useful in cases of extreme right atrial enlargement (Fig. 15.11).

CS catheterization is performed under fluoroscopic guidance. The anteroposterior (AP) projection is usually sufficient and has several advantages including lower x-ray dose rate, more comfortable posture for the operator, and better preservation of the sterile field. Angulated projections are not necessary but sometimes useful. The left anterior oblique (LAO) projection, preferred by some operators, provides left-right perspective. The right anterior oblique (RAO) projection provides anterior-posterior perspective. The 30° RAO projection often demonstrates a triangle of epicardial fat in the atrioventricular groove at the base of the heart. This “fat pad sign” provides a very reliable landmark in cases where the CS ostium is not easily located. In difficult cases, the venous phase of coronary arteriography can also help to localize the CS.

The femoral approach to CS catheterization is used for diagnostic electrophysiology, blood sampling, and angiography procedures that do not require the backup support needed to deliver pacing leads into branch veins. A variety of preformed and deflectable catheters is available for this purpose. In addition, a number of conventional angiographic catheter shapes can be utilized with or without a guidewire. The femoral approach requires clockwise rotation to enter the CS ostium (Fig. 15.12).
Entering the GCV

After locating the CS ostium, the operator must negotiate several changes in direction to enter the body of the CS and the GCV. Difficulty advancing catheters comes from using a two-dimensional fluoroscopic image to navigate a three-dimensional structure (Fig. 15.13). This is resolved by understanding the anatomy. Forceful advancement of catheters can cause dissection or perforation.

By venography in the LAO projection the CS appears to form a flat, C-shaped loop around the mitral annulus. However, from the RAO perspective, significant changes in direction are apparent. To enter the CS, a catheter is directed down, left and posterior using counterclockwise rotation (from a superior approach). After crossing the contractile portion of the CS, the catheter must be redirected upward and anterior using clockwise rotation. The catheter will eventually turn rightward with the great cardiac, reaching the base of the heart at the anterior interventricular groove.

Resistance to catheter advancement at the valve of Vieussens is common, easily recognized, and easily overcome. Small injections of contrast provide important clues to location. The valve of Vieussens is best recognized as an abrupt cutoff of retrograde-injected contrast approximately 30 mm from the CS ostium. If a OVM is visualized, the valve of Vieussens will be located immediately upstream. Finally when CS contractions are observed, the valve will mark the upstream extent of the contractile portion of the CS. Resistance to catheter advancement occurs when the tip enters a valve cusp and retrograde force closes the valve. The valve of Vieussens can produce so much resistance to catheter advancement that it is misinterpreted as a fixed stenosis or an occlusion. The valve will not yield to force, but it can always be crossed by gently probing with a steerable, hydrophilic guidewire. The guidewire will hold the pliable valve aside, allowing effortless passage of catheters and delivery systems.

It is important to learn how to catheterize the GCV because most therapeutic procedures depend on a guide catheter or delivery system that has been inserted deeply enough to be stable. The initial insertion should be beyond the area of interest. Subsequent manipulations are more precise because pull-back removes slack and improves stability while avoiding injury.

Complications of CS Catheterization

Complications of CS catheterization include dissection, perforation and contrast extravasations. Compared with other chambers, the CS is relatively thin-walled easily traumatized (31,32). The branch veins are even thinner and more fragile. Injuries occur at predictable locations and are always avoidable.

Dissections usually occur when a catheter or pacing lead is forcefully advanced to overcome resistance at valves, branch points, or changes in direction (Fig. 15.14). Common locations include the origin of the MCV, the origin the OVM, the valve of

Figure 15.11 Telescoping catheter technique for CS cannulation. The outer delivery system is directed to the anterior right atrium, the angiographic catheter is “aimed” toward the CS, and a steerable, hydrophilic guidewire is advance into the CS. The angiographic catheter can then be advance over the guidewire, followed by the delivery system over the catheter. This is a very effective technique in patients with marked right atrial enlargement. Abbreviation: CS, coronary sinus.

Figure 15.12 Coronary sinus catheterization from the femoral approach. Catheter rotation to enter the ostium is clockwise (opposite the superior approach). Source: From Ref. 30.
Figure 15.13  Three-dimensional shape of the CS and GCV. During catheterization, the operator must navigate three-dimensional anatomy with a two-dimensional fluoroscopic image.  

(A) Three-dimensional perspective. Volume-rendered reconstruction from multislice computed tomography demonstrating the CS and GCV with several changes in direction. A slight annular constriction (small arrow) marks the junction of the GCV and the CS. 

(B) Two-dimensional perspective. Fluoroscopy during the venous phase of coronary angiography. To enter the CS, a catheter must be directed down, left and posterior using counterclockwise rotation (from a superior approach). After crossing the contractile portion of the CS, the catheter must be redirected upward and anterior using clockwise rotation. The catheter will eventually turn rightward with the great cardiac, reaching the base of the heart at the anterior interventricular groove. 

Abbreviations: GCV, great cardiac vein; CS, coronary sinus. 

Source: From Ref. 35.

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Figure 15.14  Common locations for CS injury.  

(A) Catheter advancement into the wall of the CS at the MCV. The axis of force (dashed arrow) is not aligned with the CS. Injury can be avoided by using a curved catheter or steerable guidewire to negotiate the acute change in direction needed to stay coaxial with the CS. 

(B) Localized dissection caused by catheter advancement into the wall of the CS at the MCV. 

(C) Localized dissection at the origin of the oblique vein of Marshall. 

(D) Localized dissection caused by forceful catheter advancement into the valve of Vieussens. The dissection extends into a large lateral vein. 

(E) Catheter advancement into a small lateral vein. The axis of catheter force (dashed arrow) is directly into the branch vein, not into the great cardiac vein. 

(F) Localized perforation caused by catheter advancement into a small lateral vein. 

Abbreviations: MCV, middle cardiac vein; CS, coronary sinus.
Vieussens, and at the origin of lateral branch veins. Dissections can also result from balloon inflation in an undersized branch vein. Perforations occur when a catheter inadvertently enters a branch vein and force is directed perpendicular to the vessel wall. Contrast extravasations can also occur during balloon-occluded venography. The usual mechanism involves injection through an end-hole catheter when the tip is against a vessel wall.

Most catheter-induced CS injuries are clinically silent. They are recognized during venography as contrast extravasations that may appear menacing but are usually benign. Contrast extravasations are usually contained by the epicardial fat surrounding the CS. A persistent “stain” indicates that contrast does not communicate with the pericardial space. The operator should stop injecting at the first sign of contrast extravasation, mainly because extravasations can obscure the visualization of branch anatomy. Retrograde dissections close spontaneously, with blood flow, when the offending catheter is removed (33). The most significant consequence of dissection is that it can prevent cannulation of branch veins needed for optimal cardiac resynchronization. Perforations involving the low-pressure cardiac venous system usually seal spontaneously when the catheter is removed. Tamponade is a rare complication of CS catheterization—rare enough that it should alert the operator to an alternate explanation such as perforation of the right ventricular apex by a pacing lead. Branch vein obstructions are well tolerated because the cardiac venous drainage system is richly collateralized.

Injury to the CS is not necessarily a reason to terminate a procedure. After recognizing an injury, the operator can safely continue as long as the true lumen is identifiable. This may require a brief waiting period (5–10 minutes), a different choice of catheters and guidewires, and alternate imaging projections. With extensive dissection, the operator may suspend the procedure and return after allowing time (days to weeks) for healing. Most catheter-induced CS injuries heal without intervention.

Injury can be avoided by understanding the anatomy, by utilizing small injections of contrast for orientation, and by choosing curved catheters or steerable guidewires to negotiate changes in direction and remain coaxial with the vessel lumen.

Choice of Catheters
CS catheters have evolved mainly from a need to provide CRT. Left ventricular pacing leads are installed through guide catheters that provide the backup support needed to “wedge” leads securely into branch veins. Manufacturers now offer complete delivery system packages that include a variety of preformed and deflectable guide catheters, shaped catheters for CS cannulation, catheters for subselective cannulation of branch veins, guidewires and other tools (Fig. 15.15).

Delivery systems are usually advanced coaxially over smaller, steerable catheters that are used to access the CS. Some operators prefer deflectable electrophysiology catheters, while others prefer fixed-curve angiographic catheters. Angiographic catheters offer several advantages including low cost and availability in a variety of shapes. Angiographic catheters also permit injections of contrast and the use of guidewires. These attributes make angiographic catheters ideal for negotiating complex anatomy.

Hardware refinements have made cardiac resynchronization safer and more reliable, but an extensive array of catheters is no substitute for a good working knowledge of venous anatomy. Special catheter shapes may help operators to overcome technical challenges in patients with advanced heart failure and chamber dilatation, but they are usually not necessary. It is more important to remember that, even in heart failure, the anatomical relationships among structures remain constant. The CS is a large structure—approximately 10 mm diameter at the ostium and larger in heart failure—that always empties into the same location of the RA. In most cases, the CS can be cannulated easily with a few conventional catheters. No matter which catheters are selected, the objective is to place a delivery system into a deep, stable, coaxial position within the body of the CS. This provides the starting point for subsequent operations such as balloon-occluded venography, selective catheterization of branch veins, and placement of left ventricular pacing leads.

BALLOON OCCLUSION VENOGRAPHY
Rationale
Balloon-occlusion venography is the best method for visualizing the cardiac veins at the time of left ventricular lead placement. The objective is to identify the branch veins that are most ideal for placement of a left ventricular pacing lead. Optimal lead positions represent the best compromise of anatomically desirable location, stimulation threshold, stability, deliverability, and absence of diaphragmatic stimulation. To achieve optimal lead positions, the operator must visualize all potential target veins and establish priorities (best, second best, acceptable, and unacceptable). Balloon-occluded contrast venography is the only method of consistently visualizing all potential target veins. It is the cornerstone for effective CRT.

Catheter Technique
Adequate venography requires a coaxial catheter alignment to avoid subintimal injection, a stable balloon position during contrast injection, and complete visualization of all branch veins. The suggested technique reliably achieves these goals.

The first step in balloon-occlusion venography is to advance a guide catheter or delivery system beyond the valve
of Vieussens and into the GCV. It is often desirable to perform contrast injections with the balloon in the GCV because this structure is noncontractile and small enough to be easily occluded. This is important because the GCV is straight, noncontractile, and small enough to permit complete occlusion by a balloon catheter. Balloons inflated in the CS tend to be unstable and are easily ejected into the RA during contrast injection. Retrograde injections into the CS can close valve of Vieussens, creating back pressure that ejects the balloon into the RA. The balloon catheter is inserted to the tip of the delivery system, then “unsheathed” by retracting the delivery system. Alternatively, the balloon catheters may be inserted over a guidewire. Small injections of contrast should confirm that the balloon tip is beyond the valve of Vieussens, coaxial with the lumen, not in a branch vein, and not against a vessel wall. A good target for balloon inflation is the GCV just above the valve of Vieussens. The mild annular narrowing often present at this location helps to stabilize the balloon, prevent balloon migration or contrast reflux (Fig. 15.16). The balloon is then inflated until test injections of contrast indicate complete occlusion. With the balloon inflated, images are acquired as 10 to 20 mL of contrast is manually injected. Complete visualization of the cardiac venous system is facilitated by extensive vein-to-vein collaterals. The injection must be rapid enough to produce collateral filling of all branch veins. A reliable indicator of adequate filling is complete opacification of the MCV, which is invariably present and easily recognized by its location in the posterior interventricular groove. Undiluted contrast produces superior image quality but in some cases a 60% dilution reduces viscosity and allows more rapid injections needed to fill branch veins. The balloon may remain inflated long enough to obtain venograms in multiple projections and to study the images for completeness. Prolonged balloon occlusion of the GCV is remarkably well tolerated, thanks to a rich collateral network that includes the Thebesian venous system.

**Image Acquisition**
Venography should be performed in as many projections as necessary to fully define the anatomy. The AP projection is a convenient working view that minimized radiation exposure. The AP projection alone is often sufficient. The LAO view provides additional apex-to-base perspective. The LAO view provides additional superior-inferior perspective, and is best for displaying the takeoff of lateral veins draining the lateral left ventricular free wall.

Different projections can be reconciled by identifying the two planes: the plane of the interventricular septum outlined by the anterior and PIV, and the plane of the mitral valve outlined by the CS and GCV. Three-dimensional perspective can be obtained by visualizing the LV as a spherical fishbowl, with veins curving across the outer surface and the neck representing the mitral valve plane (Figs. 15.17 and 15.18).

**NONINVASIVE IMAGING OF THE CS AND CARDIAC VEINS**
One of the most challenging aspects of cardiac venous catheterization is navigating a three-dimensional structure while guided by two-dimensional fluoroscopic images. Noninvasive imaging modalities compliment catheter-based angiography by providing spatial orientation. They also show how the cardiac venous system is related to other cardiac structures—including structures that are not visible by fluoroscopy.

The CS is routinely visualized by transthoracic, transesophageal and intracardiac echocardiography. Unfortunately, these modalities provide two-dimensional images of limited portions of the CS, factors that limit their ability to support therapeutic procedures. Real-time, three-dimensional echocardiography may overcome some of these limitations (34). Intravascular ultrasound (IVUS) studies of the coronary arteries may demonstrate the major epicardial veins, which must be recognized as normal structures.

Multislice computed tomography has been utilized to depict the cardiac veins and define the range of variability (9,35). While it does require iodinated contrast and radiation exposure, multislice computed tomography can provide high-spatial-resolution images of the cardiac venous system quickly and reliably. Multislice computed tomography has become a legitimate tool for noninvasive preprocedure planning (Fig. 15.19).
Cardiac magnetic resonance imaging is another noninvasive modality that provides clear depictions of the cardiac venous system and its anatomical variations without the need for iodinated contrast or ionizing radiation. The use of cardiac magnetic resonance imaging for preprocedure planning may reduce fluoroscopy time and increase the likelihood of success (Fig. 15.20) (36).

**ABNORMALITIES OF THE CS**

Persistent left superior vena cava (PLSVC) is the most common anomaly of the thoracic veins, occurring in 0.3% of general population and in about 5% of patients with congenital heart disease (37–41). The hallmark finding is a markedly dilated CS due to increased flow. PLSVC is usually an incidental finding by echocardiography or chest CT, but it may be discovered...
while passing catheters or pacing leads from the left subclavian or jugular approach (catheters reach the right heart without passing through the SVC). The unusual trajectory can make manipulation of pacing leads difficult. PLSVC can also be discovered during right heart catheterization from the femoral approach. The markedly enlarged CS is easily entered, and catheters may appear to enter the pulmonary artery; the true location is indicated by venous pressures and venous oxygen saturations. Persistent left SVC can be thought of as a very large OVM that has failed to regress. Blood flow with PLSVC is physiologic, so there are no clinical consequences.

atrial septal defect. Unroofed CS is commonly associated with a persistent left SVC. When a left SVC is present, venous blood enters the LA and produces cyanosis. Unroofed CS is also associated with other forms of complex congenital heart disease, usually heterotaxy syndromes. The clinical manifestations of unroofed CS include right heart failure from chronic volume overload, cyanosis and paradoxical embolism. The diagnosis can be established by transthoracic or transesophageal echocardiography and catheter-based angiography, but MRI and CT are superior imaging modalities. Catheter-based interventions aimed at covering the defect or occluding the left vena cava have been described (51–53).

CS diverticulum is another malformation of the CS that can be associated with arrhythmias and sudden cardiac death (54,55). A CS diverticulum is usually discovered by contrast venography at the time of electrophysiology procedures for posterior-septal accessory pathways (Fig. 15.21) (56). Arrhythmias are mediated by muscle bridges joining LV, CS wall, and atria. These pathways can have short refractory periods that allow rapid conduction of atrial fibrillation. Rarely, CS diverticulum is an incidental finding (57).

EMERGING CS INTERVENTIONS

Mitral Annuloplasty

The proximity of the CS to the mitral valve annulus has invited researchers to explore percutaneous mitral annuloplasty. The goal is to avoid the risks of surgical annuloplasty in patients with functional mitral regurgitation secondary to dilated cardiomyopathy. CS annuloplasty mimics surgical annuloplasty by shortening the anterior-posterior dimension of the mitral annulus. Several approaches have been tried.

The VIKING and MONARC devices (Edwards Lifesciences, Irvine, California, U.S.) consist of two nitinol anchor stents connected by a spring-like bridge. One anchor is deployed in the GCV and the other near the CS ostium (58). The bridge spring contracts as biodegradable spacers slowly dissolve, pulling the stents together and shortening the annulus. The
The venous approach may facilitate percutaneous myocardial gene transfer by achieving high local concentrations of vectors with minimal systemic exposure (64).

**Cardiac Veins for Myocardial Perfusion**

The presence of arteriovenous communications within the myocardium has inspired clinicians to utilize cardiac veins as conduits to perfuse ischemic myocardium. In the 1940s Beck arterialized the cardiac veins by constructing vein grafts from the aorta to the CS and then ligating CS outflow. Unfortunately, patients developed myocardial edema, hemorrhage and fibrosis. The technique was eventually scaled back to localized arterIALIZATION of branch veins draining ischemic areas. Some patients with severe angina improved, but interest evaporated with the advent of coronary artery bypass surgery (65).

In the 1980s venous perfusion was briefly revisited. Percutaneous, synchronized CS retroperfusion was developed to manage unstable angina, and abrupt occlusion during coronary angioplasty (66–70). The objective was to inject arterial blood into the CS during diastole, and allow venous drainage during systole. CS retroperfusion failed because of cumbersome equipment, inexperience with CS catheterization, delays initiating therapy, and limited benefit. Its main purpose—support during high-risk angioplasty—was eliminated by stents.

Percutaneous in situ coronary venous arterialization (PICVA) has been performed in a few patients with ungraftable LAD disease (71). This procedure involves IVUS-guided puncture from LAD to AIV, placement of a stent to connect artery and vein, and occlusion of venous outflow. The technical challenges and complications have been substantial (72,73). Nevertheless, PICVA demonstrates a creative approach to venous perfusion.

A percutaneous, stent-based, LV-to-vein bypass procedure has been performed in animals (74). The procedure appears to be technically feasible and capable of establishing both systolic inflow and diastolic outflow. Long-term consequences are not yet known.

Patients with refractory angina who are not candidates for conventional revascularization will continue to stimulate interest in the use of cardiac veins for myocardial perfusion.
CATHETERIZATION OF THE CARDIAC VENOUS SYSTEM

Unfortunately, there are serious concerns about the durability, safety and efficacy of arterialized cardiac veins. The future of venous arterIALIZATION is still in doubt.

CONCLUSIONS

The cardiac venous system has become a vital pathway to the left heart. A good understanding of its anatomy, physiology, and catheterization techniques is essential to CRT and invasive arrhythmia management. Emerging therapies that depend on cardiac venous catheterization include percutaneous mitral annuloplasty, gene delivery, stem cell delivery, and retrograde myocardial perfusion. New interdisciplinary relationships will require the interventional cardiologist to be skilled at catheterization of the cardiac venous. The CS can no longer be ignored.

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INTRODUCTION
As with all human science, a strong understanding of normal physiologic function and many disease states requires a solid knowledge base of the normal anatomy. During the performance of coronary angiography, the anatomy of the epicardial coronary arteries including collateral vessels is the main focus. However, with the development of percutaneous techniques to treat epicardial coronary artery stenoses, an understanding of the normal anatomic structure of a coronary artery is also critical. Although this chapter will focus mainly on the anatomy of the epicardial coronary system, a brief review of the structure of a normal coronary artery is relevant.

CORONARY ARTERY ANATOMY
A normal coronary artery consists of three histologically distinct layers (Fig. 16.1). The innermost layer, which surrounds the lumen, is the tunica intima or simply the intima. It is composed of a single layer of endothelial cells in close proximity to the internal elastic lamina. The normal endothelial layer has a central role in maintaining vascular health and has three distinctive roles. First, it is a metabolically active secretory tissue. Endothelial cells secrete both vasodilator substances such as prostacyclin, nitric oxide and endothelial-derived hyperpolarizing factors and vasoconstrictor substances (endothelin and vasoconstrictor prostanoids) (1–3). Endothelial cells also produce and secrete von Willebrand factor, factor VIII antigen, tissue factor, and tissue plasminogen activator, which have important roles in coagulation and fibrinolysis. Moreover, endothelial cells secrete certain structural components of the extracellular matrix such as elastin, glycosaminoglycans and fibronectin and, along with smooth muscle cells, matrix metalloproteinases, which are critical in arterial remodeling (4,5). Finally, certain growth factors that control smooth muscle proliferation are secreted by endothelial cells (6). Second, the endothelium has an anticoagulant and antithrombotic surface. Normal quiescent endothelial cells have an antithrombotic surface that inhibits platelet adhesion and coagulation, but when stimulated by cytokines or other inflammatory mediators are capable of prothrombotic factors. Substances secreted by the endothelium include prostacyclin and nitric oxide, which affect platelet aggregation, include, plus antithrombin III, heparin-like molecules and tissue plasminogen activator (7). Although the endothelium normally exists in a functional state of balance between thrombotic and antithrombotic factors, injury or inflammation enhances the prothrombotic state of the endothelium. Finally, the normal endothelium provides a barrier to the indiscriminate passage of blood constituents into the arterial wall. Fluid and macromolecular transport functions of the endothelium are dependent on vessel size. There are two major mechanisms, which regulate the endothelial barrier function; one involves cell-to-cell contacts allowing transendothelial transport in the junctions between cells, the other involves transendothelial transport via vesicular transport directly through the cell.

The next layer of an artery is the tunica media or simply media. It surrounds the internal elastic lamina and its composition depends on the type of artery. Large arteries have additional circumferential layers of elastic tissue within the media and are thus referred to as elastic arteries. The epicardial coronary arteries are elastic arteries as are the carotids, cerebral arteries and the aorta. However, at the point the epicardial arteries turn into the myocardium, usually at a right angle from the parent vessel, they become more muscular arteries with few if any elastic fibers. In normal arteries, the vessel lumen diameter can be altered by contraction or relaxation of the medial vascular smooth muscles in response to a variety of systemic signals and locally released factors. However in certain disease states, such as restenosis following balloon angioplasty, growth and hypertrophy with migration into the intima are the usual responses (8).

Finally, the media of all arteries is contained within a connective tissue layer called the tunica adventitia, or simply adventitia. In elastic arteries, this is demarcated by a layer of elastic fibers termed the external elastic lamina. The adventitia contains a network of small blood vessels (vaso vasorum), which is responsible for the nutrition of the outer two-thirds of the artery. The inner third of the artery derives nutrition by diffusion through the endothelium. The adventitia also contains nerves, which control the tone of the artery. In various locations within the adventitia and associated with the outermost elastic layer are pressure receptors. These pressure or baroreceptors have a phasic discharge rate in harmony with the arterial stretching associated with the pulse wave. Impulses of the baroreceptors are integrated centrally and when increased or decreased cause appropriate alterations in many vascular beds.

BASIC ANATOMY OF THE CORONARY CIRCULATION
The anatomy of the coronary arteries was described by the French anatomicist Raymond Vieuxsens almost 300 years ago. Careful postmortem studies using injection techniques have provided greater detail and a more definitive description of the normal coronary anatomy. The Latin term “corona,” or crown, aptly describes coronary arteries as the branches of these two arteries traverse the atrioventricular and interventricular sulci in the shape of a crown (9). In humans as well as birds, reptiles
and mammals, the major epicardial vessels of the coronary circulation are the left main coronary artery and the right main coronary artery (RCA). The left and right coronary arteries originate at the base (root) of the aorta from openings called the coronary ostia, which are located in the left and right sinus of Valsalva, respectively. The ostia usually originate at the center of each sinus just below or no more than 1 cm above the superior edge of the aortic cusp. The left coronary orifice normally arises from the left sinus of Valsalva midway between the posterior portion of the pulmonary artery and the left atrial appendage just above the level of the free margin of the aortic valve leaflet and generally below the sinotubular junction. The left coronary ostium is usually single, giving rise to a short, common left coronary artery (LCA) trunk (the left main artery) that courses in the epicardial fat for distances varying from a few millimeters to several centimeters before bifurcating into the left anterior descending (LAD) and left circumflex (LCx) coronary arteries. The length of the left main artery as derived from pathologic examinations is 1.0 cm (10). Some premortem and postmortem angiographic studies have suggested that patients with bicuspid aortic valves have shorter left main segments, but this is not universally accepted (11). No correlation of left main coronary artery length with age, gender, heart weight, extent of coronary artery disease or left ventricular wall thickness was found in one autopsy series (12). Histologically, the left main ostium lacks adventitia and has a greater portion of elastic tissue than other segments of the coronary tree. This may account for some of the differences in response to coronary interventions involving this segment of the left main. Moreover, since the left main ostium technically lies within the wall of the aorta, it is subject to diseases affecting the aortic wall such as syphilitic aortitis, radiation-induced aortitis and Takayasu’s arteritis (13).

In some individuals, there is a trifurcation of the left main with a third branch arising in the crotch between the LAD and LCx. This third artery, called a ramus intermedius or simply a ramus branch acts functionally as a circumflex branch, supplying a portion of the obtuse margin of the heart between the LAD and LCx. In one series, a ramus intermedius occurred in 37% of the general population, and was considered a normal variant (14). In another series of 150 hearts, Baptista et al. showed that the left main bifurcated in 55%, trifurcated in 39%, and had a quadrification (ramus and separate diagonal) in 7% (15). A quadrification pattern was found in 60% of nonwhite females. The length of the ramus varies from 20 to 50 mm and its relative length varied from 21% to 50% of the length of the left ventricle (LV).

The normal location of the RCA ostium is more variable. It usually arises from the middle of the right coronary sinus just below the sinotubular junction of the right sinus of Valsalva. However, it can arise from low near the valve to high near the sinotubular ridge. The right and left coronary arteries are usually the only vessels arising immediately above the free margin of aortic valve from the ascending aorta. However in up to 30% of angiograms, the artery to the pulmonary outflow tract (conus artery) originates as a separate ostium rather than its usual position as a branch of the proximal RCA. Common variations of the location of the coronary ostia exist, which can have clinical implications as will be discussed later in this chapter.

**Coronary Dominance**

The term coronary dominance was introduced by Schlesinger in 1940 (16). The dominant coronary artery is the one from which the posterior descending coronary artery arises (Fig. 16.2). The posterior descending artery (PDA) traverses the posterior interventricular sulcus and supplies the posterior part of the ventricular septum and often a portion of the posterolateral wall of the LV. There is variability in the literature regarding the frequency of right dominance with sources varying from a low of 70% to a high of 90% (18). In a right dominant circulation, the RCA crosses the interventricular groove and continues in the atrioventricular groove beyond the origin of the PDA to supply one or more posterolateral left ventricular branches. The artery to the atrioventricular node usually arises from the RCA at an area called the crux, which represents the intersection of the interventricular and atrioventricular grooves on the inferior surface of the heart. This is noted on the posterior surface of the heart by a small indentation or dimple.

If the PDA arises from the terminal portion of the LCx, the term left dominance is applied to the circulation. The frequency of left dominant circulation varies from 8% to 15% of individuals (18). In the remaining individuals, the posterior septum is supplied by branches arising from both the RCA and LCx. In this situation the circulation is said to be “balanced” or codominant with dual posterior descending arteries (one from the RCA and the other from the LCx) or no clear PDA with multiple smaller branches arising from both arteries. It is important to note that anatomic dominance does not imply the vessel is of greater physiologic importance and thus is somewhat a misnomer. Although the RCA is most frequently the dominant artery, the left coronary artery almost always supplies a greater myocardial mass (19).

**LAD Artery**

The LAD is a direct continuation of the left main artery, with its course along the anterior interventricular groove. When the heart is viewed frontally, the LAD is seen as it curves around and emerges from behind the pulmonary artery (Fig. 16.3). The LAD in combination with the left main forms a curve that...
resembles a reverse “S” shape. The tight upper curve brings the LAD around the pulmonary artery to reach the uppermost portions of the interventricular septum, and the lower portion curves in the opposite direction as it follows the interventricular septum toward and usually around the apex. Several normal variations in the length and distribution of the LAD have been recognized. It is not essential for the LAD to reach the cardiac apex or to have well-defined branches to qualify as the LAD (19). In contrast, the LAD may course well around the apex (“wraparound” LAD) and supply a substantial portion of the posterior septum and even replace the PDA (20,21). Some individuals may have dual LAD systems with one trunk almost exclusively supplying the septum and the other trunk running almost parallel giving rise to all of the diagonal arteries (22). Along its course toward the cardiac apex, the LAD gives rise to anterior septal perforating branches and diagonal branches. As these branches arise from the LAD, the lumen diameter of the LAD is progressively reduced toward the cardiac apex. Small, branches may arise from the LAD to supply a small portion of the anterior wall of the right ventricle with isolated reports of larger vessels termed a right ventricular descending branch (23).

Diagonal Arteries
Diagonal artery branches arise from the LAD and course at downward angles to supply the anterolateral free wall of the LV (Fig. 16.3). Most individuals have one to three diagonal arteries, but up to six small diagonals have been seen. The larger diagonal arteries arise from the upper portion of the LAD and the caliber of the branches becomes progressively smaller as the LAD approaches the apex. The diagonals roughly run parallel to each other and also parallel to a ramus branch if one is present.

Septal Perforating Branches
In over 99% of individuals, the blood supply to the anterior interventricular septum is from the LAD (24). These septal perforating branches arise at nearly right angles from the LAD and penetrate deep into the interventricular septum. In the majority of individuals, there is no dominant septal artery, but several proximal septal vessels of equal size. However, in 38% of individuals, a large dominant septal perforator is present and is usually, but not always the first septal (24). Septal perforator arteries may bifurcate and trifurcate, but the branching pattern is somewhat unordered and may take the appearance of a pitchfork with multiple branches off one central point of the trunk. Septal arteries are occasionally seen arising from other arteries such as the first diagonal, proximal RCA or LCx and as a separate ostium from the right sinus of Valsalva (25,26).
LCx Artery
The LCx coronary artery arises from the left main artery at its bifurcation and courses posteriorly under the left atrial appendage to reach the left atrioventricular groove (Fig. 16.4). The origin of the LCx is often at nearly a right angle to the left main, but in some patients may have a greater or lesser degree of angulation from the left main at its origin. As it continues, it remains in the atrioventricular groove circumscribing the mitral valve annulus giving rise to as many as four obtuse marginal arteries. The extent and distribution of the LCx and marginal arteries is usually reciprocal with that of the RCA. If the LCx is has an extensive distribution over the posterior and inferior walls, the RCA will usually be small with fewer branches in this region and vice-versa. Atrial branches may arise from the LCx coronary artery and supply the sinus node in 37% of patients (27). Although the circumflex sinus node artery usually arises near the origin of the LCx, in approximately 20% of individuals who have a circumflex origin of this artery, the artery is an S-shaped vessel that originates from the posterolateral branch of the circumflex.

Obtuse Marginal Arteries
The marginal arteries run parallel to the diagonal arteries and ramus if one is present. The nomenclature of the marginal arteries is based on their origin from the LCx; that is, first marginal, second marginal, and so forth. There is considerable anatomic variation in the number and size of the marginal arteries, but there is at least one marginal branch present in most individuals (Fig. 16.5). When a single large marginal branch is present, there is usually extensive secondary and tertiary branching of the vessel. The most common pattern is to have two or three marginal branches of similar size with less extensive secondary branching. There is also a reciprocal relationship between the diagonal arteries and circumflex marginal arteries. For example, when there are only a few relatively small and short diagonals, there should be large marginal branches of the LCx, which course quite anterior to supply a portion of the anterolateral wall. Failure to see this pattern may be a hint that there is a flush occlusion of a vessel and an area of nonperfused myocardium. If a large ramus branch is present, then the proximal diagonal branches are smaller and few in number and supply an area close to the LAD. The ramus supplies the next more lateral segment of the LV (LV wall and then the LCx marginal branches pick up the supply as one approaches the posterolateral portion of the left ventricular free wall.

Right Coronary Artery
The RCA courses in the right atrioventricular groove and circumscribes the tricuspid valve annulus (Fig. 16.6). The first branch arising from the RCA is frequently the conus or infundibular branch, which courses anteriorly to supply the muscular right ventricular outflow tract or infundibulum. Alternately, in 30% to 50% of angiograms the conus artery may arise from a separate ostium close to the RCA ostium or from a common aortic ostium shared with the RCA (19,28). Another important proximal branch of the RCA is the sinus node artery. The reported frequency of the sinus node artery arising from the proximal RCA 50% to 70% with a dual blood supply from both the RCA and LCx in 3% (29,30). In its midportion, the RCA provides one or more branches that supply flow to the right ventricular free wall (right ventricular marginal branches). The RCA also...
The coronary circulation consists of three distinct components, which together facilitate the delivery of metabolic substrates and the removal of metabolic waste products from the heart muscle. These components are: the epicardial coronary arteries, the coronary microcirculation, and the coronary venous anatomy. Understanding the coronary circulation is important to the overall function of the heart and its efficient performance.

### Coronary Arterial Anatomy

The anatomic system is composed of three distinct components, which have different physiologic functions. A detailed description of coronary microvascular anatomy and function is beyond the scope of this chapter, but an overview is important to the overall understanding of the coronary circulation. Although there are three distinct components of the coronary circulation, these are not demarcated by distinct anatomic borders. The most proximal component comprises the large epicardial coronary arteries. These function primarily as conduits offering little resistance to coronary blood flow, but are subject to some flow-mediated dilatation. Therefore, the pressure drop along these conduits or conductive arteries is negligible in the absence of a coronary stenosis. The diameter of the epicardial coronary arteries, as viewed by angiography, ranges from 1 to 5 mm, but arteries as small as 500 μm can still be found on the epicardial surface.

The next component in series is the prearteriole, which range in size from 100 to 500 μm. Because of their location and wall thickness, these vessels are not directly affected by products of myocardial metabolism. Their role is to maintain pressure at the origin of the arterioles within a narrow range in response to changes in epicardial coronary perfusion pressure and flow, a function that is often referred to as the autoregulation of coronary blood flow.

The final component is the network of intramural arterioles, which have diameters less than 100 μm. The arteriole wall consists of an endothelial layer facing the blood surrounded by a layer of circumferentially oriented smooth muscle cells. These are encased by connective tissue containing a rich plexus of sympathetic and parasympathetic fibers. The smooth muscle cells are easily able to constrict the lumen of an arteriole and frequently do under physiologic and pathologic stimuli. Their role is to regulate myocardial blood supply to match myocardial oxygen consumption. This function is especially marked at their junction with the capillaries and blood passage into the capillaries is carefully controlled. The arterioles have a high resting tone and dilate in response to metabolites released by the myocardium as a result of an increase in oxygen consumption. Blood volume can be increased by 200% or more over resting values in many capillary beds by the relaxation of the arteriolar constrictors. Therefore, by regulating the resistances in the prearterioles and arterioles, blood flow is matched with oxygen requirements in the coronary circulation.

The arterioles branch into numerous capillaries that lie adjacent to the cardiac myocytes. The capillaries measure 10 to 15 μm in diameter and are the site of metabolic exchange. A high capillary to cardiomyocyte ratio and short diffusion distances ensure adequate oxygen delivery to the myocytes and removal of metabolic waste products from the cells. Capillaries are composed of a single layer of endothelium with surrounding basement membrane and an incomplete layer of pericytes. Pericytes, also known as Rouget cells or mural cells, are mesenchymal-like cells, associated with the walls of small blood vessels. As a relatively undifferentiated cell, they support the small vessel, but can differentiate into a fibroblast, smooth muscle cell, or macrophage. They are important in angiogenesis and have been implicated in blood flow regulation at the capillary level. Capillaries are also surrounded by a loosely formed adventitia of collagen, elastic fibers and matrix.

### Coronary Venous Anatomy

The capillaries terminate in small venules, vessels with a diameter of 15 μm or more. Other than size, the morphologic change from capillary to venule is not very distinctive. Small venules
have an endothelial lining, a surrounding basement lining, and collagen connections from the basement membrane to the surrounding matrix. However, the venules are unlike capillaries in that vasoactive compounds like histamine, various kinins and serotonin can affect the separation of the tight junctions of the endothelial cells resulting in the leakage of large molecular weight substances. Veins of about 0.5 mm in diameter begin to acquire a muscular coat and eventually form small epicardial veins that run in parallel with the visible epicardial arterial branches.

There is considerable variability in the cardiac venous anatomy, but there are some consistent venous structures (Fig. 16.7) (36). The most notable of these is the great (or anterior) cardiac vein, which begins at the apex of the heart and ascends along the anterior interventricular groove parallel to the LAD to the base of the ventricles. It connects with diagonal veins draining the lateral and anterolateral portion of the LV and turns posterior at the left atrioventricular groove wrapping around the left side of the heart parallel to the LCx coronary artery (38). In addition to several smaller tributaries from the left atrium and ventricles, the great cardiac vein receives two main branches, the large left marginal vein along the lateral border of the heart and the posterior left ventricular branch (also known as the posterolateral branch). The great cardiac vein terminates in the coronary sinus, a junction defined by the presence of the left atrial oblique vein. This transition point is usually marked by the presence of intravenous valves, which can obstruct catheter and pacemaker lead placement. Another fairly consistent branch is the middle cardiac vein, which runs in the posterior interventricular groove, parallel to the posterior descending coronary artery. Of all of the branches of the coronary venous system, the great cardiac and middle cardiac veins are the two most consistently present branches seen in more than 90% of individuals (39,40). However, unlike the middle cardiac vein, the great cardiac vein varies considerably in its course (41). Lateral and posterior venous branches together are seen in <50% of human hearts.

The coronary sinus is the most constant feature of the cardiac venous system, although several congenital anomalies have been described (42–44). The coronary sinus lies in the atrioventricular groove on the posterior surface of the heart and receives veins from the lateral wall, which are referred to as marginal veins. Although the coronary sinus invariably lies in the atrioventricular groove, its branches and their locations are far more variable than those of the coronary arterial system (43). The coronary sinus opens into the right atrium, posteromedially, just superior to the septal leaflet of the tricuspid valve. At the ostium of the coronary sinus is the thebesian
Valve, a semicircular fold of the lining membrane of the atrium. The valve may vary in size, or be completely absent and may prevent regurgitation of blood into the coronary sinus during contraction of the atrium. The valve can also hinder cannulation of the coronary sinus (45). The coronary sinus and its tributaries drain approximately two-thirds of the left ventricular myocardium, but they do not drain the superior part of the interventricular septum, the right atrium and ventricle or the myocardium of the roof of the left atrium. These are drained by the right cardiac (or anterior cardiac) venous system. These veins originate on the anterolateral surface of the right ventricle and drain directly into the right atrium. In addition, there are also thebesian veins (venae cordis minimae), which drain directly into the cardiac chambers. They are more common on the interventricular and interauricular septum, particularly on the right side of the heart, but prominent thebesian veins are occasionally seen entering the LV. Other variable features of the coronary venous anatomy include the presence of ostial valves of the cardiac veins (Vieussens valves), interbranch collateralization, and intramural versus epicardial course.

The knowledge of anatomical positioning of the cardiac venous structures is becoming increasingly important in the field of cardiac electrophysiology for positioning of mapping catheters and left ventricular pacing leads. Implantation of the coronary sinus lead usually involves the lateral and posterior branches, which are quite variable in their number, tortuosity, dimensions, and angulation with respect to the main trunk of the atrioventricular venous ring (46).

VARIATIONS IN CORONARY ANATOMY
Although there is considerable heterogeneity in coronary anatomy among individuals, there is greater consistency in the regions of the heart generally supplied by the different coronary arteries (Table 16.2). This anatomic distribution is important because these cardiac regions are assessed by 12-lead electrocardiograms to help localize ischemic or infarcted segments of the myocardium. This in turn, can be loosely associated with specific coronary vessels, but because of vessel heterogeneity, the specific vessel involvement requires verification by coronary angiography or other imaging techniques.

Embryology of the Coronary Arteries
Although a detailed description of the formation of the coronary vasculature is beyond the scope of this chapter, some fundamental principles are important for understanding some variations in coronary anatomy and coronary anomalies. During the earliest stages of cardiogenesis the heart is formed as an endothelial tube within a muscular tube (47). The lateral plate mesoderm is the source of both the endothelium and the muscle layers and these are the only two cardiac cell types generated. Anteriorly, in the region that will eventually become the ventricles, myogenic cells proliferate and form extensive trabeculae. In the posterior regions, however, proliferating myocytes do not form extensive trabeculations and this region eventually becomes the atria (48). By the end of the first 24 days in humans, the heart has an endocardium and a myocardium, but lacks an epicardium and there are no rudimentary blood vessels (49,50).

None of the cells that form the coronary system actually arises from within the heart. All the cells that form the coronary system come from outside the heart and then differentiate into blood vessels only when they are within the heart. All of this occurs without interaction with the blood coursing through the primitive heart lumen (50). There are at least three major anatomic components that are important in the development of the coronary arteries (19). First, the myocardial sinusoids are an elongation of the trabeculae into the primitive loosely packed myocardium and thus communicate with the heart cavities. These sinusoids are the earliest sites of metabolic exchange whereby the developing myocardium is nourished. As the myocardium becomes more compact, the sinusoids disappear, but persistence of these sinusoids may lead to coronary artery-cameral fistulae. Second, by about 32 days after ovulation a separate in situ vascular network begins to develop. This primitive network of arteries, veins, and capillaries may have connections with other mediastinal vessels, which can be a source for coronary artery fistulae. Third, as the coronary artery network evolves, endothelial buds arise from the base of the truncus arteriosus as septation is occurring. It is still unclear if there are initially only two buds or six buds, one from each potential cusp of the aortic and pulmonary sinuses with later involution of all but two buds. These buds grow and, after septation is complete, fuse with the developing in situ coronary artery network to form the coronary artery system (Fig. 16.8).

![Figure 16.8 Schematic representation of the basic components involved in the embryogenesis of coronary arteries. Aorta (AO) and pulmonary (PA) trunks are shown at completion of septation; coronary buds (3a, 3b, 3c, 3d) emerge from semilunar sinuses. Rudiments of right (Ca), circumflex (Cb), and left anterior descending (Cc), coronary arteries are shown as isolated in situ vascular networks. At this stage sinusoids (Sm) are site of metabolic exchanges between intracavitary blood and cardiac jelly. Source: From Ref. 19.](image-url)
Although the coronary ostia are formed early, the distal coronary branching pattern remains variable until the cardiac chambers are more fully developed. Abnormal involution (in the case of six initial buds), bud position, or septation of the truncus arteriosus are all factors that may contribute to the development of coronary artery anomalies.

**Variations in Coronary Anatomy of Minimal Clinical Significance**

### Right Coronary Artery

Normally, there are two main coronary ostia but several common variations may occur. As noted earlier, in 30% to 50% of angiograms the conus branch of the RCA may arise separately from the right sinus rather than its usual position as a branch of the proximal RCA (19,28). Two right conal branches have also been reported. A separate conus branch usually has a diameter at the ostium varying from 0.5 to 1.9 mm and may give rise to preventricular and ventricular branches, which nourish more than just the infundibulocardiac myocardium of the outflow tract. In patients with occlusion of the LAD or RCA, the conus artery often serves as a principal source of collateral circulation. In such patients it is important to visualize the conus artery well to adequately visualize the collateralized vessels (51).

The location of the RCA ostium is more variable than the left ostium. This variability makes it difficult to define what exactly a normal location is, but an origin below the aortic ring is definitely “low” and more than 1 cm above the sinotubular ridge is definitely a “high” takeoff. A high origin of the RCA is generally thought to be of no clinical consequence, but sudden death was reported in an amateur athlete with a high origin of the RCA plus small, hypoplastic right and LCx arteries (52). Furthermore, instead of the usual location in the middle of the sinus the RCA ostium can be located closer to the aortic valve commissures. This causes a slight alteration in the usual course of the vessel, but has no other clinical significance. The RCA may arise from the posterior (noncoronary) sinus but this is a very rare anomaly, which has never been associated with symptoms or complications (53). Finally, a RCA arising from the midsegment of the LAD has been described and presumed not to cause ischemic complications (54).

### Left Coronary Artery

The left coronary orifice usually arises from the center of the left sinus of Valsalva just above the free margin of the aortic valve leaflet. Malposition of the left coronary ostium either high or low in the sinus or near the aortic valve commissures occurs less often compared with the RCA, but should be suspected when standard angiographic catheters or manipulations fail to cannulate the artery. Similar to a high origin of the RCA, a high takeoff of the left main is not generally felt to have any clinical significance, but there is one older report of showing morphologic evidence of chronic ischemia and left ventricular scarring in a patient with a high takeoff of the left main (55). A very high origin of the left main should be noted if cardiac surgery is planned so as to avoid accidentally crossclamping or transsecting the vessel during surgery (56). Similar to the RCA, the origin of the left coronary has been rarely observed from the noncoronary cusp, but has never been associated with symptoms or complications in this location (53).

The left coronary ostium is usually single and is the origin of the left main coronary artery. The most frequent minor variation observed is absence of the left coronary, which then results in the LAD and LCx arising directly from the aortic root as separate vessels. The vessels are otherwise normal in their respective distributions. The incidence of truly separate ostia varied from 0.5% to 8% in other normal hearts (57). The wide variation in the occurrence of this finding in the literature is, in part, related to the absence of a consistent definition for this entity. If defined as two separate ostia from the aorta, the incidence is probably less than 1%. However, if it is defined simply as the absence of a proper left main trunk, the incidence is more than 1%. Rather than two distinctly separate vessels, the more common observation is a single ostium, which is shared by the origins of the LAD and LCx.

### Variation in Coronary Size

Various techniques have been used to determine the size of normal coronary arteries and it is now generally appreciated that size measurements from autopsy specimens do not correlate well with measurements made in vivo (58,59). Some of this discrepancy is due to the techniques used for fixation of the autopsy specimens (60). In practical terms, since atherosclerosis is a diffuse process it can sometimes be difficult to clinically distinguish a diffusely diseased segment from one that is just normally small in diameter. Despite a need for these data, relatively little information exists on lumen size variations in normal coronary arteries. Coronary artery diameters at multiple locations were determined in carefully selected normal coronary arteries using computer-based quantitative measurements by Dodge and colleagues (Table 16.3) (61). Using these and other measurements (62) it is possible to group the size of certain segments of normal coronaries, but the wide standard deviation makes the application of these to an individual patient of less value. Nevertheless, some associations are

<table>
<thead>
<tr>
<th>Location</th>
<th>Right dominant (mm)</th>
<th>Left dominant (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD (1st segment): midway between its origin and 1st septal</td>
<td>3.1 ± 0.5</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>LAD (3rd segment): midway between its origin and apex</td>
<td>3.6 ± 0.5</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>LCx (1st segment): midway between its origin and 1st marginal</td>
<td>4.2 ± 0.5</td>
<td>4.2 ± 0.6</td>
</tr>
<tr>
<td>LCx (3rd segment): midway between the 1st marginal and most distal marginal</td>
<td>1.6 ± 0.6</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>RCA (1st segment): midway between its origin and 1st acute marginal</td>
<td>2.8 ± 0.6</td>
<td>2.8 ± 0.6</td>
</tr>
<tr>
<td>RCA (3rd segment): midway between the 3rd acute marginal (if present) and posterior descending</td>
<td>1.1 ± 0.4</td>
<td>1.1 ± 0.4</td>
</tr>
</tbody>
</table>

**Abbreviations**: LAD, left anterior descending; LCx, left circumflex artery; RCA, right coronary artery.

**Source**: Adapted from Ref. 61.
noted. For example, the RCA or LCx is significantly larger when it is the dominant vessel, but the PDA is similar in size whether it arises from the RCA or LCx. One thing their data did show was that coronary arterial diameter in women was about 9 ± 8% smaller than in men, even after normalization for body surface area. The smaller arterial size of the left main and proximal LAD in women was confirmed in a more recent study using intravascular ultrasound (63). Other studies have shown a good correlation between the lumen area and the corresponding summed distal branch lengths and regional myocardial mass in patients with and without coronary disease, thus the greater amount of distal territory supplied the larger the caliber of the artery lumen (64).

Absent Circumflex or RCA
At the extreme of variations in coronary size are the rare anomalies of an absent circumflex artery or RCA. In this case of an absent circumflex, the RCA is a very large vessel (superdominant), which crosses the crux and ascends in the atrioventricular groove on the left to supply the posterior and lateral myocardium. In the case of an absent RCA, the circumflex continues in the atrioventricular groove in the course typical of the normal RCA (65). The LAD is usually normal in its size and distribution. Neither of these anomalies appears to be of clinical significance in the absence of coronary artery disease.

Variations in the Course of Coronary Arteries
Myocardial Bridging
As noted previously, minor variations in the course of a coronary artery may occur if the ostium is malpositioned within the aortic cusp, but these are usually of no clinical importance. One of the most common variations in the course of a coronary artery occurs when a segment of the conduit artery dips into the myocardium resulting in the overlying myocardium compressing the artery during systole (66). The muscle overlying the intramyocardial segment of the coronary artery is termed a myocardial bridge and the artery courses through the myocardium is called a tunneled artery. The most frequent site of bridging in man is the midsegment of the LAD. A typical muscular bridge in this segment is 10 to 20 mm long and 2 to 4 mm thick, but segments up to 50 mm in length have been observed (67). Muscular bridges have been identified over diagonal arteries, the left main, LCx, marginal branches and the RCA. Autopsy studies show a higher incidence of myocardial bridges than demonstrated by angiography. For example, angiographic studies show a prevalence of bridging varying from 0.5% to 7.5% of studies whereas anatomic studies show a prevalence as high as 60% in the LAD and 6% to 50% in other vessels (67–69). Factors such as the length of the tunneled segment, the degree of systolic compression and the heart rate have all been postulated to explain the difference in prevalence between angiographic and autopsy studies. In addition, for systolic narrowing to occur the external muscular compressive force must exceed the arterial pressure and the intrinsic arterial wall stiffness. During angiography, the increased intraluminal pressure related to the contrast injection may act to diminish the appearance of systolic compression and thus the appreciation of a myocardial bridge. Some anatomic variation also exists. Arteries located in the atrioventricular groove (proximal RCA and LCx) may be surrounded by scattered muscular fibers continuous with the atrial myocardium and may have systolic compression, but these are referred to as myocardial loops rather than classic myocardial bridges. As another variant, arteries such as an obtuse marginal branch or ramus located over the free wall of the LV may dive into the myocardium and not resurface.

Myocardial bridges and tunneled arteries have long been recognized clinically and are generally felt to be a benign incidental finding (66). Indeed, in most patients myocardial bridges have little clinical significance as the majority of coronary flow in the left coronary occurs during diastole when there is no compression (70). However, there are scattered reports in which typical angina with anterior wall ischemia during tachycardia, myocardial perfusion defects, acute myocardial infarction abnormal ventricular repolarization and sudden cardiac death have all been attributed to myocardial bridges (71–75). More elegant studies using intravascular ultrasound and Doppler flow velocity have documented disturbed intracoronary hemodynamics in both symptomatic and asymptomatic patients with myocardial bridging in the midportion of the LAD (76,77). In symptomatic patients, treatment by either stent placement or surgical transsection of the muscle bridge has relieved both symptoms and objective findings of myocardial ischemia (77–79). Several anatomic studies have reported a “protective” effect of myocardial bridging on the development of atherosclerosis. The mechanism of this effect is unknown, but has been postulated to be from a reduction in systolic wall stress in the tunneled segment. In humans, myocardial bridges may slightly increase the occurrence of proximal atherosclerosis while protecting the bridged segment and the distal artery. Careful autopsy studies have shown that when myocardial bridging is present, intimal thickening and macroscopic raised atherosclerotic plaques are increased just proximal to the bridge (80).

Crossing Epicardial Coronary Arteries
As the name implies, two coronary artery branches may rarely cross over each other on the epicardial surface. The true incidence of this minor variation in coronary anatomy is unknown and it is not believed to have any functional significance (81,82). Crossing of two right ventricular branches, an acute marginal branch of the RCA with the RCA in the atrioventricular groove, a diagonal and circumflex marginal branch, two obtuse marginal branches of the circumflex and the LAD and a diagonal have all been reported.

Intercoronary Continuity
Intercoronary artery continuity or “coronary arcade” is a rare variant of the coronary circulation. The true incidence is unknown, but in one report it was seen in 0.02% of nearly 10,000 coronary angiograms (83). Arterial continuities exist in other areas such as the superficial volar arch in the hand, intestinal branches of the superior mesenteric artery and the circle of Willis. Communications between the distal LCx and the distal RCA in the posterior atrioventricular groove and between the LAD and PDA in the distal interventricular groove have both been observed (Fig. 16.9). These connections occur in the absence of obstructive coronary disease and pathologically distinct from coronary collaterals (84). Compared with collaterals, these connections have a well-defined muscular layer, are larger in diameter (>1 mm) and extramural.

Small Coronary Artery Fistulas
A coronary artery fistula is an abnormal communication between an epicardial coronary artery and a cardiac chamber,
major vessel or other vascular structure. Small coronary artery fistulas occur in 0.1% to 0.2% of patients undergoing coronary angiography and usually drain into a single cardiac structure (85). One of the most commonly observed small fistulas in adults is a communication between the LAD and the common pulmonary artery. Small fistulas are usually not associated with continuous murmurs or detectable intracardiac shunts and have a benign course. Small numbers of patients have undergone serial angiographic studies demonstrating no increase in fistula size over time and patients have been followed for up to 11 years without complications attributable to their fistula (86). The detection of small fistulas in the elderly confirms their benign nature. The majority of coronary fistulas are congenital and arise from two defects in coronary artery embryogenesis. Fistulas can arise from failure of the embryonal intramyocardial sinusoids to obliterate resulting in a gradual enlargement of one of these channels or from enlargement of a thebesian veins (85). Alternatively as in the case of fistulas involving the pulmonary artery, it may evolve from persistence of a vascular bud that remains attached to the pulmonary artery as it separates from the aorta early in embryogenesis. Patients with small asymptomatic fistulas require no special treatment and can simply be followed clinically. Small fistulas can also be acquired and have been reported secondary to deceleration injuries, coronary angioplasty, repeated myocardial biopsies in heart transplant patients, pacemaker leads and after cardiac surgery.

CORONARY ARTERY ANOMALIES

The exact incidence of coronary anomalies is unknown and the reported incidence varies depending on the methods used to detect the anomalies, the population assessed and what is included as a coronary anomaly as opposed to a variant of normal. Some sources classify several of the anatomic variations described above as anomalies while other sources simply consider these to be variants of normal. In general, congenital coronary artery anomalies in the absence of other cardiac congenital anomalies have been described in approximately 1% of patients who undergo coronary angiography and approximately 0.3% of patients at autopsy (Table 16.4) (87-94).

There are several congenital syndromes that are associated with coronary anomalies. Patients with Williams syndrome (elfin facies, infantile hypercalcemia, hypoplastic teeth) may have coronary ostial narrowing as a component of supravalvar aortic stenosis, which is characteristic of this disease. Patients with congenital aortic valve disease commonly have variants in coronary ostial origin. Coronary anomalies may be commonly associated with other congenital cardiac malformations, most notably, transposition of the great arteries, tetralogy of Fallot and different forms of pulmonary atresia (95,96).

### Coronary Anomalies Not Associated with Ischemic Complications

#### Origin of the LCx from the Right Coronary Sinus

This anomaly is said to be the most common anomaly of coronary arterial origin in adults with an incidence of about 0.3% when assessed by coronary angiography and autopsy (89,93,97). The aberrant LCx can arise from either the proximal segment of the RCA or from a separate ostium near the origin of the RCA (Fig. 16.10). The LAD and RCA are normal in their distribution and the anomalous LCx invariably courses posterior to the aorta and then to its normal distribution over the lateral wall of the heart (Fig. 16.11). Most patients have no other associated anomalies. This anomaly should be suspected when angiography of the left coronary shows an unusually long, nonbranching proximal segment and no obvious LCx vessel perfusing the lateral wall (98). This anomaly can be missed during angiography of the RCA if the tip of the catheter is beyond the origin of the anomalous vessel and the force of the injection is inadequate to fill the aberrant LCx with the reflux of contrast. It can also be suspected if a “dot sign” is seen in a right anterior oblique left ventriculogram or supravalvular aortogram (Fig. 16.12). This anomaly has traditionally been considered of little clinical significance unless the operator incorrectly assumes the LCx is occluded or an important stenosis in the aberrant artery is not visualized. This is true in the majority of cases, but there are a few case reports where ischemic complications have been associated with this anomaly (99,100). Furthermore, it has been reported that the stenosis severity in this anomaly is greater than in control subjects matched for age, gender, symptoms and degree of atherosclerosis in nonanomalous coronary arteries (101). Compression of the anomalous LCx has been reported from the fixation rings of prosthetic valve (102).

### Table 16.4 Incidence of Coronary Anomalies Detected by Angiography

<table>
<thead>
<tr>
<th>Author (reference number)</th>
<th>Patients (n)</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamanaka O (94)</td>
<td>126,595</td>
<td>1.30</td>
</tr>
<tr>
<td>Wilkins CE et al. (93)</td>
<td>10,661</td>
<td>0.78</td>
</tr>
<tr>
<td>Kimbiris D et al. (91)</td>
<td>7,000</td>
<td>0.64</td>
</tr>
<tr>
<td>Baltaxe HA (87)</td>
<td>1,000</td>
<td>0.90</td>
</tr>
<tr>
<td>Chaitman BR et al. (88)</td>
<td>3,750</td>
<td>0.83</td>
</tr>
<tr>
<td>Engel HJ (90)</td>
<td>4,250</td>
<td>1.20</td>
</tr>
<tr>
<td>Cieslinski G (89)</td>
<td>4,016</td>
<td>0.97</td>
</tr>
</tbody>
</table>
Origin of a Coronary from the Posterior Sinus of Valsalva
Either the RCA or the left main coronary artery can arise from the posterior sinus of Valsalva (the noncoronary sinus). Both of these variants are considered extremely rare, although the RCA from this location is said to be more frequent (53). Origin of the left main from the posterior cusp has not been reported in the absence of other anomalies of the heart and great vessels and the simultaneous origin of both arteries from this location has never been reported (53).

Certain Variations of a Single Coronary Artery
There are many variations of a single coronary artery and several anatomic classifications have been proposed (103,104). Lipton’s classification now seems to be the most frequently used (103). In this classification, the letters “R” and “L” indicate whether the single artery arises from the right or left aortic sinus and the letters “A,” “B,” and “P” signify whether the “transverse” branch courses anterior, between or posterior to the great vessels, respectively (Fig. 16.13). The associated number in this classification indicates the number of major branches somewhat mimicking the RCA, LCx, and LAD. When found in a younger age group (<20 years) a single coronary artery is frequently associated with other anomalies of the heart and great vessels, but when identified later in life associated anomalies are infrequent (53). From the cases reported, there is a slight male predominance (male-to-female ratio 1.4:1) with a similar frequency of arteries arising from the right or left sinuses of Valsalva. Certain types of single coronary artery have not been associated with clinical complications. In general, these are the varieties where no vessel courses between the great vessels (Fig. 16.13, top). However, should coronary atherosclerosis develop in the main trunk of a single artery, the complications of atherosclerosis can be devastating.
Coronary Anomalies Associated with Clinical Complications

Origin of One or More Arteries from the Pulmonary Trunk

Coronary arteries arising from the pulmonary artery are one of the most serious congenital coronary artery anomalies. It frequently results in death during infancy and only a few individuals survive to adulthood (105). Either the left or right coronary artery, both major coronary arteries, or rarely, the LAD or LCx may originate from the pulmonary artery. Occasionally, origin of the conus artery from the pulmonary artery has been noted. The most frequent variety of this anomaly is origin of the left coronary from the pulmonary artery and a RCA arising from the usual position in the aorta with a normal course (Fig. 16.14). In infants this anomaly has been referred to as the Bland-White-Garland syndrome (107). Children with this anomaly usually present between 8 and 16 weeks after birth, but adult presentation is occasionally seen (108). During fetal life, the systemic pressure and oxygenation in the pulmonary artery provide adequate perfusion to the LV. However, within days after birth the pressure and oxygen content of the pulmonary artery decline so that the left coronary is underperfused. It is not clear why the clinical presentation is delayed for several weeks but persistence of collaterals and a delayed fall in pulmonary artery pressure are possible explanations. If a substantial collateral circulation between the RCA and the anomalous left coronary artery persists survival into adulthood is possible with a left-to-right shunt from the RCA to the pulmonary artery.

In the most common infantile presentation of this anomaly, collaterals are inadequate to support the LV and the child presents with tachypnea, cough, wheezing, pallor and cyanosis. Signs of myocardial ischemia and infarction with the associated complications of aneurysm formation, mitral regurgitation and congestive heart failure are present (105). Diagnostic testing confirms a pattern of anterior infarction on the electrocardiogram in many with important mitral regurgitation demonstrated by echocardiography and Doppler. Angiography is frequently necessary to confirm the diagnosis. Prompt surgical therapy is indicated as survival without surgery is <20% in symptomatic infants (109). Some reports suggest that up to 20% of patients with this anomaly may survive into adulthood and remain asymptomatic or have a late presentation when they develop mitral regurgitation, angina, or CHF (110). Sudden death is a complication in both infants and adults. The clinical course of the patient tends to be more favorable if extensive collateral circulation exists.

Figure 16.13 Classification of single coronary artery anomalies. In this classification, the letters “R” and “L” indicate whether the single artery arises from the right or left aortic sinus and the letters “A,” “B,” and “P” signify whether the “transverse” branch courses anterior, between or posterior to the great vessels, respectively. The associated number in this classification indicates the number of major branches somewhat mimicking the right, left circumflex and left anterior descending arteries. In the diagram, the great vessels from front to back are the pulmonary artery, aorta, and superior vena cava. Those anomalies not typically associated with complications (benign) are shown on the top and those potentially associated with ischemia are on the bottom. Source: Adapted from Ref. 103.
Anomalous origin to the RCA from the pulmonary artery is much less common and has fewer clinical consequences and the same is true for a conus branch arising from the pulmonary trunk. If the LAD alone arises from the pulmonary artery the presentation in both children and adults is often similar to that of the left main in this position. Depending on the extent of collaterals, symptoms and signs of myocardial ischemia may occur in infancy or be delayed until adulthood and surgical repair is often necessary (53). In some cases of this anomaly, only ligation of the anomalous LAD is performed while in other cases, ligation and some form of bypass is used. Anomalous origin of the circumflex alone has been reported in children with other cardiac abnormalities, but no adults have been reported with this anomaly (53).

Origin of Both Right and Left Coronary Arteries from the Same Sinus of Valsalva
When either the RCA arises from the left sinus of Valsalva (Fig. 16.15) or the left coronary arises from the right sinus of Valsalva (Fig. 16.16), the anomalous vessel traverses the base of the heart in one of four possible paths. The anomalous vessel can pass Anterior to the pulmonary trunk (type A) (Fig. 16.16), Between the aorta and pulmonary trunk (type B), through the Crista supraventricularis (within the ventricular septum beneath the right ventricular infundibulum) (type C), or posterior or Dorsal to the aorta (type D) (Fig. 16.17) (53,103). The angiographic appearance of these various courses has been well described (Fig. 16.18) (111). There is now agreement that the course of an anomalous coronary artery, rather than the actual location of the coronary ostium, is a major discriminating factor for the anomaly being benign or associated with clinical complications such as angina, ventricular arrhythmias, syncope or sudden death (53,94). Adverse outcomes occur more frequently when the anomalous coronary artery has a course that passes between the aorta and the pulmonary artery, or less commonly via a septal pathway. The mechanism of ischemia, infarction or sudden death in this situation appears related to the shape of the coronary ostium of the anomalous vessel rather
varieties have been recognized. The anomalous LAD can take a path anterior to the pulmonary artery and this course is frequently seen in association with tetralogy of Fallot. It is important to identify this course in children undergoing repair of the tetralogy of Fallot so as to avoid damage to this branch during surgery. Although this course is usually not associated with clinical complications in adults, isolated case reports of ischemic complications exist (120–122). Ischemic complications have also been reported to occur when the LAD courses between the aorta and pulmonary artery (123,124) or has a course within the interventricular septum (125). Certain variations of a single coronary artery are quite similar to a wrong-sided coronary artery and are also associated with ischemic complications (Fig. 16.13) (126).

Unfortunately, many patients with these anomalies present with sudden cardiac death, usually occurring during or immediately after intense athletic activity. In one large series of cases presenting with sudden cardiac death and proven at autopsy to have either the left or right coronary artery arising from the wrong side and passing between the aorta and pulmonary artery, only 45% had premonitory symptoms of chest pain or syncope (127). In those who had some type of cardiovascular test before death, all tests were within normal limits, including 12-lead electrocardiograms, stress ECG with maximal exercise and left ventricular wall motion and cardiac dimensions by two-dimensional echocardiography. If there is a suspicion of this anomaly, visualization of the coronary arteries by computed tomographic angiography, magnetic resonance imaging or conventional angiography is usually necessary (128,129).

Figure 16.17 Anomalous left main coronary artery from the right sinus of Valsalva. The anomalous vessel traverses the base of the heart in one of four possible paths: Anterior to the pulmonary trunk (type A), Between the aorta and pulmonary trunk (type B), through the Crista supraventricularis (within the ventricular septum beneath the right ventricular infundibulum) (type C), and posterior or Dorsal to the aorta (type D). Abbreviation: RCA, right coronary artery. Source: Adapted from Ref. 103.

than compression of the anomalous vessel by the aorta and pulmonary artery during systole. Normally, the coronary ostia are round to oval in shape, but in these anomalies the transverse course of the vessel to the opposite side of the heart results in an acute-angle takeoff that either behind the ostium into a slit-like shape (Fig. 16.19) (112,113). Clinical events, in particular sudden death, are usually seen during exertion in young individuals in the absence of coronary atherosclerosis or other cardiac abnormalities. The increased cardiac output during exercise dilates and stretches the aortic wall resulting in a further kinking and additional compromise of the slit-like opening thereby causing a transient limitation of coronary blood flow.

A left main artery arising from the right sinus of Valsalva and coursing between the aorta and pulmonary artery is the most threatening variety in this group of anomalies (53,114). Complications have not been associated with a course of the left coronary artery that is either behind the aorta or anterior to the pulmonary artery, but there are reports of ischemic complications when the course is through the upper septum (94,115,116). Although there are other anatomic possibilities, a right coronary artery arising from the left sinus of Valsalva or the proximal left main almost invariably (>99%) will pass between the aorta and pulmonary artery (94). The clinical course in these patients is variable with some having no symptoms or evidence of cardiac dysfunction and others having complications including angina, myocardial infarction, syncope and sudden death (117,118). There is some suggestion that a familial clustering of anomalous origin of a coronary artery from the wrong aortic sinus with an intra-arterial course may exist (119). An additional variation of this anomaly occurs when the LAD alone arises from the right sinus of Valsalva or the proximal RCA. This is a very rare anomaly and several

Coronary Atresia
Atresia or hypoplasia of the left main or RCA is a very rare cause of ischemia and myocardial infarction in infancy and early childhood (130). Survival to adulthood depends on the development of adequate collateral flow from the other main coronary artery. Atresia of a coronary artery can occur as an isolated lesion or in association with other congenital diseases such as supravalvular aortic stenosis, homocystinuria, Friedreich’s ataxia, Hurler’s syndrome, progeria, and pulmonary atresia (131). Successful surgical repair is possible (132).

Large Coronary Artery Fistulas
As described earlier, a coronary artery fistula is an abnormal micro- or macrovascular connection between a coronary artery and a cardiac chamber, vein, or another artery. Fistulas between a coronary artery and a cardiac chamber are also called coronary-cameral fistulas and those between a coronary artery and vein are termed coronary arteriovenous fistulas (Fig. 16.20). Small fistulas rarely are associated with clinical findings or complications and are usually detected as an incidental finding on angiography (85). About half of the patients with a coronary artery fistula are asymptomatic, but the clinical presentation in those with large fistulas depends on the type of fistula, shunt volume, site of the shunt and presence of other cardiac conditions. Detection of a continuous murmur, dyspnea with exertion, fatigue, congestive heart failure, arrhythmias, pulmonary hypertension, infective endocarditis, or myocardial ischemia are common presentations in symptomatic patients (85,134). Large fistulas are associated with the development of very tortuous ecstatic coronary arteries proximal to the origin
of the fistula. Fistulae can arise from any of the coronary arteries, but about 50% arise from the RCA, 42% from the left coronary and 5% from both arteries (135). The most common sites for drainage of the fistulas are the coronary sinus, right atrium or pulmonary artery, but many other locations have been reported. Echocardiography with Doppler studies can suggest the presence of a fistula, but confirmation requires computed tomographic or invasive angiographic imaging, the latter method often coupled with quantification of the shunt volume. If therapy if felt necessary, the treatment should obliterate the fistula yet maintain antegrade coronary flow (136). Traditional coronary artery bypass or coronary reimplantation with closure of the fistula have been used, but percutaneous methods such as catheter embolization are now being considered as an alternative (137,138). Multiple coronary-cameral fistulas causing myocardial ischemia have been reported in some patients (139). In these patients, coronary angiography shows diffuse endocardial opacification and filling of the ventricular cavity.

CORONARY COLLATERAL BLOOD VESSELS
Normal embryologic development of the coronary circulation includes the formation of collateral vessels, which connect different components of the coronary arterial circulation. In the normal adult heart, the collateral channels are small, thin-walled channels, usually less than 50 μm in diameter, that contribute little to total coronary blood flow. However, in response to coronary arterial narrowing and myocardial ischemia these collateral channels can increase in diameter to 200 to 600 μm or greater, develop muscular media and transport a substantial proportion of blood flow (140). The enlargement of native channels is termed vasculogenesis, but collaterals can also develop from the growth of new vessels (angiogenesis). Limited data exists regarding the conditions required to induce collateral growth in humans. Several clinical factors including coronary occlusion and ischemia, hypoxia and anemia have been identified as stimulating collateral development and evidence suggests this is mediated by the release of certain growth factors, cytokines and proteases from activated monocytes (141,142). Collateral development can occur quickly. At the time of acute coronary occlusion resulting in myocardial infarction, only 16% of patients had angiographically evident collateral vessels. Serial angiography showed that effective collaterals were present in 50% of the patients by two weeks and 66% of patients by seven weeks following the infarction (143). Functioning collaterals can maintain a coronary artery wedge pressure that averages nearly 40% of the mean aortic pressure thereby maintaining myocardial viability (144). The angiographic demonstration of collateral flow to an area in the
distribution of an occluded coronary artery is one of the strongest indicators on myocardial viability in the affected area.

Functional collaterals can develop between the terminal extensions of two coronary arteries, between the side branches of the two coronary arteries, between branches of the same artery or within the same branch via the vaso vasorum. Common routes for collateral blood flow to the three main coronary arteries were elegantly defined by Levin in the early days of coronary angiography and are still relevant today (Fig. 16.21) (145). Certain collaterals have been specifically identified such
Figure 16.21 Common routes of collateral supply to the three major coronary arteries. (A) Collateral channels that develop with occlusion of the LAD. (B) Collateral channels that develop with occlusion of the RCA and (C) collateral channels that develop with occlusion of the LCx. Abbreviations: LAD, left anterior descending; RCA, right coronary artery; LCx, left circumflex; AV, atrioventricular branch; D, diagonal branch; LAO, left anterior oblique; LCA, left coronary artery; OM, obtuse marginal; PDA, posterior descending artery; RAO, right anterior oblique. Source: Adapted from Ref. 145.
as Kugel’s artery (146). Although originally described as arising from the proximal LCx, most now consider a Kugel’s artery as a collateral arising from either the proximal RCA, the sinus node artery or LCx that traverses the intraatrial septum to anastomose with the atrioventricular node artery thus supplying the distal RCA or LCx branches. It is identified in 3% to 6% of angiograms in patients with significant coronary atherosclerosis (147). Another specifically identified collateral is a Vieussens’ ring (148). This is a collateral connection between the conus artery of the RCA and a proximal right ventricular branch of the LAD. This collateral circle provides flow to reconstitute a proximally occluded LAD or less frequently a proximally occluded RCA.

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Diagnostic angiographic catheters: coronary and vascular

Ryan Berg and Michael Lim

INTRODUCTION
While hundreds of catheters are available for use in the catheterization laboratory, most operators have a select few that compromise the vast majority of use. In this chapter, we provide a practical guide for many of the most important “workhorse” catheters in general use today. We do not intend to provide an exhaustive list of all available catheters; rather, we discuss the principal catheters used in the fields of coronary angiography, ventriculography, and peripheral angiography.

HISTORY OF SELECTIVE ANGIOGRAPHIC CATHETERS
Dr Mason Sones performed the first diagnostic coronary angiogram in 1958. He later developed a standard technique from a brachial cutdown approach with design of his own catheters. Sones helped develop a single catheter with a stiff body to allow for torqueability and a tapered tip that allowed it to be manipulated against the aortic cusps to take a primary curve to engage the coronary ostia. The tapered tip also prevented the catheter from completely obstructing the coronary ostia. This is known as the Sones catheter and the technique for engaging the coronary ostia through the brachial cutdown is known as the Sones technique.

The next major milestone in coronary catheter design came from Dr Melvin Judkins, who developed preshaped selective coronary catheters based on chest radiographs. These catheters are now known as the Judkins left and right catheters, and his technique of inserting them from a percutaneous femoral approach is known as the Judkins technique. While the Sones technique is of tremendous historical importance, most present-day operators have not been trained in his brachial cutdown approach with Sones catheters. A percutaneous approach and standardized preformed catheters are now the standard from both femoral and arm (radial and brachial) access for both coronary and peripheral angiography.

GENERAL DIAGNOSTIC CATHETER DESIGN
Modern vascular diagnostic catheters are typically polymer-blended catheters made of nylon, polyurethane, or other proprietary polymers. Polymer catheters are reinforced with braided steel that promotes torque transmission from the distal end to the tip. The catheter tip is usually tapered with a non-braided polymer that allows for increased flexibility and less trauma when being manipulated into a vessel ostium (Fig. 17.1). Some catheters incorporate a radiopaque tip for maximal visualization. The standard selective diagnostic coronary catheters are 100 cm in length and range in usual diameters from 4 to 6 French (Fr). While larger sizes can deliver larger volumes and increased flow rates of contrast allowing for better visualization of the selected vessel, the smaller catheters are intended to be less traumatic to the selected vessel and allow for smaller percutaneous entry sheaths. Standard selective peripheral arterial catheters are similar in construction but they come in smaller lengths as well. Most diagnostic catheters are rated to accept a maximum of 1200 psi of contrast injection.

LEFT CORONARY CATHETERS
Over two-thirds of the mortality risk associated with diagnostic coronary catheterization is related to trauma of the left main coronary artery (1). Therefore, proper diagnostic catheter selection and proper engagement of the left main is of critical importance. The most common diagnostic coronary catheter used to engage the ostium of the left main is the Judkins left. This endhole catheter has a 90° primary curve to allow the tip to enter the coronary ostium and a 180° secondary curve to allow backup support from the opposing wall of the aorta. Depending on the manufacturer, it might go by a different brand name or abbreviation, but it is usually abbreviated “JL” for Judkins left. The length of the segment between the primary and secondary curve is denoted by a number, so JL4 means there is 4 cm in length between the primary and secondary curves. The Judkins left catheter comes typically in sizes ranging from 3.5 to 6 cm (Fig. 17.2). Bigger sizes are needed for larger patients and those with dilatation of the aortic arch.

The JL catheters are the most commonly used because very little manipulation is needed to engage most left main arteries. Generally, the catheter is advanced under fluoroscopy to the ascending aorta over a wire. After the wire is removed, the catheter tends to move cranially and leftward to engage the left main artery. The left main can be engaged with usually only a slight advancement of the catheter forward at the introducer sheath, seen as a “pop” of the catheter into the left main while watching on fluoroscopy. Rarely, the left main can be out of plane either anteriorly or posteriorly and then either slight clockwise or counterclockwise torque (respectively) may be used to engage the artery. Another common problem is choosing the wrong initial catheter size. Rarely, a Judkins left of any size is not able to properly engage the left main satisfactorily for adequate angiography. This situation can occur when the left main orifice is too high or too out of plane, or when the left main is very short and selective injection of the left anterior descending and left circumflex is needed. In these cases, a more torqueable catheter such as the Amplatz left, invented by Dr Kurt Amplatz, can be used.

The most common sizes of the Amplatz left diagnostic catheters are the AL1, AL2, and AL3. They are sized on the basis of the diameter of their secondary curve (Fig. 17.3). The larger Amplatz catheters have more “reach” to engage more superior takeoffs of coronary ostia. Typically the AL2 is used as
the standard size to engage the left main coronary ostia, but higher or more superior directed left main ostia require longer catheters. The Amplatz left catheters require slightly more manipulation, with subsequent increased risk for coronary dissection for engagement and disengagement than the standard Judkins left catheters, making them a secondary choice for engaging the left main. Amplatz left catheters are inserted into the ascending aorta in standard fashion over a wire. When the wire is removed, often the catheter will be positioned with its tip pointing down to the aortic valve. If the tip is tilted toward the right cusp, the catheter must be rotated so that the tip looks toward the left cusp. The catheter must then be advanced so that the secondary curve is sitting on the aortic valve with the tip climbing up the aortic wall and pointing slightly upward. At this point, the catheter can be torqued either clockwise or counterclockwise (tip anterior or posterior) to engage the ostium of the left main (Fig. 17.4). There are various methods to disengage an Amplatz left diagnostic catheter. Commonly, once the Amplatz left catheter is engaged in the left main, pushing the catheter will advance the front of the secondary curve against the aortic wall thereby backing out the tip of the catheter. In contrast, pulling the catheter may force the tip deeper into the left main, increasing the risk of catheter dissection. Depending on how the secondary curve of the catheter is sitting on the aortic root or how deeply the tip is engaged, this “withdrawal paradox” may not occur.

**RIGHT CORONARY CATHETERS**

The most commonly used diagnostic right coronary catheter is the Judkins right. Its primary curve is a 90° bend to allow the catheter to enter the right coronary ostium. The secondary curve is a gradual 30° bend. As with the Judkins left, depending on the manufacturer, it might go by a different brand name or abbreviation, but it is usually abbreviated as “JR” for Judkins right, followed by a number representing the length of the distance between the primary and secondary curves. For most typical adults, a JR4 catheter is used to engage the right coronary artery. The Judkins right comes in sizes ranging from 3.5 to 6 cm (Fig. 17.5). Bigger sizes are needed for patients with larger or dilated ascending aortas. Unlike the Judkins left, the Judkins right catheter requires significant more manipulation to engage the coronary ostium. The standard approach involves
inserting the catheter so that it rests on the cusps of the aortic valve. The tip of the catheter starts facing toward the right of the viewing monitor (toward the patient’s left). The catheter is then pulled up to the level where it is assumed the right coronary comes off (usually a centimeter or two above the right coronary cusp), while torque in a clockwise direction is simultaneously applied to rotate the tip so it slowly turns toward the left of the screen and engages the ostium of the right coronary artery. Sometimes it will not be possible to engage from the level of the ostium, as the ostium lies just below the sinotubular junction. The sinotubular junction of the aorta in some patients is more pronounced and acts as a ridge that deflects the catheter tip away from the ostium. An alternative approach is to start with the catheter slightly above the level of the right coronary ostium, and torque clockwise while simultaneously advancing downward toward the aortic valve.

In some patients, the JR4 catheter might not torque adequately with clockwise rotation. In this circumstance, the catheter is first torqued counterclockwise to see if that resolves the problem. It is important to avoid vigorous torqueing, as this can lead to kinking of the catheter. This will be recognized by a sudden dampening of the arterial pressure waveform, despite little movement of the catheter itself. If the JR4 will not cannulate the right coronary artery, the operator must consider looking for the origin of the vessel in an anterior, posterior, or superior position and/or consider changing to an alternative catheter. A typical second-choice catheter for use in right coronary artery cannulation is the “no-torque” right catheter, also known as a Williams right or a 3DRC catheter. This catheter was designed to engage the right coronary ostium without any significant manipulation. It has a third curve out of plane of the primary and secondary curves of the usual JR4 that gives it a three-dimensional shape and allows it to engage the right coronary ostium without significant torque.

In some patients, the right coronary ostium has an alternative anatomic takeoff compared with the usual orthogonal takeoff at the level of the free margin of the aortic cusp (3). Common variants include a superior takeoff that mimics the shape of the head of a shepherd’s crook or orthogonal takeoffs from a more anterior position of the aortic wall (Fig. 17.6). In the case of a shepherd’s crook origin, a catheter that has a tip that looks superior is necessary. One example is an internal mammary (IM) artery catheter. The IM catheter is a modified JR4 with an 80° primary curve and a longer distal tip. This 10° difference in angle from the JR4 allows for a slight superior engagement. For a more superior angled takeoff, a hockey stick catheter or the El Gamal catheter (longer tip than the hockey stick) can be used. Its primary curve can vary, but typically is 75°, allowing engagement of a more superior takeoff.

For a more anterior takeoff of the right coronary ostium, and initial catheter choice may be a Williams right, as described previously. If the takeoff has a more significant anterior and superior takeoff, an Amplatz right modified catheter can be used. The Amplatz right resembles the duckbill shape of the Amplatz left catheter, but it has a much smaller secondary curve diameter. If more reach is needed for an even higher and more anterior takeoff of the right coronary artery, an Amplatz left catheter will be needed.

**BYPASS GRAFT CATHETERS**

Common grafts that need to be engaged include the left IM artery, the right internal mammary artery (RIMA), free radial or saphenous vein grafts off of the anterior aorta that can course to any of the major epicardial vessels or rarely a gastroepiploic artery.

Typically the JR4 catheter is utilized as the workhorse in angiography of grafts. While the JR4 can commonly engage most of the free grafts off of the anterior aorta going to the left-sided epicardial vessels, it may not provide engagement of the usually inferior directed takeoff of a graft to the right coronary artery. Also, the angle of the tip is sometimes not acute enough to selectively engage the ostium of the left and right internal
thoracic arteries. In cases where selective engagement of the grafts cannot be accomplished with a JR4, a specialty diagnostic catheter must be used.

Free grafts to the distal right coronary artery or posterior descending artery tend to have an inferior takeoff coming from the right and anterior wall of the ascending aorta. Most frequently, a multipurpose endhole catheter is the first choice for engaging this graft. It is advanced over a wire with the image intensifier in the left anterior oblique 30° position. The catheter begins with its tip high in the ascending aorta and is then turned so the tip faces the aortic wall to the left of the viewing screen (right of the patient). The tip of the catheter then slowly advances downward while applying torque until it is seen or felt to fall into the right-sided graft. The multipurpose catheter tends to work best in grafts that come off with a very significant downward takeoff. For more subtle inferior takeoffs, an Amplatz right modified catheter or a right coronary bypass (RCB) catheter can be helpful (Fig. 17.7). The RCB resembles a JR4 with a tip curved >90° so when it comes up and around the aorta, the tip of the catheter points slightly inferiorly.

For grafts to the left anterior descending or left circumflex arteries or their branches, a JR4 catheter is the first choice and will typically engage selectively. These grafts come off above the left main ostium with the left anterior descending grafts typically in the lowest position followed by the diagonal grafts and then left circumflex grafts most superior. In cases where the grafts are coming off with a more upward takeoff, the second choice is a left coronary bypass (LCB) catheter. The primary curve is 90° like a JR4, but the secondary curve is 70° (as compared with the gentle 30° secondary curve of the JR4), which gives the catheter more reach to the left side of the aorta as well as giving a slightly superior oriented tip of the catheter (Fig. 17.7). For grafts that cannot be engaged with a JR4 or LCB catheter, manipulation of an AL2, AL3, or multipurpose catheter frequently achieves the ability to selectively engage and image the vessel.

For engaging the IM arteries, again a JR4 can be tried for initial engagement, as it will often selectively engage both the right and left IM artery and can save a step of catheter exchange. To manipulate the JR4 to the right subclavian, the catheter is pulled back to the top of the ascending aorta in the LAO 30° view, which lays out the aorta without foreshortening of the branch vessels. In this view the tip of the JR4 is usually pointed caudally and is then rotated 180° to point in a cranial direction while the catheter is then pulled back slightly to engage the takeoff of the right subclavian artery. It is important to adjust the torque of the catheter as it is being pulled back to always keep the tip pointed directly cranial. The tip will otherwise have a natural tendency to torque out of plane and the result is that the catheter will be pulled back into the descending aorta without engagement of the arch vessels. Once the catheter is seen to jump into the brachiocephalic trunk, a test injection is given to confirm the location and to get an idea of the takeoff of the RIMA. The catheter tip can be manipulated to point more toward the right subclavian compared with the right carotid. A J-wire is then placed deep into the right subclavian and the JR4 can be advanced to the mid portion of the right subclavian, at least 2 cm distal to where the suspected takeoff of the RIMA is located. With frequent test injections, the JR4 is slowly pulled back and torqued as needed to engage the RIMA. If the angle of takeoff is steeper than can be engaged by the JR4, an exchange length guide wire is needed to exchange the JR4 for the IM diagnostic catheter. The 80° primary curve on the tip of the IM catheter as compared with the 90° tip of the JR4 should allow successful selective engagement (Fig. 17.7).

In a manner similar to engagement of the brachiocephalic trunk, the JR4 can be used to engage the left subclavian artery. Some operators prefer to engage the brachiocephalic trunk as described above, and then while keeping cranial angulation of the catheter tip, the catheter is pulled back until it is seen to jump into the left carotid artery, and then pulled back again until a second jump is seen into the left subclavian. Alternatively, some operators prefer to avoid engagement of the carotid artery in any capacity, so the JR4 is brought with tip oriented caudally around to the proximal portion of the aortic arch and from there is pointed cranially to directly engage the left subclavian. With either technique, a test injection is done to confirm that the catheter is in the left subclavian and to assess the general position of the takeoff of the left IM artery. A J-wire is then advanced into the left subclavian artery and the JR4 can be placed in the mid portion of the left subclavian, at least 1 to 2 cm distal to the suspected takeoff of the LIMA. At this point the image intensifier can be moved to the PA position if preferred. With frequent test injections, the JR4 is slowly pulled back and torqued as needed to engage the left IM artery. If the angle of takeoff is steeper than can be engaged by the JR4, an exchange length guide wire is needed to exchange for the IM diagnostic catheter.

Uncommonly, the right gastroepiploic artery might be used as a bypass graft to the posterior descending artery (5). The right gastroepiploic artery originates as a branch of the gastroduodenal artery, which is a branch of the common hepatic artery from the celiac trunk. Selective engagement of the celiac trunk will provide "nonselective" angiography of the right gastroduodenal artery. The celiac trunk originates from the anterior aorta just below the diaphragm at the level of the T12 vertebral body. Lateral angiography provides the best view of the takeoff of the celiac trunk to allow for selective engagement with a JR4 or IMA catheter. When those catheters will not selectively engage the celiac trunk, the visceral catheters such as the Cobra or Sos (see section on peripheral diagnostic catheters) can be used. If poor visualization of the distal graft anatomy and runoff is seen with nonselective angiography, super-selective angiography must be performed. This requires using an exchange length angled Terumo glide wire to advance selectively into the right gastroepiploic (Fig. 17.8). The supporting diagnostic catheter can then be exchanged for a 4-Fr soft glide catheter (Terumo) that is small and soft enough to be...
positioned deep into the right gastroepiploic without causing trauma. The 4-Fr size will allow for adequate angiography when it is selectively engaged.

MULTIPURPOSE CATHETER
As previously mentioned, the multipurpose catheter is similar in shape to the original Sones catheter with a straight tip and only one curve. It was developed by Spencer King and Fred Schoonmaker (6). There are four types of common multipurpose catheters: the MPA1 and MPA2, and the MPB1 and MPB2 (Fig. 17.9). The “A” curved catheters have approximately a 120° curve while the B catheters have a 90° gradual curve. The “1” designation refers to endhole only catheters and the “2” designation refers to the addition to two sideholes to the end-hole. The sideholes allow for ventriculography on top of selective coronary angiography. Similar to the original Sones technique, an operator can complete an entire diagnostic cardiac catheterization with just the multipurpose catheter. The soft tip allows it to be easily manipulated into a “J” shape when pressed against the aortic valve, thereby allowing it to more easily selectively cannulate the left and right coronary ostium (Fig. 17.10). Because the tip is long, it can tend to more deeply engage the coronaries, and care must be taken to avoid this predilection. With sideholes, a multipurpose catheter can be manipulated into the left ventricle and left ventricular angiography can also be performed. Since the invention of more selective catheters as described above, this technique has fallen out of favor. Most common in today’s practice, the...
A multipurpose catheter is used as a first or second choice for RCB graft angiography, or when multiple catheters have been tried and failed to engage a native coronary or bypass graft, the multipurpose can usually be manipulated into selective engagement with trial and error.

**CATHETERS FOR RADIAL OR BRACHIAL APPROACH**

Because of anatomy or patient preference, a radial or brachial approach might be used for access. The right radial or brachial approach is usually preferred as it allows the operator to stand in the usual position on the right side of the normally positioned patient. Also, approaches from the right arm allow direct access into the ascending aorta, whereas left arm approaches end in the takeoff of the left subclavian artery, which will frequently direct wires and catheters down the descending aorta preferentially. Depending on which arm is used for access, different types and sizes of catheters can be used. In general, since the left arm approach takes the same approach across the aortic arch and down the ascending aorta as a femoral approach, the typical coronary catheters described above can be used. Typically, a JL4 and JR4 can successfully be used for coronary angiography from a left arm access.

From a right arm access, because of the straight trajectory into the ascending aorta, half-size smaller Judkins left catheters must be used than would normally be used for a particular patient (e.g., start with a JL 3.5 instead of a JL4). For engaging the right coronary artery, a size larger, the JR5 tends to engage the right coronary artery better than the JR4.

The multipurpose A catheter can be used in either arm for inferiorly directed takeoffs, while the multipurpose B catheter can be more useful for horizontal and superior directed takeoffs. A modified version of the multipurpose A catheter is the Barbeau catheter. This catheter adds a 135° primary curved tip to the end of the typical multipurpose catheter, allowing better engagement of the right coronary artery and bypass grafts from the right arm approach.

Like the multipurpose catheter, others have been developed to engage both the right and left coronary ostium from arm access without switching catheters. The Kimny curve diagnostic catheter (Schneider), invented by Ferdinand Kiemeneij, has three curves: the primary curve is 145°, secondary curve is 90°, and a tertiary curve is 133° (Fig. 17.11). These curves allow backup support from the opposing aortic wall while allowing coaxial engagement of the left main, right coronary ostium, or vein grafts. To engage a Kimny catheter into the left main or right coronary artery, two general techniques can be used (Figs. 17.12 and 17.13) (7). The first involves bringing the catheter tip down from the level of the ipsilateral coronary cusp to the ostium that is to be engaged. From there the catheter can either be withdrawn and turned counterclockwise or clockwise to engage the left coronary or right coronary, respectively. The second technique involves the same torque but instead of withdrawing the catheter, it is advanced forward against the respective cusps to point the tip up and into the coronary ostium, similar to the Amplatz catheter. Similarly shaped catheters from other companies (Jacky, Tiger II, and Sarah catheters from Terumo; radialbrachial catheter from Cordis) also will engage both coronary ostium (8).

To engage aortocoronary saphenous vein grafts from a transradial approach is more difficult than the typical transfemoral approach described previously (9). As the left radial approach generally takes the same curve around the aortic arch as the femoral approach, typical catheters for bypass grafts can be tried first (multipurpose for right bypass, JR4 or LCB for left bypasses). If the JR4 or LCB is not working for the left-sided grafts, an Amplatz left, Judkins left, or multipurpose can be tried as a second option. For the right radial approach, for
grafts originating on the right side of the aorta [usually that have distal anastomoses in the right coronary artery (RCA)], again, a typical approach with a multipurpose or IMA catheter can be used. For left-sided aortic anastomoses of saphenous vein grafts, a JR4 or LCB will not have enough reach from the right radial approach. In this circumstance, an Amplatz left catheter can be very helpful.

To engage a LIMA from the right arm is difficult. The Yumiko catheter (Goodman, Nagoya, Japan) was invented specially for this purpose (Fig. 17.14) (10). It must be advanced against the aortic valve so its tip points upward. It is then torqued into the left subclavian artery, at which point the catheter is pulled back to take out slack in the aortic looped portion of the catheter, allowing it to dive forward and engage the LIMA (Fig. 17.15). This catheter is not readily available in the United States, but the special LIMA1 catheter (Cordis) has a similar shape and is available in the United States (Fig. 17.16). Alternatively, in the absence of a specially designed catheter, an angled glide wire (Terumo) can be manipulated from an IM catheter from right arm access to aim up the left subclavian (12). The wire is extended out into the left subclavian and the IM catheter is used to track over it, past the takeoff of the LIMA. After that, the wire is removed and the catheter is flushed and hooked to the manifold. Test injections are given as the IM catheter is pulled back. If the IM catheter cannot initially aim the J-wire into the left subclavian, a Judkins left catheter can be used to send an exchange length guide wire into the left subclavian, at which point the Judkins left catheter can be exchanged for an IM for selective angiography. A similar method can be used to engage the RIMA from left arm access.

VENTRICULAR ANGIOGRAPHIC CATHETERS

Left ventriculography remains a standard component of a diagnostic catheterization. A pigtail catheter has an endhole plus multiple sideholes that will inject contrast in multiple planes allowing for better filling of the ventricle with contrast. The catheter has a straight shaft with a circular tip usually 1 cm in diameter. The circular tip is a safety feature to minimize the chance of ventricular trauma and myocardial staining with contrast as compared with a straight endhole catheter like the multipurpose. Since the contrast is focused over multiple ejection points, the catheter will usually sit relatively quietly in the left ventricle, as compared with an endhole catheter, which will shoot backward with a power injection. Common variations on the typical pigtail design include $145^\circ$ and $155^\circ$ angled shafts to allow the catheter to favor a midventricle position rather than favoring the inferior wall, which can be common with a straight shafted pigtail (Fig. 17.17). A midventricle position of the catheter is important to allow for even angiography and to avoid ventricular ectopy. Pigtails are also available with radiopaque markers along the shaft to assist in quantitative angiography. As mentioned above, the “B” type multipurpose catheter can be used for ventriculography as well. However, since the catheter has fewer sideholes and a straight tip, there is more chance of myocardial staining, ventricular ectopy, and catheter movement as compared with a pigtail. In general, lower flow rate is recommended through a multipurpose catheter to minimize these complications, but this can lead to poor ventricular visualization. For these reasons, we recommend a standard angled pigtail as the first choice for left ventriculography.

Right ventriculography is less commonly done in adult catheterization but can be useful in the adult patient with
congenital heart disease, such as pulmonic stenosis, or if pulmonary artery angiography is warranted. The modern catheter of choice for right ventriculography is a Berman angiographic catheter developed by Dr. Michael Berman. This is a sidehole only catheter with a balloon flotation tip (Fig. 17.18). The balloon flotation mechanism allows safe and easy passage into the right ventricle without the risk of trauma to the right atrium or ventricle with catheter manipulation. There is no endhole so catheter recoil with injection is not an issue. It is inserted through the femoral vein and up the IVC with the use of balloon flotation in an exact manner as a pulmonary artery flotation catheter can be inserted. If the right ventricular chamber is to be visualized the balloon is kept inflated to stabilize the catheter and a power injection is given. The Berman catheter can accept flow rates and PSI similar to the typical left ventricular pigtail catheter. It can also be easily floated into

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**Figure 17.15** (A) The technique of advancing the YUMIKO-LITA catheter into the LITA via the ascending aorta. The catheter is advanced to the ascending aorta using a guide wire (left image). After the guide wire is removed, the catheter is rotated to direct the tip toward the left subclavian artery. The tip easily selects the left subclavian artery by a slight clockwise rotation (second image). Pulling the catheter with a slight counterclockwise rotation, the tip is advanced to the distal subclavian artery (third image). Further pulling of the catheter enables the tip to be engaged into the LITA (right image). (B) The technique of advancing the YUMIKO-LITA catheter into the LITA via the descending aorta. The catheter is advanced to the descending aorta using a guide wire. After guide wire removal, the catheter is turned, hanging the tip on the side branch of the descending aorta at the celiac trunk or renal artery (left image). By pulling the catheter tip to be directed to the left (second image), the tip is advanced toward the left subclavian artery (third image). Further pulling enables the tip to be engaged into the LITA (right image). Source: From Ref. 11.

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**Figure 17.16** The LIMA1 catheter is used to engage the LIMA from right radial access, similar to a Yumiko catheter.

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**Figure 17.17** Straight and angled pigtail catheters. Abbreviation: PIG, pigtail.
the main pulmonary artery for selective pulmonary artery angiography. A second choice for right ventricle and pulmonary angiography is the Grollman catheter, developed by Dr Julius Grollman. It is a modified pigtail catheter with a reversed 90° secondary curve 3 cm from the catheter tip (Fig. 17.19). This reverse curve allows it to engage the right ventricle and to be advanced to the pulmonary artery if needed. This catheter is the second choice because it requires more manipulation to advance into the right ventricle or pulmonary artery.

PERIPHERAL DIAGNOSTIC CATHETERS

The design of peripheral diagnostic catheters is similar to that of coronary catheters, and in some cases, coronary diagnostic catheters are used for a wide variety of peripheral angiography. There are also specialty-designed catheters for accessing challenging anatomy such as the carotid arteries and the visceral abdominal vessels. Frequently, a nonselective angiogram is used to visualize anatomic takeoffs of branch vessels, and then more specialized catheters are used to engage for selective diagnostic catheterization. Common peripheral angiographic catheters are described below on the basis of the anatomic location where they are used.

CAROTID

Typically, an angiogram of the aortic arch using a straight-bodied pigtail catheter is used for initial information about the location of the takeoffs of the carotid arteries and to see if there is any ostial stenosis that might make selective engagement of diagnostic catheters dangerous. In most aortic arches, a JR4 can be used to selectively engage and perform angiography of the common carotids. As described in the above section for graft anatomy, the JR4 can be advanced to the top of the ascending aorta in the LAO 30° view, which lays out the aorta and its branch vessels are not foreshortened. The JR4 can then be advanced safely over the stiff glide wire to the proximal carotid for selective angiography. Any catheter with one simple primary curve can be replaced for the JR4 for carotid angiography, with the choice currently being very operator dependent. Examples include an angled glide catheter (Terumo), IMA, vertebral, or a headhunter catheter. A headhunter has a slight secondary curve as well, but it still functions as a “simple-curve” catheter to be used for normal types 1 and 2 arches and its manipulation remains the same as the JR4. In cases of tortuous anatomy or a type 3 aortic arch, preformed complex curved catheters such as the Simmons or Vitek will be necessary for selective engagement (13).

The Simmons sidewinder (SS) catheter, named after Charles Simmons, typically comes in three sizes based on the length of the catheter from the “knee” portion (secondary curve) to the tip (Fig. 17.20) (14). The Simmons 2 is the most common size used for carotid angiography and has a 4.5 cm distance from knee to tip. The head of a Simmons catheter is shaped like a shepherd’s crook, and before it is used, it must be reformed and positioned in the ascending aorta. The preferred technique (15) for reformation (Fig. 17.21) involves pushing the catheter (with removed guide wire) over the aortic arch so that its tip is in the ascending aorta looking caudally, and the secondary curve of the catheter lies over the highest point of the aortic arch. At this point the catheter is rotated clockwise rapidly, which causes the catheter to buckle and loop over on itself at the secondary curve resembling the shape of a scissor. With continuing rotation the catheter tip will loop back over from the ascending to the descending aorta. At this point the catheter’s secondary curve is pushed over the arch and is allowed to rest on the aortic valve. With counterclockwise rotation the catheter is unwound and resumes its preformed, packaged shape. Alternatively, it can be reformed in the ascending aorta against the aortic valve to its preformed shape like an Amplatz catheter (usually by following a stiff wire that has prolapsed over the aortic valve). Once the Simmons is reformed in the aortic root, the catheter should be rotated if needed so that the tip is pointing to the right of the
The catheter is then pulled back until the tip engages the brachiocephalic trunk. This might require some clockwise or counterclockwise manipulation to successfully engage. Once the tip has engaged, it is pulled back further, which will extend the tip cranially into the great vessel. This should always be done over a guide wire. A stiff angled glide wire is ideal. The angled tip allows for directional advancement and the stiff body allows straightening and advancement of the complex curved catheter. A softer guide wire would let the complex curve keep its shape and would cause prolapse into the aorta with further advancement. For engagement of the left common carotid, the Simmons catheter is advanced without a guide wire to prolapse its body back into the ascending aorta. From here the tip is rotated 180° to look caudally so the catheter can be pulled back past the takeoff of the brachiocephalic trunk. From here the tip is rotated back 180° to look cranial, and the catheter is pulled backward until the tip pops into the left carotid artery. The Simmons catheter can tend to loop on itself or get knotted, and particular attention must be paid to avoid this complication.

The Vitek (Cook) catheter is a modified Simmons with a 90° reverse curve of the shepherd’s crook tip (Fig. 17.22). This allows for the catheter to more easily reform in the descending aorta or distal aortic arch, unlike the Simmons. It is placed over a guide wire into the top of the descending thoracic aorta. As the guide wire is removed, it returns to its preformed shape. It is pushed proximally across the arch until it engages one of the great vessels, where the tip will jump cranially into the vessel.
At this point, the catheter is pulled back straightening out the tip and sending it further cranially. In the case of left carotid angiography, no further manipulation is needed. If right carotid angiography is needed, the Vitek catheter has selectively engaged the brachiocephalic trunk. From this point a stiff angled glide wire can be advanced into the appropriate vessel, and the Vitek catheter will track over this for selective angiography. The big difference between the Simmons and Vitek catheter is location of reformation of the preformed shape. On the basis of location, the Vitek becomes a “push” catheter to engage the arch vessels while the Simmons becomes a “pull” catheter to engage the vessels. Also, since the Vitek has engaged the brachiocephalic trunk, the tip of the catheter is pointed cranially and slightly rightward, which allows easier wire manipulation into the right carotid whereas the Simmons tip will point slightly leftward, requiring slightly more manipulation to engage the right common carotid. For these reasons, the Vitek usually requires less manipulation than a Simmons catheter and is generally preferred as the first choice for difficult arch anatomy.

For a bovine arch with the left carotid coming off low in the brachiocephalic trunk, the Vitek catheter is best used to selectively engage the left carotid. As described above, upon engagement of the brachiocephalic trunk, the Vitek tip naturally points cranially and to the right. Once the Vitek has engaged the brachiocephalic trunk, if the tip is already above the left carotid takeoff, then the catheter is advanced forward until the tip moves down the brachiocephalic trunk. A stiff angled glide wire can then be used to selectively engage the left carotid. The catheter can be pulled backward to advance the tip selectively over the wire into the “bovine” left carotid. A Simmons catheter requires significantly more manipulation into a bovine left carotid as the initial tip looks rightward and should not be used.

VERTEBRAL
Angiography of the vertebral arteries is considered part of a complete cerebral circulation study (along with carotid angiography with anterior cerebral runoff) to fully evaluate the posterior cerebral circulation. Again, the first choice for selective vertebral angiography remains a simple curve catheter with the JR4 being the first choice. Alternatives include the IMA catheter, angled glide catheter, or a vertebral catheter, based on operator training and preference. The vertebral catheter has the gentlest primary curve of 150° (i.e., the tip is only angled 30° from a completely straight position) (Fig. 17.23).

SUBCLAVIAN AND UPPER EXTREMITY
Similar to carotid angiography, an aortic angiogram in the LAO 30° to 45° view will give a nonselective view of the takeoff of the right and left subclavian arteries. As described in the section “Carotid,” a JR4 or other simple curved catheter can usually be manipulated in most cases for selective left and right subclavian angiography. In the case of tortuous or type 3 arches, a Vitek or Simmons catheter is preferred to engage the left or right subclavian. Once selective subclavian angiography is performed, runoff to the upper extremity can be visualized with panning of the angiographic table. For more selective angiography of the upper extremities, a simple curved catheter like a JR4 or IMA can be used, and advanced over a wire more distally in the arm. If a complex curve catheter is used for initial angiography, an exchange length Wholey or glide wire can be placed distally in the arm. Following this, the original diagnostic catheter is walked out, and can be exchanged for a straight or angled glide catheter or a multipurpose catheter.

RENAL
Renal angiography begins with a nonselective descending aortic angiogram (utilizing a straight pigtail catheter) at the level of the takeoff of the renal arteries. The renal arteries typically...
branch off of the descending aorta at the interspace between the L1 and L2 vertebrae. The sideholes of the pigtail catheter thus will be at the level of the renal ostia. The right renal artery usually comes off at a slightly higher level than the left renal artery. The PA angiogram will give useful information regarding the orientation of the renal ostia or anatomic variants such as an accessory renal artery. Since many patients whose renal arteries are being assessed have renal insufficiency, the pigtail angiogram can be done with minimal contrast (only 10 cc needed at high flows), and the operator can proceed with selective angiography. Typically, the renal arteries have a fairly orthogonal takeoff of the lateral aspect of the aorta. The right renal artery has a slightly anterior takeoff as well. The JR4 catheter again is very useful as the first choice to engage the laterally directed renal ostia. Alternatively, a Cobra catheter (invented by Melvin Judkins) can be used to selectively engage the renal arteries. The shape of this catheter looks like a Cobra head or question mark and is similar in shape to the LCB catheter described previously. The Cobra has three curves. The primary curve has a 90° tip angled from the shaft of the secondary portion of the catheter. Along with about a 70° secondary curve in the same direction, the tip points slightly downward to be able to hook into visceral ostia (Fig. 17.24). Finally, a very broad tertiary curve is angled in the opposite direction of the primary and secondary curves. This reversed tertiary curve allows contralateral support from the opposite aortic wall. If a renal artery has an inferiorly directed takeoff, a Cobra catheter might not be able to successfully engage. In this case, an IM catheter, which has a more acutely angled tip, might be able to engage. If the takeoff has an extremely inferior takeoff, a shepherd’s crook-shaped catheter (“hooked” end similar to a Simmons catheter as described but with a smaller overall curve radius), such as the Sos Omni (Angiodynamics), can be useful (Fig. 17.25). The Sos is named after its inventor, Tom Sos. Similar to a Simmons catheter, this hooked catheter requires a pull technique to engage the renal ostia. The catheter is brought above the level of the renal ostium over a wire. As the wire is removed, the catheter will return to its prepackaged shape in the abdominal aorta since it has such a tight curve. The catheter is then manipulated either clockwise or counterclockwise to face the lateral wall of the aorta. The catheter is then brought down and when it is thought to hook a renal ostium, a test injection is given. Another method, called the “flick” technique, allows engagement of a renal artery without multiple injections of contrast (Fig. 17.26). This method involves reforming the Sos Omni in the abdominal aorta below the level of the renal arteries. A soft tipped straight guide wire like the Bentson guide wire is left in the preformed catheter with 1 cm extending from the catheter tip. Because the tip of the Bentson guide wire is very floppy, the catheter remains in its preformed shape despite having the guide wire extending from its tip. This floppy tip also allows for minimal aortic trauma. The catheter will engage the renal ostium with a push technique. The tip of
the guide wire remains parallel to the aortic wall until the catheter is pushed high enough that the wire will flick laterally into the selective renal artery. The catheter can then be advanced to the vessel ostium and the wire can be pulled out.

VISCERAL
Angiography of the major abdominal aortic branches (celiac trunk, superior mesenteric artery, and inferior mesenteric artery) begins with a nonselective abdominal aortic angiogram with a nonselective flush catheter, like a pigtail. Angiography is done in the lateral orientation to identify the origin of the appropriate vessel, as they have takeoffs from the anterior aorta. The tip of the pigtail should be placed above the level of T11 so the celiac trunk can be visualized at the level of T12. Runoff should visualize the takeoff of the SMA at the level of L1 and the IMA at the level of T3. After nonselective angiography is performed, selective angiography is usually performed with a simple curved catheter like a JR4 or IMA. If the JR4 or IMA is unable to hook the vessel, a more complex curved catheter like an Sos or Cobra can be helpful. To hook the appropriate vessel, the catheter is positioned at a level above the artery that is intended to be studied with a guide wire. The guide wire is removed allowing the complex curved catheter to reform in the descending aorta. The catheter is pulled back and rotated with its tip toward the anterior aorta (tip looking laterally in the lateral fluoroscopic angulation) until it is seen and felt to hook into a visceral ostium.

LOWER EXTREMITY
Lower extremity angiography usually begins with a nonselective angiogram with a pigtail catheter in the distal descending aorta above the level of the iliac bifurcation. Nonselective angiography is performed, and the table is panned to view runoff from the iliac artery all the way to the below the knee runoff. If a stenosis is visualized, more selective angiography can be performed with catheters selectively placed in any of the vessels (contralateral to the access sheath) or through the sheath in the femoral artery (to image the ipsilateral vessels). The common iliac arteries are usually spaced about 90° apart, so a catheter with around a 90° tip, like a JR4 or IMA, is the primary choice to selectively cannulate contralateral vessels. If the angle between the iliac arteries is <90°, a hook-shaped catheter head can be more useful to hook the ostium of the ipsilateral iliac. Examples of this include the Sos, shepherd’s hook (SHK), or KIM catheters (Fig. 17.27). Once a wire is advanced from the diagnostic catheter up and over, the diagnostic catheter is

Figure 17.26 “Flick” technique for engaging the renal artery without scraping the catheter tip against the wall of the aorta. (A) Sos catheter advanced below the level of the renal artery with a soft tipped guide wire. (B) Guidewire is withdrawn into the catheter, leaving 1 cm extended. (C) The Sos catheter is advanced. (D) As the catheter is advanced, the guide wire will flick laterally into the renal artery, at which point the catheter can be advanced. Source: From Ref. 16.
walked out and a long flexible sheath is placed up and over to the contralateral iliac artery. At this point, more selective angiography can be performed through the sheath itself or through a straight glide catheter inserted distally from the guide wire to the area of interest.

REFERENCES

Coronary imaging: angiography, CTA, MRA

Joel A. Garcia and John D. Carroll

INTRODUCTION

The central diagnostic goal of contemporary coronary arterial imaging is to completely visualize the coronary artery tree, to understand the anatomy, and to recognize and characterize pathologic findings. Beyond the diagnostic role, imaging is used to plan and execute treatment using the recognition and quantification of a variety of vessel and lesion features prior to interventions. The therapeutic planning goals are to develop an equipment strategy for each lesion to be treated. Likewise an imaging strategy is developed before interventions that allows for a working view to provide real-time visualization during the procedure. Finally, at the completion of the intervention, coronary imaging is used to confirm and quantify the therapeutic changes to the coronary arteries and detect any complications.

While the imaging technologies of computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) are now available and used clinically, catheter-based standard coronary angiography (SCA) remains the gold standard. SCA is not only widely available but also provides the highest spatial and temporal resolution for coronary imaging in 2009. SCA provides reliable angiographic information with a vast clinical experience over multiple decades of use. It is routinely used in the clinical setting to determine the appropriateness of percutaneous coronary interventions (PCI), coronary artery bypass grafting (CABG), or medical therapy. Coronary angiography, first performed by Dr. Mason Sones in 1959, has been a cornerstone in the development of the concept of transluminal angioplasty and revascularization therapies. This includes the work of Charles Dotter who performed the first transluminal angioplasty in 1964, René Favaloro who performed the first CABG in 1967, and Andreas Gröntzig who performed the first percutaneous transluminal angioplasty in 1977 (1–3). The use of diagnostic coronary angiography has significantly increased in the last decade both with the high prevalence of coronary artery disease (CAD) in the industrialized world as well as an increase in prevalence in the remainder of the world. This chapter will focus on the traditional catheter-based coronary angiography and two revolutionizing noninvasive technologies that also define the coronary anatomy, which are CTA and MRA.

Standard Coronary Angiography

Coronary angiography clearly delineates the course and size of the coronary arteries, identifies anomalies, and provides information on the location, characteristics and degree of obstructions. It provides information on coronary origin, vessel size, artery pathway, branches, lesion presence, collateral circulation, and myocardial bridging. Aneurysmal segments, thrombotic lesions, thrombus burden, and vessel spasm can be evaluated with SCA (2,3). Access to the aorta is commonly obtained by cannulation of the femoral artery although the radial, brachial and axillary approaches have been also used. Radial arterial access is particularly common outside the United States. Vascular access is described in detail in chapter 8. Shape specific catheters are then advance through the aorta to the ostium of the coronary arteries over a guidewire. Once the wire is removed and the catheter is engaged the injection of contrast with the subsequent radiographic acquisition results in an angiographic image. Hemodynamic parameters are constantly recorded before, during, and after injections. Diagnostic catheters are the focus of chapter 17.

The two-dimensional (2-D) nature of SCA requires that multiple single-view angiographic acquisitions are performed in various projections. These views are obtained by rotating the imaging system around the patient who lies supine on a radiolucent table (2,3). The imaging system can be rotated from left anterior oblique (LAO) to right anterior oblique (RAO) with an angulation toward the head (cranial) or an angulation toward the legs (caudal). While a wide array of potential combinations of rotation and angulation is possible, several standard approaches result in a comprehensive and mostly complete visualization of the coronary anatomy. The methods of performing coronary angiography have evolved substantially. Smaller catheters are currently used resulting in minimization of vascular risk, early ambulation and discharge (3). Images were traditionally stored on 35-mm cinefilm but now are almost exclusively digital recordings stored on local hard drives, servers, and occasionally compact disk (CD) or digital video disk (DVD) media.

Coronary Anatomic Considerations

The individual variability of the coronary anatomy requires that the acquisition technique and technology allow various combinations of angulation and rotation that result in a gantry position that acquires a clinically useful image. Multiple gantry positions are used in an effort to minimize the imaging inaccuracies resulting from viewing a three-dimensional (3-D) structure in two dimensions. These imaging inaccuracies and misrepresentations are mostly related to vessel overlap, ostial lesion characterization, and foreshortening (Fig. 18.1). Overlap results from the superimposed image of one vessel on another. The same concept applies for an ostial lesion that may be visually obscured by the main vessel. Foreshortening results from the relationship of a vessel segment’s longitudinal path in relation to the path of the X-ray beam. This can result in a projection image that may minimize the true length of a vessel segment as well as a coronary lesion.
Standard Coronary Angiography Limitations

Although SCA has significantly improved over the past 20 years in terms of the quality of the image, postprocessing enhancement, display on high-quality monitors, and tools for replay and lesion quantification, it is still plagued with limitations inherent to 2-D projection images of the opacified inner diameter, that is, lumen, coronary arteries, and the obvious risk of exposure to contrast media and radiation (Table 18.1) (4,5). These limitations and the so called “luminology” evaluation of the vessel have resulted in the need to have alternative technologies that allow for a more precise characterization of vessel anatomy, lesions, and stents. Intravascular ultrasound (IVUS) is one widely available technology that complements SCA in the need for a more precise coronary arterial evaluation. Another group of technologies enhances the projection images to highlight certain structures like coronary stents and other technologies transform the 2-D images into 3-D models and reconstructions. These will be discussed subsequently.

**IMAGE INTENSIFIERS AND FLAT-PANEL DETECTORS**

**Imaging-Related Coronary Fundamentals and Limitations**

The development of techniques for imaging the vasculature over the last 100 years has revolutionized the understanding and treatment of patients with cardiovascular, cerebrovascular, and peripheral vascular disease (PVD). The history of vascular imaging began shortly after the development of radiography when, in 1896, Hascheck and Lindenthal injected and imaged the vasculature of an amputated hand with a mixture of salts. Soon thereafter, femoral and cerebral arteriography using sodium bromide and strontium bromide injections were described in 1924 and 1927. With the development of less toxic contrast agents and better imaging equipment, these initial experiences resulted in surgical interventions to treat peripheral and cerebrovascular disease and formed the foundation for the field of interventional radiology (1).

Contemporary medicine has evolved along with current imaging techniques and radiographic equipment. Image intensifiers (II) have evolved into flat-panel detectors that allow for the most advanced vessel evaluations. Images are digitally enhanced and the equipment software constantly adjusts

Table 18.1  Standard Coronary Angiography Imaging and Safety Limitations

<table>
<thead>
<tr>
<th>Standard angiography</th>
<th>Standard angiography</th>
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<tbody>
<tr>
<td>Coronary imaging limitations</td>
<td>Patient safety limitations</td>
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<tr>
<td>Vessel foreshortening</td>
<td>Invasive procedure</td>
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<tr>
<td>Vessel overlap</td>
<td>Contrast exposure</td>
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<td>Ostial and bifurcation lesion evaluation</td>
<td>Radiation exposure</td>
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<tr>
<td>Lesion eccentricity evaluation</td>
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settings to provide a superior evaluation. The traditional 2-D planar imaging evaluation is now complemented by advanced imaging systems like biplane angiography, rotational angiography (RA), single- and dual-axis RA, computed tomography (CT) angiography, and magnetic resonance (MR). Most of these techniques and technologies allow for representation of vessels in 3-D utilizing workstations with advanced graphics capabilities.

3-D Acquisition and 3-D Visualization
The display and quantification of 3-D vessel properties has been a recent development in coronary imaging. Modeling and/or reconstructive techniques based on SCA have been a significant step forward in visualizing vessels in 3-D and some approaches have become commercially available (Fig. 18.1C) (6–8). The ability to produce 3-D coronary models and reconstructions has led to quantification of clinically relevant 3-D vessel properties such as tortuosity, bifurcation angles, take-off angles, vessel ostium orientation, and accurate segment length determination.

The coronary tree rests on the epicardial surface of the heart, moves with the underlying myocardium, and as a result changes in 3-D shape. Attempts to quantify the specific dynamic behavior of a coronary vessel throughout the cardiac cycle, that is, 4-D shape changes, using traditional SCA have previously been unsuccessful. The clinical relevance of 4-D shape changes have come to light with problems such as stent-induced conformational changes in coronary artery shape, that is, straightening, and the risk of stent fracture from repetitive deformation. A multimodality 3-D vessel quantification algorithm will likely be part of future endovascular therapies.

CORONARY CONTRAST DELIVERY METHODS
Optimizing coronary angiography requires reliable, adequate, and steady injections of contrast media during image acquisition. Furthermore, the use of right coronary artery (RCA) for volumetric reconstruction requires a longer coronary contrast injection. The traditional manifold allows for the injection of contrast media but suffers from the inherent limitations of being unable to provide a standard amount of flow (mL/sec). This is also coupled to the fact that the maximal contrast volume (mL) is fixed with the size of the syringe attached to the manifold. Newer power injectors allow for the combination of a variety of flows and volumes that can be predetermined by the operator (9,10). The safety of these longer direct coronary injections (<7.1 seconds) has been evaluated (10).

STANDARD CORONARY ANGIOGRAPHY
Indications
The American College of Cardiology (ACC)/American Heart Association (AHA) Task Force has delineated the indications for coronary angiography in patients with known or suspected CAD (Table 18.2) (3,9,11). Please refer to chapter 5 for a full review of cardiac catheterization patient selection including patients with stable angina.

Contraindications
There are no absolute contraindications for coronary angiography other than an individual who is not willing to consent to the study. Several conditions however do present a relative contraindication to angiography. Active bleeding, severe anemia (hemoglobin <8 gm/dL), unexplained fever, active or untreated infections, severe electrolyte imbalance, digitalis toxicity, uncontrolled systemic hypertension, previous serious contrast reaction, severe agitation and acute renal failure are relative contraindications. Others include ongoing stroke, decompensated congestive heart failure (CHF), intrinsic or iatrogenic coagulopathy [international normalized ratio (INR) > 2.0] and active endocarditis (3,11). Individuals at risk for developing serious complications from coronary angiography are also important to recognize before the procedure.

Coronary Angiography in Vulnerable Populations
There is an increased risk of complications in general in those individuals who exceed 70 years of age, have congenital heart disease, obesity, cachexia, uncontrolled glucose intolerance, arterial oxygen desaturation, severe chronic obstructive lung disease, and renal insufficiency with creatinine greater than 1.5 mg/dL (3,11). There is an increase risk of cardiac complications among patients with three-vessel CAD, left main (LM) lesions, New York Heart Association (NYHA) class IV, significant mitral or aortic valve disease, ejection fraction (EF) < 35%, high-risk exercise treadmill test (ETT), pulmonary hypertension, and pulmonary artery wedge pressure (PCWP) in excess of 25 mmHg (3,11). Another group of patients is at particular risk of vascular complications including those with anticoagulation or bleeding diathesis, uncontrolled systemic hypertension, severe PVD, recent stroke and severe aortic insufficiency (3,11).

Fundamentals
Accurate diagnosis of CAD requires multiple injections in various views to produce clinically useful images of all coronary segments by minimizing overlap and foreshortening (9). Traditionally, invasive coronary angiography has been performed with radiographic equipment that provides a simple 2-D projection image representation of a patient’s more complicated 3-D anatomy. This “flattening” of a 3-D image results in the generation of a final image that may be limited and inaccurate. To minimize these limitations, invasive cardiologists typically acquire 6 to 10 diagnostic views of the coronary arteries. In addition to the limitations of intravenous contrast, ionizing radiation, and procedural time, each angiographic view is subjectively chosen to best display an individual patient’s coronary arteries. As it has been previously demonstrated, the combination of 2-D imaging limitations and this trial-and-error technique results in some unrecognized imaging inaccuracies (Table 18.1) (12–15). Nonetheless, SCA remains the gold standard for the visualization of coronary artery anatomy and for the detailing of CAD.

Traditional Coronary Angiographic Views
Not all of the many potential views of a patient’s coronary tree are necessary for an adequate study; rather a reasonable combination of views must be acquired that adequately display the patient’s coronary tree and abnormalities. The easy positioning of the gantry allows for a wide variety of combinations of rotation and angulation. Rotation is defined as the position of the flat panel or II toward the right side of the chest (RAO) or the left side of the chest (LAO). Angulation refers to the
<table>
<thead>
<tr>
<th>Table 18.2</th>
<th>CTA/MRCA Appropriateness Criteria</th>
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</thead>
<tbody>
<tr>
<td><strong>Coronary artery disease pretest probability</strong></td>
<td>HRF NIT</td>
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<tr>
<td><strong>Chest pain syndrome</strong></td>
<td>Interm</td>
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<td></td>
<td>Interm</td>
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<tr>
<td><strong>Coronary anomaly suspected/congenital heart disease/new-onset CHF (CTA only)</strong></td>
<td>Low</td>
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<td><strong>Acute chest pain/unstable angina</strong></td>
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<td>High</td>
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<td>High</td>
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<td>Interm</td>
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<td><strong>Triple rule out/NSTEMI</strong></td>
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<td><strong>Asymptomatic</strong></td>
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<td><strong>Uninterpretable test (exercise treadmill test, perfusion, stress echo)</strong></td>
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<tr>
<td><strong>Moderate-severe ischemia</strong></td>
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<td><strong>Risk assessment (asymptomatic)</strong></td>
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<td><strong>Preoperation evaluation (noncardiac surgery)</strong></td>
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<td><strong>Low-risk surgery</strong></td>
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<td><strong>High-risk surgery</strong></td>
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<td><strong>Postrevascularization</strong></td>
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<td><strong>CABG (CP+)</strong></td>
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<td><strong>PCI (CP+) abrupt closure? Stent thrombosis?</strong></td>
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<td><strong>CABG (no CP)</strong></td>
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<td><strong>PCI (no CP) ISR</strong></td>
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<td><strong>PCI &lt; 9 mo</strong></td>
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<td><strong>CABG (CP+) constant angina</strong></td>
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<td><strong>CABG (CP-) no ischemia</strong></td>
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(Continued)
Table 18.2 CTA/MRCA Appropriateness Criteria (Continued)

<table>
<thead>
<tr>
<th>Coronary artery disease pretest probability</th>
<th>HRF</th>
<th>NIT</th>
<th>ECG</th>
<th>Exercise</th>
<th>ECG changes</th>
<th>Cardiac markers</th>
<th>Prior to CTA</th>
<th>Risk</th>
<th>CTA</th>
<th>MR</th>
<th>Coronary angiography</th>
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<td><strong>Nonspecific CP</strong></td>
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<td>Recurrent hospitalization</td>
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<td>Equivocal findings</td>
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<td>Class IIb</td>
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<td><strong>After Q-wave myocardial infarction or</strong></td>
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<td>Active ischemia</td>
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<td>Presurgical therapy (MR, VSD)</td>
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<td>Hemodynamic instability</td>
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<td>Class Ia</td>
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<td>MI due to embolism, arthritis, trauma,</td>
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<td>metabolic disease, spasm</td>
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<td>MI survivors (ejection fraction &lt; 40%,</td>
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<td>Class IIb</td>
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<td>CHF, PCI, CABG, arrhythmia)</td>
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<td>Delayed PCI for infarct related artery</td>
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<td>Left main or 3-vessel disease</td>
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<td>Recurrent ventricular tachycardia or all</td>
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<td>NQWMI</td>
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**Abbreviations:** CTA, computed tomography angiography; MRCA, magnetic resonance coronary imaging; HRF, high-risk features on noninvasive testing; NIT, noninvasive testing; Interm, intermediate; Interp, interpretable; Ca, calcium; Neg, negative; Pos, positive; NOD, nonobstructive disease; Y, yes; N, no; I, inappropriate; A, appropriate; U, uncertain; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ISR, in-stent restenosis; NQWMI, non-Q wave myocardial infarction; CHF, congestive heart failure; PCI, percutaneous coronary intervention; LM, left main; 3VD, three-vessel disease; MR, magnetic resonance; MI, myocardial infarction.

**Source:** Adapted from Ref. 69.
position of the flat panel or II toward the head of the patient (cranial) or toward the legs (caudal). The rotation (LAO vs. RAO) of a view may be recognized from the image itself by the position of tip the catheter in relation to the spine or aorta or based on the shape of the catheter (Figs. 18.2 and 18.3). In LAO the catheter shape is that of an inverted “U” (Figs. 18.2 and 18.3A, B, C), while the shape of the catheter in RAO shows it overlapped on itself (Figs. 18.2 and 18.3E, F, G, H). The tip of the catheter to the left of the spine on the screen suggests RAO (Fig. 18.3E, F, G, H, I). The tip of the catheter to the left of the spine on the screen suggests LAO (Figs. 18.2 and 18.3A, B, C, K, L). The presence of the diaphragm on the image is usually seen in cranial shots (Fig. 18.3H, I, J, K, L).

The technique used to acquire images impacts the accuracy and reproducibility of traditional angiography. To minimize imaging artifacts introduced by 2-D acquisitions, traditional angiography depends on at least two views which are orthogonal to the vessel segment of interest. This principle led to the development and widespread use of biplane angiographic equipment.

Traditionally a series of screening views have been used by operators. These screening views are ultimately complemented by additional views based on real-time interpretation of the angiogram. Any change in gantry angulation or rotation is reflected by a change in the image. Operators are required to be very proficient in real-time image interpretation and in the creation of a mental imprint of the 3-D image while acquiring only 2-D information. Over time the use of coronary angiography has resulted in the recognition of views that are usually adequate to display certain coronary segments. While this “expert-recommended” approach has evolved from the practice of angiography no scientifically based analysis of their recommended views has been performed. It is important to recognize that the variability in anatomy from patient to patient makes the recommended views only a guide and the angiographer must individualize the views acquired to produce a clinically adequate angiographic study. A detailed description of the coronary anatomy is the focus of chapter 16. Detailed knowledge of the coronary anatomy is mandatory to perform optimal coronary image acquisitions.

RAO cranial views are used to visualize the LM, proximal left anterior descending artery (LAD), and proximal circumflex (Figs. 18.3E, F, G and 18.4F). RAO cranial views visualize the mid- and distal LAD, without overlap of septal or diagonal branches, and the distal posterolateral (PL) branches (Figs. 18.3H, I, J and 18.4B, M, N). The LAO cranial views...
visualize the mid- and distal LAD in an orthogonal projection (Fig. 18.3K, L). LAO caudal views visualize the LM, ramus intermedius and the proximal circumflex (Fig. 18.3A, B, C). If uncertainty remains the supplemental views include posteroanterior (PA), lateral 60° to 90° with cranial or caudal angulation. The RCA views include LAO to visualize the proximal portion (Fig. 18.4A, D, G, J), RAO cranial for the posterior descending artery (PDA) and PL branches, RAO 30° and lateral for the mid segment (3,9,16,17).

**Universal Optimal View Map**
Recognizing views that target specific vessel segments has evolved with the practice of angiography. An approach to scientifically validate optimizing views has been studied using an in-depth analysis of a large patient population (18). A database of vessel reconstructions segment by segment results in the creation of an optimal view map, that is, a graphic representation of gantry position and the quantification of a key visualization measurement to be optimized, such as vessel foreshortening and overlap with surrounding vessels. This scientifically based evaluation validated current coronary angiographic knowledge and clinical practice but also allows extension into challenges of optimizing bifurcation regions (Figs. 18.5 and 18.6).

**Limitations of Standard Coronary Angiography**
The errors in image acquisition, evaluation and interpretation can have a significant impact on the management strategy of CAD (3,19). Ideally, a systematic approach aims at minimizing these inaccuracies and potentially avoids impacting clinical outcomes. Technical issues are generally mastered with experience. Inadequate vessel opacification due to conditions like aortic insufficiency, streaming, diluted contrast, competitive flow, anemia, non coaxial catheters can result in image interpretation limitations. Coronary angiography outlines the lumen of the vessel but is unable to provide wall thickness information, visualization of diffuse disease, quantification of nominal vessel diameter in the presence of plaque, and the...
Figure 18.4 Set of images showing various common angiographic findings. (A) RCA vessel tortuosity (black arrow); (B) left main coronary dissection and zoomed image (arrow shows oblique line to the right of the catheter); (C) eccentric mid-LAD lesion (arrow) and zoomed image; (D) RCA proximal ectasia (arrow); (E) overlap of the proximal LAD (black arrow), angulation and foreshortening of the mid-Cx (white arrow); (F) concentric distal Cx lesion (black arrow) and RCA collaterals (white arrow); (G) complete occlusion of the mid-RCA (black arrow); (H) severe ostial right ventricular marginal lesion (black arrow) and moderate posterior descending artery ostial lesion (white arrow). There is also a mild RCA ativoventricular continuation lesion which then constitutes a bifurcation lesion (in circle); (I) ostial RCA catheter induced spasm (black arrow); (J) RCA contrast streaming simulating dissection that normalized with appropriate injection flow and volume (black arrow); (K) mid-RCA thrombus (black arrow points to contrast hang out). Please note that the white arrow points toward mild calcification of the vessel wall; (L) tortuous distal vessels (black arrow points to the distal Cx mild tortuosity); (M) black arrow points to mid-LAD in diastole with an obvious myocardial bridge during systole (N); (O) distal LAD fistula to LV chamber (black arrow). Abbreviations: LAD, left anterior descending artery; RCA, right coronary artery; Cx, circumflex artery.
ability to quantify plaque composition and volume (15). The proper vessel information is highly dependent on the ability of the operator to compare with a normal vessel reference segment. Even experienced operators are subject to interpretation limitations and variability (2,19). These limitations have open the door for technologies that evaluate the vessel lumen via ultrasound or perform pressure differential evaluation of the coronary segments (2). While unrecognized occlusions, eccentric stenoses, myocardial bridging and vessel recanalization are also considered pitfalls of coronary angiography, overlap and foreshortening remain the most common and important imaging limitations associated with the projection nature of the images (3). Radiation exposure and contrast use with the subsequent risk of nephropathy remain significant limitations of current X ray–based angiographic practices as well (20–22).

Figure 18.5 Optimal view map for each coronary vessel segment. Note that the quadrants represent the angulation and rotation of the gantry. 

Abbreviations: LM, left main; LAD, left anterior descending artery; LCX, left circumflex artery; DIAG, diagonal; OM, obtuse marginal; PDA, posterior descending artery; PL, posterolateral; RCA, right coronary artery; Biff, bifurcation; p, proximal; m, mid; d, distal; RAO, right anterior oblique; LAO, left anterior oblique; CRAN, cranial; CAUD, caudal.

Figure 18.6 Basic representation of several coronary segment views. Please note the similarities in views when compared with the universal optimal view map. 

Abbreviations: RAO, right anterior oblique; LAO, left anterior oblique; LM, left main; LAD, left anterior descending artery; CX, circumflex, O, obtuse marginal; D, diagonal; RCA, right coronary artery; p, proximal; m, mid. Source: Adapted from Ref. 9.
Complications of Standard Coronary Angiography

The early days of coronary angiography relied on larger diameter catheters and high osmolar iodine containing contrast media. Several adverse effects to coronary angiography have been described but have significantly decreased over time as catheters, techniques and contrast agents have evolved. Once the coronary vessel was engaged the replacement of blood with catheters, techniques and high osmolar iodine containing contrast media. Several adverse effects to coronary angiography have been described but have significantly decreased over time as catheters, techniques and contrast agents have evolved. Once the coronary vessel was engaged the replacement of blood with contrast media resulted in several signs and symptoms. Transient hypotension, elevation of left ventricular end diastolic pressure, T-wave inversion, sinus slowing, sinus arrest, PR segment prolongation, QRS prolongation and QT interval prolongation were effects seen in response to high osmolar contrast media. Arrhythmias that included ventricular tachycardia/ventricular fibrillation, myocardial ischemia due to decreased oxygen delivery, allergic reaction and renal toxicity were also seen (9,22,28–30). Some of these adverse effects have been reduced with the use of low-osmolar contrast media. Contrast agents are the focus of chapter 4. Constant hemodynamic monitoring is therefore necessary during coronary angiography.

Major complications in contemporary practices are uncommon (<1%). They include death (0.10–0.14%), myocardial infarction (0.06–0.07%), contrast agent reaction (0.23%), and local vascular complications (0.24–0.1%) (31–33). Vascular access and complications are the focus of chapter 8. The risk of death is accentuated in vulnerable patients like those with significant LM disease (0.55%), EF < 30% (0.30%), NYHA functional class IV (0.29%), and severe aortic stenosis. Stroke is rather uncommon during angiography (3,34) but may develop because of cholesterol, atherosclerotic, or clot embolization (35–38). The results of an embolic stroke during routine angiography are generally reversible. Embolization of air is also a potential complication but can be easily prevented with newer injectors designed to minimize its risk and also following basic but necessary precautions when dealing with a manifold. Nerve damage and or pain have been also described (39). The widely publicized risk of lactic acidosis with metformin has been decreased by avoiding the medication before and after the procedure especially among those with renal insufficiency and by monitoring the serum creatinine (40).

Severe allergic reactions are uncommon and easily preventable by the premedication of those at risk 18 to 24 hours before the procedure. Prednisone 20 to 40 mg, and cimetidine 300 mg every six hours, diphenhydramine, and the use of nonionic contrast minimize risk. A dose of steroids prior to the coronary angiography has also been successful in decreasing the risk of a reaction (9). A severe in-laboratory reaction can be treated with the use of IV epinephrine (0.1 mg = 1 mL of the 1:10,000 solution) every two minutes until the systemic blood pressure and the wheezing respond favorably.

Renal insufficiency is also a potential complication of coronary angiography. Measures like early hydration (pre- and postprocedure), minimizing contrast volume and the use of low-osmolar contrast agent are of benefit. Other agents like N-acetyl-L-cysteine (NAC) and D5/NaHCO3 hydration have been used to decrease the risk of renal failure in vulnerable patients with conflicting results (22,28).

Despite the fact that more complicated and morbidly compromised patients are being referred for coronary angiography, the rates of complications have not significantly changed (31,34,41). Although radiation safety is the focus of chapter 3, it is worth mentioning that while the advances of angiography have increased utilization and allowed for patients to frequently come back for further management, this repeated exposure increases the risk of cumulative radiation injury (42,43).

SINGLE- AND DUAL-AXIS ROTATIONAL CORONARY ANGIOGRAPHY

Fundamentals of Rotational Coronary Angiography

Single-axis RA (Fig. 18.2) is a novel image acquisition technique which was designed and developed to address some of the limitations of traditional angiography (25,27,44,45). The justification for rotational acquisition is straightforward: coronary arteries and other vascular structures must be visualized from multiple projection angles to adequately appreciate their structure in the resultant 2-D X-ray projection images (Fig. 18.7). RA acquires the same images as traditional angiography but is automated, can be standardized, and provides an extensive panoramic view of key anatomic features for diagnostic and interventional purposes (Fig. 18.7).

Both standard and RA acquire runs of projections images but the imaging perspective is fundamentally different. Coronary angiography has traditionally employed acquisitions with a fixed projection during each injection and the gantry is moved to multiple positions between additional imaging runs that are acquired with different degrees of right and LAO rotation and different degrees of cranial and caudal angulation.

Single-axis RA requires a cranial (Fig. 18.2) and a caudal acquisition for the LCA and a cranial acquisition for the RCA. The preset acquisition arc rotates from the beginning position to the end position during image acquisition producing a set of
images with a changing perspective that may maximize coronary visualization. A complete study will therefore often have only three total rotational acquisitions each with an RAO to LAO arc of 110° to 120° (one cranial for the LCA, one caudal for the LCA, and a cranial for the RCA).

Dual-axis RA is a more recent development. Rather than a simple arc, dual-axis rotations may be programmed to move the gantry simultaneously in both the RAO-LAO and cranial-caudal axes. For example, the LCA angiogram has now evolved into a single acquisition that rotates from LAO caudal to RAO caudal subsequently breaking the “X”-axis (dual axis) and angulating toward RAO cranial and ending at LAO cranial (Fig. 18.3).

An additional rotational angiographic technique is the 180° to 240° acquisitions with rapid sweeps of the gantry in a single but obviously large arc. A prolonged single-axis 180° rotations from LAO 120° to RAO 60° with no angulation has been used for automatic gated vessel reconstructions providing volumetric data and thus allowing images to be displayed in cross-sectional formats similar to IVUS and in maximum intensity projection (MIP) formats similar to that of CTA which will be discussed later in this chapter (Fig. 18.8) (10).

Therefore, coronary angiography acquisition techniques have expanded with the advent of new gantry systems that are capable of performing rapid, standardized, preprogrammed, and increasingly complex changes in position that deliver images from hundreds of perspectives. These different angiographic techniques including standard angiography, single-axis RA, and dual-axis RA are further described on Figure 18.9.

**Advantages of Rotational Angiography**

The rotational representation of the coronary tree also allows a better 3-D understanding of the spatial relationships of coronary tree branches by virtue of the rotating 2-D image. RA protocols can provide up to 360 projections of the arterial tree from different angles during a single coronary injection as oppose to the limited views provided by standard angiography. The safety and efficiency of diagnostic RA have been well established with a significant reduction in contrast and radiation exposure while maintaining similar or lower procedural times. The data shows that RA has a 30% to 40% reduction on contrast exposure and at least a 15% reduction in radiation exposure when compared with standard angiography (27,44,45). Other studies show a similar contrast exposure reduction but fail to show a significant reduction in radiation exposure (44). This is in part related to the different protocols used and the inherent difference in the imaging systems (flat X-ray detector vs. an II with or without cardiac optimization). Finally, the fact that RA uses a larger field of view is an important factor in the reduction of total radiation although prior studies do show that the reduction is mostly driven by the acquisition of fewer images (27). While all the studies have been with the single-axis RA platform, newer studies with the dual-axis RA promise to deliver lower radiation exposure and total contrast volume use.
Last but not least RA provides the perfect platform for several advanced imaging applications like on-line 3-D modeling with optimal view map creation (Fig. 18.1), rapid 3-D modeling, and manual or automated gated vessel reconstructions (Fig. 18.8).

**Limitations of Rotational Angiography**

Despite the visual appeal, better safety and the standardized acquisition technique of RA, the inherent limitations of 2-D projection imaging remain. Furthermore operators and staff must isocenter the X-ray system, set up the arc of acquisition such that anticollision software does not prevent the acquisition, and learn how to review the rotational runs which contain a large amount of visual information. While RA may improve the ability to visualize a lesion, the accurate selection of the optimal single projection to show a lesion and perform a PCI is still dependent on the operator’s visual skills. Furthermore, RA cannot simulate views based on acquired images and provides no quantification of important 3-D vessel features. Hence, the need for angiographic 3-D image reconstructions. A list of attributes and limitations of all imaging technologies discussed in this chapter is provided on Table 18.3.

**3-D CORONARY MODELING AND RECONSTRUCTIONS**

Two techniques have been developed for the 3-D representation of vascular structures including the coronary tree (Table 18.4).

**Coronary Modeling**

The 3-D modeling technique uses 3-D centerline data and shaded or rendered surfaces; the diameter and 3-D morphologic structure of the vessel is subsequently derived with a computer algorithm (Fig. 18.10). The 3-D “modeling” technique uses two or more angiographic projections to extract features of the vessel and create a 3-D representation (Fig. 18.1). A 3-D modeling algorithm using single-plane angiography that does not require a calibration object has been developed and prospectively validated (6–8,14,16,24,46,47). The accuracy of the 3-D modeling method is dependent on a computer-based, four-step algorithm which integrates 2-D projections into a 3-D image. Modeling is useful in the sense that it only requires orthogonal views of a given structure. Given the lack of volumetric data it is not as precise as a reconstruction, but it allows 3-D imaging of traditionally difficult to reconstruct structures like the coronary arteries. This is mostly important in standard angiography laboratories without rotational capabilities. RA also provides images appropriate for 3-D modeling techniques (Table 18.5).

**Coronary Reconstruction**

3-D volumetric data sets can be generated from techniques that acquire volumetric data points such as RA, CT, or MR imaging (Table 18.5). Several methods that are capable of generating 3-D images have been described and in general, can be divided into surface- or volume-rendering techniques. The surface-rendering method relies on a computer algorithm to reconstruct intensity values which are above a specific defined threshold and represent volumetric surfaces within the data set; all values below the set threshold are discarded and not used for image generation. The resultant image is a representation of the surface contour and appears 3-D through computer-generated shading. While surface rendering is fast, it uses only a small portion of the acquired data and is less reliable during imaging of structures smaller than 2 to 3 mm. The MIP algorithm is another commonly used technique. 3-D imaging using volume rendering is a more powerful technique that incorporates the entire data set into the 3-D image. In contrast to surface-rendering techniques, intravascular details and spatial relationships between adjacent structures are preserved (47,48).

The 3-D “reconstruction” technique is dependent on multiple image projections for the creation of a volumetric representation of the vessel (Fig. 18.8). The 3-D reconstruction technique refers to a computer-generated representation of the true shape and size of the imaged vessel using actual volumetric data obtained from RA, CT (Fig. 18.11), or MR (Fig. 18.8) (44,45,49,50). Interest in improving patient outcomes by
optimizing the imaging of complex visual structures has been paramount in the design and creation of 3-D imaging techniques. Over the last decade, significant progress has been made in the development of new invasive and noninvasive imaging techniques that permit accurate, real-time, 3-D displays of structures.

**Coronary Optimal View Map**

3-D modeling and 3-D reconstructions are able to provide the data sets that allow for the development of an optimal view map. This optimal view map can be generated for each coronary segment and provides foreshortening and overlap quantification for all segments for all gantry positions (25). The use of these 3-D modeling technique and view maps in the contemporary laboratory has been tested (Figs. 18.1 and 18.10) (12,25,47,51).

### Advantages of 3-D Imaging

Quantifying 3-D vessel properties and characteristics of a given vessel are necessary in contemporary interventional cardiology. The ACC and the AHA outline the specific vessel properties that define the procedure outcome risk of a given lesion (Table 18.6) (52). It is important to note that these vessel characteristics are inherently 3-D in nature therefore a complete analysis requires a 3-D evaluation. Traditionally, the cardiologist has been unable to quantify some of this important variables relying on visual estimation of given characteristics like tortuosity, flexion, torsion and displacement of a vessel. Standardization of these vessel characteristics will lead to a

---

**Table 18.3** Comparison of Coronary Angiographic Imaging Technologies

<table>
<thead>
<tr>
<th></th>
<th>Invasive angiography</th>
<th>Noninvasive angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast exposure</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Radiation exposure</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Procedural time</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Invasiveness</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Image quality</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Minimizes imaging</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Inaccuracies</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Provides volumetric data</td>
<td>+(^a)</td>
<td>+++(^b)</td>
</tr>
<tr>
<td>Applicability in unstable patients</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Applicability in obese patients</td>
<td>+++</td>
<td>+/++</td>
</tr>
<tr>
<td>Compatibility with implanted devices</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Applicability to calcified vessels</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Applicability to chronic obstructive pulmonary disease patients</td>
<td>+++</td>
<td>+/+++</td>
</tr>
</tbody>
</table>

Note: +++, very favorable; ++, moderately favorable; +, least favorable.

\(^a\)Requires 3-D vessel modeling.

\(^b\)Requires 3-D modeling or 3-D/4-D vessel reconstruction.

**Abbreviations:** 3-D, three-dimensional; 4-D, four-dimensional; HR, heart rate; BP, blood pressure.

**Table 18.4** Coronary Angiographic Data Processing Techniques

<table>
<thead>
<tr>
<th></th>
<th>3-D modeling—3-D representation</th>
<th>3-D reconstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image input</td>
<td>&gt;2 orthogonal views (&gt;30(^\circ))</td>
<td>Multiple images required</td>
</tr>
<tr>
<td>Image source</td>
<td>3-D centerline based</td>
<td>True shape reconstruction</td>
</tr>
<tr>
<td>Vessel measurements</td>
<td>Size and diameter are derived from a computer algorithm</td>
<td>Uses actual volumetric data</td>
</tr>
<tr>
<td>Surface rendering</td>
<td>n/a</td>
<td>3-D surface appearance is the product of shading</td>
</tr>
<tr>
<td>Volume rendering and maximum intensity projection</td>
<td>n/a</td>
<td>Incorporates entire data set in image; Intravascular details, spatial relationship and structures are preserved</td>
</tr>
</tbody>
</table>

**Abbreviations:** 3-D, three-dimensional; n/a, not applicable.
more comprehensive evaluation of the vasculature that should subsequently improve procedural outcomes.

3-D images via optimal view maps or simple direct evaluation can provide information on images with minimal foreshortening and minimal overlap (12,13,18,25). In addition recent X ray–based advancements have allowed for the direct visualization of in vivo stents with 3-D reconstructions (53).

**LESION CHARACTERISTICS**

There is still controversy as to what diameter stenosis defines significant CAD. It is well known that typically a 70% lesion can provoke ischemia (54). The CASS criteria for defining significant disease was diameter stenosis >50% in the LM or diameter stenosis >70% in any other major epicardial vessel or branch. An inherent limitation of coronary angiography is in the assessment of stenosis severity due to the problems of

**Table 18.5 Comparison Between 3-D Modeling and 3-D Reconstruction**

<table>
<thead>
<tr>
<th></th>
<th>3-D modeling</th>
<th>3-D reconstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of use</td>
<td>+++</td>
<td>++ a</td>
</tr>
<tr>
<td>Coronary measurements reliability</td>
<td>Vessel size +</td>
<td>+++</td>
</tr>
<tr>
<td>Vessel length +++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Image acquisition requirements (number views)</td>
<td>+ + +</td>
<td>+ (requires rotational angiography)</td>
</tr>
<tr>
<td>Standard angiography compatible</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Rotational angiography compatible</td>
<td>Yes</td>
<td>Yes (requires 180° rotation)</td>
</tr>
<tr>
<td>Computed tomography angiography based</td>
<td>n/a</td>
<td>Yes</td>
</tr>
<tr>
<td>Magnetic resonance angiography based</td>
<td>n/a</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note: ++++, very favorable; ++, moderately favorable; +, least favorable.

aNewer algorithms are now fully automated.

**Table 18.6 Type B1 Lesions Have One Characteristic of Type B Lesions, Whereas Type B2 Lesions Have Two or More of the Type B Lesion Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length</strong></td>
<td>&lt; 10 mm</td>
<td>10–20 mm</td>
<td>&gt; 20 mm</td>
</tr>
<tr>
<td><strong>Lesion morphology</strong></td>
<td>Concentric</td>
<td>Eccentric</td>
<td>Excessive tortuosity</td>
</tr>
<tr>
<td><strong>Pathway to lesion</strong></td>
<td>Easy access</td>
<td>Moderate tortuosity</td>
<td>Extreme angulation &gt; 90°</td>
</tr>
<tr>
<td><strong>Angulation</strong></td>
<td>&lt; 45°</td>
<td>&gt; 45° but &lt; 90°</td>
<td>&gt; 90°</td>
</tr>
<tr>
<td><strong>Lesion contour</strong></td>
<td>Smooth</td>
<td>Irregular</td>
<td>-</td>
</tr>
<tr>
<td><strong>Calcium in vessel</strong></td>
<td>Little or none</td>
<td>Moderate to heavy</td>
<td>-</td>
</tr>
<tr>
<td><strong>% Stenosis</strong></td>
<td>Not occluded</td>
<td>Occlusion &lt; 3 mo</td>
<td>-</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Not ostial</td>
<td>Ostial</td>
<td>-</td>
</tr>
<tr>
<td><strong>SB</strong></td>
<td>No major SB</td>
<td>True bifurcation lesion</td>
<td>Unable to protect SB</td>
</tr>
<tr>
<td><strong>Thrombus presence</strong></td>
<td>None</td>
<td>Some</td>
<td>Degenerative vein graft</td>
</tr>
</tbody>
</table>

**Abbreviation:** SB, side branch.

**Source:** From Ref. 52.
defining a normal reference segment when disease is diffuse and the eccentric nature of atherosclerosis. Lesion morphology and lesion characteristics are equally important when defining CAD (Table 18.6). This lesion classification allows the estimation of PCI procedural risk. Type A are simple lesions, type B are moderately complex lesions divided into B1 (lesions with only one B characteristic), and B2 (lesions with more than three B characteristics), and C are high risk (52–56). Further angiographic lesion characteristics are shown in Figure 18.4 and Table 18.7.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY Fundamentals

The cardiac applications of CT are a rapidly growing diagnostic area because of the ability to visualize plaque burden, artery calcification, and luminal obstruction noninvasively (57,58). Several studies have shown the indications that could aid physicians in the management of symptomatic and asymptomatic patients. A symptomatic patient that has no calcification is associated with both a lower risk of an abnormal nuclear study and angiographic obstruction. The invasive nature, expense, and risk resulting from invasive angiography have been instrumental in encouraging the development of new diagnostic methods that allow the coronary arteries to be visualized noninvasively (57). Electron beam tomography and multidetector spiral computed tomography (MDCT) have been used in an effort to visualize the coronary arteries after the administration of intravenous contrast. Both have high spatial and temporal resolutions as well as excellent signal-to-noise ratios, which allows major branches of the coronary tree to be depicted (59). The axial images are then used by the software to generate a volume rendering or reconstruction (Fig. 18.11). Although reconstructions are used for the diagnosis of CAD because the images are visually appealing, the most reliable images come from the MPI of the vessels (Fig. 18.12). 3-D reconstructions have no added diagnostic value other than the documentation of the overall findings, a better understanding of 3-D branching patterns, and vessel tortuosity (3).

Currently, there is much interest in the assessment of CAD using MDCT. Recent advances in MDCT have provided the opportunity to noninvasively and three-dimensionally evaluate the coronary vasculature in a safe and efficient manner. Newer CT imaging technology with faster gantry rotations, dual X-ray source scanners, multidetector 64, 128, 256, and recently 320 row acquisitions and ECG gating has substantially improved both temporal and spatial resolutions to adequately visualize the moving coronary vasculature. Current-generation MDCT scanners are able to achieve a spatial resolution of 0.4 mm with a temporal resolution as low as 83 milliseconds during a less than 15-second cardiac acquisition. Initial relatively small studies evaluating the diagnostic accuracy of 64-slice MDCT compared with diagnostic cardiac catheterization have demonstrated sensitivities ranging from 80% to 94% and specificities ranging from 95% to 97% (60,61).

Routine evaluation of coronary MDCT involves segmentation of the individual visualized coronary vessels. From the resulting coronary tree, determinations are easily made regarding vessel length, curvature, branching angles, stenosis length, location and severity (Fig. 18.12). Additionally, atherosclerotic plaque composition can be easily assessed. Because of high CT attenuation of calcified lesions, they are differentiated from fibrous or lipid-rich lesions. These angiographic features are easily displayed on MDCT-derived 3-D volumetric and anatomic representations (62-65).

Imaging of coronary stents with CTA is also possible. Newer algorithms do allow for the evaluation of post intervention patients although the image quality of the stented segment lacks reliability. The evaluation of the in-stent restenosis is therefore possible but limited in certain patients and difficult to quantify with any precision. The visualization of the patency or occlusion of bypass grafts is also possible but limitations do exist when accurately and completely evaluating the anastomosis sites.

Table 18.7 Coronary Angiographic Lesions and Their Respective Description

<table>
<thead>
<tr>
<th>Angiographic lesion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angulated lesion</td>
<td>Angle from the vessel to the proximal lesion</td>
</tr>
<tr>
<td>Collaterals (Fig. 18.4)</td>
<td>Networks of tiny anastomotic branches interconnect the major coronary arteries</td>
</tr>
<tr>
<td>Contrast streaming (Fig. 18.4)</td>
<td>Inadequate vessel opacification results in uneven contrast lining of the vessel suggesting pseudolesions</td>
</tr>
<tr>
<td>Coronary aneurysm (Fig. 18.4)</td>
<td>Focal dilation of a coronary segment that includes all elements of the vessel wall</td>
</tr>
<tr>
<td>Coronary artery fistula (Fig. 18.4)</td>
<td>Communication between a coronary and the pulmonary artery, aorta, a cardiac vein, another artery or a chamber</td>
</tr>
<tr>
<td>Coronary ectasia (Fig. 18.4)</td>
<td>Enlargement or increase of the size of a coronary artery</td>
</tr>
<tr>
<td>Coronary spasm (Fig. 18.4)</td>
<td>Transient vessel contraction (can be catheter induced)</td>
</tr>
<tr>
<td>Coronary thrombus (Fig. 18.4)</td>
<td>Filling defects consistent with clot within the arterial lumen</td>
</tr>
<tr>
<td>Diffuse disease (Fig. 18.4)</td>
<td>Long segments with varying degrees of stenosis</td>
</tr>
<tr>
<td>Eccentric lesion (Fig. 18.4)</td>
<td>Vessel lesion characterized by an uneven distribution of the plaque in relation to vessel wall</td>
</tr>
<tr>
<td>Foreshortening (Fig. 18.1D)</td>
<td>Imaging phenomenon that occurs on the basis of perpendicularity of the vessel to X-ray beam</td>
</tr>
<tr>
<td>Muscle bridge (Fig. 18.4)</td>
<td>A dip in the coronary artery below the epicardial surface under small strips of myocardium</td>
</tr>
<tr>
<td>Ostial lesion and bifurcation lesion (Fig. 18.1B)</td>
<td>Ostial is a lesion located 3 mm of the origin of the vessel. Bifurcation disease is that o the main branch and the side branch</td>
</tr>
<tr>
<td>Total occlusion (Fig. 18.4)</td>
<td>A complete lack of flow into a closed segment</td>
</tr>
<tr>
<td>Vessel calcification (Fig. 18.4)</td>
<td>Presence of calcium in the vessel</td>
</tr>
<tr>
<td>Vessel dissection (Fig. 18.4)</td>
<td>Creation of a false lumen between the intima and the media</td>
</tr>
<tr>
<td>Vessel overlap (Fig. 18.1A)</td>
<td>Imaging phenomenon that occurs when vessels or coronary segments are one on top of the other</td>
</tr>
<tr>
<td>Vessel tortuosity (Fig. 18.4)</td>
<td>Refers to the lack of longitudinal path of the coronary. Frequent turns are of the vessel are seen</td>
</tr>
</tbody>
</table>

Coronary aneurysm (Fig. 18.4) Focal dilation of a coronary segment that includes all elements of the vessel wall.

Coronary artery fistula (Fig. 18.4) Communication between a coronary and the pulmonary artery, aorta, a cardiac vein, another artery or a chamber.

Contrast streaming (Fig. 18.4) Inadequate vessel opacification results in uneven contrast lining of the vessel suggesting pseudolesions.

Collaterals (Fig. 18.4) Networks of tiny anastomotic branches interconnect the major coronary arteries.

Ostial lesion and bifurcation lesion (Fig. 18.1B) Ostial is a lesion located 3 mm of the origin of the vessel. Bifurcation disease is that of the main branch and the side branch.

Total occlusion (Fig. 18.4) A complete lack of flow into a closed segment.

Vessel calcification (Fig. 18.4) Presence of calcium in the vessel.

Vessel dissection (Fig. 18.4) Creation of a false lumen between the intima and the media.

Vessel overlap (Fig. 18.1A) Imaging phenomenon that occurs when vessels or coronary segments are one on top of the other.

Vessel tortuosity (Fig. 18.4) Refers to the lack of longitudinal path of the coronary. Frequent turns are of the vessel are seen.
Indications

The visualization of plaque is paramount in the diagnosis of CAD. The ability of CT to evaluate plaque has been the product of a significant amount of research. The detection, quantification, and characterization of coronary plaque do play a significant role in risk assessment. Under the assumption that lipid-rich, thin fibrous cap plaques are at risk of rupture with subsequent thrombosis more so than fibrotic plaque, researchers have tried to use CT attenuation values to differentiate plaque types (66–68). The implications and clinical value of stenting vulnerable plaques has not been established. While one of the strongest indications for CT relies on its ability for risk stratification based on plaque presence evaluation very few clinical guidelines exist in the United States for this imaging technology and MR. The appropriate use and indications for coronary angiography with CT are shown on Table 18.2. It is based on the ACCF/ACR/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for “Cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology.”

Contraindications

A list of appropriate/uncertain/inappropriate indications for CT is shown on Table 18.2. There are no absolute contraindications to perform CTA other than a patient unwilling to consent. Risks, such as radiation exposure and contrast adverse effects, should be considered. It is expected that patients being evaluated can achieve a breath hold, which is required for the acquisition, are under the weight limit of the table, and have no significant heart rate variability. For the most part it is expected that patients not present with any of the following:

a. Irregular heart rhythm (e.g., atrial fibrillation/flutter, frequent irregular premature ventricular contractions, or premature atrial contractions, and high grade heart block)
b. Obese patients (body mass index > 40 Kg/m²)
c. Renal insufficiency, creatinine greater that 1.8 mg/dL
d. Heart rate greater than 70 beats/min refractory to heart rate–lowering agents (e.g., a combination of β blocker and calcium channel blocker)
e. Metallic interference (e.g., surgical clips, pacemakers, and/or defibrillator wires, coils, or tissue expander) (69)

For CT angiography patients should be able to

a. hold still,
b. follow breathing instructions,
c. take nitroglycerin (for performing coronary CT angiography only),
d. take iodine in spite of steroid prep for contrast allergy, and
e. lift both arms above the shoulders (69).

Improvements in CTA technology that are now coming to market allow for much faster acquisition that lessen the need for slower heart rates and longer breath holds.

Advantages

Although patients are still exposed to radiation and contrast CTA delivers a noninvasive coronary angiographic evaluation without the added risk of the more invasive SCA. Furthermore, some studies support the use of CTA as a safe and effective noninvasive imaging modality for defining coronary arterial anomalies in an appropriate clinical setting, providing detailed 3-D anatomic information that may be difficult to obtain with invasive angiography (70).
The use of CTA in the risk stratification, triage, and evaluation of patients continues to be evaluated with very promising results (Table 18.2).

Having the CTA images available for evaluation in planned PCI has now introduced the concept of preplanning. Operators are able to evaluate a myriad of coronary features that help in preparation for the case. Lesion characteristics (e.g., occlusion, calcification, side branch), pathway to the lesion (e.g., angulation, tortuosity), and even the shape of the aorta can be evaluated before an actual procedure. Potential equipment selection (e.g., stent size, stent length, guide catheter) is now a decision that the operator can make even before the procedure starts. The usefulness of this approach is formally being evaluated by several groups (71,72).

3-D imaging using volume rendering is a powerful technique that incorporates the entire data set into the 3-D image. In contrast to surface-rendering techniques, intravascular details and spatial relationships between adjacent structures are preserved (Tables 18.4 and 18.5). The vascular model can be refined further if data from the heart structures and vessel wall are available (e.g., IVUS and the 3-D coronary lumen from X-ray image-based reconstruction as an example. This new multimodality fusion concept that incorporates imaging technologies like CTA- and X ray-based images during a procedure holds the future of image guidance (Fig. 18.13) (73,74).

**CORONARY MAGNETIC RESONANCE CORONARY ANGIOGRAPHY**

Cardiac MR imaging is a rapidly evolving noninvasive imaging modality that will further advance the goal of providing 3-D imaging. Cardiac MR has become an established imaging modality for the assessment of various cardiac disorders including myocardial viability, infiltrative cardiomyopathies, congenital heart disease, anomalous coronary arteries, bypass grafts, cardiac masses, aortic and pericardial diseases (75-79).

Magnetic resonance coronary angiography (MRCA) is a technique that allows a noninvasive visualization of coronary arteries. MRCA has gained considerable importance as a noninvasive method to diagnose coronary artery stenoses and is an area of active research (80-82). The benefit of MRCA is to not only visualize the coronary arteries, but also to evaluate cardiac morphology and function in one setting (78,79).

Current techniques with 3-D navigator MRCA imaging can obtain a coronary artery data set in approximately 10 to 15 minutes. Analogous to MDCT, from a MRCA volumetric data set, 3-D vessel features including vessel tortuosity, lesion lengths, bifurcation angles can be evaluated, quantified and translated to the interventional cardiologist.

**Fundamentals**

Since the concept of ionizing radiation has been discussed in chapters 1 and 3 an abbreviated understanding of MR is required. The physical interaction required for MR is related to the atomic nucleus. The frequency of the radio wave absorption depends on the strength of the external magnetic field. Because MR therefore does not interfere with the atomic shell, which is responsible for chemical binding, it is fundamentally safe, unlike ionizing radiation, which may interact with electro binding, damaging molecules such as DNA. MR only interacts with unpaired spin atomic nuclei, which are basically seen in water and fat (hydrogen-1 abundant tissues) (3). Since these tissues are abundant in the body images with a high signal-to-noise ratio can be easily obtained. The nuclei when exposed to a magnetic field will behave as a magnet. The nuclei precess...
randomly about 1.5-T magnetic field at a resonance frequency of 63 MHz, which is in the radio wave range. When excited by radio waves the nuclei will rotate away from the direction of the main magnetic field and precess in a coordinated manner that causes a net magnetization. In its relaxation form this signal is then captured as radio wave echo by the scanner in a form that can be subsequently transformed into an image by the receiver antenna (3).

The CMR scanner consists of several pieces: (i) the superconducting magnet that produces the static magnetic field, (ii) the radiofrequency amplifier that generates the pulses, (iii) the radiofrequency antenna or receiver that captures them, and (iv) the computer hardware and software that allows for the management of the data with subsequent image creation. The gating of the images based on the electrocardiographic R-R is what allows for the system to minimize the movement through the changes of the cardiac cycle and respiratory motion. The acquisition sequence is composed of the following block components: (i) cardiac triggering to suppress cardiac motion, (ii) respiratory motion suppression, (iii) pre-pulses to enhance contrast to noise ratio (CNR) of the coronary blood, and (iv) image acquisition enhancement. Multiple methods for coronary evaluation exist and include conventional spin-echo coronary MRI (very limited), 2-D segmented k space gradient echo coronary MRI, 3-D coronary MRI methods (the predominant approach for the past decade), the more advanced spiral and radial coronary MRI method, and 3-T coronary MRI method.

Coronary CMR angiography is still technically challenging and relatively expensive but several studies have shown its value (76,83). Although the imaging limitations of CMR related to its spatial resolution due challenge its ability to evaluate CAD with confidence, it is very useful in the diagnosis and recognition of anomalous coronary origins (84). CMR has also been used in the evaluation of coronary flow (adenosine stress related evaluation) reserve and the subsequent diagnosis of a significant coronary lesion and on saphenous vein graft evaluations (85,86).

**Indications**

There is no formal guideline for use of MRCA but Table 18.2 does include the appropriateness criteria from the ACCF/ACR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for “Cardiac computed tomography and cardiac MR imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardio Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology.”

**Contraindications**

Unlike CTA there are currently several contraindications to the use of MRCA. Patients are assumed not to present with severe claustrophobia or specific metallic devices that are contraindicated such as pacemakers, defibrillators, and certain aneurysm clips.

Although studies are ongoing and have evaluated the safety of pacemakers and defibrillators when exposed to MR the appropriateness criteria document from ACCF/ACR/SCMR/ASNC/NASCI/SCAI/SIR 2006 still does not reflect does changes (69). In April 2005, the Food and Drug Administration approved MR imaging studies immediately after implantation of sirolimus and paclitaxel-eluting stents (69).

Although in the past gadolinium based contrast for MR was used in all patient populations’ appropriate patient selection and caution should be exercised when using Gadolinium in patients with renal failure due to the risk of nephrogenic fibrosing dermopathy (87–89).

**Advantages**

MRCA without its requirement for more nephrotoxic contrast agents or exposure to ionizing radiation is an ideal noninvasive imaging modality to help plan and execute PCI. It allows for the evaluation of the coronary anatomy, pathway to the lesion, shape of the aorta, aneurysms, bypass patency, anomalous coronary origin, vessel wall characteristics, lesion characteristics, coronary flow reserve, and most importantly can couple that with myocardial viability and potentially function. Because of its specificity a normal coronary MRI suggests the absence of severe multivessel disease.

**Limitations**

Although the safety of MR is well described the full implications of magnetic field exposure have not been well established as it has been for ionizing radiation. It is certainly reasonable that in the modern climate of safety priority, radio wave technology shares with echocardiography a sizable advantage over ionizing radiation.

The challenges for coronary MRA include compensation for cardiac and respiratory motion, spatial resolution and coverage, high level of tortuosity of the coronary vessel, and signal-to-noise limitations due to adjacent epicardial fat and myocardium. Another limitation is that provided by the bare metal nature of stents (not so much tantulum). MRI has a sizable problem when evaluating coronary stents because of signal voids artifacts at the site of the stent. Bypass graft imaging is limited by local signal loss/artifact caused by implanted metallic objects (hemostatic clips, ostial stainless steel graft markers, sternal wires, prosthetic valves, struts, rings, and graft stents). The technical aspects of MRCA are however quickly evolving and multiple methods have been used to improve imaging (cardiac and respiratory motion compensation, breath-hold method, free-breathing methods, MR navigators—triggering alone, MR navigators—gating and slice tracking, electrocardiographic timing, and respiratory suppression methodology). Similar to cardiac CTA, ECG triggering is mandatory to prevent vessel blurring due to intrinsic cardiac motion. To suppress the effects of respiration, MRCA using respiratory gating (navigator echo technique) is performed to monitor diaphragmatic motion. Current isotropic fast 3-D techniques provide thinner slices, superior signal-to-noise ratios and total coverage of coronary arteries over 2-D MRCA techniques. Introduction of new intravascular contrast agents, novel data (k space) sampling strategies, and higher field strength (3 T) imaging will further enhance MRCA (90).

A serious disadvantage of MR is related to its inability to image patients with metallic implants. Although it is safe on valve prosthesis, vascular stents and orthopedic implants it has a serious limitation with pacemakers and defibrillators (programming may change). Flying projectiles in the magnetic field have the potential to strike the patient or a staff member when
the magnet is activated. Caution to avoid any metallic objects should be constantly exercised.

CONCLUSIONS

Contemporary medicine has a diverse armamentarium of invasive and noninvasive imaging technologies to evaluate the coronary anatomy. The risk and benefits of each available imaging technique should be taken into consideration and tailored to the individual need of the clinical situation. This diversity allows the clinician the luxury of choosing an imaging evaluation that minimizes the patient risk while delivering superior results.

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REFERENCES


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INTRODUCTION
Cardiac catheterization is an important diagnostic and therapeutic procedure in pediatric patient with congenital heart disease. The four commonly used indications for cardiac catheterization in the pediatric patient are to make an anatomic diagnosis, to obtain a hemodynamic assessment, to perform a pharmacologic or catheter-based intervention, and to make an electrophysiologic diagnosis and/or perform an electrophysiologic intervention. With improvements in noninvasive imaging (echocardiography and magnetic resonance imaging) the use of cardiac catheterization to make an anatomic diagnosis has significantly reduced. Today, the decision to catheterize a child with congenital heart disease is based on whether the anatomic diagnosis by noninvasive methods is incomplete or inconsistent with the clinical findings. In the preoperative patient, the physician recognizes an unanticipated indication for intervention that may become evident during the course of a diagnostic catheterization and perform these interventions when necessary. Therefore, this chapter will also discuss the following areas that are important when performing a cardiac catheterization in a pediatric patient: sedation for the procedure, vascular access, hemodynamic assessment, and angiography.

CATHETERIZATION LABORATORY SEDATION FOR THE PEDIATRIC PATIENT
The approach to premedication and sedation varies widely among institutions. In some institutions all catheterizations are performed under general anesthesia, and in many others conscious sedation is performed either supervised by the pediatric cardiologist or by a pediatric anesthesiologist. The goals of sedation are to ensure patient comfort without airway compromise, to promote amnesia, and to facilitate performance of the procedure so it may be undertaken in a safe and efficient manner.

Indications for General Anesthesia
The decision to use general anesthesia is determined by both patient and procedural factors. In the following circumstances general anesthesia is necessary: airway issues such as having either paralysis of a diaphragm or vocal cord, and/or obstructive sleep apnea; when hemodynamic compromise is likely to occur during an intervention, such as placement of a ventricular septal defect (VSD) device; if the child is very uncooperative or likely to become very agitated with sedation (e.g., a child or young adult with severe developmental disabilities); and if the child must remain absolutely still during a critical phase of an intervention, such as a device or stent placement. Not all interventions require general anesthesia, for example, conscious sedation works well for most individuals who require pulmonary or aortic valvuloplasties and patent ductus arteriosis (PDA) closure and coil occlusion of venous or arterial collaterals.

Appropriate conscious sedation protocols will enable the majority of diagnostic catheterizations to be managed by nurses trained in both pediatric sedation and the catheterization laboratory setting.

Pharmacologic Agents
The drugs and doses commonly used to sedate children in the catheterization laboratory are shown in Table 19.1. These agents have minimal hemodynamic effects in a well-compensated patient and the main consideration is airway maintenance and avoidance of respiratory depression (1).

Choral hydrate is commonly used to sedate infants. The onset of action is 15 to 30 minutes and duration of action is two to four hours. About 10% to 20% of children will become excitable and uncooperative with choral hydrate. It is also important to remember that choral hydrate is metabolized to trichloroethanol and trichloroacetic acid both of which are pharmacologically active with a long half-life of over 24 hours (2).

Midazolam is a short acting benzodiazepine commonly used in pediatric catheterization laboratories. If oral midazolam is used as a premedication, its onset of action is 15 to 30 minutes with duration of action of two to four hours. In addition, if cardiac output and splanchnic perfusion is reduced, hepatic metabolism of midazolam will be reduced and the drug will accumulate. Intravenous midazolam can cause significant hypotension in patients with poorly compensated cardiac failure.

Opioids provide excellent analgesia and commonly used opioids in the catheterization laboratory are morphine and fentanyl. Unlike the synthetic opioid fentanyl, morphine has sedative properties in addition to providing analgesia. However, fentanyl has a shorter duration of action and generates much less histamine release and resultant vasodilation and hypotension than morphine. Chest wall rigidity may occur with a rapid bolus of fentanyl, although this is an idiosyncratic and dose-related reaction (3).

Ketamine is a phencyclidine derivative that effectively dissociates the thalamic and limbic systems and provides intense analgesia. It provides hemodynamic stability through sympathomimetic actions resulting from central stimulation and diminished post ganglionic catecholamine uptake that results in an increase in both heart rate and blood pressure.

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A disadvantage of using the umbilical vessels is that the umbilical vein directs the catheter posteriorly in the right atrium toward the foramen ovale and left atrium; therefore it is ideal for advancing the catheter into the left atrium and ventricle and undesirable for advancing the catheter into the right ventricle and pulmonary artery. Another disadvantage is that the umbilical arteries enter the internal iliac artery and add an additional curve to the catheter that makes it difficult to maneuver.

**Femoral Access**

The Seldinger technique is used to obtain percutaneous entry into the femoral vessels in the vast majority of cases (6,7). The child should be positioned with the hips elevated and the leg should be straightened with slight outward rotation. The landmarks for determining site of vessel entry are the anterior superior iliac spine, the pubic tubercle, the inguinal ligament, and the femoral pulse. The vessel should be entered below the inguinal ligament to ensure the ability to obtain hemostasis at the end of the procedure. The area is prepped with a
chlorhexidine gluconate solution and the skin and subcutaneous tissue anesthetized with lidocaine. Venous access is usually obtained first but this is not mandatory. In infants, the vessel should be entered about 1 cm below the inguinal ligament. The vein is medial to the artery and will be quite close, within 2 mm of the artery, in infants; whereas, in older patients it may be a centimeter away from the artery. The angle between the needle and the skin should be 45° or less. The needle should be advanced almost to bone and then slowly withdrawn with or without gentle aspiration with a syringe. Once blood is seen, the needle is stabilized and the soft end of a wire is advanced into the femoral vein. If any resistance is felt while advancing the wire, the wire should be withdrawn and the needle re-adjusted. After using fluoroscopy to confirm that the wire is in the correct vessel, a small skin incision is made, the needle is removed, and a sheath and dilator are advanced over the wire. If the wire cannot be advanced despite having excellent blood return, contrast should be injected into the vein to ensure that the common iliac vein is not occluded. A plexus of collateral will be seen if the vessel is occluded or stenotic. If collaterals fill the contralateral iliac vein it is likely that the contralateral femoral vein is patent. A similar technique is used for obtaining femoral artery access.

The most common complications of femoral access are hematomas, arteriovenous fistulae, pseudoaneurysms, retroperitoneal hemorrhages, venous thrombosis, and loss of the arterial pulse. Absence of the arterial pulse is not uncommon in young infants immediately following removal of the arterial sheath. If the pulse has not returned within 2 hours the infant should be heparinized with 100 units/kg, followed by an infusion of 20 units/kg/hr for up to 12 to 24 hours or until the pulse returns. If the pulse is still absent at 24 hours, streptokinase or tissue plasminogen activator can be started (8,9). Surgical thrombectomy may be required in rare cases (10). A pseudoaneurysm of the femoral artery can frequently be treated with ultrasound-guided compression and thrombin injection (11).

Subclavian Access
The subclavian vein is routinely used in individuals with a Glenn anastomosis, after a hemi-Fontan procedure, or if the femoral vessels are occluded. The major disadvantage with subclavian access is difficulty in crossing a patent foramen ovale and the inability to perform a trans-septal puncture.

The patient is positioned with the arm down at the side, with a small roll under the spine, and the head turned to the opposite side. The landmarks are the depression in the lateral third of the clavicle and the suprasternal notch. The skin and subcutaneous tissues and clavicular periosteum are infiltrated with lidocaine. A needle with a syringe attached is inserted at the junction of the medial and middle third of the clavicle (at the depression) and is advanced gently until it contacts the clavicle. It is then advanced under the clavicle and then advanced parallel to the floor and toward the suprasternal notch. Care must be taken to avoid passing the needle through the periosteum as this will make it nearly impossible to introduce the sheath. Once blood is freely being aspirated from the needle, the syringe can be removed and the soft end of a wire advanced under fluoroscopic guidance into the right atrium or cavopulmonary anastomosis. If access is not obtained after several attempts, contrast injection through an IV in the hand or arm should be performed to document vessel patency and location. Complications include pneumothorax, hemothorax, and subclavian artery or aortic puncture.

Internal Jugular Access
The internal jugular approach is frequently used for right heart endomyocardial biopsies, to access the pulmonary arteries in children with a cavopulmonary connection, and when the femoral vessels are occluded. An advantage of the internal jugular approach over the subclavian approach is that the vessel is entered well outside the thorax making pneumothorax an unlikely complication. As with subclavian access, the internal jugular approach is not well suited to cross a patent foramen ovale or perform a trans-septal puncture. The other disadvantage in an infant with the internal jugular approach is that it is difficult to immobilize uncooperative patients and more sedation or general anesthesia may be required.

The right internal jugular is preferred as it offers a more direct route to the right atrium. The patient is positioned with the neck hyperextended by placing a roll under the shoulders and the head turned to the opposite side. Always use ultrasound guidance to enter the internal jugular vein. The vein is imaged in short axis and the needle can be visualized as it enters the vein. Once the needle appears to be in the vein and is confirmed by free return of blood into a syringe, the soft end of a guidewire is passed through the needle and entry into the right atrium or pulmonary is confirmed by fluoroscopy. A hemostatic sheath should then be positioned into the vein. Complications include hemothorax, pneumothorax, carotid artery puncture, and tracheal puncture.

Hepatic Access
Percutaneous transhepatic venous access is an excellent alternative to the femoral vein, especially in cases where it is necessary to cross an atrial septal defect or perform a trans-septal puncture (12).

A Chiba needle is introduced into the skin at the costal margin near the anterior axillary line. The needle is advanced cephalad and posteriorly toward the intrahepatic inferior vena cava. The needle is usually advanced to within a few centimeters of the right border of the spine and the obturator is removed and a syringe with contrast is attached. As the needle is slowly withdrawn contrast is simultaneously injected until contrast is observed to freely fill the hepatic vein. The syringe is removed and a guidewire inserted. The desired sheath is then advanced over the guidewire into the hepatic vein. At the end of the case, hemostasis is achieved with a Gianturco coil placed in the hepatic tract. This is accomplished by placing the dilator of the sheath into the hepatic vein. The dilator and sheath are slowly withdrawn while injecting contrast into the dilator. Once it is determined that the dilator is out of the hepatic vein and into the tract an appropriately sized coil is placed in the tract.

Abdominal pain is frequent following transhepatic access but a significant peritoneal hematoma is rare (12).

Percutaneous Transthoracic Puncture
Percutaneous transthoracic puncture can be used to obtain access to the ventricles in a patient with a mechanical valve in the aortic and mitral, or tricuspid position (13). It can also be used to puncture a surgically isolated left atrium in individuals following the Fontan procedure (14).
The procedure should be performed under general anesthesia and requires either transesophageal or transthoracic echocardiographic guidance. A modified triaxial system can be used with an 18-gauge lumbar needle inserted in a dilator/sheath combination. The subxiphoid position is used for right ventricular (RV) puncture and left atrial puncture after the Fontan procedure, whereas an apical position is used for left ventricular puncture. Initially, a 4- to 6-Fr sheath is placed for diagnostic hemodynamics and angiography and this sheath can be up-sized to facilitate an intervention. Following completion of the procedure the sheath is removed and a purse-string suture is placed in the superficial skin wound.

Complications can include pericardial effusion and hemothorax. The procedure should only be done in individuals who have had previous cardiac surgery, since a surgically-scarred pericardium is important for hemostasis especially after a ventricular puncture.

HEMODYNAMICS

Four important areas in the hemodynamic evaluation of an individual with congenital heart disease include measurement of pressures, measurement of blood oxygen content, measurement of cardiac output, and measurement of shunt size, vascular resistance, intracardiac pressure gradients, and valve areas.

Pressure Measurement

In both adult and pediatric catheterization laboratories, pressures are usually measured with fluid-filled catheters. Six common errors can lead to inaccurate measurement of pressure.

1. Air in the system which usually leads to a damped (artificially lower) pressure; however, occasionally air results in amplification of the pressure wave leading to overshoot of the wave (artificially high pressure) (Fig. 19.1).

2. Loose connection in the system usually results in overdamping of the wave form.

3. Partial catheter obstruction leading to a damped pressure tracing (this is especially common when using small thin walled catheters).

4. Catheter fling resulting from the catheter being in a turbulent jet or if the catheter is struck by a cardiac structure such as the anterior leaflet of the mitral valve, will result in an artificially high pressure.

5. Inaccurate calibration can result from either movement of the patient and/or the transducer during the study.

---

**Figure 19.1** The effect of an air bubble in the pressure transducer. (A) The left ventricular pressure in a 10-month-old with valvar aortic stenosis. This pressure was recorded with a small bubble in the transducer. The arrows depict the overshoot (“fling”) produced by the air bubble. If one used this pressure tracing to measure LV pressure the systolic pressure of 177 mmHg would have markedly overestimated the pressure. (B) The LV pressure after the air bubble was removed from the transducer. Notice the now normal LV pressure wave form without the fling. The true LV pressure is 150 mmHg not 177 mmHg. Abbreviation: LV, left ventricle.
6. Catheter entrapment occurs when an end-hole catheter is placed in a small or heavily trabeculated chamber and traps a small volume of fluid that results in an exaggerated systolic pressure elevation.

Table 19.2 summarizes the normal hemodynamics for a child.

Blood Oxygen Measurements

Oxygen is carried in the blood either dissolved in plasma or attached to hemoglobin. The amount of oxygen dissolved in the plasma at 37°C is about 0.03 mL/mmHg/L (or 3 mL of dissolved oxygen per liter, for every 100 mmHg partial pressure of oxygen). This amount of oxygen is quite small in comparison with the amount of oxygen bound to hemoglobin and is therefore usually ignored. However, if the child is in supplemental oxygen, with a PO2 > 100 mmHg, then dissolved oxygen must be considered in the calculation of total oxygen content.

Most of the oxygen in blood is bound to hemoglobin. The amount is dependent on the type of hemoglobin, temperature, partial pressure of oxygen and carbon dioxide, and the level of 2,3-DPG. The maximum amount of oxygen that can be taken up by hemoglobin in blood is referred to as the oxygen capacity. Oxygen capacity can be directly measured by the method of Van Slyke (15); however in current practice it is assumed that the maximal oxygen capacity is 1.36 mL/g of hemoglobin, thus,

\[
O_2 \text{ capacity} (\text{mL/L}) = Hb (\text{g/dL}) \times 1.36 (\text{mL/g}) \times 10 \text{ dL/L}.
\]

The oxygen content is the amount of oxygen present in a sample of blood, and this includes both dissolved oxygen and oxygen bound to hemoglobin.

\[
O_2 \text{ content (mL/L)} = (O_2 \text{ capacity}) \times (O_2 \text{ saturation}) + (0.03 \text{ mL/mmHg/L}) \times (PO_2 \text{ mmHg})
\]

When the child is breathing room air, this can be simplified to

\[
O_2 \text{ content (mL/L)} = (O_2 \text{ capacity}) \times (O_2 \text{ saturation})
\]

Oxygen saturation is usually measured using the spectrophotometric method. Measuring oxygen saturation directly rather than calculating it from the oxygen-hemoglobin dissociation curve makes the measurement independent of factors that may increase (alkalosis, hypothermia, fetal hemoglobin) or decrease (acidosis, fever) hemoglobin/oxygen affinity.

Measurement of Cardiac Output

The most common methods for measuring cardiac output use the indicator dilution technique first described by Fick (16). The indicators most commonly used in congenital heart disease are oxygen and cold saline (thermodilution) (17). The basic principles of the indicator dilutions method are that an indicator is present in the fluid in a measurable concentration, and the indicator is added or removed at a known rate. If, for example, oxygen is the indicator, the equation to measure cardiac output is as follows:

\[
Q_s = \frac{V_{O_2}}{(AO \text{ O}_2 \text{ content} - MV \text{ O}_2 \text{ content})}
\]

\[
Q_p = \frac{V_{O_2}}{(PV \text{ O}_2 \text{ content} - PA \text{ O}_2 \text{ content})}
\]

where \(Q_s\) is systemic blood flow, \(AO\) aortic, \(MV\) mixed venous, \(PV\) pulmonary venous, \(PA\) pulmonary artery, \(Q_p\) pulmonary blood flow, and \(V_{O_2}\) oxygen consumption.

Using oxygen as the indicator, the most difficult parameter to measure is oxygen consumption. This is either measured directly using a flow-through method (18) or using an assumed value based on the formulas of Lafarge and Miettinen (19).

In the thermodilution method, the indicator is temperature. A double lumen catheter is used and saline is injected in the proximal port usually in the right atrium and the thermistor for measuring temperature is positioned on the distal end of the catheter usually in the pulmonary artery.

The thermal dilution method is inaccurate in the following circumstances: significant pulmonary or tricuspid regurgitation, the presence of significant intracardiac shunts, and if the baseline temperature is unstable (i.e., patient has a fever or at the end of strenuous exercise).

Measurement of Shunt Size, Vascular Resistance, Valve Areas, and Intracardiac Pressures

Shunt Detection and Quantification

An increase in oxygen saturation between different sites on the right side of the heart is used to detect the presence of left-to-right shunt; whereas a decrease in saturations between different sites on the left side of the heart is used to detect the presence of a right-to-left shunt. Since the oxygen saturations of blood in the superior vena cava, inferior vena cava, right atrium, right ventricle, and pulmonary artery are not the same even in individuals with no intracardiac shunting, it is important to be able to define the minimum change in blood oxygen saturation that is needed to reliably demonstrate an intracardiac shunt. In adults it has been reported that an interchamber oxygen saturation difference of as small as 3% (right ventricle to pulmonary artery) or as large as 9% (superior vena cava to pulmonary artery) can reliably detect a left-to-right shunt (20). Table 19.3 lists the minimum saturation difference to detect a shunt at the 99% confidence limit for children (21). If more than one set of saturations is obtained the minimum saturation difference is reduced (22).

<table>
<thead>
<tr>
<th>Chambers sampled</th>
<th>Minimum saturation difference (%)</th>
<th>Multiple samples difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior vena cava–right atrium</td>
<td>8.7</td>
<td>7</td>
</tr>
<tr>
<td>Right atrium–right ventricle</td>
<td>5.2</td>
<td>4</td>
</tr>
<tr>
<td>Right ventricle–pulmonary artery</td>
<td>5.6</td>
<td>4</td>
</tr>
</tbody>
</table>
CARDIOVASCULAR CATHETERIZATION AND INTERVENTION

If the aortic saturation is <94% or there is a 2% or greater step down from left atrium or left ventricle (LV) to aorta then a right-to-left shunt is suspected.

The Fick principle is used to calculate pulmonary and systemic blood flows. To calculate right-to-left and left-to-right shunts, the concept of effective pulmonary blood flow must be used. Effective pulmonary blood flow ($Q_{ep}$) is defined as the desaturated blood that flows to the lungs. In the absence of a right-to-left shunt, effective blood flow equals pulmonary blood flow. The equation to calculate effective pulmonary blood flow is

$$Q_{ep} = \frac{V_{Qp}}{(PV \text{ O}_2 \text{ content} - MV \text{ O}_2 \text{ content})}$$

When intracardiac shunts are present, the superior vena cava is probably the best estimate of mixed venous blood. The three situations where this may not be the case are individuals under general anesthesia, the presence of supracardiac partial or total anomalous pulmonary venous return, and in many individuals with an atrial septal defect in which atrial blood refluxes into the proximal portion of the superior vena cava.

The volume of left-to-right shunt is equal to the difference between pulmonary blood flow and effective blood flow.

$$Q_L - l = Q_L - Q_{ep}$$

The volume of a right-to-left shunt is equal to the difference between systemic blood flow and effective blood flow.

$$Q_L - r = Q_R - Q_{ep}$$

The important exception to this definition is in an infant with D-transposition of the great arteries who has parallel circulations. In these infants the $Q_{ep}$ is the amount of blood that is mixing between the pulmonary and systemic circuits (i.e., the left-to-right and right-to-left shunting).

The ratio of pulmonary to systemic blood flow is a useful estimate of the magnitude of left-to-right shunting. Small left-to-right shunts are defined as $Q_{ep}$ of <1.5, moderate 1.5 to 2, and large >2. The formula to calculated $Q_{ep}$ is

$$Q_{ep} = \frac{(MV \text{ saturation} - AO \text{ saturation})}{(PV \text{ saturation} - PA \text{ saturation})}$$

If the patient is in oxygen, then dissolved oxygen must also be taken into account. The formula then becomes

$$Q_{ep} = \frac{(MV \text{ O}_2 \text{ content} - AO \text{ O}_2 \text{ content})}{(PV \text{ O}_2 \text{ content} - PA \text{ O}_2 \text{ content})}$$

Vascular Resistance

One of the most common reasons for performing a diagnostic cardiac catheterization is to assess pulmonary vascular resistance. This is especially important in the following situations:

- To determine if an individual can have their cardiac defect repaired, that is, child with a VSD device and pulmonary artery hypertension (Table 19.4)
- To determine if the child is a candidate for cardiac transplantation
- To determine the hemodynamic response of a child with pulmonary artery hypertension who is/or may have to be treated with pulmonary artery vasodilators

The calculation of vascular resistance is based on Poiseuille’s law, which states that flow in a tube is directly related to pressure and cross-sectional area of the tube and inversely to the length of the tube and the viscosity of the fluid flowing in the tube. In the vascular system the length of the tube and the viscosity of the fluid are assumed to be constant so that the pressure gradient across a vascular bed divided by the flow through the bed is equal to the resistance of the bed. Therefore, the formulas for pulmonary and systemic vascular resistance are as follows:

$$R_p = \frac{(PA \text{ mean pressure} - LA \text{ mean pressure})}{Q_p}$$

$$R_s = \frac{(AO \text{ mean pressure} - RA \text{ mean pressure})}{Q_s}$$

There are two different types of pulmonary resistance: arteriolar resistance is resistance calculated across the vascular bed ($\frac{PA \text{ mean pressure} - LA \text{ mean pressure}}{Q_p}$) and total resistance of the lungs ($\frac{\text{mean PA pressure}}{Q_p}$). In the clinical setting we are usually only interested in arteriolar resistance.

The units for this expression of vascular resistance are called Wood’s units (named after Paul Wood) and are in mmHg/L/min. To convert this to metric units, the Wood’s unit is multiplied by 80 to yield the units of dyne·sec·cm⁻². Because of the considerable size range of pediatric patients most cardiologists index the Wood’s units to body surface area (Wood’s unit·m⁻²). The normal values for systemic and pulmonary resistance are <20 units for systemic and <3 Wood’s units for pulmonary.

Pulmonary Vasodilator Testing

In patients with pulmonary hypertension in whom it is important to determine if their hypertension is fixed or reactive, pulmonary vasodilator testing is performed at the time of a diagnostic catheterization.

The two pulmonary vasodilators that are used are oxygen and nitric oxide (23,24). The usual protocol is to initially obtain pulmonary artery, pulmonary venous wedge and aortic pressures, saturations and blood gases, along with a measurement of pulmonary blood flow (either with using the Fick procedure or with thermodilution if other cardiac lesions are not present). Following these baseline measurements, the individual is placed in 100% oxygen for 10 minutes and repeat measurements are made. If oxygen does not result in normalization of pulmonary vascular resistance then the individual receives oxygen along with nitric oxide either at 50 ppm through a nasal cannula or at 20 ppm though an endotracheal tube. After 10 minutes of the nitric oxide, repeat hemodynamic measurements are made. Combination testing with NO + O₂ provides additional pulmonary vasodilation in patients with a reactive pulmonary vascular bed in a selective, safe, and expedient fashion during cardiac catheterization (25). Pulmonary vasoreactivity can also be assessed by using aerosolized iloprost (a stable carbacyclin derivative of prostacyclin, intravenous epoprostenol, and/or intravenous adenosine) (26). These agents are comparable to inhaled NO in their ability to induce pulmonary vasodilation and since they do not require a special delivery system they may even be more cost effective. A reactive pulmonary bed is defined by a drop in pulmonary vascular
Table 19.4  Example of Pulmonary Vasodilator Testing in a 12-Month-Old Infant with a Large Ventricular Septal Defect

<table>
<thead>
<tr>
<th>Site</th>
<th>Saturation</th>
<th>Pressure</th>
<th>PO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC</td>
<td>60%</td>
<td>Mean = 5 mmHg</td>
<td>42 mmHg</td>
</tr>
<tr>
<td></td>
<td>65%</td>
<td>88/50 (63) mmHg</td>
<td>47 mmHg</td>
</tr>
<tr>
<td>LA/PV</td>
<td>97%</td>
<td>Mean = 12 mmHg</td>
<td>88 mmHg</td>
</tr>
<tr>
<td>Aorta</td>
<td>93%</td>
<td>88/55 (66) mmHg</td>
<td>69 mmHg</td>
</tr>
<tr>
<td>SVC</td>
<td>70%</td>
<td>Mean = 5 mmHg</td>
<td>45 mmHg</td>
</tr>
<tr>
<td>PA</td>
<td>92%</td>
<td>90/30 (49) mmHg</td>
<td>68 mmHg</td>
</tr>
<tr>
<td>LA/PV</td>
<td>100%</td>
<td>Mean = 17 mmHg</td>
<td>425 mmHg</td>
</tr>
<tr>
<td>Aorta</td>
<td>100%</td>
<td>90/60 (70) mmHg</td>
<td>425 mmHg</td>
</tr>
</tbody>
</table>

Siteb  Saturation Pressure PO2

| SVC   | 70%        | Mean = 5 mmHg     | 45 mmHg |
| PA    | 99%        | 88/25 (46) mmHg   | 108 mmHg|
| LA/PV | 100%       | Mean = 17 mmHg    | 400 mmHg|
| Aorta | 100%       | 88/65 (72) mmHg   | 400 mmHg|

The following hemodynamics were present after the child was in 100% O2 for 10 minutes.

\[
Q_p = \frac{188 \text{ mL/min} \cdot \text{m}^2}{[13 \cdot 1.36^{10} + (0.03 \cdot 425)] - [13 \cdot 1.36^{10} + 0.03 \cdot 68]} = 7.5 \text{ L/min} \cdot \text{m}^2
\]

\[
Q_s = \frac{188 \text{ mL/min} \cdot \text{m}^2}{[13 \cdot 1.36^{10} + (0.03 \cdot 425)] - [13 \cdot 1.36^{10} + 0.03 \cdot 68]} = 2.9 \text{ L/min} \cdot \text{m}^2
\]

\[
Q_p/Q_s = 2.6; Q_d = Q_s
\]

\[
R_p = \frac{(49 - 17)}{7.5} = 4.2 \text{ Wood's units} \cdot \text{m}^2
\]

The following hemodynamics were present after the child was on O2 and 50-ppm NO for 10 minutes.

\[
Q_p = \frac{188 \text{ mL/min} \cdot \text{m}^2}{[13 \cdot 1.36^{10} + (0.03 \cdot 400)] - [13 \cdot 1.36^{10} + 0.03 \cdot 108]} = 17 \text{ L/min} \cdot \text{m}^2
\]

\[
Q_s = \frac{188 \text{ mL/min} \cdot \text{m}^2}{[13 \cdot 1.36^{10} + (0.03 \cdot 400)] - [13 \cdot 1.36^{10} + 0.03 \cdot 108]} = 2.9 \text{ L/min} \cdot \text{m}^2
\]

\[
Q_9/Q_s = 5.9; Q_d = Q_s
\]

\[
R_p = \frac{(46 - 17)}{17} = 1.8 \text{ Wood's units} \cdot \text{m}^2
\]

**Abbreviations:** PA, pulmonary artery; LA, left atrium; PV, pulmonary vein; SVC, superior vena cava.

Note: In this child, the combination of O2 and NO normalized Rp by increasing pulmonary blood flow while only slightly decreasing pulmonary artery pressure.

The following hemodynamic measurements were made on diagnostic cardiac catheterization.

Hb = 13 g/dL and VO2 measured at 188 mL/min/m2.

Abbreviations: PA, pulmonary artery; LA, left atrium; PV, pulmonary vein; SVC, superior vena cava.

resistance. This can be due to an increase in pulmonary blood flow with no or little change in pulmonary artery pressure (i.e., the child with a large VSD and pulmonary hypertension), a decrease in pulmonary artery pressure without a change in pulmonary blood flow (i.e., the child with idiopathic pulmonary artery hypertension), or a combination of both. An example of the calculations association with pulmonary vasodilatory testing is depicted in Table 19.4.
Valves areas are infrequently used in the management of children with congenital heart disease. Most decisions as to whether or not to perform surgery or balloon angioplasty are based on peak-to-peak pressure gradients at the time of a heart catheterization. When valve areas are calculated, either the Gorlin formula (27) or Bache’s modification of the Gorlin formula (28) is used.

In addition to measuring absolute systolic, diastolic, and mean pressures, analysis of the intracardiac pressure wave forms and pressure gradients between chambers are very important in performing a diagnostic cardiac catheterization in a patient with congenital heart disease. For example, the dominant pressure wave form in the right atrium is the “a” wave, whereas the “v” wave is the dominant pressure wave in the left atrium; however with an atrial septal defect the a and v are nearly the same in both atrium (Fig. 19.2).

The pressure wave forms are critical for making the diagnosis of both cardiac tamponade and pericardial constriction. In tamponade, the pericardial fluid causes equalization of all diastolic pressures. The atrial pressures increase with inspiration rather than decreasing and there is a marked fall in arterial pressure (>10 mmHg) with inspiration. In individuals with chronic pericardial constriction, a fluid bolus (10–20 cc/kg of warm saline) uniformly increases all pressures; whereas, if the individual has chronic myocardial constriction the fluid bolus will increase pressure to a greater degree in the cardiac chamber most severely affected (29).

Pressure pullbacks with end-hole catheters are very useful in identify the precise site of obstruction, that is, a patient with multiple sites of left ventricular outflow tract (LVOT) obstruction.

ANGIOGRAPHY
Angiography still remains an essential component of the diagnostic evaluation of the patient with congenital heart disease. The selection of the appropriate angiographic projection is critical for obtaining diagnostic images (30,31). The standard angiographic projections currently used in individuals with congenital heart disease are frontal (posteroanterior), lateral, right anterior oblique (RAO), left anterior oblique (LAO), long-axial oblique, hepatoclavicular (four-chamber), and the caudal views. All congenital heart disease angiography is performed...
using bi-plane angiography to reduce the amount of contrast agent given to the individual. Table 19.5 lists the commonly used angiographic projections.

In addition to selecting the appropriate angiographic view it is important to remember that the anatomy of any chamber is best delineated when the chamber is selectively filled with the appropriate amount of contrast at the appropriate rate. For the best anatomic definition, contrast should be injected in one second or less. The volume of contrast should be modified according to both the size and flow rates of the chamber or vessel being imaged. For example, higher volumes and flow rates are required to define the ventricular anatomy of a child with a large intracardiac shunt than a child with ventricular outflow obstruction. In general, most angiograms in patients with congenital heart disease use 1.0 to 1.5 cc/kg of contrast.

**Clinical Aspects (Angiography in Specific Lesions)**

**Ventricular Septal Defects**

Membranous defects are best visualized in the long-axial oblique projection (lateral tube at 60–70° LAO with 30° cranial angulation). This view elongates the LVOT. This view also is useful in evaluating the LVOT for possible outflow tract obstruction produced by a subaortic membrane and/or possible prolapse of the aortic valve into the VSD. The companion RAO projection is useful in identifying potential RV outflow tract obstruction and for making the diagnosis of associated LV-RA shunts.

Muscular VSDs require multiple views depending on the exact location of the defect or defects. The RAO projection is helpful in profiling the infundibular septum and defects in the anterior conal septum (subpulmonary defects). The long-axial oblique projection is useful for malalignment defects and defects in the midtrabecular portion and some defects in the apical portion of the ventricular septum (Fig. 19.3). The hepatoclavicular (four-chamber view) projection is helpful to evaluated defects in the posterior trabecular septum, apical septum and around the atrioventricular valves.

**Atrioventricular Septal Defects**

The RAO and companion long-axis oblique views are useful in assessing the degree of atrioventricular valve regurgitation and the status of the LVOT. The hepatoclavicular view is excellent for evaluation of the inlet (posterior interventricular) septum.

**Table 19.5 Commonly Used Angiographic Projections and Cardiac Lesions Best Imaged with These Projections**

<table>
<thead>
<tr>
<th>View</th>
<th>Frontal plane angle</th>
<th>Lateral plane angle</th>
<th>Cardiac lesion best imaged using these planes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posteroanterior and</td>
<td>0°</td>
<td>90°</td>
<td>Posteroanterior projection for complex heart disease, right ventricle in most conditions, pulmonary veins, left ventricle, coarctation, pulmonary stenosis, PDA</td>
</tr>
<tr>
<td>LAO</td>
<td>30° RAO</td>
<td>60° LAO</td>
<td>RAO useful for mitral valve, RPA, PDA and anterior VSDs, RAO with 30° cranial angulation useful to see RPA after a hemi-Fontan; LAO for coarctation, aortic valve abnormalities</td>
</tr>
<tr>
<td>Long-axial oblique</td>
<td>30° RAO</td>
<td>60° LAO and 20° cranial</td>
<td>Membranous, outlet, midmuscular, and some apical VSDs, left ventricular outflow tract obstruction, and the left pulmonary artery</td>
</tr>
<tr>
<td>Hepatoclavicular</td>
<td>40° LAO and 40° cranial</td>
<td>120° LAO and 15° cranial</td>
<td>Atrioventricular septal defects, apical and midmuscular VSDs, truncus; with a little less LAO on frontal projection good to see atrial septal defect</td>
</tr>
<tr>
<td>Cranial caudal</td>
<td>20° RAO and 40° cranial</td>
<td>90° and 20–30° caudal</td>
<td>Frontal plane; RPA and main pulmonary artery in TOF, lateral for Main pulmonary artery, truncus in TOF and after Hemi-Fontan or Bicaval shunt</td>
</tr>
<tr>
<td>Laid back</td>
<td>0° and 45° cranial</td>
<td>90°</td>
<td>Coronary arteries in D-transposition of the great arteries or double-outlet right ventricle</td>
</tr>
</tbody>
</table>

**Abbreviations:** RPA, right pulmonary artery; TOF, tetralogy of Fallot; VSD, ventricular septal defect; PDA, patent ductus arteriosis; RAO, right anterior oblique; LAO, left anterior oblique.
This view is also well suited to evaluate abnormal position of the atrioventricular valve attachments and the size of the ventricles. It is also useful in assess the type and severity of atrioventricular valve regurgitation. The companion cranially angled RAO projection is useful to evaluate the infundibular septum and the possibility of RV outflow tract obstruction.

**Tetralogy of Fallot**

The RV infundibular narrowing is best visualized by performing a RV angiogram in a slightly RAO projection with 30° of cranial angulation with the companion projection being a straight lateral (Fig. 19.4). These views provide excellent visualization of the anterior deviation of the infundibular septum. The pulmonary arteries are best imaged with the frontal plane in an RAO projection with cranial angulation and with the lateral plane in a LAO projection with 30° to 40° of cranial angulation. The RAO projection defines the right pulmonary artery (RPA) and the LAO projection delineates the left pulmonary artery. The coronary arteries should always be visualized in any preoperative patient with tetralogy of Fallot who is undergoing a heart catheterization. An aortogram positioned in the RAO and long-axis oblique positions usually result in adequate delineation of the coronary anatomy.

**D-Transposition of the Great Arteries**

A left ventricular angiogram in the long-axis oblique projection is useful to assess the size of the LV, status of the ventricular septum, and the LVOT anatomy. The RAO projection of the left ventricular angiogram is helpful to evaluate the mitral valve and anterior ventricular septum. The origins of the coronary arteries are best evaluated by performing an aortogram with marked caudal angulation and with a balloon angiographic catheter positioned antegrade across the aortic valve and with the balloon inflated (Fig. 19.5) (32).

**Complex Congenital Defects**

The standard posteroanterior and lateral projections are the initial views for evaluating a child with complex congenital heart disease (Fig. 19.6). Other views can then be performed to define any structures that need better anatomic evaluation. The echocardiogram can be used to help determine the best angiographic view. An angiographic view that is perpendicular to the transduce position and provides the best echocardiographic definition of the anatomy is usually a good starting point.

**Peripheral Pulmonary Artery Anatomy**

In patients with pulmonary atresia the first angiogram is usually an aortic angiogram in the posteroanterior and lateral projections (Fig. 19.7). Once the source of pulmonary blood flow is identified, selective angiograms in the aortopulmonary collaterals can be performed.

In the neonate, balloon occlusion angiography is useful (Fig. 19.8) (33). To perform balloon occlusion aortogram, the aorta is catheterized antegrade with a balloon-tipped angiographic catheter. The balloon is inflated immediately prior to contrast injection and is then rapidly deflated.

Finally, if pulmonary arteries or segments of the pulmonary arteries are not visualized on the aortic angiogram, selective pulmonary venous wedge angiograms can be performed.

---

**Figure 19.4** RV angiogram from a four-month-old with tetralogy of Fallot who has had a previous right BT shunt. (A) The frontal camera projection in the RAO cranial projection. The RV infundibular narrowing is marked by the two white arrows, the main, right and left pulmonary arteries are visualized. One can note stenosis and hypoplasia of the proximal RPA at the site of the BT shunt. The fact that the aorta (AO) is opacified on the RV injections suggests the presence of a VSD with right-to-left shunting. (B) The companion LAO cranial projection in the same patient. This projection again demonstrates the infundibular narrowing (solid white arrowhead) and the outlet malalignment VSD (two smaller white arrows). One can also note that the aorta overrides this VSD. Abbreviations: RV, right ventricle; BT, Blalock Taussig; RAO, right anterior oblique; LAO, left anterior oblique; LPA, left pulmonary artery; RPA, right pulmonary artery; PA, pulmonary artery; LV, left ventricle.
Figure 19.6 Left ventricular angiogram of a child with tricuspid atresia. The angiogram was performed in the posteroanterior projection. The LV opacifies the hypoplastic RV infundibular chamber (a line outlines the chamber) and PA. There is no apical portion of the right ventricle identified. Abbreviations: LV, left ventricle; RV, right ventricle; PA, pulmonary artery.

Figure 19.7 Aortogram in an infant with pulmonary atresia with VSD. The angiogram was filmed in the posteroanterior projection. The PA are filled by a PDA. Abbreviations: PA, pulmonary arteries; AsAo, ascending aorta; PDA, patent ductus arteriosus.

Figure 19.8 Balloon occlusion descending aortogram for documentation of the source of pulmonary blood flow in a neonate with pulmonary atresia with ventricular septal defect. The balloon-tipped angiographic catheters has been advanced from the right ventricle into the ascending and then the DsAo. Contrast injected behind the inflated balloon (arrow) produces dense opacification of single large collateral arising from the mid thoracic aorta that opacifies confluent right and left pulmonary arteries. One should also note that the infant has a right aortic arch. Abbreviation: DsAo, descending aorta.
The technique involves advancing an end-hole catheter across the atrial septum into the pulmonary vein that is best for delineating the portion of the pulmonary tree that could not previously be visualized. The catheter should then be advanced until it is wedged in the pulmonary vein. If the catheter has a balloon tip, the balloon can be inflated and wedge position confirmed by the injection of a small amount of contrast. A 10-cc syringe in which contrast and saline have been layered such that the saline is drawn up first and contrast second is used for the injection. The catheter is then wedged and the contrast/saline is injected by hand as fast as possible. Serious complications from this technique have been reported with the use of a nonballoon end-hole catheter (34).

CONCLUSION
Although advances in noninvasive imaging have reduced the role of diagnostic cardiac catheterization in the patient with congenital heart disease, recent developments in transcatheter interventions as well as marked advancements in surgical
management of many forms of extremely complex congenital heart disease, have resulted in diagnostic cardiac catheterization remaining a critical component of the evaluation and treatment of children with congenital heart disease. This chapter has summarized four of the areas that are critical to know when performing a cardiac catheterization in a pediatric patient: sedation for the procedure, vascular access, hemodynamic assessment, and angiography.

REFERENCES


Cardiac catheterization for the adult with complex congenital heart disease

John F. Rhodes, Jr. and Jorge R. Alegria B.

INTRODUCTION
The incidence of congenital heart disease is 0.8% (8/1000) live births (1). These patients have a cardiovascular abnormality that is secondary to an altered embryonic development with abnormal shunting patterns that result in further problems in the structure and function of the cardiovascular system. Currently, there are more adults than children in the United States with congenital heart disease making this chapter of critical importance to the cardiologist (2). Many of these patients with adult congenital heart disease (ACHD) will require additional catheter-based procedures that are either diagnostic to assess the complex anatomy or interventional procedures that allow therapeutic options to the patient. Over the past few decades, with the evolution of noninvasive imaging techniques including real-time 3-D echocardiography as well as magnetic resonance and CT angiography, the catheterization laboratory is now used more often for interventional procedures. The objective of this chapter is to provide the cardiologist with a general overview of complex ACHD and its management options in the congenital cardiac catheterization laboratory.

ANATOMIC AND PRECATHER CONSIDERATIONS
Congenital cardiac catheterization is performed with either general anesthesia or moderate sedation with a combination of opiates and benzodiazepines. Percutaneous access using standard Seldinger technique in the femoral artery and/or vein is performed and alternative venous access could include the internal jugular, subclavian or transhepatic approaches. Arterial access may also be obtained from the femoral and radial arteries. Hemodynamic measurements are obtained initially always in room air precluding the need for a pulmonary vein PO2. Subsequently, angiograms will further delineate the anatomy or lesion severity. For therapeutic procedures, a catheter is passed across the target area, such as stenosis or abnormal shunt. A guide wire is then passed through the catheter to provide a track over which therapeutic devices are delivered. Balloon catheters are threaded directly, whereas stents and occlusion devices are protected or constrained within a long delivery sheath. Anticoagulation is managed with heparin 100 units per kg body weight (maximum 5000–7000 units) for a goal activated clotting time (ACT) > 200 to 250 seconds, depending on the procedure to be performed. In addition, antibiotics are given to patients who receive an implanted device.

FUNDAMENTALS FOR CONGENITAL CARDIAC CATH
Hemodynamic Assessment: Oxygen Satuations Obtained in Room Air
Oxymetry can detect shunts and be utilized in the calculation of cardiac output. It is critical to avoid obtaining the data with the patient on nasal canulae oxygen. It is important to obtain the saturation date while the patient is in room air and the saturation should be drawn from a location distal to the shunt lesion. Oxygen saturation is the percentage of hemoglobin that is present as oxyhemoglobin and is measured by reflectance. Oxygen content is the total amount of oxygen present in the blood. This includes the oxyhemoglobin plus the oxygen dissolved in the plasma. The oxygen content is calculated with the following formula:

\[ \text{O}_2 \text{ content} = (\text{O}_2 \text{ saturation} \times 1.36 \times 10 \times \text{Hgb concentration}) \]

In this formula 1.36 represents the amount of O2 1 g of hemoglobin carries when fully saturated. A left-to-right shunt is diagnosed when a significant oxygen step-up is found. Specifically, a step-up of >11% from the SVC to RA indicates a left-to-right shunt at the atrial level, >7% from the RA to the right ventricle (RV) is consistent with a shunt at the RV level, >5% from the RV to the pulmonary artery indicates a systemic to pulmonary artery shunt, and >9% from the SVC to the pulmonary artery has a high predictive accuracy to detect a 2:1 left-to-right shunt.

To calculate blood flows, oxygen contents and oxygen consumption are used.

Systemic blood flow \( Q_s \) =

\[ \frac{V_O_2 (\text{mL/min})}{\text{SA O}_2 \text{ content} - \text{MV O}_2 \text{ content}} \]

Pulmonary blood flow \( Q_p \) =

\[ \frac{V_O_2 (\text{mL/min})}{\text{PV O}_2 \text{ content} - \text{PA O}_2 \text{ content}} \]

where SA is systemic arterial saturation, MV mixed venous, PV pulmonary vein, and PA pulmonary artery saturation.

The mixed venous saturation is calculated with the following formula:

Mixed venous saturation (MV) =

\[ \frac{(2\text{SVC} + 1\text{IVC})}{3} \]

Another flow that is calculated in the study of congenital heart defects in the cardiac catheterization laboratory is the effective flow \( Q_e \), that is, the quantity of systemically mixed venous blood that circulates and is oxygenated in the lungs and
then circulates through the systemic capillaries. On the basis of this, the effective flow is calculated using the pulmonary vein and mixed venous saturations, and in the absence of shunts equals \( Q_p = Q_s = Q_v \).

Effective pulmonary flow = \( \frac{O_2 \text{ consumption}}{\text{PV } O_2 \text{ content } - \text{MV } O_2 \text{ content}} \)

In the absence of shunting, the mixed venous saturation is equal to the pulmonary artery saturation. The left-to-right shunt (flow) is obtained by subtracting the effective pulmonary blood flow from the total pulmonary blood flow: left-to-right shunt = \( Q_p - Q_v \).

**Hemodynamic Assessment: Intracardiac and Intravascular Shunts**

Shunts allow the intermixing of saturated blood with unsaturated blood. Various shunts can be either cardiac or vascular and are classified as left to right, right to left, and bidirectional. Left-to-right shunting results in increased pulmonary blood flow. Right-to-left shunt results in a lower arterial saturation, generally less than 95%. In bidirectional shunts the left-to-right shunting is calculated as \( Q_p - Q_s \) and the right-to-left shunting as \( Q_s - Q_v \). In patients with residual shunts and pacemaker leads there is a >2-fold increase in thromboembolic events (3).

**Hemodynamic Assessment: Pressure Data (Room Air)**

Normally in the right atrial pressure tracing the “a” wave is dominant and in the left atrial pressure tracing the “v” wave is dominant. In secundum atrial septal defect there is a larger \( v \) wave in the right atrial pressure (equal \( a \) and \( v \) waves). Elevation of the \( a \) wave can be seen in pulmonary stenosis. Large \( “cv” \) waves are seen in tricuspid insufficiency. Rise in right ventricular pressure is seen in outflow tract obstruction or pulmonary hypertension. Ventricular septal defects occasionally are close and are associated with anomalous and hypertrophied muscle bands, creating the so-called double-chamber RV, which results in a proximal chamber with elevated pressure and a distal one with low pressure in the RV. Abnormal aortic tracings can be the result of abnormal gradients such as in coartation of the aorta or supravalvular stenosis. A wide pulse pressure is seen in aortic insufficiency, aortopulmonary shunts or systemic AVM.

**Hemodynamic Assessment: Angiography**

To understand congenital heart diseases it is necessary to be familiar with normal features of the different cardiac segments (Fig. 20.1). Angiography is performed and each structure is evaluated for anatomy, function and connections. Contrast injection of the innominate vein is done to rule a persistent left superior vena cava or other anomalies. Inferior vena cava venograms are needed in patients with Fontan circulation to assess for inferior baffle obstruction and shunts resulting in systemic hypoxemia. Right ventriculogram is frequently performed for either function or anatomy. If for function the injection rate can be slowed down to see the systolic function over several heart beats but for anatomy the injection should be approximately 0.5 to 1 cc/kg over a single heart beat. This is usually 30 to 40 cc contrast at 30 to 40 cc/sec when the heart rate is 60 beats/min. Pulmonary angiography is used to evaluate pulmonary valve regurgitation or branch pulmonary stenoses. When doing these angiograms the levophase angiogram is useful to identify the pulmonary vein drainage and additional left-sided structures and function. Pulmonary wedge angiogram is occasionally used to assess the pulmonary vascular anatomy and its changes when there is important pulmonary vascular obstructive disease. In congenital heart diseases biaxial imaging should be used. To visualize the atrial septum a cranial 45°, left anterior oblique (LAO) 45° view is useful. To see the transverse arch and the area of aortic coartation a direct lateral view if a biaxial laboratory and a steep caudal/LAO view are performed (Fig. 20.2).

**CATHETERIZATION FOR COMPLEX CONGENITAL HEART DEFECTS**

**Patent Ductus Arteriosus**

Patent ductus arteriosus (PDA) is a cardiac derangement usually detected early in life and occasionally during adulthood. The finding of an audible PDA is generally regarded as an indication for treatment since patients with an audible PDA typically have a shortened life expectancy (4) and a potential increase risk for endarteritis. Survival with an audible PDA to an advanced age is unusual without significant morbidity (5). However, with a small or restrictive PDA clinical findings such as murmur and clinical symptoms are uncommon other than a potentially higher risk of endarteritis compared with the general population. Historically, over half of the mortalities from PDA in the pre-antibiotic era were from endarteritis rather than
heart failure (6). In the presence of significant shunting, con-
gestive heart failure initially and pulmonary hypertension later
can occur. In addition, by 40 years of age nearly a third of
patients with an unrepaired PDA develop heart failure, pul-
monary hypertension, or endarteritis and two thirds do not
survive beyond the fifth decade (7). Therefore, the current
standard of care is surgical or device PDA closure when a
PDA is auscultated (8). In the ACHD patient, coexistent path-
oologies like dilation of the aorta secondary to the chronic left-to-
right shunt, calcified atheromatous lesions, and aneurysm of
the ductus may result in surgical correction requiring cardio-
pulmonary bypass (9). Consequently, percutaneous occlusion
of the PDA as an excellent lower risk alternative for the ACHD
patient and precludes the need for a potentially high-risk
cardiopulmonary bypass procedure (Fig. 20.3) (10).

Both a femoral venous and femoral arterial sheath is
placed to perform percutaneous PDA closure and patients are
given local anesthesia, moderate sedation, and heparin. If pos-
sible the PDA is crossed retrograde from the pulmonary artery
into the aorta for the purpose of coil or device delivery. When
the ductus can only be crossed antegrade (from the aorta),
either the coil may be deployed in that fashion or the delivery
catheter may be advanced retrograde by using a snare and rail
technique (11). A biplane aortogram in the 40 RAO (AP camera)
and direct lateral is preferred but if the lab is single plane the
lateral projection or steep LAO is utilized. This angiogram is
used to delineate the location, anatomy, and narrowest diam-
eter of the PDA. A single or multiple 0.038-in Gianturco coils
are deployed in the PDA using a tapered catheter for enhanced
control as previously described (12). The goal is to deploy ≤1
loop of the coil in the main pulmonary artery and the remain-
ing loops in the ductal ampulla. More recently, many centers
have moved toward using the Amplatzer duct occluder (AGA
Medical Corporation, Golden Valley, Minnesota, U.S.) almost
exclusively for PDA closure in adults (13). A repeat aortogram
is performed to evaluate for coil or device position and for

residual shunts. The goal is to achieve complete closure of the
ductus by angiography prior to leaving the catheterization
laboratory. If residual shunt, other than slow filtration through
the device, is seen on angiography, the PDA is crossed again
and additional coils can be deployed in the same fashion.
Prophylactic antibiotics are administered at the time of coil
delivery and for 24 hours thereafter. The risk for adverse events
is low with reported complications including coil or device
embolization, hemolysis from high-velocity residual shunting
and infection. Adult patients can present with a calcified PDA
and are at higher risk for surgical closure when calcification is present.

Chest X ray (CXR) and transthoracic echocardiography are performed before discharge the next morning. Standard endarteritis prophylaxis is recommended for six months after closure to allow coil or device endothelialization to occur and echocardiography should confirm complete closure prior to releasing the patient from routine follow-up with cardiology.

**Persistent Left Superior Vena Cava with Hypoxemia**
This is a common congenital anomaly of the venous system. It is relevant to be aware of this malformation before pacemaker lead placement from the left subclavian vein approach. The most common anatomy is absence or hypoplasia of the left innominate vein and a direct connection of the left internal jugular vein and left subclavian vein to either the left atrial appendage to the left atrium or through the coronary sinus to the right atrium. The coronary sinus anatomy should be suspected when a prominent coronary sinus ostia is seen by echocardiography or MRI. The direct connection to the left atrium (Fig. 20.4) should be suspected when patients present with resulting in systemic hypoxemia or a history of brain abscess after dental procedures.

**Interrupted Inferior Vena Cava**
This anomaly is commonly but not always associated with complex congenital heart diseases or forms of heterotaxy. The inferior vena cava below the hepatic veins but above the renal veins is absent and thus the venous return is interrupted with subsequent systemic venous drainage via the azygous vein to the left-sided superior vena cava (Fig. 20.5). The hepatic veins enter the right atrium directly but although usually together they can enter contra lateral to each other.

**Myocardial Bridging**
The intramural course of a coronary is very common congenital coronary anomaly although its clinical significance remains to be elucidated. In selected cases percutaneous or surgical intervention is warranted (generally severe bridging and evidence of ischemia) but in the majority with adequate antegrade flow during diastole do not warrant any intervention (Fig. 20.6).
Anomalous Coronary Arteries

They can occur isolated or in conjunction with other structural heart disease abnormalities. The recognition and evaluation of coronary anomalies has become a very important part of the evaluation of congenital heart diseases. The left coronary artery arises from the left sinus of Valsalva the right coronary artery from the right sinus of Valsalva. The right or left coronary artery may arise from inappropriate sinus of Valsalva, the most common one is when the left circumflex artery arises from the right coronary sinus. Other types includes anomalous right coronary artery from the left coronary sinus, single coronary artery, anomalous left coronary artery from the pulmonary artery (ALCAPA) also called Bland-White-Garland syndrome. ALCAPA is characterized by pathologic q waves in leads I, aVL, and precordial leads V4 to V6. It is possible to find a small left-to-right shunt at the pulmonary level. The left ventriculogram demonstrates left ventricular dysfunction (anterolateral wall) and mitral valve regurgitation. Aortogram will demonstrates a large right coronary artery and filling of the left coronary by collaterals from the RCA with passage of contrast from the left main to the pulmonary artery.

Coronary Fistulae

They commonly arise from the proximal portion of the native coronary artery and enter either the pulmonary artery or the atria. Coronary fistulae can produce ischemia due to steal of coronary perfusion. If large enough they can produce a left-to-right shunt. Transcatheter intervention is indicated when there is coronary steal and symptoms (Fig. 20.7).

Coarctation of the Aorta

Coarctation of the aorta has been estimated to occur with a frequency of 7% to 9% (14). It is usually diagnosed in infancy or early childhood but can go undetected to become apparent well into adulthood. The natural history suggests that isolated coarctation may represent one aspect of more diffuse arteriopathy. Late complications can include aneurysm formation and dissection of the ascending aorta rather than the region of prior repair or intervention. Cerebrovascular events from rupture of berry aneurysms may occur before or after surgical repair of coarctation. Persistent hypertension has been reported despite apparently complete relief of obstruction either surgically or by angioplasty. Life expectancy beyond the sixth decade is unusual if the coarctation is not repaired with a mean survival
of approximately 35 years (15). The coarctation site is typically just beyond the origin of the left subclavian artery across from the ampulla of the ductus arteriosus. Collateral circulation often is present in older patients to bypass the coarctation and provide blood flow to the lower extremities. The most common origins of these vessels are from the subclavian arteries through the internal thoracic arteries and the thyrocervical and costocervical branches. These vessels communicate with the intercostal arteries, which then perfuse the descending aorta distal to the coarctation. This can produce diminished but palpable lower extremity pulses and mask substantial coarctation. MRI is particularly helpful in the evaluation of coarctation among adult patients and cine Careful hemodynamic assessment across the coarctation is essential to find a peak systolic gradient. Intervention typically is indicated when the peak gradient it can be classified as mild (<30 mmHg), moderate (30–49 mmHg), or severe (>50 mmHg). Pulmonary valvotomy, or placement of an RV to pulmonary artery conduit should be used since right ventriculotomy entails the risk of injuring the LAD. Long-term follow-up studies have demonstrated that patients with TOF will have right ventricular enlargement and dysfunction due to chronic volume overload secondary to severe pulmonary valve regurgitation. Pulmonary valve replacement is often indicated. An evolving interest in performing percutaneous pulmonary valve replacement exists, although further data is needed.

**Right Ventricular Outflow Tract Obstruction: Native or Postoperative**

When severe a large wave will be seen in the right atrial tracing because of decreased compliance of the RV. A gradient will be found in the right ventricular outflow tract. Right ventricular angiography should be performed with AP and lateral views. The valve will be thickened and with restricted motion (doming). Usually infundibular hypertrophy is present. On the basis of the peak gradient it can be classified as mild (<30 mmHg), moderate (30–49 mmHg), or severe (>50 mmHg). Pulmonary valve can be dysplastic. Dysplastic pulmonary valve is present in the Noonan Syndrome.

For non-dysplastic valves the treatment of choice is percutaneous pulmonary balloon valvuloplasty. Because of

**Figure 20.8** Stent angioplasty for native coarctation of the aorta.
infundibular hypertrophy, immediately post valvuloplasty the gradient can increase (dynamic obstruction). In some rare cases there is severe increase in the gradient immediately post valvuloplasty, with hypotension and hypoxemia (“suicidal RV”). Infundibular contraction can be decreased with β-blocker therapy.

More recently, ongoing clinical trials are looking at percutaneous pulmonary stent valve placement for severe insufficiency of a surgically placed homograft. The two clinical trials include the Melody valve (Metronic BV, Heerlen, Limburg, The Netherlands) and the Edwards stent valve (Edwards Lifescience, Irvine, California, U.S.) (Fig. 20.9). Although preliminary data from Europe and via these two FDA approved feasibility studies, long-term data remains pending (17).

Branch Pulmonary Stenoses or Distortion
For the most part, transcatheter therapies in the care of adult patients with TOF are limited to patients who have undergone surgical treatment with attention to residual obstructive lesions in the main pulmonary artery, RV to pulmonary artery conduit, or distal pulmonary arteries. Prior shunt sites may become stenotic with time and necessitate balloon angioplasty and possibly stent placement. Success has been achieved in these situations, but many residual lesions necessitate surgical re-intervention. Hypoplasia or stenosis of branch pulmonary arteries will result in an increased afterload to the RV and hypoperfusion to one lung or segments, with subsequent over-circulation to other segments. Branch pulmonary stenosis can be congenital in origin or acquired as a complication of surgical interventions. In adults they are treated with stenting.

Sinus of Valsalva Aneurysms
The sinus of Valsalva aneurysm can potentially rupture and produce a left-to-right shunt and right-sided volume overload. In addition, postoperative adverse events with the right coronary artery can result in severe systemic hypoxemia in the presence of a patent foramen ovale or atrial level shunt because of sudden compliance change within the RV.

D-Transposition of the Great Arteries
D-Transposition is a malalignment of the great vessels with the pulmonary artery arising from the morphologic left ventricle (LV) and the aorta arising from the morphologic RV. Today, all newborns with this form of CHD and many teenagers have been treated with arterial switch operation, described by Dr. Janten (18). Unfortunately though, most of the young adults evaluated with this form of CHD were treated earlier with an atrial rather than arterial switch known as either a Mustard or Senning operation depending on if the atrial baffle was made of pericardial tissue or Dacron material (19). The main hemodynamic and thus cardiac catheterization concerns for these patients as adults include the systemic RV function because of the poor morphology of the RV for the systemic work load, baffle leaks predominantly within the connection of the superior vena cava baffle to the right atrium resulting in a right-to-left shunt, systemic hypoxemia or systemic embolic events, baffle obstruction resulting in superior vena cava syndrome or enlargement of the azygous vein as it “pops” off to the inferior vena cava and arrhythmias especially sick sinus syndrome and the need for a pacemaker insertion. Non-interventional catheter-based evaluation is reserved mainly for hemodynamic interpretation of the failing systemic RV to obtain an end diastolic pressure, filling pressures, and pulmonary vascular resistance. These data are critical prior to proceeding for a possible cardiac transplantation.

The patient with multiple baffles leak is often the most difficult intervention to undertake. These patients have very irregular and abnormal connections within the baffle and the morphologic right atrium and right atrial appendage. Techniques previously described (20) for this situation include Gianturco coils (Cook, Bloomington, Indiana, U.S.), Amplatzer vascular plugs (AGA Medical, Minneapolis, Minnesota, U.S.), and
Amplatzer ASD and PDA devices (AGA Medical, Minneapolis, Minnesota, U.S.). More recently a few centers have used the Gore cuffed “covered” stents (WL Gore, Flagstaff, Arkansas, U.S.) within the SVC baffle to essentially exclude the baffle leak (21).

The patient with SVC baffle obstruction will require stent angioplasty with balloon expandable peripheral diameter stents (12–18 mm). The position of the stent is important to avoid too much overlap of the inferior baffle but long enough to include the more distal SVC. Often a second stent more distal may be necessary. We recommend considering the balloon-in-balloon catheter so these positioning issues can be addressed. Also, the lesion often can be either scarred and resistant to the balloon or compliant and more of a kink in the baffle. We therefore often use a soft noncompliant balloon to “test” the lesion resistance measuring in the AP and lateral projections and then choosing an angioplasty-stent and balloon that will be large enough to adhere well to the walls and not dislodge toward the atroventricular (AV) valves. If a patient already has pacing wires across the baffle a temporary wire is placed from the lower extremity and the pacing wires are then removed allowing the stent to be placed. Once the stent is fully dilated the pacing wires are replaced across the superior vena cava and the lower extremity temporary wire is subsequently removed.

The final possible derangement to discuss is baffle obstruction in the pulmonary venous baffle. This obstruction is quite difficult to diagnose and is often within the midpulmonary venous baffle between the entrance of the pulmonary veins to the morphologic left atrium and the tricuspid valve apparatus. Multiple imaging modalities including MRI, CT angiography or cardiac catheterization with pulmonary artery wedge pressures and angiograms are utilized to delineate this abnormality. Despite these techniques, it remains difficult to image thus if the wedge pressures are elevated compared with the RV end diastolic pressures we use a pigtail and floppy wire to position a hemodynamic catheter retrograde from the aorta near the pulmonary veins and thus across the midpulmonary baffle obstruction. Once the hemodynamic data is obtained this catheter is exchanged for an angiographic catheter to perform a power injection directly in the morphologic left atrium. The main importance of these maneuvers is that long standing pulmonary venous obstructions can result in pulmonary hypertension or elevated pulmonary vascular resistance and subsequently make the patient possibly a poor candidate for cardiac transplantation.

**Congenitally Corrected Transposition of the Great Arteries**

This defect is characterized by AV discordance and ventriculoarterial discordance. The RV is the systemic ventricle and with time will develop left ventricular dysfunction. The tricuspid valve is the systemic AV valve and can develop significant regurgitation. Cardiac catheterization is indicated to assess the degree of systemic AV valve regurgitation, to rule out pulmonary hypertension and to assess the systemic right ventricular function potentially prior to consideration for cardiac transplantation later in life (22).

**Ebstein’s Anomaly**

This lesion is due to a lack of delamination of the tricuspid valve, resulting in different degrees of TV regurgitation. There is as portion of the RV that is “atrialized.” Associated lesions include PFO, ASD, and pulmonary stenosis (23).

**Single-Ventricle Physiology: Postoperative Physiology**

A patient with a functional single ventricle typically proceeds with palliation, including the systemic shunt (Norwood operation, Potts shunt, Waterston shunt, or other central shunts), followed by the superior vena caval shunt or Glenn operation, and ultimately the completion of the caval pulmonary shunt with the Fontan operation (Fig. 20.10). Examples of congenital defects that may necessitate such palliation include hypoplastic left heart, tricuspid atresia, pulmonary atresia with intact ventricular septum, or unbalanced complete AV canal. The adult congenital patient with single-ventricle physiology is usually palliated with a Fontan but few patients remain with single lung supplied by a superior vena cava to the pulmonary artery shunt (Glenn) or a systemic artery to pulmonary artery shunt. The Fontan procedure represents the final palliative procedure for single-ventricle physiologic status. This procedure completes the direction of the remaining systemic venous blood from the inferior vena cava and hepatic veins to the pulmonary arteries. This is accomplished in most cases by means of either an external conduit or an intra-atrial lateral tunnel, which courses from the lateral and inferior aspect of the right atrium (24). The atrial appendage or superior vena caval stump transected during the Glenn procedure is directed to the pulmonary artery, effectively “septating” the circulation. Pulmonary blood flow is achieved passively without the assistance of a ventricular pumping chamber. For this reason it is imperative to have low pulmonary pressures and vascular resistance.

Important derangements include the Fontan pathway obstruction, persistent fenestration, or venovenous fistulae both of the later resulting in systemic hypoxemia and increased risk of cerebrovascular events.

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**Figure 20.10** AP projection demonstrating an external conduit Fontan pathway around the right atrium and directly connecting to the pulmonary arteries.
Fontan Pathway Obstruction

There are multiple locations for Fontan pathway obstruction. These include the distal Fontan anastomosis along the hepatic veins, the proximal anastomosis at the pulmonary arteries due to the Fontan pathway or the SVC anastomosis, and bilateral branch pulmonary artery stenoses. Also, the left innominate vein can become narrowed especially if there is a history of upper extremity central line placement during previous procedures. All of these locations are amendable to stent intervention using peripheral size 10 to 22 mm diameter stents. Hemodynamic derangements are assessed using mean pressures and careful pullbacks as only a 2- to 3-mmHg gradient can be significant especially if there are venovenous “pop-off” routes for the blood flow.

Persistent Fenestration

This is fairly unusual in the adult population but many younger teens and the rare adult may require transcatheter closure of the fenestration if there is concern regarding systemic hypoxemia with or without exercise and if there is a concern regarding possible or previous cerebrovascular events. Multiple different septal occluder devices have been successfully used to close the Fontan fenestration and few data exist using the covered stent technology to essentially isolate the fenestration within the Fontan baffle (Fig. 20.11).

Venovenous Fistula

As with the patient with a persistent fenestration the venovenous fistulae will manifest itself as systemic hypoxemia, with or without exercise, or a route for systemic embolic events. The standard angiograms to assess the Fontan circuit for these malformations is a biplane cineangiogram in the inferior vena cava distal to the hepatic veins, a biplane cineangiogram at the proximal anastomosis of the Fontan, a biplane cineangiogram in the left innominate vein for the patient with a right-sided Glenn shunt and angiograms in both SVC in those patients with bilateral Glenn shunts. If these angiograms do not demonstrate the explanation for the patients systemic hypoxemia or embolic events we recommend agitated saline injections in the proximal right and left pulmonary arteries with simultaneous TEE or chest wall echocardiography to assess for tiny arteriovenous malformations in either lung. The lung with the least or no blood from including the hepatic veins is most likely to have the malformations. Transcatheter closure (25) of the venovenous fistulae or larger arteriovenous malformations can be performed using Gianturco coils, Amplatzer vascular plugs, or the Amplatzer PDA occluder (Fig. 20.12). Final angiography or agitated saline injections can be utilized to assess for immediate closure and systemic oxygen saturations at rest or during follow-up exercise testing can be checked to confirm improvement and future risk for embolic events.

Aortopulmonary Collaterals

A significantly decreased pulmonary blood flow is a stimulus to the development of collateral vessels from the systemic circulation. Major aortopulmonary collaterals (MAPCAs) are present in patients with pulmonary atresia and ventricular septal defect.

SPECIAL ISSUES

Pulmonary Hypertension in Congenital Heart Disease

Changes in the pulmonary vasculature are common in patients with congenital heart diseases and can be related to increased blood flow secondary to left-to-right shunting, distortion of the pulmonary arteries due to shunts or others (26). Pulmonary angiography is frequently performed. The objectives are to rule out pulmonary branch stenosis (proximal, distal, bilateral, or unilateral), assess PCWP, and evaluate response of pulmonary pressures to vasodilator tests. Catheterization will help in the decision-making process of selection for heart or heart and lung transplantation in selected patients.
Secundum atrial septal defects with elevated pulmonary vascular resistance or left ventricular diastolic dysfunction should be carefully evaluated before proceeding with device closure. Transient balloon occlusion of the defect can be performed to assess the changes in cardiac output and left atrial pressure.

In patients with D-TGA with atrial switch procedures (Mustard or Senning) and pulmonary hypertension, pulmonary venous baffle obstruction must be ruled out. When a catheter is wedged in a pulmonary vein, the pressure may reflect the pulmonary artery pressure. In cases that the pulmonary artery pressure cannot be measured, for example, in a patient with pulmonary valve atresia, pulmonary vein wedge pressure is used.

**Eisenmenger Syndrome**

Without treatment, the increased pulmonary blood flow resulting from a left-to-right shunt will produce progressive structural changes in the pulmonary vasculature (26). These changes will consist of medial thickening and hypertrophy, endothelial damage, and in situ thrombosis, resulting in an increase in pulmonary vascular resistance due to the decrease in the cross-sectional area of the pulmonary circulation and vasoconstriction. As the pulmonary pressures continue to increase, the degree of left-to-right shunt will diminish, and eventually there will be right-to-left shunting, resulting in cyanosis. Eisenmenger syndrome refers to reversal of a left-to-right shunt to a right-to-left shunt due to the development of pulmonary vascular disease. Patients can present with syncope, cyanosis, palpitation, hyperviscosity symptoms, hemoptysis, stroke, or brain abscess.

The diagnosis is based on physical examination, which will disclose clubbing, cyanosis, a right parasternal heave, and loud P2 with a high pitch decrescendo diastolic murmur of pulmonary valve regurgitation. If the RV fails, signs of right-sided heart failure will be present, with worsening tricuspid valve regurgitation.

Patients are advised to avoid dehydration, heavy exertion, or systemic vasodilators that can increase the right-to-left shunting. If a surgical procedure is planned, careful anesthetic management (cardiac anesthesia) should be available, and use of an air filter in all intravenous access to avoid paradoxical air embolism is mandatory.

Avoidance of hypotension is important; otherwise, the degree of right-to-left shunting will increase and progressive hypoxemia will develop, with the risk of death. If coronary angiography is needed, the most experienced operator should perform the procedure with minimal contrast to minimize the risk of kidney failure. Cyanotic patients are more susceptible to developing nephropathy with the use of contrast, NSAIDs, or other drugs such as aminoglycosides (27).

**CONCLUSIONS**

Congenital heart disease in the adult population, more than any other type of malformation, is taxing the current medical system as the number and complexity of patient issues is outgrowing the limited facilities established to care for them. With better survival from childhood, it is evident that few of our surgical and catheter-based interventions are curative, and that a lifetime of care will be required. The education of both internal medicine/cardiology trainees as well as those already in practice, in addition to the development of national databases for tracking patients and their responses to therapy, are critical to the future care of this complex and diverse population. Clinical systems designed for the transition of these patients out of the Pediatric clinics, where many continue to receive their care, and into organized, regional ACHD centers of excellence will facilitate this process.
REFERENCES


Ventriculography and aortography

José G. Díez and James M. Wilson

VENTRICULOGRAPHY

Introduction

Reliance upon radiographic cardiac-chamber imaging has substantially declined in recent years because of the success of echocardiography and, more recently, magnetic resonance imaging (MRI). In 1980, ventriculography was recommended as a routine part of the evaluation of patients undergoing cardiac catheterization (1). More recently, other methods of accurately determining left ventricular (LV) function or the aortic anatomy have supplanted cavity angiography to such a degree that the techniques and technical details of obtaining diagnostic images with ventriculography are being lost.

Nonetheless, cavity imaging (also referred to as “cavitography” for lack of a better word) remains important because it allows efficient, timely diagnosis and guides intervention, particularly for structural heart disease. The LV ejection fraction (LVEF) provides diagnostic and prognostic information in patients with known or suspected heart disease. In clinical practice, the LVEF can be determined with any of five currently available imaging techniques: contrast angiography, echocardiography, radionuclide blood-pool and first-pass imaging, electron-beam computed tomography (CT), and MRI (2). In studies comparing different imaging techniques, the results have suggested that LVEF measurements are not interchangeable (3). Therefore, conclusions and recommendations should be interpreted in the context of locally available techniques. In addition, there are wide variances in the estimation on volumes and LVEF between different techniques, especially when using echocardiography. The principal reason for this variance is the method used to convert two-dimensional (2D) images to three-dimensional (3D) information. Ventrilocigraphy typically uses the equations of Sandler and Dodge; the heart is assumed to be symmetrical and shaped like a prolate spheroid. However, this assumption is valid only for the normal heart. Similarly, echocardiographic methods are encumbered by geometric assumptions, which may result in estimates that vary widely from those of ventriculography. Nuclear methods that are add-ons to perfusion imaging reconstruct the ventricular walls and measure the volume and LVEF with Simpson’s rule. Unfortunately, these methods are hampered by poor spatial resolution (implying a larger error range) and difficulty in assessing transmural myocardial infarction (where the LV wall is not visible, the result must be inferred), that is, the location of the infarcted wall during systole must be inferred.

Count-determinant, multigated acquisition (MUGA) scanning provides an accurate LVEF but is not reliable for determining wall motion. Improvements in the efficiency of medical diagnosis have virtually excluded MUGA from the evaluation sequence unless other imaging methods are contraindicated or unsuccessful. In essence, the only available technique that can provide accurate spatial and temporal resolution without relying on geometric assumptions is cardiovascular MRI. Therefore, MRI is to be considered the new, true gold standard for measuring LV systolic function.

Left ventriculography can also be performed with digital subtraction angiography (DSA), which uses either an intravenous or a low-dose intraventricular contrast agent. Advantages over standard radiography include a reduced use of radiation and contrast media, an ability to visualize with very low concentrations of contrast medium, and an image format that can be directly analyzed by means of quantitative techniques (4). By enhancing the contrast-to-background signal, DSA allows angiography to be done with reduced doses of contrast medium. Nichols and coauthors performed a validation study that measured LV volume and segmental contraction while also comparing the hemodynamic effects of low- and high-dose contrast injections in 28 patients (5). The group that received the low-dose contrast injections underwent digital left ventriculography and received an intraventricular injection of 7 mL of contrast medium diluted in saline solution. This step was followed by conventional cineangiography of the left ventricle, using 45 mL of undiluted contrast medium. After injection of the diluted contrast medium, LV systolic and end-diastolic pressures did not change significantly, and patients had no discomfort. LV volumes calculated from digital ventriculograms correlated well with volumes calculated from conventional ventriculograms. Thus, DSA eliminates the hemodynamic effects that result from injecting conventional doses of contrast medium, thereby permitting the use of left ventriculography with markedly reduced doses of contrast medium.

To determine the validity of intravenous DSA–left ventriculography (IVDSA-LVG) in evaluating the LV ejection fraction, Kuribayashi and coauthors compared IVDSA-LVG using 30 mL of contrast medium with direct left ventriculography in 18 patients (6). There was a good correlation between the two methods (r = 0.877) in determining the LVEF, and 90% of the interpretations of regional wall motion were in agreement between the two methods. Intravenous DSA-LVG was useful and accurate in evaluating the LV and regional wall motion. The results of this study suggest that this method may be used in patients with impaired LV function to avoid hemodynamic derangement induced by conventional, direct left ventriculography using large doses of contrast medium.

The above-described ventriculography methods and techniques are experimental. They use contrast media, and the radiation doses are actually higher than those used in standard angiography. As these diagnostic imaging methods have evolved, improvements in standard angiography have kept pace. Cavitography allows clinicians to draw upon angiographic data; these are the data on which they base most of their decisions in the cardiac catheterization laboratory.
Anatomic Considerations and Fundamentals

In imaging any cardiac cavity, the following variables must be considered: anatomy, systolic function, regurgitant fraction, shunting, cavity size, cavity output, heart rate, the maximum flow rate of the diagnostic system chosen, and the catheter position and injection technique. For standard ventriculography, midcavity positioning of the catheter just below the inflow of the mitral valve is crucial. This position allows mitral inflow to carry the injected contrast material forward, opacifying the apex of the left ventricle. The preferred angiographic view is usually the 30° right anterior oblique (RAO) projection. To evaluate ventricular septal defects or obstructions of the LV outflow tract, a 30° to 60° left anterior oblique (LAO) projection with 20° cranial angulation is necessary (Table 21.1).

An underlying principle of cavitography is that the contrast volume of the chamber being imaged should reach at least 10% of the total contrast volume for the period of imaging in question. Because of the volume of contrast needed for aortography and ventriculography, a power injector is typically used. Power-injection parameters include the volume of contrast medium to be infused, maximum injection pressure, injection rate, and timing of the pressure increase used to minimize catheter movement. The settings for adequate cavity imaging are condition dependent. For example, a single beat stroke volume of 70 mL would be expected in a patient with no cardiac murmurs and with presumed normal LV function. Therefore, to achieve the 10% threshold over the target of three to five heartbeats, a volume infusion of 30 mL is more than sufficient. Assuming that the heart rate is 60 to 70 beats per minute (bpm), this volume may be infused over a period of three seconds. The maximum allowed pressure will be influenced by the necessary injection rate and the size of the catheter used. For example, power injection with a 4-Fr catheter system mandates the use of higher maximum allowed pressures and relatively low infusion rates (7 mL/sec), as well as longer infusion periods (4 seconds) to provide diagnostic-quality images.

Consider a patient suspected of having severe aortic valve insufficiency. Upon injecting the ascending thoracic aorta with contrast medium, one should be able to quantify the severity of aortic valve insufficiency and, if it is severe, properly opacify the LV and quantify its volume and function. This goal requires rapidly injecting a large volume of contrast material over a period of three heartbeats, which is the threshold for distinguishing moderate from severe aortic valve insufficiency. It may not be possible to complete an adequate study with small-diameter catheters. To meet the above-mentioned threshold, let us assume that the LV end-diastolic volume (LVEDV) is 300 mL, the stroke volume is 200 mL, and the LVEF is 66%. When the regurgitant volume is 140 mL, the contrast injection flow rate should exceed 20 mL/sec so that the aorta and left ventricle are opacified. Any catheter smaller than 6 Fr would not be able to achieve the flow rate necessary for opacifying both chambers at a normal heart rate. At a maximum pressure of 1000 psi (for which most systems are rated) in patients with a normal resting heart rate, a 7-Fr diagnostic system is necessary to inject more than 60 mL of contrast material over the required three-second period.

Planimetry is more objective than ventriculography for quantifying LV function. With planimetry, the projection image of the chamber in question is outlined and the area quantified. By means of a series of geometric assumptions, this area is used to derive the LV volume. The first and most important assumption is that a ventricle that is somewhat triangular in shape in the RAO view is an ellipsoid. In a 2D view, something that looks like a football is an ellipse. In 3D, such a structure is referred to as an ellipsoid. To be precise, a football is a prolate spheroid. This assumption is not uniformly valid and is clearly violated in patients with previous myocardial infarction (the population for whom the ejection fraction estimation is most important) and other patient populations in whom diastolic or systolic anatomy deviates from normal. This is the principal reason why echocardiography and MRI are preferred for measuring LV function.

The volume of an ellipsoid is calculated with the following formula:

\[ V = \frac{4}{3} \pi \times \frac{D_1}{2} \times \frac{D_2}{2} \times \frac{L}{2} \]

In the 2D representation, the ellipsoid is an ellipse. Therefore, one may measure the area of the ventricle and the length of its long axis. This allows one to calculate the short-axis diameter for the imaginary ellipse with the following formulas: RAO, \( D_1 = 4A_1/nL_1 \) and LAO, \( D_2 = 4A_2/nL_2 \).

After the axes are derived, these formulas can be used to calculate the ventricular volume. Because the ventricle is some distance from the detector, it will be magnified. Unless an object of a known size is present within the ventricle when the image is being captured, some means of correcting for magnification is required. The correction factor can be calculated from this formula: \( CF = (H - P)/H \), where \( H \) is the distance from the tube to the detector and \( P \) is the distance from the object to the detector. Alternatively, an object of a known size may be placed in the field of view and used for calibration. If the object is placed on or behind the patient, use of the correction factor is required (Fig. 21.1).

The single-plane method of measuring the ventricular volume assumes that the long-axis and the calculated short-axis diameters are the same in both the RAO and LAO projections. This assumption is acceptable. However, in patient populations

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<td>Evaluation</td>
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**Abbreviations:** LVEF, left ventricular ejection fraction; LV, left ventricle; RAO, right anterior oblique; LAO, left anterior oblique; MR, mitral regurgitation; LVOT, left ventricular outflow tract; VSD, ventricular septal defect; ASD, atrial septal defect; RV, right ventricle; AP, anteroposterior.
with abnormal LV anatomy, in systole or diastole, this assumption is unreliable and may lead to errors in the calculation of the LV volume or function. The formula used in this method is

\[ V = \frac{0.81}{C^2} \times \frac{D^2}{C^2} \times L \times CF + 1.9 \text{ mL} \]

Automated edge-detection algorithms may be used to outline the borders of the LV cavity, thereby decreasing intra- and interobserver variability and the analysis time (7). In addition, new modalities using 180° rotational LV injections and a series of projection images may be used for 3D reconstructions and potentially for 4D reconstructions (8).

**Indications**

Left ventriculography is indicated for the assessment of global LV function and regional wall-motion abnormalities (Fig. 21.2). It can also be used to assess the severity of mitral regurgitation and to identify and assess muscular and membranous ventricular septal defects. Other indications include proper positioning of the CardioKinetix Ventricular Partitioning Device (CardioKinetix, Redwood, California, U.S.), which isolates the malfunctioning portion of the left ventricle in patients with symptoms of heart failure due to ischemic heart disease.

**Equipment**

Ventriculography is best performed with an angled pigtail catheter, which avoids some of the pitfalls of end-hole catheters such as inadequate opacification, ectopy, myocardial staining, and catheter movement (recoil). The straight pigtail catheter frequently becomes oriented beneath the posterior leaflet of the mitral valve, resulting in poor opacification of the LV or apically produced premature ventricular complexes (PVCs).

The angled catheter is more appropriately located within the LV; this position reduces the incidence of PVCs. Pigtail catheters have an end loop that keeps the end hole (required for wire advancement) away from the endocardium, and the other holes along the distal shaft provide offset jets that help stabilize the catheter and reduce recoil (9).

Alternative catheters include those with multiple side holes (e.g., the NIH and Eppendorf catheters). As mentioned above, in obtaining measurements from angiographic data, a structure of known size may be placed within the ventricle. This is most effectively done by using a pigtail catheter with radiopaque markers (1 cm from front edge to front edge). Additionally, the Langston catheter (Vascular Solutions, Inc., Minneapolis, Minnesota, U.S.) is a dual-lumen 6-Fr to 8-Fr device with end or side holes 8 cm apart. It is available in angled pigtail, multipurpose, and straight configurations. This catheter provides the ability to obtain precise simultaneous measurements of aortic and LV pressures. However, the lumen size limits the maximum contrast infusion rate, and the pigtail catheter often creates a spurious gradient. The multipurpose version of this dual-lumen catheter is much easier to use for hemodynamic measurements.

Smaller catheter diameters have been used in recent years to reduce the probability of groin-access complications. However, very small catheter diameters may limit maximum injection rates, impairing the evaluation of the severity of regurgitant lesions. Small catheter diameters (4 Fr and 5 Fr) are usually sufficient for performing coronary angiography, left ventriculography, and aortography in patients whose LV size and function and aortic diameter are normal. However, for the evaluation of dilated chambers or regurgitant lesions, larger catheter diameters (6 Fr or 7 Fr) may be necessary.

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**Figure 21.1** Ventriculogram obtained in right anterior oblique 30° view. LV measurements obtained with available software from commercial workstations. Abbreviation: LV, left ventricular.

**Figure 21.2** Ventriculogram obtained in right anterior oblique 30° view, showing a dilated LV chamber in diastole. Abbreviation: LV, left ventricular.
In most instances, a standard 0.035-in. J wire is sufficient for positioning the catheter and crossing the aortic valve. In the setting of aortic valve stenosis, a smaller, soft-tipped, 0.032-in. straight wire is frequently used. If multiple exchanges are necessary after the valve is crossed, a stiff exchange-length wire is highly useful. Examples include the J-tipped Amplatz (Cook Medical, Bloomington, Indiana, U.S.) or 3-cm tipped Amplatz devices.

**Clinical Aspects**

**Crossing the Aortic Valve**

Once an indication for performing ventriculography has been established, the first step is to cross the aortic valve. As in several other invasive procedures, crossing the aortic valve in patients without significant aortic stenosis is regarded as straightforward. The presence of significant aortic stenosis necessitates a modified technique (see later in text). Although bioprosthetic valves may be crossed with catheters, it is not advisable for any catheter or wire to be placed across a tilting-disc valve prosthesis, because the equipment can be entrapped. In addition, crossing a mechanical prosthetic valve may cause sudden severe aortic regurgitation, leading to hemodynamic complications.

The classic approach for crossing the aortic valve in patients without stenosis requires the use of a 0.035-in. wire, which is placed in the pigtail catheter and positioned slightly back from the tip. The catheter is placed above the valve, and is advanced until it prolapses above the valve and forms a loop resembling a reverse J shape or the number 6. The loop is then pulled back and rotated slightly in a clockwise direction. During systolic opening of the aortic valve, the catheter will fall into the LV outflow tract, it is advanced into the LV cavity. On occasion, the body of the catheter will prolapse across the valve, but the tip will stay in the aortic root. In this event, advancing the 0.035-in. wire will usually cause the catheter to prolapse into the ventricle. This can result in severe ventricular ectopy and may even damage the valve leaflets. Having the patient take a breath while the pigtail catheter is advanced into the ventricle during systole will sometimes facilitate entry.

Aortic valve stenosis poses a more complex situation. This condition carries a risk of embolization from the valve or from thrombus that may form on the wire or catheters if multiple attempts are required, thereby prolonging the procedure. In these cases, anticoagulation with heparin (3000–5000 units bolus) is recommended. Because of the heightened risk, crossing the valve should be done only if noninvasive assessment is inconclusive or interventions (e.g., valvuloplasty or percutaneous prosthetic valve deployment) are planned.

In patients with aortic stenosis, a preliminary aortic root angiogram will allow visualization of the valve opening. Fluoroscopic and cineangiographic guidance of the wire through the calcified opening can also be done, in both the RAO and LAO projections. Once the opening has been identified, a straight-tipped 0.032-in. wire is inserted through an Amplatz left 1 catheter or a similarly configured device such as an Amplatz left 2, an Amplatz right 1 modified, a multipurpose 1, or a Feldman catheter. Once the wire crosses the valve, the diagnostic catheter is advanced, and pressures are recorded. If an angiography catheter or other catheter is required, it is exchanged over an exchange-length wire (usually a soft-tipped, shaped wire, because it will be less likely to induce ventricular ectopy). With a 6-Fr dual-lumen pigtail catheter, one can simultaneously measure pressures in the left ventricle and the ascending aorta. Although the proximal connector tubing allows angiography, we have found that it tends to rupture at high pressures.

An alternative technique for entering the left ventricle of patients with acquired aortic valve stenosis uses the right Judkins and Amplatz right-modified catheter and a soft-tipped 0.032-in. straight wire. The alternative technique may be used for normal patients or aortic valve stenosis. In normal patients, a standard J-wire may be used. In patients with acquired aortic valve stenosis, the soft-tipped 0.032-in. straight wire is preferred. The catheter is advanced over the wire to the right coronary sinus. The straight wire is then placed outside the catheter and oriented so that it can be advanced to the non-coronary cusp. The catheter is rotated clockwise until aortic ejection creates visible wire oscillation. The catheter is then withdrawn by means of the exchange technique, so that the wire is oriented within the aortic valve orifice. The wire may then be advanced into the left ventricle. After the catheter is inserted into the left ventricle, the 0.035-in. J wire may be used to exchange for the catheter of choice to be used for additional measurements or angiography.

**Ventriculography Technique**

Hemodynamic measurements should be performed before ventriculography to obtain baseline information.

With single-plane equipment, ventriculography will provide only a 2D projection of the ventricle, and individual images will not include all the LV segments. The standard views for ventriculography are the RAO (30°), which shows the anterolateral, anterior, apical, and inferior ventricular walls, and the LAO 60° or 20° cranial view, which allows better imaging of the lateral, posterior, and septal ventricular walls (Fig. 21.3). The...
LAO views are particularly useful in patients with lateral ischemia (especially circumflex ischemia), suspected ventricular septal defect, and mitral regurgitation (Fig. 21.4). Some operators prefer to use biplane ventriculography.

The LV cavity is usually visualized with 30 to 50 mL of contrast material. Some clinical scenarios call for a modification of this volume. For example, in patients with known or suspected mitral regurgitation, 50 to 60 mL of contrast material is needed to completely opacify the left atrium. In elderly patients with hypertensive disease and small LV cavity, smaller volumes (30–36 mL) are adequate. If the patient has severe valvular disease, LV dysfunction, or an elevated end-diastolic pressure, use of a nonionic contrast agent is recommended. In patients with a severely elevated LV end-diastolic pressure (LVEDP), ventriculography should be performed only after pharmacologic interventions (e.g., nitroglycerin or furosemide administration) have been carried out to prevent subsequent pulmonary edema (Fig. 21.5).

Once advanced into the left ventricle, the pigtail catheter should be positioned in the midventricular cavity over the region of mitral inflow. Apical positioning of the catheter might lead to excessive ectopy, which could interfere with the interpretation of wall-motion abnormalities. A position that is too basal may interfere with the mitral apparatus, leading to an overestimation of mitral regurgitation. A catheter that is difficult to manipulate, ectopically positioned, or visibly entangled may indicate that the mitral apparatus is involved. In this setting, proper catheter positioning usually requires catheter withdrawal (preferably over a wire) and replacement into the left ventricle.

Repositioning the catheter usually requires countering and pulling it (ideally over the wire) and then advancing it once the tip is free (Fig. 21.6).

If the patient is in unstable condition and DSA is available, manual injection may be attempted while the patient holds his or her breath. This method should be used only for a quick estimate, because important abnormalities such as a ventricular septal defect may be missed due to incomplete opacification.

**Settings**

Optimal ventriculography is performed with a power injector so as to fill the LV cavity. Adjustable settings on the power injector include pressure and flow rates, volume, and the rate of pressure increases. In each case, the settings will vary slightly,
low-volume ventriculography has been shown to be similar to standard, larger-volume ventriculography for the estimation of LV systolic function. In 102 patients, Hodges and coworkers compared low-volume ventriculography to standard-volume ventriculography using standard (15 mL/sec for 3 seconds) and low-volume (15 mL/sec for 1 second) contrast agents (12). Each patient served as his or her own control. Of the 204 ventriculograms, 27% were not interpretable because of ectopy. Ectopy involving ≥3 beats was more common with standard-volume angiograms (41% vs. 14%; P < 0.001). With both methods of contrast-agent injection, the LVEDP increased from baseline levels (P < 0.005). In patients for whom both angiograms could be interpreted (n = 58), no differences were noted between LVEFs measured with planimetry (low-volume method = 61 ± 20% vs. standard-volume method = 62 ± 20%; r = 0.87; P < 0.001). Therefore, low-volume ventriculography reduces the contrast load and ectopy while providing estimates of the LVEF similar to those obtained with standard volumes.

Quantification of Ventricular Function

Depending on the angiographic projection, specific ventricular wall-motion abnormalities may be identified. These include hypokinesia (decreased but not absent motion of a ventricular segment); akinesia (a complete absence of wall motion); tardi-kinesia (delayed contraction of a ventricular segment); and dyskinesia (paradoxical expansion or wall motion, usually due to tethering from the adjacent segments). The LVEF calculated with ventriculography will usually be slightly higher than that calculated with echocardiography.

The American College of Cardiology (ACC), American Heart Association (AHA), and other cardiovascular organizations recognize the importance of having clinical data standards that define and standardize platforms and conditions. These elements are described in the ACC/AHA’s 2008 publication titled “Key Elements and Definitions for Cardiac Imaging” (10). The authors acknowledge that each imaging modality uses a unique range of values for quantitatively determining the LVEF and that, even within a single modality, different quantitative methods may yield disparate results. The consensus is that systolic function should be classified into four categories: normal, mildly reduced, moderately reduced, and severely reduced. The quantitative value may be reported as a
specific value (e.g., 64%) or as a 5% range (e.g., 30-35%). The midpoint of the range would be used for data collection and storage. Regional function of myocardial segments assessed by means of contrast LV angiography should be described as normal, hypokinetic, akinetic, dyskinetic, or not visualized. The authors also suggest the use of a 10-segment division in the RAO or LAO views. In the RAO view, the segments should be described as anterobasal, anterolateral, apical, diaphragmatic, and posterobasal. In the LAO view, they should be described as basal septal, apical septal, posterolateral, inferolateral, and superior lateral (Fig. 21.3).

Quantification of Mitral Regurgitation
Valvular regurgitation affects the cardiac chambers upstream or downstream from the leaking valve. The ability of these chambers to accommodate the excess workload is highly variable and at least partly related to the time span over which the regurgitation has developed. For example, if the left atrium has had insufficient time to dilate after rupture of a chorda tendina, that chamber’s compliance produces striking increases in the left atrial pressure in response to the volume introduced from the left ventricle. Conversely, in chronic, slowly regressive regurgitation, the compliance characteristics of the left atrium are altered so that the volume of blood ejected into the left atrium may be accommodated with little change in pressure. As a result, the pressure measured within the accepting chamber may be a poor measure of the severity of regurgitation. Moreover, regurgitant severity may not be the sole determinant of the hemodynamic effect of valvular failure.

Angiographic quantization of valvular regurgitation severity depends on opacification of the proximal chamber during contrast injection. Therefore, the visual measures that are commonly used depend on the severity of regurgitation, as well as the volume of the accepting chamber and the volume of flow through the affected chamber. High-volume flow may limit opacification and result in rapid clearance, and low-volume flow may do the opposite. A severely dilated chamber may be relatively difficult to opacify sufficiently to reach a threshold for assigning maximal severity. Thus, angiographic methods are accurately characterized as “semiquantitative.” Valvular regurgitation may be readily visualized angiographically. This requires sufficient contrast administration for excellent opacification of the distal chamber and relies on the degree of opacification of the proximal chamber and the time required for the contrast agent to clear. Administration of 40 to 60 mL of contrast agent over three seconds is generally necessary.

Both the RAO and the LAO cranial projections can be used to identify significant mitral regurgitation. Grading the amount of regurgitation is based on the degree of opacification of the atrium and ventricle, as well as the atrial size, and the number of cycles required for maximal opacification (Table 21.2). Both elevation of the left atrial pressure in acute regurgitation and dilation of the left atrium in chronic regurgitation can interfere with the use of this grading system.

Regurgitant Fraction
Perhaps the most valuable indicator of regurgitation severity is the regurgitant fraction (RF). The regurgitant volume is the amount of ejected blood that is returned to the chamber in question during the period of preparation for the next beat. The RF is the regurgitant volume divided by the stroke volume (SV). The effect of regurgitation may be estimated by combining the RF and LVEF with the LVEDV, which gives an idea of the effective forward flow (EFF). The following formula can be used to calculate the EFF:

\[
\text{EFF} = (1 - \text{RF}) \times \text{EF} \times \text{EDV}
\]

The same formula may be used to quantify the regurgitant volume if the SV and net cardiac output are known. As a general rule, when the EFF begins to decrease because the chamber has enlarged and cannot accommodate the excess load, the valve needs to be repaired.

The difference between the angiographic SV and the forward SV is the regurgitant volume. The angiographic SV is computed from the left ventriculogram, and the forward SV is derived from the cardiac output, as determined by the Fick or thermodilution method and the heart rate. The RF is the portion of the angiographic SV that does not contribute to the net cardiac output. It is computed as the regurgitant SV divided by the angiographic SV (Table 21.3).

Limitations
Ventriculography has been compared with other methods and technologies for assessing LV function and morphology. In 65 consecutive patients, Takenaka and associates compared 2D echocardiography, thermodilution techniques, and biplane cineventriculography with respect to LVEDV, LV end-systolic volume (LVESV), SV, and LVEF (calculated with the modified Simpson rule). 2D echocardiography was performed within three days of cardiac catheterization (13). The results were compared with those obtained by means of the thermodilution technique and biplane cineventriculography. The heart rate and SV were significantly different among the three techniques, and ventriculography yielded the highest values. These findings suggest that patients may have been in a hyperadrenergic state caused by anxiety during invasive cineventriculography and thermodilution examinations. The inter- and intraobserver variabilities for echocardiography differed little from the variability for ventriculography. Although there were good correlations between the echocardiographic and cineventriculographic findings for the LVEDV ($r = 0.67$), LVESV ($r = 0.80$),
and LVEF ($r = 0.78$), as assessed by two independent observers, there was a lack of agreement for the LVEDV, LVESV, and LVEF. The echocardiographic LVEDV values were significantly lower than the cineventriculographic values.

3D echocardiography, being exempt from the need for geometric assumptions, correlates highly with ventriculography for estimating ventricular volumes. The former technique has approximately half the variability of 2D echocardiography in making these measurements (14).

Radionuclide ventriculography is a valuable tool in the risk stratification of postinfarct patients (15), but in this patient population, LVEF correlates poorly with radiographic ventriculography ($r = 0.42$). Therefore, in this setting an alternative method is warranted. Nonfluoroscopic electromechanical mapping of the left ventricle is feasible and safe. The LVESVs obtained with this method strongly correlate with those measured by means of ventriculography, but the LVEF does not (16).

The utility of ventriculography in providing an estimation of the LVEF that is reproducible and correlate with survival has been well demonstrated. Many LVEF calculations used for prognosis in the literature are, in fact, angiographic. However, it should be clear that LVEF values obtained with alternative methods cannot be “interchanged” with values obtained by means of ventriculography.

**Special Issues (Complications and Other Cardiac Cavities)**

The following relative contraindications are shared by cardiac catheterization and angiography: severe uncontrolled hypertension, ventricular arrhythmias, acute stroke, severe anemia, active gastrointestinal bleeding, allergy to radiographic contrast agents, acute renal failure, decompensated congestive heart failure (the patient cannot lie flat), unexplained febrile illness and/or untreated active infection, electrolyte abnormalities (e.g., hypokalemia), and severe coagulopathy. Some of these factors can be corrected before the procedure, thereby lowering the risk.

In patients with cardiogenic shock undergoing percutaneous revascularization, contrast ventriculography is deferred until after coronary angiography has been performed (17) or is avoided to prevent further hemodynamic compromise resulting from arrhythmias or increases in ventricular pressure and renal failure. Contrast medium–induced hypotension and bradycardia were once serious concerns in patients with severe aortic stenosis and left main or severe three-vessel coronary artery disease, but these complications have been decreased by the use of low-osmolar or nonionic media (18). In cases of severe coronary artery disease (including left main) disease, it is uncertain whether the risks of a left ventriculogram are outweighed by its benefits (19). However, as discussed above, ventriculography can be safely performed with less than 40 mL of a low-osmolar contrast agent. Proper access technique and careful manipulation of the catheter are required because hemodynamic instability can be caused by a catheter-induced arrhythmia or vasovagal response.

Left ventriculography should be performed only in patients in whom the benefits from the information obtained are greater than the risks related to the procedure. Otherwise, noninvasive assessment of ventricular function and mitral regurgitation by means of echocardiography and nuclear or MRI techniques is more appropriate (20).

**Contraindications**

Contraindications for left ventriculography include critical left main disease, a tilting-disc aortic prosthesis (the catheter can cause acute aortic regurgitation, become entrapped, or damage the tilting mechanism), decompensated heart and/or renal failure, and a recently diagnosed (freshly formed) intracardiac thrombus. Because thrombi more than six months old may have a lower risk of dislodgement, some operators may proceed with ventriculography in their presence. However, because of the uncertainty involved in appropriately estimating the age of an intracavitary thrombus, we suggest deferring ventriculography and proceeding with noninvasive evaluation.

**Complications**

Among the complications that have been encountered during ventriculography are ventricular arrhythmias, embolization of air or thrombus, contrast agent–related complications, worsening of hemodynamic values in patients with decompensated heart failure, and myocardial staining or “tattooing.”

Air or thrombus embolization has been observed during ventriculography and left-sided heart catheterization. Transcranial Doppler (TCD) imaging has shown that these complications commonly occur when patients are evaluated with ventriculography. To assess the prevalence, time of occurrence, and potential significance of microembolic signals (MESs) detected with TCD during left-heart catheterization, Leclercq and coworkers monitored the right and left middle cerebral artery in 51 consecutive patients (36 men, 15 women) (21). MESs were detected in all except two patients (mean number of signals, 17.1 ± 12.8 per patient) mainly during left ventriculography. The MESs were asymptomatic and probably of gaseous origin because they occurred predominantly during contrast media injection and were not related to the patients’ cardiovascular history or to atheroma risk factors. No neurologic events occurred within 24 hours after ventriculography in the 49 patients who had MESs.

An unusual but potentially dangerous complication of left-sided heart catheterization is massive air embolization (22,23). Therefore, the system should be meticulously checked for air before performing the injection. If air bubbles embolize to the brain or coronary arteries, they can cause transient or permanent neurologic complications and hemodynamic collapse, respectively. The operator should be alerted if a sensory deficit is noted after a contrast medium has been injected for left ventriculography. Theoretically, the preferred treatment for cerebral air embolization is hyperbaric oxygen. However, in clinical practice this is rarely performed.

**Left Atrial Angiography**

The left atrial anatomy is complex, and the chamber borders are poorly defined, making assessment of left atrial function and volume somewhat difficult. However, opacification of the left atrium may be useful for the anatomic evaluation of an atrial septal defect (ASD) or a patent foramen ovale (PFO). Similarly, it may be important to evaluate the left atrial anatomy before and after radiofrequency ablation procedures. In most instances, the anatomy may be assessed quite well with noninvasive means. In fact, due to the complex and highly variable anatomy of the pulmonary veins, MRI and CT are superior to angiographic projection imaging. However, angiographic guidance is necessary for placement of ASD, PFO, or left atrial occluder devices. Left atrial angiography is best performed with the NIH
Right Ventriculography

The right ventricle’s shape is poorly conducive to evaluation by means of projection imaging. It is both triangular in the anteroposterior projection and discoid in the lateral projection. Therefore, use of angiographic imaging for volume estimates is fraught with error, and the geometric assumptions used in imaging the right ventricle are of little value. However, right ventricular (RV) angiography may be useful for evaluating tricuspid regurgitation, global RV function, suspected RV cardiomyopathy, or arrhythmogenic RV dysplasia, and for planning a pulmonary valvuloplasty. The severity of tricuspid regurgitation is evaluated qualitatively, and the grading system is similar to that used for mitral regurgitation: 1+, trivial; 2+, mild; 3+, moderate; and 4+, severe. Given that access to the right ventricle requires crossing of the tricuspid valve, evaluation of tricuspid insufficiency is as potentially erroneous as imaging of the right ventricle.

Ideally, right ventriculography is best performed with a biplane system. When performed with a single-plane system, it is usually done in the AP projection. With a biplane system, the 60° LAO projection is added. The contrast volume ranges from 20 to 40 mL, injected over two seconds. In general, lower maximum pressures may be used when RV pressures are low.

Either an angled pigtail catheter, a variant of the angled pigtail catheter known as the Grollman catheter, or the NIH catheter may be used for this procedure. The authors prefer the NIH catheter because it is easily maneuverable in patients who have a difficult anatomy, and it can be concurrently used for subselective pulmonary artery angiography. The catheter is placed in the midcavity position, and injection parameters similar to those of left ventriculography are used. When RV pressures are elevated, pulmonary artery catheterization should be performed before right ventriculography. In the setting of severe pulmonary hypertension, main pulmonary angiography or right ventriculography may result in hemodynamic compromise, so alternative methods for assessing RV anatomy and function should be chosen.

Conclusions: Ventriculography

Catheterization of the left ventricle to obtain hemodynamic measurements and to visualize the left ventricle with contrast ventriculography is an important component of a complete angiographic study because it provides essential anatomic and functional information. Although noninvasive testing techniques continue to improve and become more accurate, cardiac catheterization remains the standard for evaluating hemodynamic parameters. In some instances, catheterization is preferred (e.g., when patients present acutely with a myocardial infarction). By assessing myocardial and valvular function with ventriculography, the clinician may quickly gain information vital to making sound decisions about a patient’s acute care. In obese patients who have suboptimal echocardiographic windows, ventriculography may provide information not obtainable from the echocardiogram.

As new technologies and interventions become available, such as percutaneous aortic valve replacement, it is important that cardiologists become skilled at crossing the aortic valve and appropriately assessing LV function and morphology. Meanwhile, cavitography remains an important tool for diagnostic evaluation and for planning interventional procedures. Its principles are straightforward, but close attention to detail is necessary to obtain diagnostic-quality images.

AORTOGRAPHY

Introduction

Aortography is the radiographic technique used for opacifying the lumen of the aorta, the superior aspect of the aortic valve leaflets, and all of the vessels that arise from the aorta (24). Noninvasive radiographic evaluation of the aorta and its branches has evolved rapidly because of advancements in imaging techniques such as computed tomography angiography (CTA) and magnetic resonance angiography (MRA). Nevertheless, catheter-based angiographic evaluation remains an integral part of the diagnostic process and the main guide to choosing an intervention (either endovascular or surgical). An ascending aortogram allows one to determine the competency of the aortic valve, the anatomy and diameter of the ascending thoracic aorta, and the presence of patent aortocoronary bypass grafts. When the catheter is positioned proximal to the innominate artery, the examiner may evaluate the anatomy of the aortic arch and its major arterial branches, detect the presence of a persistent ductus arteriosus or coarctation, and gain information about the descending thoracic aorta. When the catheter is positioned more distally, one may evaluate aneurysms, dissections, and abnormalities of the abdominal aorta and its arterial branches (Fig. 21.7).

Figure 21.7 Aortogram in 60° left anterior oblique projection from a patient who had previously undergone repair of an ascending aortic aneurysm with a Dacron graft (white arrows indicate the beginning and end of the graft). Aortic dilatation distal to the graft compromises the arch and descending aorta (black arrows).
Anatomic Considerations and Fundamentals

During aortography, variants in the anatomy may be identified. To understand and appropriately identify these variants, some basic concepts need to be reviewed. In the earliest stages of embryogenesis, the vessels are plexiform. As the fetus grows, the vessels become recognizable as conduits. The adult aorta and the aortic arch system result from the regression and fusion of six pairs of aortic arches (Table 21.4). Normal regression of the right dorsal aortic root results in the normal left aortic arch. Aortic arch branch variants can be identified in 30% to 35% of individuals. The most frequent variant (20%) is a common origin of the innominate and left common carotid arteries (bovine arch). Other variants include a left vertebral artery arising from the arch (5%), an aberrant right subclavian artery or lusoria (1%), and, less frequently, a right-sided aortic arch, double aortic arch, or cervical aortic arch (Fig. 21.8).

The abdominal aorta is formed from the right and left dorsal aortas. The numerous splanchnic branches that supply the primitive digestive tract are reduced to become the celiac, superior, and inferior mesenteric arteries. Anomalies of the abdominal aorta itself are rare, but they are common in the primary branches (Fig. 21.9) (25). Multiple renal arteries can be present in a third of the population. Approximately 2% to 7% of patients have bilateral accessory renal arteries. Persistence of the ventral connection results in the rare condition known as celiosomesenteric trunk. In addition, the hepatic, left hypogastric, or splenic arteries may have separate origins from the aorta. The presence of multiple branches accounts for the parietal collateral systems that can be identified in occlusive diseases of the aorta. (Intercostal, subcostal, and lumbar arteries can provide collaterals to the iliolumbar and superior gluteal branches of the internal iliac artery and to the circumflex branches of the external iliac artery.) The visceral pathways for collaterals arise from the superior and inferior mesenteric arteries.

Even in healthy humans, the aorta lengthens with age, primarily because the ascending aorta elongates over time (26). This elongation is also a function of blood pressure. At the same time, an increase in collagen augments aortic wall stiffness. Because these changes are balanced by changes in body morphology, the changes in the physical characteristics of the aorta cannot be detected by measuring the pulse wave velocity. Aged, hypertensive patients will frequently have a tortuous aorta that challenges the interventionalist with regard to catheter passage, catheter placement, and proper angiographic imaging. Because of the difficulties that the abdominal aorta may present when it is severely diseased (e.g., with an

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Origin</th>
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<tbody>
<tr>
<td>Proximal ascending aorta</td>
<td>Truncus arteriosus</td>
</tr>
<tr>
<td>Distal ascending aorta, innominate artery, and arch until left common carotid artery</td>
<td>Aortic sac</td>
</tr>
<tr>
<td>Right subclavian artery</td>
<td>Fourth aortic arch</td>
</tr>
<tr>
<td>Common carotid arteries</td>
<td>Third aortic arch</td>
</tr>
<tr>
<td>Aortic arch between the left common carotid artery and the left subclavian artery</td>
<td>Fourth aortic arch</td>
</tr>
<tr>
<td>Left subclavian artery</td>
<td>Left intersegmental artery</td>
</tr>
<tr>
<td>Ductus arteriosus</td>
<td>Sixth aortic arch</td>
</tr>
<tr>
<td>Descending aorta</td>
<td>Left dorsal aorta</td>
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</tbody>
</table>

Figure 21.8 Digital subtraction angiogram from a woman with a history of dysphagia who presented with right-arm claudication. The occluded, aberrant right subclavian artery originates distal to the left subclavian artery. Collateral flow is reconstituting the aberrant vessel (arrow).

Figure 21.9 Abdominal aortogram from a patient with diffuse atherosclerosis, dyslipidemia, and hypertension who presented with claudication. This image, obtained in the anteroposterior view, shows bilateral renal artery stenosis (white arrows) and severe distal aortic stenosis (black arrow).
aneurysm, a dissection, a luminal thrombus, or tortuosity), a radial or brachial approach may be needed during aortography to obtain adequate images yet avoid complications.

Optimal aortography requires the use of a power injector to opacify the aorta adequately. In each case, a slight variation in settings will be required, based on the size of the aortic root, presence of aneurysms, degree of aortic valve insufficiency, diameter of the catheter lumen, and patient size. The catheters used for aortography are similar in shape to those used for ventriculography (pigtail catheters), but, because diameter measurements are required, a marker pigtail catheter is preferred. Alternatively, other angiographic catheters such as the Omniflush or the tennis racket can be used.

**Indications**

Although aortography has been supplanted by transesophageal echocardiography (TEE), CTA, and MRA for many disorders of the aorta, angiographic imaging may be useful to exclude aortic dissection (Fig. 21.10) in patients referred for urgent coronary angiography. This technique is also useful for measuring the aortic diameter—preferably with a marker pigtail—when other studies have rendered conflicting information, for measuring the severity of aortic insufficiency, for delineating the aortic and coronary anatomy before surgical repair of an aneurysm, and for verifying the presence of an aortoenteric fistula (27,28).

Perhaps the most important advance in aortography in recent years has been the use of digital subtraction, which allows anatomic details to be accurately delineated with relatively small quantities of contrast media. Digital subtraction angiography is superior to standard imaging for evaluating congenital and acquired lesions of the arch and great vessel origins (29).

**Figure 21.10** Aortogram in left anterior oblique demonstrating an ascending aortic dissection. The dissection extends from the sinuses of Valsalva to the origin of the innominate artery (arrows).

Contrast aortography has gained a central role in guiding aortic endovascular aneurysm repair (EVAR) and other percutaneous interventional procedures at the level of the aorta (Fig. 21.11) and the supra-aortic vessels.

**Figure 21.11** Aortogram from a critically ill patient with multiple comorbidities who presented with a large pseudoaneurysm several months after undergoing surgical repair of an ascending aortic aneurysm. (A) Evidence of a perforation at the level of the distal suture in the Dacron graft (arrow). (B) Successful closure of the graft perforation with an Amplatzer™ Cribriform Occluder (diameter, 18 mm) AGA Medical Corporation, Plymouth, Minnesota, U.S. (off-label indication) (arrow).
Equipment
For contrast aortography, angiographic equipment that provides a spatial resolution of at least 3 to 4 lines/mm is required. Ideally, large image intensifiers up to 16 in. (40.6 cm) in diameter should be used to provide a field of view large enough to show the entire arch and its branches or the entire abdominal aorta at the same time. Current technologies include postprocessing and image-reformatting modalities, which allow diameter analysis, 3D rendering, and rotational 3D rendering. Flat-panel technology has significantly increased image resolution.

For arterial access, 4-Fr to 7-Fr systems can be used. Dedicated radial sheaths or micropuncture devices (usually 4–6 Fr) are used for radial or brachial access. The length of the guidewire is determined by its intended use and varies from 145 to 175 cm. However, if multiple catheter exchanges are required, or if maintaining position is important (i.e., in the presence of aortic dissections, complex aneurysms, severe tortuosity, or a large atherothrombotic burden), a long (260–350 cm) exchange wire is used. While the guidewire’s diameter may range from 0.014 to 0.038 in., most of the time a 0.035-in. guidewire is used.

Angiographic catheters are usually pigtail, marker pigtail, Omniflush, or tennis racket devices or catheters with multiple side holes. A power injector is required for optimal opacification. Low-osmolar or iso-osmolar contrast agents are preferred because they cause less intravascular volume augmentation, fewer side effects, and possibly less contrast-induced nephropathy.

Clinical Aspects
In general, careful planning for the procedure is required. The access site needs to be determined first. Choosing the appropriate site of access for peripheral arteriography is a most important procedural decision, which is analogous to planning a surgical incision (30). The site of access is determined on the basis of anatomic knowledge acquired from previous noninvasive studies (if available), the patient’s clinical history (including ascending or abdominal aortic pathology), and the physical examination (including the presence of pulses). In our practice, the most common sites of access are the common femoral (70%) (Fig. 21.12) and radial (30%) (Fig. 21.13) arteries. With the aid of fluoroscopic guidance, access via the common femoral artery is usually obtained with a micropuncture system, which is later exchanged for a catheter with a larger French size.

In most of our angiographic studies, a 5-Fr system is used. Also, we most commonly use exchange-length wires of 0.035 in., including the Wholey Hi-Torque model (Mallinckrodt Inc., St. Louis, Missouri, U.S.), the Bentsen model (Cook, Inc., Bloomington, Indiana, U.S.), and the hydrophilic Glidewire (Terumo, Somerset, New Jersey, U.S.). If diameter measurements are important, a marker pigtail catheter is used...

When we are dealing with a complex anatomy (involving an aortic dissection, previous aneurysm repair with a Dacron graft, or severe tortuosity) and are uncertain about reaching the aortic root via the femoral approach, we usually obtain access with a micropuncture system. We advance a 0.035-in. Wholey wire until it reaches the ascending aorta. After establishing that the wire is in the true lumen (by verifying that the wire moves freely, responds to flow from the aortic valve, and loops easily at the sinuses), we exchange the micropuncture system for a 5-Fr system (including a long sheath if necessary) and then advance the angiographic catheters. Severe aortic tortuosity can cause difficulties in advancing and manipulating the catheter. In such cases, a long access sheath may help when one is
working from a femoral approach (Fig. 21.14). However, one should carefully consider using a radial or brachial approach. With the radial approach (Fig. 21.15), we prefer to use a dedicated radial sheath (Terumo) and to perform exchanges over an hydrophilic wire (e.g., Glidewire). At all times, careful manipulation of wires and catheters is essential to prevent traumatic disruption of intraluminal thrombus and/or wall atheromas.

**Ascending Aortography**

When the ascending aorta is visualized in the 30° LAO projection with 30° cranial angulation, dissections of the ascending aorta, anomalous coronary origins, and some saphenous bypass grafts may best be seen (Fig. 21.16). In contrast, the aortic arch and branch origins are best displayed in the 45° LAO projection with no cranial angulation. The catheter (preferably a regular or marker pigtail) is placed in the ascending thoracic aorta at the level of the sinotubular ridge (2–3 cm above the aortic valve). This allows the catheter to stiffen and lengthen during power injection without encountering the aortic valve. Unintentional contact with the aortic valve may either produce iatrogenic aortic valve insufficiency or result in poor opacification of two of the three sinuses of Valsalva. If the catheter is positioned just proximal to the right innominate branch, the aortic arch and the origin of the great vessels can be seen. The 30° RAO projection is best reserved for visualizing saphenous vein grafts, but it may also be used to demonstrate aortic insufficiency.

**Technique**

A 4-Fr to 7-Fr pigtail catheter is generally used to perform aortography. The size is critically dependent on the specific situation in question. To assess the aortic anatomy, the injection velocity from a 4-Fr catheter is sufficient with the assistance of DSA. For aortic insufficiency, a catheter with a larger diameter (7 Fr) will allow rapid contrast injection. However, any catheter without end holes may be used. With end-hole catheters, there may be a risk of aortic dissection or aortic valve damage during power injection (Figs. 21.17 and 21.18).

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**Figure 21.14** Aortogram performed via a common femoral approach, showing an ascending aortic aneurysm that extends into the arch.

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**Figure 21.15** (A) Aortograms in anteroposterior projection from a 65-year-old man with a history of hypertension. The descending aorta was completely interrupted below the level of the left subclavian artery. A small collateral vessel is seen (arrow). (B) Aortogram obtained via the left radial approach, showing aortic coarctation, with collaterals reconstituting the descending aorta.
During injection, the high-viscosity contrast agent encounters resistance along the length of the catheter lumen. This resistance produces a force within the catheter, making the device as straight as possible within the constraints placed on it by the anatomy of the aorta. To reduce this “kick” during injection, the rate of pressure rise during power injection is modulated. A period of pressure rise of 0.5 to 1.0 second is often used, the rise time being a function of the size of the catheter lumen. The pressure settings are typically 600, 900, and 1200 psi for a 6-, 5-, and 4-Fr system, respectively. Generally, injection of 40 to 50 mL at 20 to 25 mL/sec is sufficient for imaging a normal aorta. To prevent a catastrophic embolism during aortography—particularly if performed at the level of the ascending aorta or aortic arch—careful attention must be paid to removing air from the injector system before it is used. According to anecdotal case reports, air injection of 50 cc in the ascending aorta has proven fatal.

**Quantification of Aortic Insufficiency**

Quantification of aortic valve regurgitation requires injection of a sufficient volume of contrast material (about 60 mL) into the aorta via a catheter that is near, but not in contact with, the aortic valve. The severity of regurgitation is rated according to a semiquantitative scale similar to the one used for mitral regurgitation (Table 21.5).

**Abdominal Aortography**

Abdominal aortography is usually performed via the common femoral approach with a multi-side-hole catheter (4–6 Fr). Depending on the patient’s history and physical findings, radial or brachial access may be preferred. Once access has been obtained, a soft-tip wire is placed across the area of interest with the aid of fluoroscopy, and the angiographic catheter is advanced so that its tip is at the level of the T12 or L1 vertebra. If available, a biplane system allows the visceral branches to be visualized with only one injection of contrast.
Table 21.5 Angiographic Assessment of Aortic Insufficiency

<table>
<thead>
<tr>
<th>Grade</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+</td>
<td>Brief and incomplete ventricular opacification. Clears rapidly.</td>
</tr>
<tr>
<td>2+</td>
<td>Moderate opacification of the ventricle that clears in less than 2 cycles. Not greater than aortic root opacification.</td>
</tr>
<tr>
<td>3+</td>
<td>Opacification of the ventricle equal to aortic root opacification in more than 3 cycles. Delayed clearing of ventricle over several cycles.</td>
</tr>
<tr>
<td>4+</td>
<td>Opacification of the ventricle almost immediately or in less than 3 cycles that is equal to or greater than that of the aortic root with delayed clearing of the ventricle.</td>
</tr>
</tbody>
</table>

Figure 21.19 Abdominal aortogram from a 68-year-old woman with a history of Takayasu's arteritis, showing bilateral renal artery stenosis (arrows) and a significant decrease in the diameter of the distal abdominal aorta.

Special Issues
A severely diseased aorta can present multiple technical difficulties during angiography, resulting in potential complications. A difficult anatomy may necessitate excessive manipulation of catheters, causing distal embolization of atherothrombotic debris. In the presence of aortic wall dissections, the operator may not realize that the catheter is in the false lumen; these dissections can be extended by the catheter, causing organ perfusion compromise and perforations.

During the procedure, wires, catheters, and other devices may penetrate the aortic wall, initiating dissection and/or rupture. The International Registry of Aortic Dissection (35) indicates that up to 5% of acute aortic dissections are iatrogenic (27% being due to percutaneous procedures). Patients with iatrogenic dissections are more likely to have myocardial ischemia (36% vs. 5%; P < 0.001) or a myocardial infarction (15% vs. 3%; P < 0.001) than are patients with noniatrogenic dissections. The former group also has a higher mortality (35% vs. 24%). In addition, when the ascending aorta and arch are manipulated, stroke can occur with devastating consequences (36,37).

Atheroembolism can also lead to renal insufficiency, which develops slowly over several weeks. Other systemic manifestations of atheroembolism include livedo reticularis, abdominal or foot pain, and purple toes associated with systemic eosinophilia (blue toe syndrome) (38). Systemic complications may also occur. They are related to allergic and anaphylactoid reactions in 3% of cases (<1% of which involve hospitalization) (39).
Conclusions: Aortography

The multiple noninvasive imaging modalities that have evolved for evaluating the aorta and its branches include MRA, CTA, and duplex ultrasonography. These methods allow clinicians to appropriately diagnose patients, follow up their conditions, and plan appropriate therapeutic strategies while avoiding the complications inherent in invasive percutaneous procedures. Aortography still plays a primary role in the invasive evaluation of aortic disorders (valvular, traumatic, aneurysm, and atherothrombotic). Before elective surgical repair of thoracic aortic aneurysms, aortography and coronary angiography provide important information about the relationship of nearby vessels to the aneurysm and about coronary artery locations and patency. Aortography is also fundamental in guiding therapeutic endovascular interventions. Careful procedural technique is required to maximize benefits and minimize the risk of complications.

REFERENCES

INTRODUCTION
Even though the diagnostic imaging modalities for the evaluation of pulmonary vasculature have made considerable advancements over past couple of decades, pulmonary angiography still remains the gold standard technique for the diagnosis of pulmonary embolism (PE). However, because of more widely available noninvasive imaging techniques such as multislice computed tomography (CT) and magnetic resonance imaging (MRI), the utilization of pulmonary angiography as a primary diagnostic modality has declined considerably. Catheter angiography is now more commonly used for various endovascular interventions on the pulmonary circulation, such as mechanical embolectomy, embolization for tumors or retrieval of foreign bodies, as well as for the diagnosis and treatment of a variety of congenital heart diseases.

ANATOMIC CONSIDERATIONS
Pulmonary Circulation Anatomy
The main pulmonary artery originates from the right ventricle and travels anteriorly on the left side of the aorta and then follows a posterior course, bifurcating into the right and left pulmonary arteries (Fig. 22.1). The right pulmonary artery gives rise to right upper-lobe branch during its course in mediastinum that further divides into three upper-lobe segmental arteries. The right pulmonary artery continues and then divides into middle-lobe and lower-lobe segmental arteries. The left pulmonary artery continues in the mediastinum and gives rise to variable number of small segmental arteries to the upper lobe. It then bifurcates into interlobars and basalis branches that give rise to two lingular and four lower-lobe segmental arteries, respectively. Further branching of these vessels is remarkably variable. The segmental pulmonary veins are also variable; however, they form superior and inferior vein on each side before draining into the left atrium.

FUNDAMENTALS
Patients referred for pulmonary angiography almost invariably have acutely or chronically elevated right heart pressures and may be hemodynamically unstable. Therefore, pulmonary angiograms should be performed by experienced operators in laboratories with staff and equipment capable of invasive hemodynamic monitoring.

INDICATIONS
Pulmonary Embolism
PE is one of the important causes of cardiovascular morbidity and mortality with an annual incidence of 1 per 1000 in the adult general population (1,2). The main cause of death in the acute setting is right ventricular failure. Patients may present with wide range of symptoms and, therefore, a high index of suspicion is necessary for the prompt diagnosis. Symptoms may include dyspnea, hemoptyis, cough, and pleuritic chest pain. Syncope indicates a hemodynamic compromise. Clinical signs include elevated jugular venous pressure, decreased pulmonic component of second heart sound, right ventricular heave and tachycardia—all indicating right ventricular dysfunction. Wells and coworkers have described clinical means to estimate the probability of deep venous thrombosis and PE (3,4).

Electrocardiography (ECG) in acute PE usually shows sinus tachycardia. The presence of classic SIQ3T3 pattern may help in making diagnosis; however, this is not commonly seen. Other findings may include incomplete or complete right bundle branch block and right axis deviation. The presence of Qr pattern in lead V1 and inverted T waves in anterior precordial leads indicates increased risk of poor clinical outcomes (5). A negative D-dimer has high negative predictive value (>90%) and low specificity (45%) for PE (6–8). Therefore, the test is useful only as a “rule-out” modality in the office setting or emergency room. Arterial blood gas analysis should not be used for screening purposes because of its low specificity in PE, but may help direct therapy. The presence of hypoxemia, hypocapnia, respiratory alkalosis, and increased alveolar-arterial gradient is usually seen (9).

Chest CT is now considered initial imaging test for the diagnosis of PE. Chest radiographs and ventilation perfusion lung scanning should precede pulmonary angiography and serve as a planning aid. The ventilation perfusion scan is very useful for diagnosis of PE when the chest radiograph is normal and CT chest with intravenous contrast cannot be performed (10). A normal or a high probability lung scan are diagnostic of PE. To interpret low or intermediate probability scans, clinical history should be considered to help direct any further use of diagnostic modalities and management.

The sensitivity of multidetector CT ranges from 70% to 90% (11,12). MR imaging can also be utilized for diagnosis of PE and can reach sensitivity and specificity as high as pulmonary angiography. MR angiography is more time demanding and less available in the acute setting than CT angiography. In addition, highly symptomatic patients may not comply sufficiently to have adequate quality images with MR. Venous ultrasonography can be performed in patients with symptoms of deep venous thrombosis and, if a thrombosis is confirmed, the finding is sufficient to diagnose PE if the patient has a suggestive clinical presentation. Contrast venography is rarely performed except when catheter-directed thrombolysis or other percutaneous intervention are planned, or an inferior vena cava filter is to be inserted. Transthoracic echocardiography is an important tool for risk stratification in PE. Accordingly, right
ventricle dysfunction is associated with increased mortality and in the presence of hemodynamic instability warrants thrombolysis, catheter intervention, or surgical embolectomy.

Predictors of a positive angiogram include the following:

1. Presence of one or more risk factors for pulmonary thromboembolism (bed rest, surgery, or trauma within 6 weeks, previous history of deep vein thrombosis or PE, malignancy, congestive heart failure);
2. Chest radiograph showing infiltrates, pleural effusion, or atelectasis;
3. Ventilation perfusion scan interpreted as indeterminate or high probability.

When only one of the three predictors is present, the likelihood of angiographically demonstrable PE is <5%, with two of three predictors positive, about 20% and with all three predictors being positive, the likelihood is >70%.

The natural history of pulmonary thromboembolism suggests that most patients will have identifiable emboli for at least one week following the acute episode. However, the number of false-negative studies will increase after 48 hours and the performance of angiography after 7 days may not be advisable.

Other Indications
Pulmonary angiography and right heart catheterization can be utilized to both confirm the diagnosis and for the evaluation of possible surgical treatment in a patient with pulmonary hypertension secondary to chronic thromboembolic disease. The characteristic angiographic findings of chronic thromboemboli include pooling of contrast in organized thrombus with obstruction of the distal artery, the presence of thin or thick webs or bands that appears as radiolucencies in lobar or segmental vessels and can cause stenosis with or without poststenotic dilatation. Luminal irregularities are common with vessel tapering of large pulmonary arteries and obstruction of lobar arteries, usually at their origin. Such findings were confirmed surgically in one study of 250 patients (13). In addition to chronic anticoagulation, placement of an inferior vena cava filter should be considered. Patients with proximal pulmonary artery emboli should be considered for surgical pulmonary thromboembolectomy. Pulmonary hypertension may persist after thromboembolectomy and identifies patients with poor outcomes. Lung transplantation may be an option in patients with extensive chronic embolic disease.

Primary pulmonary hypertension is a disease of unknown etiology. Angiography in such patients shows nonspecific dilatation of the proximal arteries with smooth, rapid tapering of distal vessels with corkscrew appearance of the distal arteries. If untreated, the right ventricle fails secondary to gradual increase in pulmonary vascular resistance. Vasodilator challenge with IV adenosine or inhaled nitric oxide is often performed before initiation of vasodilator therapies. Reduction of ≥20% in pulmonary vascular resistance with decrease in mean pulmonary artery pressure ≥20% is considered a positive response. A vasodilator challenge may also be performed to document reversibility in pulmonary vascular resistance in a patient being considered for heart transplantation.

Pulmonary arteriovenous malformations are usually asymptomatic. However, patients may present with dyspnea, hemoptysis, cyanosis, and clubbing. Polycthemia and paradoxical embolism may occur due to extracardiac right-to-left shunting. A contrast-enhanced spiral chest CT can be utilized to establish the diagnosis, and pulmonary angiography is usually performed only to guide percutaneous embolization.

Pulmonary artery stenosis is usually seen in patients who survive repair of congenital heart diseases such as tetralogy of Fallot, truncus arteriosus, pulmonary valvular stenosis, patent ductus arteriosus, aortic stenosis, ventricular septal defects, or transposition of great vessels during childhood. Pulmonary angiography is both diagnostic and part of therapeutic procedures in which such lesions can be treated with angioplasty and stents.

Pulmonary artery aneurysms—are usually secondary to pulmonary hypertension—are seen in patients who underwent corrective surgery for congenital heart disease; in infectious diseases like tuberculosis and syphilis; and in rheumatologic processes such as Behcet disease. Percutaneous embolization can be performed after pulmonary angiography.

Partial anomalous pulmonary venous return can be diagnosed by pulmonary angiography with oxygen saturation run and delayed filming to identify the venous phase and to quantify left-to-right shunting.

EQUIPMENT AND PROCEDURE
Venous Access
The right common femoral vein is the most often utilized access site for pulmonary angiography due to the ease of cannulation and of compression, and its relatively straight course into right side of the heart through the inferior vena cava. The left common femoral vein is used if the right side is not accessible for reasons such as proximal deep venous thrombosis, fibrosis, infection, or recent hematoma. If iliac or inferior vena cava thrombosis is suspected at the time of the procedure, 15 mL of contrast can be injected into the femoral vein to confirm or rule out the presumptive diagnosis.

The internal jugular vein can be utilized if no femoral approach is possible. The basilic vein at the antecubital fossa is preferred over the internal jugular vein if thrombolytic therapy is being considered because it allows for a better hemostasis at the puncture site. The cephalic vein may not be a good choice due to its relatively smaller size and presence of acute angle when it joins the axillary vein.
Choice of Contrast and Injection Rates

Traditionally, low-osmolar contrast agents are used for pulmonary angiography. The advantage of such agents includes less frequent side effects of flushing, hypotension, nausea, or cough reflex. Currently, there is limited data regarding iso-osmolar, nonionic agents for use in pulmonary angiography. The determinants of contrast injection rate include the rate of blood flow in the catheterized vessel, pulmonary artery pressure, the type of catheter used for angiography, and the imaging mode. Digital imaging techniques require less contrast to be injected for adequate opacification of selected arteries. The injection rate and volume should be less if more subselective catheterization is performed in smaller vessels. This should also be considered in patients with pulmonary hypertension and right ventricular overload to avoid hemodynamic side effects (14). Right ventricular end-diastolic pressure of 20 mmHg is usually considered the upper limit for safe use of contrast media in chronic pulmonary hypertension (15). If available, biplane angiography may also be used to further reduce both total contrast volume and catheter dwell time.

Imaging Modes

Digital subtraction angiography (DSA) is equivalent to conventional angiography in image quality and diagnostic performance (16). In one study, comparable accurate detection of PE was noted by use of DSA as compared to conventional angiography (17). There are many advantages of DSA as the imaging mode. It allows the use of less contrast media, which is particularly important in patients with pulmonary hypertension or renal insufficiency. The images are acquired rapidly in flexible display format, in which images can be viewed individually or in cine format for both DSA and conventional angiography.

The main disadvantage of DSA is requirement of image acquisition without motion that may be suboptimal in patients with severe cardiac or pulmonary symptoms, and in patients who are unable to breath hold. Motion artifacts can be reduced by mask-shifting techniques that may improve cardiac motion; however, it is less helpful in respiratory motion artifacts. For that reason, DSA is usually not possible in patients undergoing angiography for massive PE other than if the patient is intubated, a situation in which DSA should be performed after induction of an anepa.

The two standard views that have been validated in a large clinical trial are the anteroposterior and the 45° ipsilateral oblique view (18). Lateral views are not useful because the frequently observed reflux of the contrast into the opposite lung may hinder interpretation.

Technique

Pulmonary angiography is usually performed in the acute setting for evaluation and catheter-directed treatment of massive PE. Close invasive blood pressure and electrocardiographic monitoring is required for early detection of hypotension, brady- or tachyarrhythmias, and atrioventricular block during the procedure. Angiography is initiated by performing complete right heart catheterization. Special considerations are made depending on the measured pulmonary artery and right ventricle end-diastolic pressures.

The catheters usually used for diagnostic pulmonary angiography range in sheath size between 5 and 7 Fr. However, lower-size 4-Fr nylon pulmonary catheter that allows flow rates of 20 mL/sec can be used to reduce access site complications. The pigtail catheter has multiple side holes with curled tip that provides safety during right heart catheterization as well as provides easy access to any segmental artery (Fig. 22.2). The retrieval of such catheters should, however, always be made after straightening with a guidewire under direct fluoroscopic visualization to avoid entrapment in the tricuspid valve or subvalvular apparatus. The balloon-tipped catheters have side holes in the shaft of the catheter proximal to the balloon and power injection after balloon occlusion allows for selective high-quality injections. After deflation of the balloon, the catheter can be removed without the use of fluoroscopy.

In general, contrast medium is injected separately into right and left pulmonary arteries rather than the main pulmonary artery, with an injection rate per artery of approximately 20 mL/sec for total of 30 to 40 mL depending on the patient size at a maximum pressure of 600 psi. The regions that are suspected to be abnormal are examined first in anterior posterior or oblique planes or with biplane angiography. Further injections may be required to better define the anatomy.

CLINICAL ASPECTS

A normal pulmonary angiogram is demonstrated in Figure 22.3. Often selective or superselective injections with magnification may be required when suspicious areas require closer examination (Figs. 22.4 and 22.5). These may be performed with balloon-tipped catheters following balloon occlusion. The findings depend on the size and number of emboli, on the location of the lesion—central or peripheral, and if the lesion results in partial or complete flow obstruction. Angiography may detect intraluminal filling defects of various sizes, shapes, and locations; abrupt arterial cutoffs and localized pruning or lack of branching (Fig. 22.6). The extent of these findings correlates with
the severity of pulmonary arterial occlusion. As a correlate of hemodynamic compromise—cardiogenic shock—patients may have in addition oligemia, asymmetrical filling, prolongation of the arterial phases, and bilateral lower-zone filling delay.

LIMITATIONS
Pulmonary angiography studies are challenging to interpret. The reading physician, therefore, should give some estimate of the degree of certainty of the diagnosis, though arbitrary, based on a judgment of the completeness of visualization of pulmonary circulation.

COMPLICATIONS
Pulmonary angiography is a remarkably safe procedure in experienced hands. Reported major complications are approximately 1.5% and include death, respiratory distress requiring cardiopulmonary resuscitation or intubation, renal failure requiring dialysis, or access site complications requiring transfusion (18). Patients with pulmonary artery hypertension are at higher risk of having acute right heart failure (19). However, in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, increase mortality was not observed among 755 patients who underwent pulmonary angiography (10). Nevertheless, due to this potential risk, pulmonary
CONTRAINDICATIONS AND SPECIAL ISSUES

There is no absolute contraindication to pulmonary angiography. However, minimization of contrast and special care should apply for high-risk patients such as those with severe pulmonary hypertension, known allergic reaction to iodine-based contrast media, renal insufficiency, left bundle branch block, and right heart or biventricular congestive heart failure (14). Patients with history of severe allergic reactions should be pretreated with corticosteroids and antihistamines, and use of nonionic low osmolar contrast agents should be considered, as conventional ionic monomer contrast media transiently increase pulmonary artery and right ventricle pressure.

CONCLUSIONS

Although rarely needed for diagnostic purposes, pulmonary angiography remains the gold standard imaging modality for acute and chronic PE. In addition, angiography may, on occasion, be indicated in the evaluation of pulmonary hypertension, congenital heart disease, pulmonary arteriovenous malformations, and pulmonary aneurysms. Finally, angiography guides all catheter-based interventions in the pulmonary circulation. Pulmonary angiographic studies should be performed by experienced operators in catheterization laboratories capable of invasive hemodynamic monitoring. Pulmonary angiography requires venous access, passage of the angiographic catheter under fluoroscopic guidance, and contrast injection during cineangiography. In addition to technical expertise, angiographic interpretation requires great experience.

REFERENCES


Transseptal catheterization

Zoltan G. Turi

INTRODUCTION

Left atrial access has been a challenge in cardiac catheterization since the earliest cardiac surgical procedures mandated accurate assessment of left atrial pressure in the 1940s. The occasional direct measurement was by a number of hazardous routes, including transbronchial and direct left atrial puncture. Modern left atrial catheterization by puncture of the interatrial septum is a half-century-old. It resulted from the pioneering efforts of a young medical resident at the East Orange New Jersey Veteran’s Administration Hospital, Constantine Cope, who developed an apparatus working with the Becton Dickinson Company (1). This led to animal and clinical investigation at Hahnemann Hospital in Philadelphia, in conjunction with Charles Bailey, the pioneering cardiac surgeon who performed the first successful mitral commissurotomy in 1948 (2). Ross and colleagues at the National Institutes of Health subsequently described a similar approach (3). The technique was inherently dangerous (4), and was used primarily for pressure measurement and angiography. Several factors contributed to its near disappearance from clinical practice. First, right heart catheterization, developed in the 1940s, allowed indirect left atrial pressure measurement through the pulmonary arterial wedge pressure (5). Second, the introduction of balloon flotation catheters simplified and enhanced the safety of right heart catheterization (6). Finally, the availability of echocardiography further decreased the need for a highly invasive means of assessing hemodynamics. As a result, there was a dramatic decrease in use of transseptal puncture, and by the late 1970s most adult catheterizers had either stopped doing the procedure or had never been trained to perform it. Occasional transseptal puncture was still mandated by prosthetic aortic valves that were inherently dangerous to cross retrograde, in particular the Bjork-Shiley tilting disk valve. However, the declining emphasis on structural heart disease in favor of coronary angiography and the introduction of ever more sophisticated cardiac ultrasound in lieu of hemodynamic studies resulted in few operators with training, experience, or maintenance of skills at transseptal puncture (7).

Although the technique continued to have adherents for high fidelity hemodynamic measurements, and for antegrade access in patients with aortic stenosis (8) or hypertrophic obstructive cardiomyopathy (9), the reappearance of transseptal catheterization owed much to the introduction of percutaneous balloon mitral valvuloplasty in the 1980s, a procedure that requires primarily antegrade left atrial access. The real stimulus to the rebirth of transseptal catheterization however has been in the electrophysiology laboratory, where left-sided ablations have resulted in exponential growth (Fig. 23.1) (10). Further utilization is related to the expansion of structural heart disease interventions in the past decade, and a number of currently experimental technologies will likely continue the trend. A list of procedures for which transseptal catheterization is required is provided in Table 23.1.

Transseptal technology was relatively stagnant for the first 20 years after its introduction. In 1979, Mullins introduced a dilator and sheath combination that provided a platform for advancement of a variety of catheters into the left atrium (LA), and enhanced the safety of the procedure overall (11). The primary tools for left atrial access have remained the Mullins sheath, along with the Brockenbrough needle, a combination with origins 30 and 50 years old, respectively. More recently, however, with increasing utilization of transseptal puncture, a number of novel technologies have appeared, and will be discussed later in this chapter (12).

ANATOMY OF THE INTERATRIAL SEPTUM

The interatrial septum is embryologically derived from growth of the septum primum and secundum toward the endocardial cushions (Fig. 23.2A). During prenatal development, a circular opening, the foramen ovale, develops in the inferior-posterior portion of the septum secundum. As the septum primum resorbs, it continues to overlap the foramen ovale, forming a flap that functionally acts as a valve. Because of high pulmonary vascular resistance during gestation, right atrial pressure drives the valve to open and allow blood to flow from the right atrium (RA) to the LA. After birth, pulmonary vascular resistance decreases, right atrial pressure falls below left atrial pressure, and the valve fuses to the septum secundum. Because the septum primum is thin and membranous compared with the thicker and more muscular septum secundum, the fossa ovalis is only approximately 2 mm thick, and is recessed unless the left atrial pressure is high. It averages less than 2.5 cm² in diameter, making for a relatively small target (Fig. 23.2B). A patent foramen ovale (PFO), present in approximately one quarter of the population, allows for easy transseptal access, but may not be the ideal entry route to the LA as discussed subsequently. Important anatomic variants include a prominent Eustachian valve, which can limit access to the septum from the inferior vena cava, and left superior vena cava (SVC), which may result in a markedly enlarged adjacent coronary sinus ostium.

EQUIPMENT FOR TRANSSEPTAL PUNCTURE

The standard Mullins technique calls for use of the Brockenbrough needle, a dilator and sheath as shown in Figure 23.3. The needle is curved to allow access to the fossa ovalis; several curvatures are available, with typical ones ranging from a relatively shallow 19° angle to a steeper 53° angle (Fig. 23.4A). We prefer the steeper angle for easier access to the septum in the
average patient. Some operators gently bend the needle (with the stylet in place) to provide a custom configuration, in particular to provide a steeper angle to access the septum when the RA is large, or the anatomy is distorted, such as when a prominent Eustachian valve interferes with access. Patients with high left atrial pressure, where the entire septum protrudes toward the RA, may require a less angled approach. An example of the latter is mitral stenosis, where the fossa is both enlarged as well as more horizontally aligned (13). Needles are typically 71 cm in length and taper from a proximal 18 to 21 gauge at the distal tip. A number of needle modifications exist, including a 16-gauge needle that does not taper. The Mullins sheath is typically 59 cm, with a 67-cm dilator, and is available in a wide range of diameters, typically 6 to 8 Fr for routine diagnostic procedures, but 14 to 21 Fr for use with interventions requiring large diameter devices.

Table 23.1 Indications for Transseptal Puncture

I. Diagnostic studies
a. Hemodynamic assessment where noninvasive data are equivocal
   i. Aortic outflow obstruction
   1. Tilting disk prosthetic aortic valve dysfunction
   2. Hypertrophic obstructive cardiomyopathy
   3. Inability to cross a stenotic native aortic valve
 ii. Mitral stenosis—particularly prosthetic valve obstruction
 b. Arterial angiography when access can only be obtained by antegrade access through the aortic valve

II. Interventions
a. Electrophysiology mapping and ablation
   i. Atrial fibrillation
   ii. Left atrial tachyarrhythmias (left atrial tachycardia/left atrial flutter)\(^a\)
   iii. Left-sided accessory pathways\(^a\)
   iv. Left ventricular arrhythmias\(^b\)
 b. Structural heart interventions
   i. Balloon mitral valvuloplasty
   ii. Left atrial appendage occlusion\(^a\)
   iii. Percutaneous mitral valve repair\(^a\)
   iv. Prosthetic paravalvular leak closure\(^a\)
   v. Pulmonary vein stenosis dilatation and stenting\(^a\)
   vi. Percutaneous aortic valve implantation\(^a\)
   vii. Patent foramen ovale closure\(^a\)
   viii. Left atrial pressure monitor placement\(^a\)
   ix. Atrial septostomy
 c. Percutaneous cardiac assist

\(^a\)procedure off-label, experimental, or pending FDA approval.
\(^b\)transseptal approach used when aortic stenosis, peripheral vascular disease, or mechanical prosthetic valve prevents retrograde access to the left ventricle.

Figure 23.1 Growth of transseptal puncture in a survey of 33 hospitals in Italy over a 12-year period. This exponential growth was driven primarily by atrial fibrillation ablation procedures. Source: From Ref. 10.
Figure 23.3  (A) Transseptal needle, stylet, sheath, and dilator. Note the parallel orientation of the needle arrow, sheath sidearm, dilator and needle tip. The pointer allows for orientation of the needle and the rest of the Mullins assembly as it is withdrawn from the superior vena cava and maneuvered against the fossa ovalis. (B) The transseptal needle, dilator and sheath showing the distance markers that identify the length of the dilator protruding from the sheath (A) and the relative distance between the position arrow of the transseptal needle and the dilator hub when the needle tip is just inside the end of the dilator (B). The Bing stylet is seen to protrude from the needle hub at the extreme left (arrow). The double arrow points to the site of entry of the needle into the dilator; finger compression of the space adjacent to the needle (inset) is necessary to prevent air from being sucked into the assembly during careful drawback of blood through the needle to establish an air-free fluid column for pressure recording and dye injection. (C) The sheath with (A) the dilator and (B) needle both fully inserted into the hub. Since there are several commonly available lengths of the Brockenbrough needle, it is essential to confirm that the needle and sheath sizes are matched. Source: Courtesy of Medtronic, Inc. and St. Jude Medical.
Transseptal sheaths with a wide range of shapes are available (Fig. 23.4B), primarily designed for electrophysiology access to various structures within or originating from the LA. A transseptal sheath that allows the operator to vary the distal curvatures (Fig. 23.4C) is widely used in ablations (14) and some specialized left atrial interventions such as percutaneous closure of prosthetic mitral paravalvular leaks (Agilis, St. Jude Medical, St. Paul, Minnesota, U.S.) (15). The Agilis can be used in the initial transseptal puncture (in which case a longer needle is required to accommodate the additional length added by the control handle) or introduced by an exchange technique after access to the LA is already achieved.

INDICATIONS
Diagnostic Studies
The initial use of transseptal puncture for direct hemodynamic assessment of left heart pressures has become uncommon given the small but significant risk associated with the procedure, the low risk of pulmonary wedge pressure measurement, and the availability of noninvasive alternatives in most cases. Nevertheless, in settings where echocardiographic data are equivocal, transseptal catheterization remains an important alternative means of access to the LA and the left ventricle (LV).

Mitral Valve Hemodynamics: Wedge Vs. Left Atrial Pressure
Pulmonary artery wedge pressure differs from left atrial pressure measured directly in several clinically important ways. First, the additional resistance in the pulmonary vascular bed dampens the phasic excursion of the wedge derived A and V waves. Second, a substantial phase delay is introduced. Thus, as shown in Figure 23.5A, although the mean wedge and left atrial pressures are usually identical (barring the still uncommon but no longer rare phenomenon of pulmonary veno-occlusive disease) (16), the height of the A and V waves is prone to significant underestimation when pulmonary wedge pressures are recorded (Fig. 23.5B). Since the rate of fall in left atrial pressure (negative \( \frac{dP}{dt} \)) is substantially diminished by recording across the pulmonary vascular bed, the gradient between pulmonary wedge and left ventricular pressure is artifactually higher than that noted between left atrial and left ventricular pressure. An example is shown in Figure 23.6. This in turn leads to substantial overestimation of the severity of mitral stenosis, especially when any degree of mitral insufficiency is superimposed on preexisting valve obstruction. This phenomenon has led to overestimation of prosthetic mitral valve stenosis and unnecessary repeat mitral valve surgery when wedge pressure rather than left atrial pressures has been relied on to assess prosthetic valve dysfunction (18).

Aortic Outflow Obstruction
Technical failure to cross the aortic valve retrograde should be rare and is usually associated with severe calcification and an eccentric orifice; this can be addressed by the alternative of transseptal antegrade access (8). In addition, some mechanical valves should not be crossed retrograde because of the risk of catheter entrapment and potential difficulties with extracting the catheter (19). Furthermore, entrapment of the catheter in a
mechanical aortic valve will distort hemodynamics since a leaflet is pinned in an open position resulting in artifactual aortic insufficiency. Simultaneous measurement of left ventricular pressure via antegrade access to the LV and retrograde access to the central aorta does address two concerns: artifact induced by measurement of left ventricular pressure against femoral artery sheath sidearm pressure and the potential for a small reduction in systemic pressure created by the obstruction of the aortic valve by the catheter itself (Carabello’s sign) (20); the latter is uncommon with 6-Fr catheters. Using femoral artery rather than central aortic pressure does result in underestimation of the transvalvular gradient regardless of whether the left ventricular pressure is measured via transseptal access (21) or by retrograde left ventricular entry (Fig. 23.7) (22). There is also a concern that retrograde passage of catheters across the aortic valve is associated with cerebral emboli (23) in over 20% of patients, although most are not clinically apparent. Furthermore, the frequency of these initial findings has not been confirmed (24). Importantly, left ventricular and central aortic pressures can be measured simultaneously using several techniques that avoid transseptal puncture, including use of a catheter designed for simultaneous measurement using a retrograde technique (Langston, VascularSolutions, Minneapolis, Minnesota, U.S.) (25), a simultaneous catheter and pressure wire method (26), and dual arterial punctures. Overall, routine transseptal puncture for hemodynamic evaluation of aortic stenosis does not appear warranted.

A second setting for use of transseptal puncture to assess left ventricular hemodynamics via an antegrade approach has been in patients with hypertrophic cardiomyopathy with obstruction. The transseptal route can avoid catheter entrapment and artifact (27); pullback to the mitral valve allows differentiation between apical or midcavitary obliteration and true outflow obstruction (Fig. 23.8).

Figure 23.5 (A) Left atrial and simultaneous pulmonary artery wedge pressures, 40-mm Hg scale. Note that the height of the A wave in this patient is higher on the left atrial pressure tracing, while the V wave is similar. An arrow points to diastasis between the pressure waveforms; the mean pressures are typically identical, with the exception of patients with pulmonary venous outflow obstruction. (B) Simultaneous left atrial and pulmonary artery wedge pressures at 40-mm Hg scale in a patient with severe prosthetic mitral perivalvular regurgitation. Although the mean pressures are the same, note that the peak left atrial pressure (diamond-shaped arrow) is 42-mm Hg, while the peak wedge pressure is 24-mm Hg, with a significant phase delay. The gradient between wedge pressure (double arrows) and left atrial pressure (single arrows) is substantial, but entirely artifactual, induced by measuring the wedge pressure indirectly across a high resistance system: the pulmonary capillary bed. Abbreviations: LA, left atrium; PCW, pulmonary capillary wedge.
Transseptal Access to the Arterial Circulation
In selected patients, access to the arterial circulation cannot be obtained by any practical means. These patients typically have obstructions of the subclavian arteries and aorta, and limited approaches such as carotid or lumbar transaortic access are almost always high risk. An alternative has been transseptal access, typically for aortography. Coronary angiography is technically difficult, but has been described (28). In addition, carotid stenting has been performed via the transseptal route in Takayasu’s arteritis (29) as well as in the setting of a Type III aortic arch, where neither femoral nor arm access was deemed suitable (30).

Interventions
Electrophysiology
Ablation for atrial fibrillation and other left-sided electrophysiologic interventions has accounted for the largest segment of the growth of transseptal puncture in the past two decades (Fig. 23.1). Treatment of preexcitation syndromes transitioned from medical therapy to an investigational retrograde left ventricular approach to a transseptal access based procedure as first line therapy (31). The advantages of the transseptal approach include avoidance of several potential complications associated with retrograde left atrial access. These include large femoral artery puncture related adverse events, potential damage to the aortic valve or subvalvular apparatus from extensive catheter manipulation, and perforation, dissection or embolization from catheter manipulations in the LV and aorta. In addition, some patients are not suitable for retrograde ablations, such as those with severe peripheral vascular disease and those with mechanical aortic valves. Treatment of atrial fibrillation and other atrial arrhythmias by catheter ablation in the LA and the pulmonary vein ostia is now widely performed (32). Dual transseptal access to the LA is required for some procedures, and is achieved either by performing two separate transseptal punctures or by placing two catheters across a single puncture site; the safety implications are discussed subsequently.

Structural Heart Interventions
Since the introduction of percutaneous balloon mitral valvuloplasty with a device originally designed for atrial septectomy (33), transseptal catheterization has been utilized for a variety of structural heart interventions. In patients with rheumatic mitral stenosis with favorable anatomy, balloon dilatation and other atrial arrhythmias by catheter ablation in the LA and the pulmonary vein ostia is now widely performed (32). Dual transseptal access to the LA is required for some procedures, and is achieved either by performing two separate transseptal punctures or by placing two catheters across a single puncture site; the safety implications are discussed subsequently.

Figure 23.6 The patient whose hemodynamics are presented in this figure was initially misdiagnosed as having severe mitral stenosis and referred for balloon mitral valvuloplasty. The tracing at left demonstrates a substantial gradient measured using a pulmonary arterial wedge pressure against left ventricular diastolic pressure (40-mm Hg scale). Two clues to the true nature of the actual diagnosis are present: first, note the V wave peak is more than twice the mean wedge pressure, and second, note the presence of diastasis at end-diastole. In contrast, a simultaneous left atrial and left ventricular pressure measured in the same patient clarifies these hemodynamics: the gradient is primarily due to the sizeable V wave, with decompression of left atrial pressure only slightly delayed by the presence of mild mitral stenosis; diastasis can now be seen to occur much earlier in diastole. Source: From Ref. 17.

\[ V \text{ wave} \]
\[ \text{Diastasis} \]
Percutaneous balloon valvuloplasty of the aortic valve via the antegrade approach has a number of adherents, in particular because of superior immediate hemodynamic results with the Inoue balloon compared with cylindrical balloons (39). The Inoue balloon is typically not long enough for retrograde access to the aortic valve but is of sufficient length to place transseptally. However, long-term benefit of this technique compared with the conventional retrograde approach has not been shown.

Figure 23.7 (A) Severe aortic valve stenosis with left ventricular, central aortic and left atrial pressure on 200-mm Hg scale. The left ventricular pressure was obtained by antegrade introduction of a pigtail catheter into the LV through a Mullins sheath. Aortic pressure was measured through a pigtail catheter in the central aorta (Ao). The peak-to-peak gradient is approximately 60-mm Hg peak to peak. The arterial pressure upslope \( (dP/dt) \) is markedly blunted. The arrow points to the start of the upstroke of central aortic pressure coincident with opening of the aortic valve. (B) Left ventricular, femoral artery and left atrial pressure on 200-mm Hg scale in the same patient obtained moments after the tracing in 23.7A. The gradient is underestimated and the arterial pressure upslope \( (dP/dt) \) appears relatively well preserved, both the result of recruitment of harmonics as the pulse waveform travels distally through the arterial tree. The arrow points to the substantial delay in pressure upstroke seen when femoral artery rather than central aortic pressure is compared with the left ventricular pressure. Although left ventricular-femoral artery gradient measurement is the most commonly used, it leads to inaccurate estimation of aortic valve area. Several less invasive means of obtaining the gradient are discussed in the text. Abbreviations: LA, left atrium; LV, left ventricle; FA, femoral artery. 

Source: From Refs. 17 and 21.
Finally, percutaneous aortic valve implantation was initially performed antegrade via the transseptal route (41). This approach has been abandoned because of complexity and associated morbidity, in particular trauma to the subvalvular apparatus (42) caused by shortening of the catheter loop in the LV that effectively “filleted” the chordae and papillary muscles.

Cardiac Assist
Transseptal access is required for a percutaneous cardiac assist device that provides extracorporeal circulation by shunting oxygenated blood from the LA using a 21-Fr transseptal cannula that needs stable positioning in the LA (TandemHeart, CardiacAssist, Inc., Pittsburgh, Pennsylvania, U.S.) (43). Blood is then pumped into a large femoral arterial cannula. The technology provides circulatory support during high-risk percutaneous interventions, perioperatively during cardiac surgery, and temporarily augments cardiac output in a variety of settings (Table 23.1).

CONTRAINDICATIONS
Relative contraindications to transseptal puncture include uncorrected anticoagulation as well as significant coagulopathy (although some operators puncture with the patient fully anticoagulated as discussed subsequently) (44), thrombus in either the right or LA, and anatomic abnormalities that alter landmarks and interfere with septal access. The latter include severe kyphoscoliosis, giant LA, prominent Eustachian valve, left SVC, vena caval interruption, and an azygous continuation of the inferior vena cava. While transseptal puncture has been described in most of these settings, the risks are augmented. Some other features that make transseptal puncture technically more complex include a thickened or fibrotic septum and atrial septal aneurysm (which increases risk of perforating the left atrial free wall). Repeat transseptal puncture has been reported as more difficult, in part because of increased atrial septal thickness (45). Finally, the presence of a prior atrial septal defect (ASD) closure either by surgery or percutaneously placed device has been addressed using intracardiac (ICE) or transesophageal (TEE) echocardiographic guidance. Limited experience in these setting has suggested that transseptal puncture can be performed with reasonably high success and low complication rates (46).

TECHNIQUE
Preprocedure Evaluation
Knowledge of the anatomy of the septum, the LA and its appendage, and the RA can be extremely helpful prior to transseptal puncture. This is particularly true in patients predisposed to thrombus. Although most clot occurs in the left atrial appendage, it occurs with much higher frequency in the rest of the LA in the setting of atrial fibrillation and rheumatic heart disease (47). Thrombus along the septum, on prosthetic valves, and on pacemaker wires adds substantial risk, and most operators consider these absolute contraindications to transseptal puncture. However, safe performance of procedures such as balloon mitral valvuloplasty despite the presence of appendage thrombus has been described (48). The relative thickness of the septum, aneurysmal excision, deviation into the RA (more common with left atrial hypertension such as is seen with mitral valve stenosis (49), and presence of a PFO are all potentially important variables to know prior to attempting the transseptal.
Imaging
The most common techniques for adjunctive imaging are ICE (49) and TEE (50), both of which can blunt the learning curve for transseptal puncture, and provide for a margin of safety even for highly experienced operators. Transthoracic echo alone has been used as an adjunct when transseptal puncture with fluoroscopic guidance alone was difficult (51), but this technique has largely been supplanted. TEE preprocedure in patients at high risk of left atrial thrombus is a Class I indication (34), and both TEE and CT angiography have been used to assess for thrombus (52,53). The consensus statement published by the Heart Rhythm Society lists TEE as the “gold standard,” with a recommendation that all patients with atrial fibrillation at the time of ablation should be screened with a TEE (54). More recently, real-time three-dimensional echo guidance has been utilized to facilitate transseptal puncture (Fig. 23.9) (55). Preprocedure CT angiography, in conjunction with electroanatomic mapping (56) has been used as an adjunct to transseptal puncture, and an animal model using intraprocedural magnetic resonance imaging to guide laser driven transseptal puncture has been described as well (57).

In certain settings, such as pregnant patients where the operator has deemed fluoroscopy to be hazardous, the procedure has been done with echo guidance alone (58) or with fluoroscopy plus echo designed to minimize radiation (59). Since minimal radiation is required for a transseptal, most operators continue to use fluoroscopy in pregnant patients to minimize procedure duration and for the added margin of safety provided by the additional imaging guidance (60).

TRANSSEPTAL PROCEDURE
Preparation
Although transseptal puncture has been performed by venous access from a variety of approaches, including the internal jugular, subclavian and even hepatic veins, the standard remains the right femoral route. Left femoral venous access requires negotiating the additional curvature of the left iliac vein, in particular as it enters the inferior vena cava, and provides technically more difficult access to the interatrial septum; it is nevertheless quite feasible. We place a short 7-Fr sheath in the right femoral vein, and perform right heart catheterization if clinically warranted. This helps identify hemodynamics before transseptal puncture, including the pressure to expect when the needle enters the LA, and establishes the baseline hemodynamics should a subsequent suspicion of tamponade occur. We also fluoroscope the left heart border in the anterior-posterior view, to note the degree of motion seen before puncture. At this point, we advance a pigtail catheter retrograde to the aortic valve, usually from the femoral artery, although a radial approach can also be used. Because the fossa is usually below the level of the aortic cusps, placement of the pigtail at the aortic valve is an important adjunct to prevent entry into the aorta or perforation of the RA secondary to a high puncture (Fig. 23.10) (61). Electrophysiologists performing transseptal puncture will frequently place a catheter in the coronary sinus to provide an alternative or additional anatomic landmark (Fig. 23.2B) (62). The pigtail catheter is connected to a pressure manifold, and systemic pressure is continuously displayed during the procedure, from pretransseptal puncture to at least five minutes after withdrawal of the transseptal sheath, to ensure that sheath withdrawal does not unmask a stitch perforation (discussed subsequently) or other errant puncture that may result in early tamponade.

Maneuvering to the Septum
After withdrawal of the right heart catheter, the venous sheath is carefully flushed. The Mullins assembly is potentially quite thrombogenic and should not be introduced into the vein until all the equipment is completely prepared and the operator is ready to perform the puncture. A 0.032-in J-tipped guidewire is...
then advanced through the femoral venous sheath (some Mullins assemblies will accept a 0.035-in wire); when advanced from the femoral vein directly (rather than inside a catheter), the wire tends to enter the SVC easily. If introduced through the Mullins dilator, the curvature tends to steer the wire away from the ostium of the SVC, and more manipulation is typically required. Once the wire is in place in the SVC, the venous sheath is removed and the Mullins dilator and sheath are advanced; some operators place the assembly into the left subclavian vein. The dilator is flushed, taking care to make sure there is venous return, since aggressive flushing of the dilator buried in the vessel wall can cause local dissection. The Brockenbrough needle and Bing stylet (Fig. 23.3A) are advanced through the dilator, with care taken to allow the needle to rotate freely as it traverses toward the SVC. If the needle is held rigidly during advancement and prevented from rotating freely, there is a small risk of perforation; in addition, it places pressure against structures that abut the vena cava, particularly Glissen’s capsule of the liver, and can cause considerable discomfort. The Bing stylet helps prevent perforation of the sheath and dilator as the needle is advanced. Once the needle and stylet enter the RA, the needle can be turned to face toward the patient’s left (3 o’clock) as it is advanced up into the SVC, and the stylet withdrawn when the needle is a few centimeters from the tip of the dilator. The needle is then connected to extension tubing attached to the manifold. Flushing the needle requires some care while drawing back on the column of fluid in the needle and should be done slowly with the operator using his fingers pressed against the point where the needle enters the dilator hub to prevent air from entering around the needle (Fig. 23.3B). The needle should be kept at least a few millimeters proximal to the dilator tip. If it is too proximal, there is a risk of the dilator kinking when the assembly is pressed against the septum and can result in perforation of the dilator when the needle is advanced. If it is too distal, there is a risk of inadvertent needle deployment and perforation of the SVC or RA. The operator should maintain his fingers in the space between the needle arrow and the dilator hub to prevent inadvertent movement of the needle proximally or distally. The alignment of the Mullins sheath, dilator and needle should be parallel (Fig. 23.3A). Care should be taken to maintain this alignment throughout the subsequent movement of the Mullins assembly.

Once properly flushed and an undamped pressure tracing is seen on the monitor, the entire assembly is pulled down into the RA with the needle pointer aimed in a posterior medial direction (approximately 4–5 o’clock, with 6 o’clock being straight posterior). The tip of the dilator can usually be seen to deflect off the SVC-right atrial junction, and then to fall below the limbus. We typically pull it back an additional centimeter and advance into the fossa. At this point, unless the fossa is displaced toward the RA by elevated left atrial pressure, resistance should be felt.

**Localization at the Fossa Ovalis**

Several maneuvers can confirm appropriate location of the dilator prior to attempted puncture. Fluoroscopy should demonstrate that the tip of the Mullins assembly is below the pigtail that was placed in the aortic root; the relevant relationship of the dilator to the pigtail catheter and anatomic structures can be seen in different views in Figures 23.10 and 23.11. Although puncture can also be performed in the 20° RAO view (Fig. 23.12) (63) or the anterior-posterior view as well, in our experience the
Figure 23.11  The correct position for transseptal puncture in the (A) anterior-posterior and (B) 20° right anterior oblique planes. The fossa ovalis has been stained (white arrow), and the Mullins assembly can be seen to have entered the fossa. Note that the target for transseptal puncture is approximately 1 to 2 cm below the bottom of the aortic cusp (as demarcated by the location of the pigtail catheter in the aorta). In the 20° right anterior oblique view, the fossa is typically located below the center of a line drawn from the right anterior free wall to the bottom of the aortic cusp.

Figure 23.12  The Mullins assembly in simultaneous (A) anterior-posterior and (B) 90° left lateral views; the needle is too low and too posterior to consider attempted transseptal puncture. In the image on the left, the tip of the catheter can be seen to be well below the aortic cusps; in the image on the right the catheter tip abuts the posterior free wall of the right atrium. Needle advancement in this position would lead to pericardial entry and risk of tamponade. This patient had severe mitral stenosis and was undergoing transseptal puncture for mitral valvuloplasty; note the double density caused by the enlarged left atrium (short arrows).

best guidance to avoiding the left atrial free wall is the 90° lateral (Fig. 23.13). (Adequate imaging in this view requires that the patient’s arms be raised out of the field; if the procedure is done under anesthesia the arms should be moved prior to induction or with great care afterward, since brachial plexus injury can result if inadvertent traction is placed on the arms.) The relationship of the fossa ovalis to the aortic cusps and posterior LA is most likely to be fixed in the center of a line drawn at a 45° angle between the
If the catheter is low, it can be moved into position with a gentle 'windshield wiper' maneuver: clockwise turns the assembly posteriorly and counterclockwise anteriorly. Aggressive manipulation should be avoided; besides trauma to the RA, patients in sinus rhythm predisposed to atrial arrhythmias, such as those with mitral stenosis and dilated LA, are prone to develop atrial fibrillation. With normal anatomy, the dilator tip will be tented against the fossa; contrast injection to “tag” the septum is benign and can assist visualization but is not ordinarily necessary (Figs. 23.11 and 23.13). If the operator is uncertain of location, however, this is a useful maneuver.

If ICE (49) or TEE is performed as an adjunct to the procedure, tenting of the fossa (Fig. 23.9) should be seen. The advantages of intraprocedural echocardiographic guidance have been extensively demonstrated (64), although operators should be sufficiently versed in transseptal anatomy that they are not unduly dependent on echo guidance. However, additional benefits of ICE or TEE beyond anatomic guidance for transseptal puncture include early warning of pericardial effusion. A review of tamponades during ablation procedures revealed echocardiographically apparent pericardial effusion before hemodynamic compromise in 11 of 13 patients (65). A characteristic electrogram recorded through the Brockenbrough needle and associated with the fossa ovalis has been described (66), although this technique is rarely if ever used. A number of other schemes (Fig. 23.14) for assessing location of the septum and the fossa have been described and include right atrial angiography in a variety of views, including visualization of the LA in the levo phase of the injection.

At this point, with pressure applied by the dilator tip against the fossa ovalis, and without deployment of the needle, it is possible to advance into the LA through the foramen ovale in a significant percent of patients, variably described as 25% to 90% (68). Although a classic PFO may not be present, prolonged gentle pressure may allow “peeling” apart the
overlapping layers of septum secundum and residual septum primum when the foramen does not ordinarily open with the usual maneuvers. Catheter passage through a PFO is suitable for diagnostic catheterization but causes problems for many interventional procedures, since the foramen tunnel restricts pivoting of the sheath, and the orientation is relatively superior and posterior. In some cases, passage without needle deployment is not through the foramen tunnel but directly across an extremely thin fossa, the latter in keeping with the membranous nature of the septum primum that forms the embryonic fossa valve.

Although transseptal puncture at the center of the fossa is usually ideal, some interventions require high or low puncture. The former is desirable when a relatively perpendicular plane of access is required toward the mitral valve, such as for percutaneous mitral valve repair with a clip device (35), or left atrial appendage occlusion (36). Low puncture is desirable when a relatively shallow entry to the mitral valve is ideal, such as was the case for percutaneous metallic mitral commissurotomy (69).

**Puncture and Device Advancement**

Once the operator has ascertained that the location is suitable, it is essential that only the needle and not the rest of the assembly perforate the septum (Fig. 23.13B). A video demonstrating transseptal entry using a 90° lateral view can be downloaded from an article by Cheng and colleagues (70). The technique shown does not include use of the pigtail catheter in the aortic root to identify the level of the aortic cusps, and features combined entry of the dilator and needle into the LA, a technique best avoided because needle entry alone is usually benign, while errant entry of both needle and dilator is much more likely to lead to tamponade.

The operator has several means of confirming left atrial entry. A tactile sensation of the catheter popping through the septum is usually felt. Entry of the needle into the LA should be immediately apparent when a distinctive left atrial pressure is seen on the monitor (Fig. 23.15). When the fossa is thickened, or the operator advances into the thick septal wall outside of the fossa, a damped pressure is usually seen; in older patients the septal wall can be fibrosed or calcified, in which case the waveform may occasionally appear to be a reflection of a slightly damped left ventricular pressure. In some cases, a higher velocity of needle entry will allow for penetration of the thickened or fibrosed septum; it is occasionally necessary to pass the needle and dilator together in this setting. It is essential that the operator be reasonably certain of the needle’s location against the fossa before committing to such combined entry. In addition to tactile sensation and pressure monitoring, contrast injection will confirm needle location in the LA. Oxygen saturation can also be obtained through the transseptal needle. If ICE or TEE is being performed, the needle and catheter are usually visualized in the LA (Fig. 23.9), the tenting of the septum resolves, and saline or contrast injection appears as “bubbles” in the LA on echo. Some operators use a coronary guidewire immediately after needle puncture to confirm entry into the LA (Fig. 23.16) (71).

At this point we rotate the image intensifier to visualize catheter advancement in an anterior-posterior plane. If the

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**Figure 23.15** One of several modalities for confirming catheter entry into the LA. Damped right atrial pressure (RA, double arrow) was recorded while the dilator tip was against the fossa. Immediately after transseptal puncture, the phasic waveform characteristic of left atrial pressure is seen (LA, black arrow). Right and left atrial pressures, 40-mm Hg scale; aortic pressure (AO), 200-mm Hg scale. Abbreviations: LA, left atrium; RA, right atrium.
If the septum is thin, it may be possible to advance the dilator and sheath without further advancement of the needle. If the septum is thick, it may be necessary to advance the entire assembly to have enough support to prevent the sheath from buckling as it advances against the septum. Care needs to be taken at this point since it is possible to have the entire assembly prolapse back into the RA if the septum offers resistance. Of greater concern is the risk of perforating the LA as the assembly is advanced. Continuous pressure monitoring through the needle with immediate discontinuation of advancement if pressure damping is noted, as well as small puffs of contrast to identify if the assembly is near to the left atrial wall will protect the LA (Fig. 23.17). If the septum is relatively soft, it may be possible to withdraw the needle completely once the dilator has crossed the septum, in which case a J-tipped guidewire can be placed through the dilator to allow safe advancement of the sheath and dilator assembly. Alternatively, if support from the shaft of the needle is required, a 0.014” coronary guidewire can be advanced through the needle into the LA or a pulmonary vein, to visualize approach to the left atrial wall, and provide some protection from perforation (Fig. 23.16) (72). A significant risk for perforation occurs during blind advancement of needle or dilator (with no guidewire of any kind used), and an abrupt forward movement frequently occurs as the sheath penetrates the septum over the dilator, especially if the sheath is overcoming resistance caused by a thickened septal wall. For certain procedures, such as percutaneous balloon mitral valvuloplasty, sheath entry is optional, since the Inoue guidewire can be advanced through the dilator alone.

Anticoagulation

There has been a dramatic change in the approach to anticoagulation for transseptal puncture in the last several years. This represents a dichotomy between interventional cardiologists performing structural heart disease interventions who have been concerned predominantly about tamponade and electrophysiologists performing ablations whose primary focus has been the avoidance of thrombus formation and stroke. Ablations tend to be of longer duration and have several features that increase the predisposition to clotting, including platelet activation by the catheters themselves and char formation that triggers thrombus formation. Some operators, including many electrophysiologists, give at least a small amount of heparin before the puncture (73) on the basis of data suggesting a lower rate of intraprocedural left atrial thrombus, while others perform transseptal puncture with patients fully heparinized (70) or maintained on therapeutic oral anticoagulation (44). A comparison of warfarin discontinuation plus bridging of anticoagulation with enoxaprin versus maintenance of therapeutic range oral
anticoagulation during the periprocedure period did not demonstrate a difference in complication rates (74).

In contrast, interventional cardiologists have focused on avoidance of tamponade, with most deferring transseptal puncture if the international normalized ratio is greater than 1.6 or patients are heparinized. However, stroke secondary to thrombus formation is an important source of morbidity and mortality during prolonged structural heart disease interventions as well, an example being closure of prosthetic paravalvular leaks (75). And while aggressive anticoagulation may help prevent thrombus formation, it is important to note that the most common single cause of peritransseptal mortality with structural heart disease interventions as well as ablation procedures remains pericardial tamponade (76). Importantly, when anticoagulation is deferred until after puncture, the tamponade rate is higher than 1% (77). The exact peri- and postprocedure anticoagulation management of these patients remains a focus of investigation (78).

If patients are not anticoagulated at the time of needle entry into the LA, transseptal puncture should be performed expeditiously to allow anticoagulation as soon as the LA has been entered to prevent thrombus formation on the catheter tip or guidewire. The target for activated clotting time (ACT) has increased in the recent literature to a range of 300 to 400 seconds (79); comparison of two groups with ACTs of 250 to 300 seconds versus ACT greater than 300 seconds demonstrated a reduction of catheter associated thrombus from 11% to 3% (80). The consensus statement by the Heart Rhythm Society recommends continuous heparin infusion at 10 units/kg/hr with ACT checked every 10 to 15 minutes until therapeutic anticoagulation is achieved, and then every 30 minutes thereafter (53). Despite the relatively aggressive anticoagulation regimen, stroke continues to be a factor after transseptal puncture; in the ablation literature, transient ischemic events and stroke continue to occur in the 0.5% range (77). However, transcranial Doppler does demonstrate that a significant portion of microembolic signals are unrelated to the puncture itself (81).

Sheath Management
Handling of the transseptal sheath for the rest of the procedure needs to follow certain basic principles. Wires and catheters should be withdrawn from the Mullins sheath slowly, since abrupt negative pressure caused by rapid catheter or wire withdrawal can induce air to enter the sheath. Similarly, flushing should be performed with care to avoid sucking air in through the sheath diaphragm; we prefer to allow back bleeding through the sheath sidearm and do not put negative pressure on the sheath since the diaphragm can leak air into the fluid column when negative pressure is applied. Passive air embolization due to the gradient between atmospheric pressure and low left atrial pressure, a phenomenon most common in the setting of sedation and exacerbated by placement of a guidewire through a sheath hemostatic valve, is an important and relatively common occurrence, and requires careful technique to avoid (82). If the left atrial pressure is low, it may be necessary to suspend the end of the Mullins sheath below the patient to ensure that pressure at the open sidearm is lower than left atrial pressure. Some operators keep the proximal end of the sheath inside a large bowl of saline or other solution. Introduction of air during introduction of devices through the Mullins sheath is a common occurrence. We maintain a column of diluted contrast in the sheath so that as a device is introduced, bubbles in the column are readily detected under fluoroscopy, in which case the device can be withdrawn and the sheath repreared as necessary. The Mullins sheath needs to be flushed regularly, or a drip maintained with a system designed to prevent air from entering the column of fluid.

COMPICATIONS
Complications of transseptal puncture are significant and potentially life threatening (Table 23.2). The event rates are quite variable, and are influenced by several important factors, including level of anticoagulation, duration of the procedure, size of catheter used, intracavitary pressure, status of pericardium (intact or removed), use of echocardiographic guidance, and most importantly the operator learning curve (83). The major complication rate is far lower in diagnostic (1%) (84) than interventional procedures (4%) (85), likely because of less aggressive anticoagulation in most diagnostic studies, shorter duration of diagnostic procedures, and the addition of morbidity associated with the interventions themselves. In the era before ablation procedures were common, the incidence of tamponade was more than 10 fold higher (1.2%) than the incidence of stroke (0.1%) (84). While the profile of complications seen after transseptal puncture for structural heart disease interventions may be significantly different than that seen with electrophysiology procedures, as the complexity and duration of the former increase, these differences may be muted.

Tamponade
As discussed, the most dreaded complications of transseptal puncture remain pericardial tamponade and clot or air embolization. The incidence of tamponade is highly variable, but remains a significant concern in a wide variety of procedures associated with transseptal puncture (86), and has been described to range from 0.5% to 4% in patients undergoing percutaneous balloon mitral valvuloplasty (87). In patients undergoing ablation, tamponade has been described as occurring in up to 6% of cases (54), associated with the type (linear) and

<table>
<thead>
<tr>
<th>Table 23.2 Complications of Transseptal Puncture</th>
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<tr>
<td>I. Mechanical</td>
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<tr>
<td>a. Perforation</td>
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<tr>
<td>i. Pericardial tamponade</td>
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<tr>
<td>ii. Hemothorax</td>
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<td>b. Persistent atrial septal defect</td>
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<tr>
<td>c. Right to left shunting</td>
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<td>d. Aortoatrial fistula</td>
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<td>II. Embolization—peripheral or central nervous system</td>
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<td>a. Thrombus</td>
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<td>III. Arrhythmias</td>
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<td>a. Atrial fibrillation</td>
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<tr>
<td>b. Supraventricular tachycardia</td>
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<tr>
<td>c. Inferior ST segment elevation</td>
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<td>d. Bezold-Jarisch reflex</td>
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<tr>
<td>e. Sinus node dysfunction</td>
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<td>IV. Death</td>
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energy of ablation (88) and therefore presumably not necessarily related to the transseptal puncture itself. The occurrence of tamponade underestimates the frequency of pericardial effusion secondary to small iatrogenic effusions: in one study of 1150 patients with left atrial access preparatory to planned atrial fibrillation ablation, effusion occurred in 2.7% while tamponade requiring pericardiocentesis occurred in approximately one-third of these patients (1%) (89). An uncommon but important cause of tamponade is stitch perforation (90). In this scenario, the needle exits the RA and enters the LA while traversing tissue folds or periadventitial fat (Fig. 23.18). The separation between the chamber walls is limited, and the operator is typically unaware of extracardiac passage of the needle. During most of the subsequent procedure, tamponade may not occur because the fenestration is sealed by catheters or sheaths; when these are removed at the end of the case, effusion and tamponade may occur. The phenomenon is most likely to occur with a low stick. Some operators address this possibility by leaving a guidewire in place prior to withdrawal of all hardware from the septum and observing for a few minutes to detect any pericardial effusion. If in fact this occurs, the guidewire can provide access for placing a sheath to tamponade the hole temporarily while anticoagulation is reversed (86).

Embolization

Once the Mullins sheath has been placed, maintenance of adequate anticoagulation, proper flushing and avoidance of introduction of air are integral to the safety of the procedure.

Air as well as clot embolization remain important sources of morbidity (91); setting up a continuous flush through the sheath during extended procedures has been described as preventing air and clot embolization, and the stroke risk appears to be lower when a high-flow state is maintained through the transseptal sheath (92). If bolus flushing of the sheath is performed, consideration should be given to using a high heparin concentration, since there is evidence that thrombus formation is inversely related to the concentration (93). Stroke and transient ischemic attack secondary to transseptal catheterization have been widely reported to occur in the range of approximately 1% with values as high as 5% in patients with ablation procedures for atrial fibrillation (94). A phenomenon that appears to be migraine has been described in approximately 0.5% of patients, and may occur up to one week after transseptal puncture (95).

Persistent Atrial Septal Communication

The creation of a communication between left and right atria commonly results in postprocedure shunting (96). Use of balloon dilatation to allow larger sheaths to enter the septum increases the risk of persistent ASD (97) as well as tamponade. Some transseptal flow after the procedure is almost always seen on TEE, and correlates with size of the puncture as well as driving pressure determined by disparity between left and right atrial pressures. Thus, early in the era of percutaneous balloon mitral valvuloplasty, when the septum was routinely dilated with peripheral angioplasty balloons ranging in size from 5 to 10 mm, and two transseptal sheaths were usually placed, left-to-right flow was detected by TEE in 87% of patients, although the majority of these resolved within six months (98). These patients usually had a degree of residual mitral stenosis; thus, a 10-mm Hg or more driving pressure across an iatrogenic 5- to 10-mm defect in the septum would result in a significant sized permanent ASD. In addition, balloon dilatation of the septum can cause ripping rather than stretching of the septal opening. At present, dilators are typically used to create a sufficient size fenestration, even for devices larger than the typical 14 Fr used for mitral dilatation. Persistent ASD after electrophysiology procedures, particularly when two catheters are placed across the septum, is also seen in approximately 87% of patients, with resolution in all except 4% by one year (99). Using two transseptal punctures rather than placing two catheters across a single fenestration appears to decrease the risk of a persistent shunt (100). Because the left-to-right gradient is smaller in electrophysiology procedures, the presence of a residual shunt remains more common with mitral valvuloplasty (85).

Transseptal puncture in patients with high right-sided pressures increases the risk of right to left shunting and systemic arterial desaturation. One scenario is the use of a transseptally placed percutaneous ventricular assist device (TandemHeart) in the setting of right heart failure or right ventricular infarction when a PFO is also present. The simultaneous decompression of the LA has been demonstrated to result in substantial cyanosis because the iatrogenic pressure gradient drives large amount of blood across the PFO from right to left (101). For similar reasons, in the rare case of percutaneous dilatation of both tricuspid and mitral stenosis, the tricuspid valve should be dilated first, to prevent a setting in which left atrial pressure is substantially
lower than right atrial pressure after mitral valve dilatation results in right to left shunting (102).

Bezold-Jarisch Reflex
ST segment elevation, accompanied by chest pain, hypotension, bradycardia and diaphoresis has been reported by a number of operators to occur during or immediately after transseptal access. While the phenomenon resembles a Bezold-Jarisch reflex, the mechanism is unclear. It occurs in somewhat less than 1% of cases (89). Although introduction of air with consequent right coronary embolization has been postulated (103), coronary angiography during such episodes has failed to confirm this (104), and a neurally mediated mechanism remains the likely etiology. The phenomenon is typically transient, and may respond to atropine.

TREATMENT OF COMPLICATIONS
Tamponade
Prompt recognition of tamponade is essential to successful outcome. If ICE or TEE is performed during the procedure, it can provide early recognition of pericardial effusion in over 80% of cases prior to the onset of hemodynamic compromise (65). Hypotension is commonly the first sign, although early in tamponade hypertension and tachycardia may occur, likely secondary to catecholamine stimulation (86). In some patients there is an abrupt slowing of heart rate, likely a vasovagal response to sudden pericardial stretch. Knowledge of the patient’s baseline hemodynamics is helpful; incipient or actual tamponade should be accompanied by familiar hemodynamic findings, including a narrow pulse pressure with pulsus paradoxus, near-obliviation during inspiration, and elevation with equalization (in most cases) of right and left heart filling pressures. Early diagnosis of tamponade is greatly facilitated by continuous arterial pressure display during the procedure. One of the earliest and most specific findings in the catheterization laboratory is straightening and immobility of the left heart border that is readily seen on fluoroscopy in the anterior-posterior view. This reflects the profile of the tense pericardium along with the markedly diminished stroke volume that accompanies tamponade. Although ICE or TEE can provide immediate confirmation of the diagnosis, if the procedure is done without continuous echo guidance, a transthoracic echo can be obtained. However, if the echocardiographic equipment is not already in the cardiac catheterization laboratory, waiting for its arrival prior to performance of pericardiocentesis may be fatal and the operator needs to proceed promptly in the setting of critical hemodynamic compromise. Once the pericardium has been tapped, a catheter should be left in place for drainage; the average withdrawn after tamponade in anticoagulated patients was greater than 800 mL in one study of 15 periblation tamponades (65). Reversal of anticoagulation is helpful in this setting, and is one reason that we routinely use heparin rather than bivalirudin in patients undergoing transseptal puncture. Surgical evacuation of the pericardium is usually not necessary, frequently results in the surgeon finding no obvious locus of perforation, and may expose the patient to substantial unnecessary morbidity and some mortality. Nevertheless, in certain scenarios, such as inadvertent laceration of a coronary artery, there may be no alternative to surgery (65). If the patient is in extremis, transthoracic pericardiocentesis is unsuccessful, and the delay to surgical evacuation is likely to be fatal, one other alternative has been described: access to the pericardium using an intracardiac approach with the transseptal apparatus purposely utilized to perforate the heart and enter the pericardial space (105).

Air or Clot Embolism
Treatment of air embolism is variably successful. Aggressive oxygenation, particularly in a hyperbaric chamber, and especially if performed promptly, is the procedure of choice (91). Infusion of volume to maintain cerebral perfusion and administration of lidocaine to protect cerebral tissue may also be beneficial. Aggressive transcatheter suctioning of air if trapped in a cardiac chamber has occasionally prevented clinically significant embolism. Treatment of clot embolization is more complex. Iatrogenic embolization of thrombus has been treated by intravenous (106) and intraarterial (107) thrombolysis, as well as a variety of clot disruption (108) and extraction techniques (107), although the evidence base remains minimal (109). We have successful experience with thrombus embolization from a transseptal sheath to the left main coronary artery treated with aspiration using techniques primarily employed for primary coronary intervention in acute myocardial infarction (110).

NEW TECHNOLOGIES AND FUTURE CONSIDERATIONS
To facilitate safe transseptal puncture and modernize the Mullins apparatus, a transseptal access device, ACross (St. Jude Medical), has been developed. The device prevents inadvertent advancement of the needle while still inside the dilator, a concept that had been described previously using a safety stop (111). Several new technologies provide alternatives to the Brockenbrough needle and are designed to require less force to cross the septum, avoiding the typical high velocity movement with a rigid needle and attendant risks associated with uncontrolled advance of both needle and Mullins assembly. The techniques are particularly appealing when there is a thick or fibrosed septum that may be difficult or impossible to penetrate. One of the technologies uses radiofrequency energy to puncture the septum and includes a catheter system (112) that is approved by the U.S. Food and Drug Administration (Baylis Medical, Montreal, Quebec, Canada). The system has a curved and flexible tip designed to decrease the risk of trauma to the LA, and sideholes to facilitate dye injection. Using a similar approach, radiofrequency has been applied directly through a transseptal needle to facilitate transseptal puncture (113).

Another technique to minimize the force required to cross the septum and decrease perforation risk is a 0.014-in nitinol wire with a needle like tip that assumes a J shape once free in the LA and functions as a guidewire to facilitate dilator access (114) (SafeSept, Pressure Products, San Pedro, California, U.S.). Two other technologies should be mentioned. One experimental device under development is the LACross (St. Jude Medical). It features a sheath placed in the RA either from the internal jugular or femoral vein, with a sidehole that allows a catheter with a hollow screw to drill through the septum. Once in the LA, an Inoue wire can be advanced allowing atraumatic introduction of additional catheters. Finally, laser catheters have been used for controlled access to the LA, both in an
animal model using magnetic resonance guidance (57) and in a small series of patients (115) (Fig. 23.19).

Training for competence to perform transseptal punctures has been challenging. There is no consensus on the number of procedures required to achieve or maintain competence despite the significant learning curve and periprocedural risks associated with the procedure. Training with a minimum of 20 transseptals (116) and proficiency at emergency pericardiocentesis have been proposed (117) as minimal requirements. Transseptal puncture meets the criteria for procedures where simulator training is appealing: high-risk, relative low volumes of procedures to which most trainees are exposed, and potential for additive risk to the patient when the procedure is done under supervision rather than entirely by an experienced primary operator. Accordingly, several simulation systems have been developed.

Figure 23.19 A gallery of novel technologies for transseptal puncture: (A) The A Cross device is a Mullins apparatus with needle and safety lock (St. Jude Medical, St. Paul, Minnesota, U.S.); (B) the Toronto catheter is designed to allow controlled radiofrequency entry, contrast injection and sheath introduction (Baylis Medical, Montreal, Quebec, Canada); (C) radiofrequency applied through a transseptal needle; (D) magnetic resonance imaging used for laser transseptal access in an animal model; (E) a nitinol needle system (SafeSept, Pressure Products, San Pedro, California, U.S.); (F) the LACross (St. Jude Medical) is designed to allow transseptal puncture with a catheter deployed through a side fenestration of a sheath placed in the RA. Technologies in (C–D) and (F) are experimental or offlabel. Abbreviations: LA, left atrium; RA, right atrium; LAA, left atrial appendage. Source: Courtesy of the manufacturers (A–B and E–F) and the publishers (C–D) (see text for manufacturer name and location), Refs. 57 and 111–113.
CONCLUSIONS
Transseptal puncture, the gateway to the LA for a growing variety of structural heart disease and electrophysiologic procedures, is of increasing importance in invasive cardiology. The significant benefits of proficiency in performing transseptals is somewhat offset by the substantial learning curve and complication profile associated with the procedure. However, the dramatic rise in number of transseptals performed has been accompanied by an expanding evidence base in the literature addressing issues such as optimal periprocedure management, in particular anticoagulation. A number of technologies, including adjunctive imaging and, more recently, equipment to facilitate the transseptal puncture itself, may improve the overall success rate and safety of this now half-century-old procedure.

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INTRODUCTION
Catheter-based contrast angiography remains the “gold standard” in the diagnosis of mesenteric and renal artery disease and usually follows a high index of clinical suspicion and corroborative noninvasive testing. Duplex ultrasonography, computed tomography angiography (CTA), and magnetic resonance angiography (MRA) have become extremely helpful in the initial assessment of patients with suspected disease, but invasive angiography is often required for definitive diagnosis. Catheter-based angiography has the added benefit of providing simultaneous interventional therapy if required. This chapter reviews the vascular anatomy and equipment essential to conducting a proper mesenteric and renal angiographic examination and highlights the proper indications for invasive testing of these vessels. Percutaneous mesenteric and renal interventions are addressed in separate chapters.

INDICATIONS
Mesenteric Angiography
The principal indication for mesenteric angiography is evaluation of intestinal ischemia that may be acute or chronic (1). Classically, patients with acute intestinal ischemia present with sudden or recent onset pain and little or no findings on abdominal physical exam. These patients often have a history of coronary artery disease, peripheral arterial disease, or other cardiovascular risk factors (Table 24.1). Acute intestinal ischemia should also be suspected in patients with severe abdominal pain following endovascular procedures that involve catheter traversal in the abdominal aorta. The decision to perform angiography on patients with suspected acute intestinal ischemia needs to be individualized. For instance, patients presenting with acute abdominal pain due to suspected arterial occlusion with intestinal infarction should be referred for immediate laparotomy instead of angiography. Alternatively, patients with nonocclusive disease may benefit from a strategy that incorporates initial angiography.

As in those with acute ischemia, patients with chronic mesenteric ischemia often have coexisting atherosclerotic disease (Table 24.2). In cases of suspected chronic intestinal ischemia, there is often time for initial assessment with noninvasive testing including duplex ultrasound, CTA, or MRA. Angiographic evaluation should be performed in patients with abnormal or indeterminate noninvasive testing. Alternatively, diagnostic mesenteric angiography may be performed as an initial diagnostic tool if these noninvasive testing modalities are not available.

Renal Angiography
Renal angiography is indicated in patients in whom renal artery stenosis (RAS) is clinically suspected and who have also corroborative noninvasive testing suggesting significant disease. Renal arterial disease is prevalent in patients with other forms of atherosclerotic disease such as multivessel coronary artery disease and peripheral arterial disease. The clinical clues suggesting the diagnosis of RAS are detailed in Table 24.3. Of these, the strongest clinical indicators are early onset of hypertension prior to age of 30 years; multidrug-resistant hypertension; development of renal failure or declining renal function after institution of angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB); atrophic kidney or 1.5-cm size discrepancy between kidneys; flash pulmonary edema; and unexplained renal failure. When renal arterial disease is suspected, noninvasive imaging with duplex ultrasound, MRA with gadolinium enhancement, or CTA is recommended to first establish the diagnosis of RAS.

CLINICAL ASPECTS
Acute Mesenteric Ischemia
Although relatively infrequent, acute mesenteric ischemia is a life-threatening condition caused by a sudden decrease in blood flow to the intestines. Prolonged intestinal hypoperfusion can culminate in bowel necrosis and death, and mesenteric ischemia is associated with mortality ranging from 60% to 100% (2,3). While the early use of angiography has resulted in a decline in mortality rates over the past 30 years, patient outcome is highly dependent on prompt recognition and early treatment of this disease process (4).

Acute mesenteric ischemia is characterized with duration of hours to days and may be caused by embolic, thrombotic, or nonocclusive etiologies (Table 24.1) (5,6). Classically, patients present with sudden severe abdominal pain out of proportion to the findings on clinical exam and may have fever and bloody stool. With occlusive acute mesenteric ischemia, patients often have coexisting atherosclerotic disease or risk factors that predispose them to embolism or thrombus formation. Most often, occlusive acute mesenteric ischemia involves the proximal superior mesenteric artery (SMA) either by thrombosis of preexisting plaque or by embolism to this site (7). In nonocclusive mesenteric ischemia, intestinal hypoperfusion results from a low-flow state in the splanchnic circulation caused by a sudden drop in systemic blood pressure, severe arterial vasospasm (e.g., from cocaine use or treatment with vasopressin or norepinephrine), or cardiogenic shock (2,6,8). The splenic flexure, a watershed area supplied by the SMA and inferior mesenteric artery (IMA), is particularly susceptible to ischemia in low-flow states. Overall, the incidence of acute mesenteric ischemia is rising (3). The reasons for this are unclear, but may in part be due to a growing elderly population with atherosclerotic disease and increased proportion of patients with shock states requiring vasoactive medications (3).
Table 24.1 Risk Factors for the Development of Acute Mesenteric Ischemia

- Advanced age
- Low cardiac output
- Cardiac arrhythmia (e.g., atrial fibrillation)
- Valvular heart disease
- Recent myocardial infarction
- Malignancy
- Hypercoagulable states
- Critical illness or prolonged intensive care unit stay
- Trauma

Table 24.2 Risk Factors for the Development of Chronic Mesenteric Ischemia

- Peripheral arterial disease
- Coronary artery disease
- Advanced age
- Diabetes mellitus
- Smoking
- Obesity
- Hyperlipidemia
- Sedentary lifestyle

Table 24.3 Clinical Clues to the Diagnosis of Renal Artery Stenosis

- Early onset of hypertension before the age of 30 yr
- Onset of severe hypertension after the age of 55 yr
- Multidrug-resistant hypertension
- Development of new renal failure or worsening renal function following initiation of ACE (angiotensin converting enzyme) inhibitor or ARB (angiotensin receptor blocker) therapy
- Size difference between kidneys of more than 1.5 cm or unexplained atrophic kidney
- Systolic-diastolic epigastric bruit
- Unexplained renal failure
- Multivessel coronary artery disease
- Unexplained or recurrent pulmonary edema
- Angina refractory to medical management

Chronic Mesenteric Ischemia

In comparison to acute mesenteric ischemia, chronic mesenteric ischemia is more indolent in nature, with duration of onset over weeks to months. Patients are most commonly female and present with abdominal pain, weight loss, and no alternative explanation. The abdominal discomfort is variable in character and may have associated bloating; it typically occurs 30 minutes to 3 hours after food ingestion. Recurrent intestinal angina causes sitophobia (fear of food). Patients suffering from chronic intestinal ischemia often reduce their food intake and on an average lose 10 to 20 kg prior to diagnosis.

The patients are typically smokers and have additional cardiovascular risk factors or evidence of systemic atherosclerosis (Table 24.2). Indeed, progressive atherosclerotic disease causes the vast majority of chronic mesenteric ischemia. Less common etiologies include vasculitis, fibromuscular dysplasia (FMD), and aortic dissection. The classical teaching has been that chronic mesenteric ischemia is nearly always caused by narrowing of two or more mesenteric vessels. The mesenteric vessels—celiac trunk, SMA, and IMA—can develop collaterals at multiple levels such that a high-grade stenosis of any single vessel is generally well tolerated. Patients who have had surgical interruption of these splanchnic collateral networks are more likely to be symptomatic from single-vessel mesenteric disease (10,11). Additionally, single-vessel disease involving the SMA has been reported to cause chronic mesenteric ischemia. Chronic mesenteric ischemia can also result from mesenteric vein thrombosis, most often involving the superior mesenteric vein. Primary venous thrombosis is caused by hereditary hypercoagulable states, while secondary venous thrombosis results from etiologies associated with malignancy or inflammation. While the mortality rate in chronic mesenteric ischemia is far lower than that of acute mesenteric ischemia, the natural history of chronic mesenteric ischemia is less well defined and some patients with chronic ischemia progress to acute mesenteric ischemia (12).

Median Arcuate Ligament Syndrome

Median arcuate ligament syndrome (also known as celiac artery compression syndrome, celiac axis syndrome, and Dunbar syndrome) is a rare clinical entity thought to be caused by the compression of the celiac axis by anomalous fibrous diaphragmatic bands. It is characterized by postprandial abdominal discomfort and weight loss and is occasionally associated with an abdominal bruit (13). While the pathophysiology of this disorder is not clearly understood, some have suggested a congenital origin (14). Since the SMA and the IMA remain widely patent in these cases, there should, in theory, still be ample blood supply to the bowel. As such, the diagnosis of median arcuate ligament syndrome remains controversial and is often one of exclusion (15–17). Expiration may accentuate regional stricture in patients with median arcuate ligament syndrome, and catheter angiography during respiratory maneuvers is often helpful in evaluating these patients.

Visceral Artery Aneurysms

Aneurysms of the mesenteric vessels are uncommon. The majority of patients with these visceral aneurysms are asymptomatic, and these aneurysms are found incidentally during unrelated abdominal imaging (18,19). However, these aneurysms do carry a risk of rupture and hemorrhage that can be fatal. Splenic artery aneurysms are the most common occurring in 60% of cases. In one series, fewer than 20% of patients with splenic artery aneurysms presented with abdominal pain or rupture (20). The mortality rate for nonpregnant patients with splenic artery aneurysms ranges between 10% to 25% but may be as high as 70% for pregnant females (21). In general, splenic aneurysms greater than 2.0 cm in diameter are thought to be of sufficient risk of rupture to warrant treatment. Aneurysms do carry a risk of rupture and hemorrhage that can be fatal. Splenic artery aneurysms are the most common occurring in 60% of cases. In one series, fewer than 20% of patients with splenic artery aneurysms presented with abdominal pain or rupture (20). The mortality rate for nonpregnant patients with splenic artery aneurysms ranges between 10% to 25% but may be as high as 70% for pregnant females (21). In general, splenic aneurysms greater than 2.0 cm in diameter are thought to be of sufficient risk of rupture to warrant treatment. Aneurysms involving the hepatic artery are increasingly common and presently make up 20% of cases. This is probably due to an increase in percutaneous biliary procedures being performed today as well as increased recognition from incidental imaging (22). Aneurysms of the SMA are less common accounting for only 6% of total cases. Aneurysms of the renal arteries are most commonly associated with FMD, which is discussed in the following section. Vasculitis and trauma have also been associated with renal artery aneurysms (23).

Renal Artery Stenosis

Renovascular disease is well recognized as a potentially reversible cause of hypertension and renal failure. RAS has been associated with coronary artery disease and congestive heart
failure, and patients with RAS have a markedly reduced survival rate. RAS by ultrasound is also prevalent in patients with other forms of atherosclerotic disease such as peripheral arterial or coronary artery disease. Population-based studies have demonstrated that approximately 20% to 60% of patients with peripheral arterial disease also have RAS (24). In a study of patients who underwent screening aortography at the time of coronary angiography, 4.8% had significant renal stenoses of more than 75% narrowing (25).

Clinically, RAS may present as uncontrolled hypertension, flash pulmonary edema, intolerance to ACE-I or ARB treatment, progressive renal deterioration, or refractory angina. The presence of renal arterial disease does not necessarily indicate that the patient’s hypertension or renal failure is caused by RAS, and outcomes in renal revascularization studies have been discordant (26–28). When hypertension is attributed to RAS, the term “renovascular hypertension” is commonly used. Flash pulmonary edema or renal failure following administration of ACE-I or ARB usually indicates significant bilateral renal arterial disease or significant disease in a solitary kidney.

RAS is most commonly due to either atherosclerotic disease or FMD (29). Atherosclerosis is the main mechanism of RAS in patients older than 55 years. Atherosclerotic renal arterial lesions are most often aorto-ostial in location, involving the ostial and proximal segment of the vessel; distal or branch vessel involvement is uncommon (28). Progression in atherosclerotic RAS occurs in more than 40% of patients (30). Fibromuscular dysplasia is seen predominately among young female patients. The etiology of FMD is unknown, but a genetic predisposition has been suggested (31). Degenerative changes lead to fibroplasia and arterial wall weakening resulting in fibrous, band-like stenoses often interposed with aneurysmal dilatations. The angiographic appearance of FMD has thus been characterized as “beads on a string” (Fig. 24.1). Unlike in atherosclerotic RAS, distal or branch vessel involvement in FMD may occur. Disease progression occurs in more than 30% of patients in FMD (30).

ANATOMIC CONSIDERATIONS

Mesenteric Circulation

The mesenteric arteries arise from the anterior aspect of the lower thoracic and abdominal aorta. These vessels—the celiac trunk, SMA, and IMA—are responsible for the blood supply to all organs located within the abdominal cavity. The celiac trunk is the first major branch of the abdominal aorta and is an essential source of blood supply to the liver, stomach, and parts of the esophagus, spleen, duodenum, and pancreas. Its origin from the anterior aorta is typically midline at the level of the T12 vertebral body; and it courses inferiorly for 1 to 2 cm before branching into the left gastric, common hepatic, and splenic arteries (Fig. 24.2). The common hepatic divides into the proper hepatic artery and, typically, also the gastroduodenal artery. The proper hepatic gives off the right gastric artery before branching into the right and left hepatic arteries. The gastroduodenal artery then goes on to divide into the right gastroepiploic artery and the anterior and posterior superior pancreaticoduodenal arteries. The right gastroepiploic artery and the left gastroepiploic artery (from the splenic artery) join together along the greater curvature of the stomach. The right gastric artery and the left gastric artery join together to run along the lesser curvature of the stomach. Because of the redundant blood supply to the stomach, gastric ischemia is uncommon.

Figure 24.1 Selective right renal angiogram demonstrating fibromuscular dysplasia (FMD). Degenerative changes lead to fibroplasia and arterial wall weakening resulting in fibrous, band-like stenoses often interposed with aneurysmal dilatations. The angiographic appearance of FMD has thus been characterized as “beads on a string” (arrow).

Figure 24.2 Normal anatomy of the celiac artery. (A) Common hepatic artery; (B) left gastric artery; (C) esophageal branches; (D) splenic artery; (E) short gastric branches; (F) splenic branches; (G) left gastroepiploic artery; (H) right gastric artery; (I) right gastroepiploic artery; (J) superior pancreaticoduodenal artery; (K) gastroduodenal artery; (L) hepatic artery. Source: From Ref. 32.
The SMA usually originates 1 cm lower than the celiac trunk and anterior to the L1 vertebral body. The SMA travels inferiorly and slightly rightward to supply the duodenum and pancreas. In its course, the SMA passes beneath the pancreas and divides into the inferior pancreaticoduodenal, middle colic, right colic, ileocolic, and intestinal branches (Fig. 24.3). In general, the middle colic artery provides blood supply to the proximal and mid-transverse colon. In some individuals, the middle colic may provide the main source of blood to the splenic flexure. The right colic artery provides the blood supply to the middle and distal ascending colon, while the ileocolic artery supplies the distal ileum, cecum, and proximal ascending colon. The middle, right, and ileocolic branches join together with the left colic artery (from the inferior mesenteric) forming the marginal artery or artery of Drummond that courses along the inside border of the colon. Multiple anatomic variations of the colic arteries exist.

The IMA is the smallest of the mesenteric vessels. It originate below the level of the renal arteries and approximately 6 to 7 cm below the SMA. The IMA courses inferiorly and leftward giving off the left colic artery and several sigmoid branches before terminating in the superior rectal artery (Fig. 24.4). The IMA is responsible for providing the blood supply to the distal transverse colon, descending colon, and the rectum. The left and middle colic branches may join together, effectively anastomosing the SMA and IMA circulations in what is known as the arc of Riolan.

Renal Arteries

The renal arteries originate from the lateral abdominal aorta immediately below the SMA at the level of the lower border of the L1 vertebral body. There are slight anatomic differences between the two renal arteries. In one study of 100 patients who underwent spiral CTA, the right and left renal arteries originated at the same level in 50% of patients (33). In the other 50% of cases, the right renal artery arose higher than the left. The right renal artery also typically courses downward to the supply the more inferiorly located right kidney; the left renal artery typically has a horizontal course. The right renal artery has an anterolateral origin from the aorta while the left renal artery has a posterolateral origin. Both renal arteries typically give off small inferior suprarenal branches before dividing into segmental branches. These segmental branches subsequently divide into arcuate and multiple interlobular branches terminating within the renal cortex and medulla. Accessory renal arteries are the most common vascular variant (34). These accessory vessels may be of similar or smaller caliber and typically originate lower than the main artery, supplying the inferior pole of the kidney (Fig. 24.5). Another variant occurs when the main artery divides early in its course into segmental branches. Finally, it should be noted that the renal arteries can be surgically bypassed or reimplanted in the pelvis (“autotransplant”).
EQUIPMENT AND TECHNICAL CONSIDERATIONS

Abdominal Aortography

Prior to selective engagement, initial abdominal aortic angiography should be performed with a pigtail or Omniflush catheter (Omni Flush, AngioDynamics Inc., Queensbury, New York, U.S.) (Table 24.4). The Omniflush catheter is designed to minimize the amount of upward-refluxed contrast and thus may result in more contrast concentrated at the level of the renal and mesenteric vessels. Usually, the aortogram is adequate to demonstrate patency but often is insufficient to adequately assess degree of stenosis of the mesenteric and renal vessels. The aortogram does, however, provide important adjunctive information regarding the presence of aortic calcification, aneurysmal dilatation, and anatomical anomalies (e.g., number of accessory renal arteries) as well as the location of the renal and mesenteric ostia (Fig. 24.6). The catheter should be placed with its side holes placed at the T12-L1 intervertebral space (i.e., above the origin of the renal arteries). For optimal imaging, the field of view should be maximized, the table elevated to its highest setting, and the table positioned such that the catheter tip is at top of the screen. If a recent prior abdominal aortogram is available for review, repeat study is not necessary and the operator should proceed to selective assessment of the arteries of interest.

The abdominal aortogram is first performed in a standard posteroanterior (PA) projection using digital subtraction. Our practice is to use a 5-Fr system with a total volume of 10 to 20 mL of contrast at a rate of 10 mL/sec. Patients should be instructed not to breath or move prior to angiography. Lateral projection aortography may then be performed to visualize the mesenteric arteries since these vessels arise anteriorly (Fig. 24.7). This should also be done with digital subtraction, and similar settings may be used. If the renals are the sole focus of the study, a 15° left anterior oblique (LAO) projection is recommended and can be performed using a smaller amount of contrast.
contrast (10 mL/sec for 10 mL total). For these studies, the contrast may be diluted as 70% dye and 30% heparinized saline. This dilution technique reduces the total contrast exposure and still results in acceptable image quality.

Selective Mesenteric Angiography

A 5-Fr system is usually adequate for diagnostic mesenteric angiography (Table 24.5). Femoral access is commonly used; but in general, an arm approach is easier for the selective engagement of the mesenteric vessels. From a femoral access, our preference is to use a reverse angulation catheter such as a Sos (AngioDynamics) catheter that allows easy access to the inferiorly directed ostia of the celiac trunk, SMA, and IMA (Figs. 24.8–24.11). A JR 4 diagnostic, internal mammary artery or left coronary bypass (LCB) catheter can also be used to engage these vessels. Reverse angulation catheters should be positioned by moving them caudally with a generous amount of wire extending from the tip that allows for a relatively atraumatic bend of wire over which the catheter can pass. Once the catheter is positioned superiorly to the vessel ostia, its curve is formed by the slow withdrawal of the wire. If kept in an anterior orientation and walked down the aorta, such reverse angle catheters should readily find the mesenteric ostia, but care should be taken as these catheters also will readily catch onto sidewall atheroma.

Table 24.5  Equipment for Selective Mesenteric Angiography

- Sheath
  - 5 Fr or 6 Fr
- Catheters
  - JR 4
  - IMA
  - Sos
  - Simmons 1, 2, 3
  - Cobra C2
  - Hockey Stick
  - Multipurpose (arm approach)
- Wires (0.035 in.)
  - Standard J-wire
  - Glidewire
  - Wholey
  - Rosen

Figure 24.7  Lateral abdominal aortogram demonstrating the anterior origins of the celiac artery (A) and superior mesenteric artery (B). Nonobstructive narrowing of the proximal celiac artery (C) is present.

Figure 24.8  Selective angiography of the celiac trunk. As the first major branch of the abdominal aorta, the celiac trunk (A) originates from the anterior aorta at the level of the T12 vertebral body and branches into the left gastric (B), common hepatic (C), and splenic (D) arteries. The common hepatic artery further divides into the proper hepatic and gastroduodenal (E) arteries. This angiogram demonstrates an anomalous left hepatic artery arising from the gastroduodenal artery.

Figure 24.9  Selective angiography of the superior mesenteric artery (SMA). The SMA (A) travels inferiorly and slightly rightward to supply the duodenum and pancreas. In its course, the SMA gives off the inferior pancreaticoduodenal arteries (B), the middle colic artery (C), and several intestinal arteries (D).
Alternatively, many operators prefer an arm approach in selective mesenteric studies. From a brachial or radial approach, the mesenteric arteries can usually be easily engaged using a multipurpose diagnostic catheter. In most cases catheters that are 125 cm in length are necessary with the (right) radial approach. Arm access is particularly helpful in patients with severe aortoiliac tortuosity and highly angulated vessel origins. Arm access should also be used in patients with known abdominal aortic aneurysms and patients with severe aortoiliac disease.

Selective angiography of the celiac trunk is performed with a 15° to 30° LAO angulation to demonstrate the celiac axis origin and trifurcation into the left gastric, common hepatic, and splenic arteries. In cases of suspected celiac artery compression, comparative, selective views should be obtained at end-inspiration and end-expiration as expiration may exacerbate vessel compression (Fig 24.12). Given its course to the rightward pelvis, angiography of the SMA should be performed in a 15° to 30° LAO. In comparison, the IMA has a leftward course; and thus, selective angiography of this vessel should be performed in a 15° to 30° right anterior oblique (RAO) projection. As with abdominal aortography, digital subtraction angiography is recommended. The field of view should be adequate to visualize the mesenteric vessel of interest as well as all potential collateral networks in cases of occlusion.

**Selective Renal Angiography**

When performing renal angiography, we predominately use femoral access with a 5-Fr system (Table 24.6). Arm access is reserved for those patients with severe aortoiliac disease or known abdominal aortic aneurysm. The JR 4 catheter is our workhorse catheter for selectively engaging the renal arteries. Alternatively, an internal mammary or renal double curve
catheter can also be used. In cases of aortoiliac tortuosity, a Cobra C2 (Terumo, Somerset, New Jersey, U.S.), Sos, or Simmons catheter may be necessary to reach the ostia (Fig. 24.13). Regardless of the equipment chosen, the catheter must never be advanced to the renal ostia without the use of a wire. Such manipulation can result in advancement of atheromatous debris into the renal ostium (“snowplow effect”). Using a 0.035-in. wire, the catheter should be positioned anteriorly at the L1 level. Gentle retraction with clockwise (left renal artery) or counterclockwise (right renal artery) manipulation of the catheter allows for selective engagement.

Aortic calcifications and prior-placed renal artery stents serve as important landmarks indicating the renal ostia (Fig. 24.14). Bear in mind, the renal arteries do not originate directly from the lateral aorta. The right renal artery originates about 20° to 30° anteriorly, and the left originates only slightly posteriorly. Therefore, PA projection angiography may not adequately illustrate the renal ostium. Accordingly, one study demonstrated optimal visualization of the right renal ostia in only 26% of cases and of the left in 38% of cases (32). Our practice is to perform selective right and left renal angiography with a 10° to 20° LAO angulation. Occasionally, additional slight (10°) cranial or caudal angulation may be necessary for optimal visualization. Since the right renal artery travels down below the inferior vena cava, additional RAO projections may be necessary to adequately visualize the entire course of this vessel. Care should be taken to visualize any accessory renal arteries since these occur commonly.

Prior to injection, the catheter must be aspirated well and the pressure waveform should reflect a crisp arterial tracing. The field of view should be large enough to incorporate the kidney, and the cineangiogram run should also be long enough to visualize the influx of contrast into the renal cortex. This nephrogram yields important insight into renal size and regional function. Such adjunctive information becomes particularly important in individuals with suboptimal or equivocal noninvasive studies.

With selective renal angiography, a few additional technical points should be mentioned. The operator should be careful to avoid unnecessary trauma to the renal ostia with engagement as this may lead to showering of aorto-ostial atherosclerotic debris. Care should also be taken not to deep-seat the catheter past the renal ostium as this may lead to underestimation of the lesion severity due to insufficient opacification of the ostium.
Damping of the pressure waveform on selective engagement may indicate significant ostial stenosis.

**SPECIAL ISSUES/CONSIDERATIONS**

**Contrast Selection and Renal Insufficiency**

An optimal diagnostic angiographic should allow for complete examination of the arterial bed with the least amount of contrast used. In patients with renal insufficiency, it is critical to minimize the amount of contrast used during the angiographic study. Low osmolar contrast agents are preferred as they minimize patient discomfort and both reduce the risk of contrast-induced nephropathy (CIN) and allergic reactions. The only available iso-osmolar contrast agent, ioxagloïn, may be associated with a lower risk of nephropathy than low osmolar agents, particularly among patients at high risk for contrast nephropathy (35). Despite the lower risk of complications with these agents, the possibility of CIN and allergic reaction remain. Carbon dioxide (CO2) angiographic imaging is an alternative in patients who remain at high risk for these complications. CO2 is a very dissolvable gas that is nontoxic to the kidneys and is nonallergic (36,37). It works by displacing blood cells inside the vessel, effectively reducing the radiographic density within the lumen. There are certain limitations to this form of imaging that should be noted. Importantly, contrast resolution with CO2 angiography, while often adequate, is inferior to that with traditional iodinated contrast agents (38). CO2 angiography must also be performed in a controlled fashion with carefully administered gas volumes to avoid gas trapping in the pulmonary circulation (39). Gadolinium also has been studied as a possible alternative agent in patients at risk for CIN. However, this agent has not been proven to have any significant advantage over low osmolar agents in reducing CIN and has been largely abandoned (40).

**Difficulty in Visualizing Renal Ostia**

Renal artery ostial disease may be missed by standard angiography. If clinical suspicion of RAS is high, nontraditional views with added cranial or caudal angulation should be attained. Intravascular ultrasound (IVUS) is an alternative modality that can be used for better visualization of the renal arteries and to determine the presence of renal artery ostial disease. The operator should pay attention to hemodynamic clues such as catheter damping that may indicate a significant ostial lesion. Finally, measurement of fractional flow reserve across intermediate lesions has emerged as an attractive technique to assess indeterminate lesions. A translesional pressure gradient of 20 mmHg or greater is generally considered indicative of a hemodynamically significant stenosis.

**Difficulty Using Arm Approach**

As discussed above, an arm approach for mesenteric and renal angiography can be very helpful in certain circumstances. However, in cases of subclavian stenosis, innominate stenosis, or tortuous aortic arch, the passage of diagnostic catheters and equipment from an arm approach can be challenging. In these cases, a long sheath should be used and advanced into the descending aorta and placed above the level of the mesenteric vessels. For right radial approach, catheters that are 125 cm in length must be used. A stiff 0.035-in. wire such as a Rosen or a stiff Glidewire may also facilitate catheter and sheath placement in this circumstance.

**CONCLUSIONS**

The invasive assessment of patients with suspected mesenteric or renal vascular disease needs to be performed cautiously and meticulously. These patients, particularly those with preexisting renal insufficiency, can have a high risk of procedure-related complications. However, if careful technique is observed and minimal contrast used, such angiographic assessment can yield critical clinical information and potentially set the stage for important interventional therapies.

**REFERENCES**


Peripheral arterial angiography

Ivan P. Casserly

INTRODUCTION
The widespread availability of noninvasive angiographic techniques, notably computed tomography (CT) and magnetic resonance (MR) angiography, has had a dramatic impact on the practice of routine peripheral angiography of the upper and lower extremities (1–3). Most invasive angiographic studies are now performed to confirm the findings on noninvasive studies for the purpose of performing vascular intervention or to image small diameter extremitv vessels for which the resolution of CT or MR angiography is insufficient. The result is a more targeted and individualized approach to angiography that answers a clinical question or helps direct a therapy. This chapter will outline the angiographic anatomy of the arterial supply of the upper and lower extremities, and provide a practical approach to angiography of these territories.

LOWER EXTREMITY
Anatomic Considerations
Arterial Anatomy of the Lower Extremities
The distal abdominal aorta typically bifurcates at the level of third or fourth lumbar vertebra into right and left common iliac arteries (CIA) (Fig. 25.1) (4,5). Each CIA passes in an anterior direction in the pelvis before bifurcating into external (EIA) and internal (IIA) iliac artery branches. The IIA generally divides into two trunks (in 60% of patients) but may have four or more trunks. In addition to branches to the pelvic organs (i.e., bladder, rectum, female, and male reproductive organs), the IIA provides the superior and inferior gluteal branches that supply the gluteal muscles and the obturator branch. These branches serve as an important source of collaterals to the ipsilateral and contralateral limb in the presence of iliac occlusive disease.

The EIA continues with an anterior trajectory, becoming the common femoral artery (CFA) at the level of the inguinal ligament. There is some variability in the location of the CFA bifurcation into superficial (SFA) and profunda (PFA) branches (Fig. 25.2). One prospective angiographic study found the bifurcation below the middle and inferior border of the femoral head in 99% and 80% of individuals, respectively (6). Arising from the proximal portion of the PFA are the medial and lateral circumflex femoral branches, which serve as important collateral pathways in the presence of occlusive disease affecting the iliac arteries and CFA. The PFA continues laterally into the thigh supplying three or four perforator branches to the muscles of the thigh, which serve as the main source of collaterals to the leg when the SFA is occluded (Fig. 25.3), underscoring the importance of the PFA. Fortunately, the PFA rarely has significant occlusive disease in patients with extensive disease in the SFA.

The primary function of the SFA is to provide an arterial conduit for arterial flow to the knee, leg, and foot. Under normal circumstances, it provides no significant angiographic branches in the thigh. While in the thigh, it sequentially runs through the femoral triangle, the muscular adductor canal, and the adductor hiatus, at which point it becomes the popliteal artery. The popliteal artery initially runs in the popliteal fossa posterior to the distal third of the femur, and subsequently along the posterior surface of the tibial plateau, providing articular branches to the capsule and ligaments of the knee joint, and sural branches that supply the calf muscles (Fig. 25.2). Although the popliteal artery is typically described as having a trifurcation, this is a misnomer, as the most typical pattern is a bifurcation into an anterior tibial (AT) artery and tibioperoneal trunk (Fig. 25.4). Passing anteriorly through the interosseous membrane between the tibia and fibula, the AT reaches the anterior compartment of the leg and courses inferiorly to a point midway between the malleoli where it becomes the dorsalis pedis artery. The tibioperoneal trunk has a variable length (typically 2–4 cm), before dividing into the posterior tibial (PT) and peroneal arteries. Both of these arteries continue inferiorly in the posterior compartment of the leg. The PT passes posterior to the medial malleolus before dividing into medial and lateral plantar branches (Figs. 25.5 and 25.6), whereas the peroneal branch typically terminates above the level of the ankle joint. All three tibial branches provide the major arterial supply to the calf muscles. Although variable, the terminal portions of the three tibial branches typically provide important collateral communications that provide flow to the foot in the presence of proximal occlusive disease of one or more tibial branches (Fig. 25.7).

Within the foot, the plantar branches of the PT, and the dorsalis pedis branch of the AT, variably contribute arterial inflow to the metatarsal arch, which runs along the base of the metatarsal bones. The metatarsal branches arise from this arch and course toward the interdigital spaces, providing digital branches to the toes.

Arterial Anatomy of the Upper Extremities
The arterial inflow to the right and left upper extremities is provided by the right and left subclavian arteries (SCA), respectively (3,7). While the left subclavian artery arises directly from the aortic arch as the third and terminal great vessel, the right subclavian arises from the bifurcation of the innominate artery. In approximately 0.5% of patients, the right subclavian artery arises as the terminal vessel from the descending thoracic aorta (Fig. 25.8).

The subclavian artery extends from its origin to the lateral border of the first rib (Fig. 25.9). Its course is divided into three segments based on the relationship of the artery to the scalenus anterior muscle. The first segment that lies medial to the scalenus anterior muscle provides the most important branches of the subclavian artery, notably the vertebral and
internal thoracic arteries and the thyrocervical trunk. While the vertebral and internal thoracic arteries are largely constant in their origin and course, the thyrocervical trunk greatly varies between individuals, in terms of the pattern and size of its various branches. In 4% to 6% of individuals, the left vertebral artery had a direct origin from the aortic arch, typically between the origins of the left common carotid and left subclavian arteries.

The axillary artery reflects the continuation of the subclavian artery and extends from the lateral border of the first rib to the inferior border of the teres major muscle. During angiography, the latter anatomic border roughly corresponds to the position of the anatomical neck of the humerus. Similar to the subclavian artery, the axillary artery is divided into three segments on the basis of its relationship to the pectoralis minor muscle. Significant interindividual variation is seen in the location and size of branches of the axillary artery.

**Figure 25.1** Angiographic anatomy of the distal abdominal aorta and pelvic arteries. (A) Right anterior oblique view; (B) left anterior oblique view. 1, Inferior mesenteric artery; 2, lumbar branch; 3 and 4, right and left common iliac artery; 5 and 6, right and left internal iliac artery; 7 and 8, right and left external iliac artery; 9 and 10, right and left common femoral artery.

**Figure 25.2** Angiographic anatomy of the right common femoral artery (A), profunda femoral (A), superficial femoral (B, C), and tibial arteries (C). 1, Common femoral artery; 2, profunda femoral artery (PFA); 3, superficial femoral artery (SFA); 4, perforating branch of PFA; 5, muscular branches of SFA; 7, distal SFA; 8, approximate location of adductor hiatus; 9, descending genicular branch; 10, popliteal artery; 11, articular branch of popliteal artery; 12, sural branch of popliteal artery; 13, anterior tibial artery; 14, tibioperoneal trunk; 15, peroneal artery; 16, posterior tibial artery.

**Figure 25.3** (A) Collaterals branches from right superficial femoral artery (SFA) in presence of significant stenosis (arrowhead); (B) collateral filling of distal right SFA and popliteal artery via collaterals from the profunda femoral artery (PFA) in the presence of a distal SFA occlusion (extent of occlusion shown by arrows). 1, SFA; 2, SFA collateral; 3, PFA; 4, PFA collateral to distal SFA/popliteal artery; 5, popliteal artery.
Figure 25.4 Examples of variant angiographic anatomy of the tibial vessels. (A) True trifurcation of the left popliteal artery; (B) long tibioperoneal trunk in right leg; (C) bifurcation of the left peroneal artery; (D) absent tibioperoneal trunk, with origin of the posterior tibial artery as the first branch of the left popliteal artery, followed by the peroneal artery and anterior tibial artery. 1, Popliteal artery; 2, anterior tibial artery; 3, tibioperoneal trunk; 4, peroneal artery; 5, posterior tibial artery; 6 and 7, bifurcation branches of peroneal artery—one of these branches supplied the medial plantar branch to the foot.

Figure 25.5 Angiograms from two patients (A,B) demonstrating the collateral circulation between the distal portion of all three tibial vessels. 1, Anterior tibial artery; 2, peroneal artery; 3, posterior tibial artery; 4, posterior communicating branch; 5, perforating branch; 6, dorsalis pedis artery; 7, lateral plantar artery; 8, medial plantar artery; 9, metatarsal arch.

Figure 25.6 Angiographic anatomy of the left foot. (A) Lateral projection; (B) posterior-anterior projection with cranial angulation. 1, Anterior tibial artery; 2, peroneal artery; 3, posterior tibial artery; 4, dorsalis pedis artery; 5, lateral plantar artery; 6, medial plantar artery; 7, metatarsal arch; 8, metatarsal branches.

Figure 25.7 Angiographic anatomy of the right foot in a patient with an occluded dorsalis pedis artery. (A) Lateral projection; (B) posterior-anterior projection with cranial angulation. 1, posterior tibial artery; 2, peroneal artery; 3, lateral plantar artery; 4, medial plantar artery; 5, metatarsal arch; 6, metatarsal branches.
it divides into radial and ulnar branches (Fig. 25.10). The profunda brachii branch of the brachial artery is considerably smaller and clinically insignificant compared with its counterpart in the lower extremity (i.e., the PFA). Other major branches of the brachial artery include muscular branches to the arm muscles, the nutrient artery to the humerus, and vessels to the elbow joint.

Analogous to the posterior tibial artery of the lower extremity, the ulnar artery is the major vessel to the forearm and is usually larger than the radial artery. It arises from the brachial artery bifurcation at the level of the neck of the radius and runs through the arm to the pisiform carpal bone. Its main branch is the interosseous artery, which courses lateral to the ulnar artery, supplying the forearm muscles and interosseous membrane. In addition, the ulnar artery supplies branches to the elbow joint, muscular branches to the forearm, carpal branches to the palmar and dorsal aspect of the wrist, contributes to the deep palmar arch, and continues into the hand as the major source of blood flow to the superficial palmar arch.

Analogous to the AT artery of the lower extremity, the radial artery is the smaller of the terminal branches of the brachial artery. It runs from the brachial artery bifurcation toward the styloid process of the radius, contributing to the deep palmar arch, and carpal branches to the forearm, and carpal branches to the wrist.
the palmar and dorsal aspects of the wrist. In the hand, it contributes to the superficial palmar arch and continues into the hand as the major source of flow to the deep palmar arch.

The superficial and deep palmar arches provide the arterial flow to the hand (Fig. 25.11). Angiographically, the superficial arch lies distal to the deep arch and is generally more prominent. Formed primarily from the terminal portion of the ulnar artery, the superficial arch is less commonly complete (80%). The deep arch is formed primarily from the terminal portion of the radial artery and is complete in the majority of individuals (>95%). Common palmar digital arteries arise from the superficial arch and fuse with palmar metacarpal branches from the deep arch. In the interdigital space, each of the common palmar digital arteries divides into two proper palmar digital arteries that run along the borders of the 2nd to 5th digits and supply the arterial network of the finger pads. The princes pollicis branch typically arises from the terminal portion of the radial artery and supplies the thumb.

PERIPHERAL ANGIOGRAPHIC TECHNIQUE

General Comments
As outlined earlier, the current approach to peripheral angiography is typically targeted to confirm the findings of a prior noninvasive imaging study and guide an endovascular intervention or to define anatomic detail that cannot be provided by such imaging modalities, such as the tibial and pedal anatomy in a patient with critical limb ischemia. With the recent reports of nephrogenic systemic fibrosis following the administration of gadolinium-based contrast agents with MR angiography in patients with renal insufficiency (8,9), there has been a minor resurgence in demand for routine contrast angiography with X-ray equipment without dedicated vascular imaging capability is strongly discouraged. Tables 25.1 and 25.2 summarize the most commonly used catheters and wires used during lower and upper extremity angiography.

Lower Extremity Angiography
Lower extremity angiography generally encompasses imaging the distal abdominal aorta and pelvic vessels, in addition to the lower extremity vessels. This is most commonly achieved using retrograde femoral access. Using this access, a flush catheter is

Figure 25.11 Angiographic anatomy of the left hand in a patient with vasculitis and occlusion of the ulnar artery (black arrow). 1, Radial artery; 2, ulnar artery; 3, interosseous artery; 4, deep planter arch; 5, superficial planter arch; 6, common palmar digital branch; 7, proper palmar digital branch; 8, digital pad network.
advanced over a wire to the level of approximately L3 in the distal abdominal aorta. With the catheter in this position, left anterior oblique (LAO) 30° to 40° and right anterior oblique (RAO) 30° to 40° pelvic angiograms are acquired with the patient holding their breath (typically in exhalation). Injection rates of 10 to 15 cc/sec for a total of 20 to 30 cc are adequate in most patients (using psi of 800–1000). Acquisition of these oblique angulations is important to allow for optimal visualization of eccentric lesions, and definition of obstructive disease involving the aortoiliac and common iliac bifurcations (e.g., LAO to view the right aortoiliac and common iliac bifurcations).

Below the level of the iliac arteries, angiography of the lower extremity may be performed using one of two basic methods: the bolus chase technique or sequential static imaging. Using specially equipped angiographic X-ray systems, the bolus chase technique is achieved by administering a large volume of contrast in the lower abdominal aorta to image both lower extremities (~30 cc/sec for a total of 90 cc) or the EIA to image an individual lower extremity (~15 cc/sec for a total of 45 cc) that is coordinated with activation of cineangiographic acquisition. Depending on the particular X-ray system, the table is subsequently moved proximally using an automated or manual (according to the speed of the contrast runoff) mechanism, allowing imaging of the entire lower extremity. While this method certainly decreases the total procedure time and X-ray dose required to obtain angiographic images of the extremity, and eliminates the need to selectively engage the individual limb vessels, it has a number of limitations. In the authors’ experience, the definition of the infrapopliteal arterial anatomy using this technique is typically poor, and the presence of asymmetric occlusive disease, which creates significant differences in the rate of contrast runoff in both lower extremities, invariably results in suboptimal imaging from one of the limbs. The inability to alter the angulation of image acquisition along the length of the lower extremity also decreases the sensitivity of the technique for the detection of disease, particularly at bifurcation points. As a result, while the bolus chase technique is promoted as a method to limit contrast use, if additional static imaging is required to answer remaining diagnostic dilemmas, overall contrast use may be increased.

Although more time consuming and requires more catheter manipulation, sequential static imaging of the lower extremity remains the authors’ preferred method for lower extremity angiography. Image quality is usually superior, and with careful technique, the total contrast use is often comparable to that using the bolus chase method. Imaging of the lower extremity ipsilateral to the femoral sheath is achieved by injecting contrast through the sidearm of the sheath, or through a flush catheter positioned in the ipsilateral EIA. By moving either the image intensifier or the X-ray table, the entire region of interest is sequentially imaged. With modern image intensifiers with a 20 in. field of view, the lower extremity may be imaged using three to four overlapping acquisitions. Injection rates of 3 to 5 cc/sec for a total of 9 to 15 cc (using psi of 500–600) will provide uniform opacification of the entire length of vessel within the field of view.

An ipsilateral oblique projection (~30°) is optimal for imaging the CFA and its bifurcation into the PFA and SFA. Between the level of the mid-SFA and ankle, images are generally acquired in the posteroanterior (PA) or ipsilateral oblique projection (15–25°). In the leg, the relationship of the tibial vessels is variable, and multiple views may be required to provide views without vessel overlap. High-quality imaging of the foot is generally reserved in the assessment of patients with critical limb ischemia to assess the dominant arterial inflow to the foot or the site of tissue loss. In the authors’ experience, the combination of a steep contralateral oblique image of the externally rotated foot and a cranial image of the foot in the neutral position allows the best assessment of the small vessel anatomy of the foot for clinical decision making (Figs. 25.5 and 25.6). Peripheral X-ray angiographic imaging systems allow a programmed time delay between the injection of contrast and image acquisition. This becomes increasingly important with prolonged transit times (i.e., in the presence of total occlusions) and increased distance between the site of contrast injection and image acquisition (i.e., the foot with the catheter placed in the CFA).

To imaging the contralateral limb using the sequential static technique, a diagnostic catheter must be placed in the contralateral EIA or CFA. This clearly requires patency of the iliac system, and the major factors impacting the complexity of this task include the angulation of the aortic bifurcation and the tortuosity of the iliac system. In most patients, an internal mammary (IM) artery catheter allows for successful engagement of the contralateral CIA. However, for patients with acute angulation of the aortic bifurcation, prior aortoiliac stent placement or prior aortobifemoral bypass surgery, an SoS (Angio-Dynamics, Queensbury, New York, U.S.) or Simmons (Cordis Endovascular) catheter may be required. Following successful placement of a diagnostic catheter in the contralateral CIA, a road map of the iliac system (using 3 cc/sec for total of 6 cc) is performed with the image intensifier in the contralateral oblique projection. This allows passage of a stiff angled Glidewire (Terumo, Somerset, New Jersey, U.S.) into the contralateral CFA. Severe angulation of the aortic bifurcation or iliac tortuosity may require that the wire be advanced further into the PFA or SFA to provide increased wire purchase and support. Typically, the IM catheter is then advanced over this wire, which is exchanged for a Super stiff Amplatz wire (with 1-cm soft tip) (Boston Scientific Corp., One Boston Scientific Place, Massachusetts, U.S.) or Supra-Core wire (Abbott Vascular, Santa Clara, California, U.S.) for support. The IM catheter is then exchanged for a straight flush catheter through which angiography of the extremity is performed. Occasionally, the IM catheter cannot be advanced over the stiff-angled glidewire. In this case, a more flexible catheter such as a Glide catheter (Terumo) may be used, and by adopting a strategy of using increasingly supportive wires and catheters, the straight flush catheter can be ultimately delivered, although angiography through a glide catheter is also possible.

The principles for imaging the contralateral limb are identical to those for the ipsilateral limb, as outlined earlier. In selected patient subsets, such as those with renal insufficiency, and/or patients with critical limb ischemia requiring high-quality images of the infrapopliteal anatomy, the flush catheter may be advanced more distally over a wire into the distal SFA or popliteal artery with the goal(s) of reducing contrast use and improving image quality.

Alternative Arterial Access for Lower Extremity Angiography

Both antegrade CFA access and upper extremity arterial access (brachial or radial artery) may also be used to perform lower extremity angiography. While antegrade CFA access is typically used for complex lower extremity interventional procedures, it may also be necessary for diagnostic purposes where
the iliac anatomy prohibits contralateral access. Upper extremity arterial access may be required in patients who have a contraindication to CT or MR angiography and have complex iliac disease or an aortic occlusion preventing retrograde CFA access. The angiographic principles of lower extremity angiography from these alternative access sites are identical to that described earlier.

**Upper Extremity Angiography**

Diagnostic angiography of the upper extremities is typically performed using retrograde femoral access. An initial assessment of the anatomy of the aortic arch is helpful in determining the appropriate diagnostic catheter for engagement of the right and left SCA and the detection of anomalies (e.g., anomalous origin of right SCA distal to left SCA, direct origin of the vertebral artery from the arch) that might influence these engagements. In the authors’ experience, good quality angiography of the aortic arch is achieved using a 6-Fr pigtail catheter placed in the descending thoracic aorta, and injecting 40 cc of contrast at a rate of 20 cc/sec and a pressure limit of 1000 psi with the image intensifier or flat panel in the LAO 40° position.

In patients with normal anatomic origin of the great vessels and a benign configuration of the arch (i.e., type I), the innominate artery and left subclavian artery can be selectively engaged with either a Bernstein (Cordis Endovascular, Miami Lakes, Florida, U.S.), Judkins right (JR) 4, or angled glide diagnostic catheter. With increasing complexity of the aortic arch (i.e., type III), a Vitek catheter (Cook Inc., Bloomington, Indiana) or Simmons catheter (Cordis Endovascular) may be required. While the Vitek catheter can typically be shaped in the descending thoracic aorta, the Simmons catheters (i.e., Simmons 1, 2, and 3) require more skilled manipulation in the aortic arch and great vessels to help shape the catheter for vessel engagement.

The bifurcation of the innominate artery (i.e., including the ostium and proximal portion of the right SCA) is best imaged in the RAO oblique projection, whereas the LAO projection typically provides the best assessment of the origins of the right vertebral and right internal mammary arteries. For the left SCA, the RAO projection generally allows the most accurate assessment of the origins of the left vertebral artery and left internal mammary artery (LIMA). When imaging the SCA specifically for the purpose of assessing the presence of arterial compression due to thoracic outlet syndrome, angiography should be performed in the PA projection with the arm in the neutral position (i.e., arm at side in adducted position) and repeated with the shoulder in full abduction, external rotation, and retroversion (as if pitching a baseball).

Imaging of the upper extremity vessels beyond the level of SCA artery usually requires that a diagnostic catheter be advanced from the origins of the innominate and left SCA to the level of the axillary artery. In patients with friendly aortic arches (i.e., type I), this is usually straightforward and is achieved by advancing the diagnostic catheter over a long (300 cm) soft tipped 0.035 in. wire (e.g., Wholey (Mallinckrodt, St. Louis, Missouri, U.S.), Magic Torque (Boston Scientific Corp., Natick, Massachusetts, U.S.)] that is placed in the brachial artery using the road-mapping function for guidance. The presence of significant tortuosity in the subclavian artery may occasionally require the use of a glidewire (floppy or stiff body) to achieve this maneuver. With complex arch anatomy that necessitates the use of a Vitek or Simmons catheter for engagement of the left SCA or innominate artery ostia, these catheters need generally to be exchanged for a gentle shaped catheter (e.g., angled glide, straight flush, Bernstein) that can be delivered to the axillary artery after the 0.035 in. wire has been advanced into the brachial artery.

Axillary artery angiography is performed with the arm in the neutral position or slightly abducted. Angiography of the arm, forearm, and hand is performed with the patients forearm and hand placed in the supine position on an arm board, and the digits splayed apart. Tape is required to maintain the hand in this position and avoid motion artifact. Prior to imaging of the hand vessels, the administration of vasodilators is recommended, and the surface temperature of the hand should be kept warm to remove any component of spasm. After achieving the appropriate positioning of the patients upper extremity, sequential overlapping static images of the upper extremity vessels are acquired in the PA projection, using angulated views when required. Again, the use of an automated power injection that allows the injection of 12 cc over a 3-second period (psi of 500 to 600) for a 20 in. field of view is optimal for imaging above the level of the hand. In the hand, higher magnification images are required with use of shorter injection lengths (e.g., 5 cc/sec for total of 10 cc).

**CONCLUSIONS**

Peripheral angiography of the upper and lower extremities remains important in the assessment of patients with a variety of vascular disorders. A thorough understanding of the normal and anomalous arterial anatomy of the upper and lower extremities and a thoughtful approach to the angiographic technique will maximize the angiographic information required to answer specific clinical questions or guide endovascular intervention.

**REFERENCES**

INTRODUCTION
Traditionally, cerebral angiography has been performed by neuroradiologists, but the application of percutaneous intervention for chronic brachiocephalic occlusive diseases and acute stroke has resulted in the increasing involvement of interventional cardiologists. Accordingly, cardiologists are expected to have an understanding of diseases that impact the circulation to the brain, including diseases of the aortic arch, carotid artery, subclavian and vertebral artery, and intracranial diseases. This chapter discusses the purpose, specific goals, technique, and complications of catheter-based cerebral angiography. Subclavian artery intervention, extracranial carotid and vertebral intervention, and intracranial and stroke intervention are covered in separate chapters.

PURPOSE OF ANGIOGRAPHY
Despite the availability of noninvasive techniques such as duplex ultrasound, computerized tomography angiography, and magnetic resonance angiography, invasive angiography remains the gold standard for the diagnosis of extra- and intracranial arterial diseases because of superior spatial and temporal resolution. In general, invasive angiography may be recommended to clarify ambiguous results of noninvasive imaging, to obtain baseline angiographic evaluation prior to extra- or intracranial interventions, and to assess some patients with unusual diseases such as vasculitis, fibromuscular dysplasia, dissection, and prior arterial bypass surgery.

While noninvasive imaging techniques are often used for the diagnosis of carotid and vertebral artery diseases, the quality of these studies is dependent on the acquisition technique and the skill of the physician interpreting the study. Some noninvasive studies are limited by vessel tortuosity, heavy calcification, or other difficult anatomy. Overreliance on noninvasive imaging can result in misdiagnosis or the performance of unnecessary surgery (1,2). It is not unusual for interventions scheduled purely on the basis of noninvasive imaging to be abandoned or modified once invasive angiographic images have been obtained.

SPECIFIC GOALS OF ANGIOGRAPHY
The specific goals of cerebral angiography are to provide a detailed assessment of the aortic arch, extracranial brachiocephalic vessels, intracranial circulation, and collaterals (Table 26.1).

Arch Aortography
Every arch study must include an assessment of three key characteristics: the type of aortic arch, the configuration of the great vessels, and the extent of atherosclerosis. The aortic arch type depends on the relationship between the point of origin of the great vessels and the apex of the arch. Although several classifications are available, we rely on a modification of the Myla classification (3) (Fig. 26.1): type 1, in which all three great vessels originate from the apex of the arch; type 2, in which the first two great vessels [usually the innominate artery (IA) and left common carotid artery (CCA)] originate below the apex of the arch, and type 3, in which all three great vessels originate below the apex of the arch. Regardless of which classification is used, the goal is to distinguish “simple” (type 1) from “complex” (type 2 or 3) arches. Simple arches are conducive to selective cannulation of the great vessels from a femoral approach, whereas complex arches make selective cannulation more difficult due to aortic uncoiling, tortuosity, and the angle of origin of the great vessels. Aging itself, as well as the long-term consequences of atherosclerosis and hypertension, lead to elongation of the aortic arch, superior displacement of the aortic knob, inferior and posterior displacement of the great vessels, and elongation and sharp angulation of the left CCA (Fig. 26.1). Together, these morphological changes substantially increase the technical difficulties of selective cannulation and angiography, and may partially explain the increased risk of carotid interventions in octogenarians.

In contrast to the arch type, the arch configuration refers to the usual or anomalous origin of the great vessels. In the usual configuration, the IA, left CCA, and the left subclavian artery (SCA) originate as the first, second, and third great vessels from the arch, respectively (65% of individuals) (Fig. 26.1). Anomalous configurations include common origin of the IA and left CCA (so-called bovine configuration, 25%) (Figs. 26.2 and 26.3), origin of the left CCA from the proximal IA (7%), separate origin of the left vertebral artery (VA) from the arch (0.5%), separate origin of the right SCA from the distal arch (arteria lusoria, 0.6%), and origin of the left CCA and left SCA from a left IA (1.0%). A true bovine configuration is extremely rare and consists of a single IA that trifurcates into a right SCA, a single CCA, and a left SCA; the single CCA divides into right and left CCA.

The extent of arch disease should be described in detail, including the presence of stenosis, degree of calcification and tortuosity, as well as the presence of aneurysm or ulceration. In general, it is important to perform arch aortography prior to selective angiography, since the arch type, arch configuration, and degree of atherosclerosis will influence the need for catheter manipulation and catheter selection.

While arch aortography details the anatomy of the proximal intrathoracic brachiocephalic circulation (Fig. 26.1), selective angiography is preferred for more detailed assessment of the intrathoracic, cervical, and intracranial segments (Table 26.2). The purpose of selective angiography is to assess...
the presence, location, severity, and length of stenosis; normal reference vessel dimensions; morphological features of the stenosis (calcification, thrombus, ulceration, angulation); vessel tortuosity proximal and distal to the stenosis; patency of the major branches; and the integrity of the intracranial circulation and collateral pathways. Clinically, selective SCA angiography is often performed to assess SCA or internal mammary artery (IMA) graft patency, symptoms of vertebrobasilar insufficiency, or arm claudication. Subclavian arteriography should be performed in all patients who require cardiac catheterization after IMA bypass surgery (Fig. 26.4). Subclavian arteriography during coronary angiography prior to coronary artery bypass surgery (CABG) is reasonable in patients with known occlusive disease of the brachiocephalic circulation, cervical or supraclavicular bruits, discrepant blood pressure between both arms, symptoms suggestive of vertebrobasilar insufficiency, or arm claudication (4).

In most situations, selective SCA angiography provides sufficient images of the SCA and VA without selective VA angiography, particularly since most VA stenoses are located at the VA origin. In selected cases, particularly if VA intervention is performed, selective VA angiography is required. The SCA is considered in four sections (Fig. 26.5): proximal (origin of SCA to origin of VA), mid (segment of SCA involving the origin of the VA, IMA, and thyrocervical trunk), distal (segment of SCA distal to thyrocervical trunk and extending up to the axillary artery), and the axillary artery (Table 26.3). Although angiography of the brachial artery circulation is not routine during arch and cerebral angiography, it is important to have an understanding of the arterial circulation to the arm and hand.

Selective carotid angiography is performed most often to assess symptomatic or asymptomatic carotid artery atherosclerosis (Fig. 26.6). Less commonly, carotid angiography is performed to evaluate patency of a carotid-subclavian artery bypass, fibromuscular dysplasia, or spontaneous carotid dissection (Fig. 26.7). The carotid artery is considered in four segments (Table 26.3): the CCA (intrathoracic and cervical regions), the external carotid artery (ECA), the cervical internal carotid artery (ICA), and the intracranial circulation (intracranial ICA, middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior communicating artery (PCOM)).

### SPECIFIC VASCULAR TERRITORIES

#### External Carotid Artery

After its intrathoracic origin, the CCA bifurcates into the ECA and ICA at the level of the C3-C5 interspaces. The ECA is important because it supplies blood flow to most extracranial...
structures in the head and neck (Fig. 26.8), provides numerous anastomoses to the ICA and VA (Table 26.4), and may supply blood to intracranial neoplasms and vascular malformations. Some of these diseases may be outside the expertise of interventional cardiologists, but may be encountered during angiography for other reasons. For physicians interested in carotid artery stenting, the anatomy of the ECA is important for use of proximal embolic protection devices. Branches of the ECA include five anterior and three posterior arteries, which are visualized best in the lateral projection. Variations in the origin, size, and distribution of ECA branches are fairly common (Fig. 26.9), but anomalies of the ECA are rare.

**Internal Carotid Artery**

In most patients, the ICA has no extracranial branches and is longer than the ECA. Aberrant origin of the occipital artery or ascending pharyngeal artery from the ICA is very rare. The ICA provides most of the blood flow to the cerebral hemispheres, and vascular diseases of the ICA and its branches are important causes of serious morbidity, disability, and mortality. There are several classifications of the segments of ICA (Table 26.5), but we prefer a simplified classification based on cervical (extracranial), petrous (intracranial but extradural), cavernous (within the cavernous sinus), and cerebral (intradural) segments (Figs. 26.10 and 26.11). The cervical segment of the ICA is the most common site for carotid atherosclerosis, and consists of the carotid bulb and the ascending ICA (Fig. 26.12). The proximal cervical ICA is anatomically related to the cervical sympathetic ganglion, the vagus nerve, and the hypoglossal nerve, which may explain vasovagal and vasodepressor responses during ICA stimulation. The petrous segment of the ICA has a characteristic appearance that includes a vertical segment and sharp horizontal segment (upside-down “L” or genu), whereas the cavernous segment has two sharp genii (short vertical segment, longer horizontal segment, and a short vertical segment) (Figs. 26.10 and 26.11). Operators who perform carotid artery stenting will commonly position a distal embolic protection device in the upper cervical segment, and the guidewire tip will often reside in the petrous segment, avoiding the cavernous and cerebral segments (Fig. 26.12).

**Circle of Willis**

It is important to have an understanding of the normal anatomy, common anatomic variations, and vascular anomalies of the circle of Willis. The circle of Willis provides blood flow to the anterior, posterior, left, and right portions of the brain, and
Figure 26.4  Subclavian and coronary steal after coronary artery bypass surgery. (A) Selective left subclavian arteriogram (30° RAO projection) demonstrates total occlusion of the left subclavian artery, and no antegrade filling of the left vertebral artery or the left internal mammary artery (LIMA) graft to the LAD (left). After initial angioplasty, there is high-grade residual stenosis, extending up to the origin of the left vertebral artery (right). Note the lucency at the origin of the left vertebral artery (arrowhead), which represents bidirectional blood flow and should not be mistaken for thrombus. (B) After successful stenting, there is prompt antegrade flow in the left subclavian and vertebral arteries (left, arrowhead), as well as the internal mammary bypass graft (arrow). Selective angiography demonstrates patency of the LIMA graft to the LAD (right). Abbreviation: RAO, right anterior oblique.

Figure 26.5  Selective angiography of the left subclavian artery. RAO projection (left), LAO projection (right). The proximal (1), mid (2), and distal segments (3) are evident; the axillary artery is not shown. Abbreviations: RAO, right anterior oblique; LAO, left anterior oblique.
is a key source of collateral blood flow in occlusive diseases of the intra- and extracranial circulation. A complete circle of Willis is present in 50% of individuals, and consists of a nine-sided polygon (nonagon) and the basilar artery (Fig. 26.13). The complete “circle” includes the anterior communicating artery (ACOM), two precommunicating anterior cerebral arteries (A1), two intracranial ICA; two precommunicating posterior cerebral arteries (P1); and two PCOM (Table 26.6). The postcommunicating anterior (A2) and posterior (P2) cerebral arteries and the MCA are not part of the circle of Willis. The entire circle of Willis is rarely identified during a single-vessel angiogram, so visualization of the individual components depends on the extent of the cerebral angiogram.

Anatomic variations in the circle of Willis are very common (~50%), particularly aplasia or hypoplasia of PCOM and P1 (Fig. 26.14), and may impair potential collateral pathways. Individuals with ipsilateral aplasia or severe hypoplasia of A1 and P1 have an isolated cerebral hemisphere and cannot receive collateral flow from the vertebrobasilar system or from the
contralateral ICA; these patients are especially prone to cerebral ischemia if they develop proximal occlusive disease. Anomalies of the circle of Willis and other intracranial arteries are uncommon. However, duplication and fenestration of intracranial vessels are associated with intracranial aneurysms and arteriovenous malformations (AVM) (Table 26.7).

Anterior Cerebral Artery

The ACA and its branches supply the majority of blood flow to the anterior, medial, and anterobasal portions of the brain (Figs. 26.15–26.20). The most common classification of the ACA includes three segments (A1, A2, A3), which provide perforating and cortical branches to the brain (Table 26.8). Perforating branches usually arise from A1 and A2 (basal ganglia, internal capsule, corpus callosum) and cortical branches usually arise from A3 (ventral medial frontal lobe) and A3 (corpus callosum, medial cerebral hemisphere, cortical convexity) (Table 26.9). Most of the penetrating and cortical branches can be readily identified by selective ipsilateral carotid angiography in anteroposterior (AP)-cranial and lateral projections. The pericallosal artery represents the distal continuation of the main ACA (Fig. 26.19). Aplasia or hypoplasia of A1 is observed in 12% of individuals, but other anatomic variations are rare. Two ACA anomalies (infraoptic origin, azygous ACA) are associated with intracranial aneurysm and AVM, but bihemispheric ACA is not (Table 26.7).

Middle Cerebral Artery

The MCA and its branches supply most of the blood flow to the superior, lateral, and central portions of the brain (Figs. 26.15 and 26.17–26.21). The most common classification of the MCA includes four segments (M1, M2, M3, M4); M2 and M3 are conduit segments between M1 and M4, and usually do not provide significant branches (Table 26.10). Perforating branches arise from M1 (lateral lenticulostriate branches to basal ganglia and internal capsule), and cortical branches arise from M1 (anterior temporal artery to anterior and inferior temporal lobe) and from M4 (supplying large sections of the temporal, frontal, parietal, and occipital lobes) (Tables 26.11 and 26.12; Figs. 26.15 and 26.21). A common anatomic variation is early MCA bifurcation (20% of individuals), but other variations are rare. MCA anomalies such as fenestrations, duplications, and accessory MCA are associated with intracranial aneurysm and AVM (Table 26.7).

Vertebrobasilar Circulation

The vertebrobasilar system provides virtually all of the blood flow to the posterior circulation, including the pons, medulla, midbrain, and cerebellum (Figs. 26.15–26.17). The vertebrobasilar system consists of extracranial (vertebral arteries) and intracranial [vertebral arteries, basilar artery, posterior cerebral arteries (PCAs)] components (Table 26.13). The most common classification of the VA includes four segments (V1, V2, V3, V4) depending on the relationship to the cervical transverse foramina and foramen magnum (Table 26.14; Figs. 26.22 and 26.23). Cervical branches originate from the V1 segment (branches to the spinal cord and skeletal muscles of the head and neck); meningeal branches originate from V2 and V3; and intracranial branches originate from V4 (branches to the cerebellum, pons, medulla, and spinal cord). Anatomic variations in the size of the VA are common; although the left VA is large and

![Figure 26.8 Schematic illustration of branches of the external carotid artery. 1, Superior thyroid artery; 2, lingual artery; 3, facial artery; 4, maxillary artery; 5, superior temporal artery; 6, occipital artery; 7, posterior auricular artery; 8, ascending pharyngeal artery. Note that the internal carotid artery has been cut away for clarity.](image_url)

![Table 26.4 Major Anastomoses of the External Carotid Artery](image_url)

<table>
<thead>
<tr>
<th>ECA branch</th>
<th>Destination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior thyroid artery</td>
<td>SCA&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ascending pharyngeal artery</td>
<td>ICA, ECA, SCA, VA</td>
</tr>
<tr>
<td>Lingual artery</td>
<td>ECA</td>
</tr>
<tr>
<td>Facial artery</td>
<td>ICA&lt;sup&gt;a&lt;/sup&gt;, ECA</td>
</tr>
<tr>
<td>Occipital artery</td>
<td>ECA, SCA, VA</td>
</tr>
<tr>
<td>Posterior auricular artery</td>
<td>ECA</td>
</tr>
<tr>
<td>Superior temporal artery</td>
<td>ICA&lt;sup&gt;a&lt;/sup&gt;, ECA</td>
</tr>
<tr>
<td>Inferior maxillary artery</td>
<td>ICA, ECA</td>
</tr>
</tbody>
</table>

<sup>a</sup>Collateral to ipsilateral SCA via inferior thyroid artery and thyrocervical trunk, or to contralateral SCA via opposite superior thyroid artery.

<sup>b</sup>These branches usually have posterior origin from the ECA.

<sup>c</sup>Via ophthalmic artery.

Abbreviations: SCA, subclavian artery, ICA, internal carotid artery, ECA, external carotid artery, VA, vertebral artery.
Figure 26.9  Selective angiography of the left carotid artery, demonstrating the distal common carotid artery (CCA), internal carotid artery (ICA), and branches of the external carotid artery (ECA). (A) Note the severe stenoses at the origin of the ICA and ECA. (B) Note the variation in the ECA in which the lingual and facial arteries originate from a common trunk (TR), rather than as separate branches from the ECA. Abbreviations: STA, superior thyroid artery; L, lingual artery; F, facial artery; MAX, maxillary artery; TA, temporal artery; OCC, occipital artery; APA, ascending pharyngeal artery; PAA, posterior auricular artery.

Table 26.5  Cervical and Intracranial Segments of the Internal Carotid Artery

<table>
<thead>
<tr>
<th>Region</th>
<th>Segment</th>
<th>Description</th>
<th>Notable branches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>C1 Cervical</td>
<td>Carotid bulb and ascending cervical ICA (extracranial)</td>
<td>None</td>
</tr>
<tr>
<td>Petrous</td>
<td>C2 Petrous</td>
<td>ICA contained within petrous bone; characteristic genu</td>
<td>Vidian artery, caroticotympanic artery</td>
</tr>
<tr>
<td></td>
<td>C3 Lacerum</td>
<td>ICA travels above FL between petrous bone and PL ligament (extradural, intracranial)</td>
<td>None</td>
</tr>
<tr>
<td>Cavernous</td>
<td>C4 Cavernousa</td>
<td>Only artery that courses through a vein (cavernous sinus); characteristic genu (extradural, intracranial)</td>
<td>Posterior trunk, lateral trunk, capsular arteries (medial)</td>
</tr>
<tr>
<td></td>
<td>C5 Clinoida</td>
<td>Short wedge of ICA in terminal cavernous sinus (intradural)</td>
<td>None</td>
</tr>
<tr>
<td>Cerebral</td>
<td>C6 Ophthalmica</td>
<td>ICA exits cavernous sinus (intradural)</td>
<td>Ophthalmic artery, superior hypophyseal artery</td>
</tr>
<tr>
<td></td>
<td>C7 Communicating</td>
<td>Origin of PCOM to ACA/MCA bifurcation</td>
<td>PCOM, anterior choroidal artery</td>
</tr>
</tbody>
</table>

aC4, C5, C6, carotid siphon.

May cause a pituitary blush (meningohypophyseal artery).

Abbreviations: ICA, internal carotid artery; FL, foramen lacerum; PL, petrolingual ligament; PCOM, posterior communicating artery; ACA, anterior cerebral artery; MCA, middle cerebral artery.
dominant in most individuals, the right VA is dominant in 25% of cases (Table 26.7). The most common VA anomaly is direct origin from the arch rather than from the SCA, which occurs in 5% of individuals. Although anomalous origin of the VA is not associated with serious intracranial diseases, duplications and fenestrations of the VA are associated with fused vertebrae, intracranial aneurysms, and AVM (Table 26.7).

The basilar artery is a large midline artery that is formed by the merging of the left and right VA, and extends to the bifurcation of both PCAs (Figs. 26.13, 26.16, 26.17, 26.22, and 26.23). Although only 3 to 4 mm in diameter and 30 mm in length, the basilar artery has several important branches, including pontine perforators and two of three major cerebellar arteries [anterior inferior cerebellar artery (AICA), superior cerebellar artery] (Table 26.13; Figs. 26.16, 26.17, and 26.23). The third major artery to the cerebellum [posterior inferior cerebellar artery (PICA)] is a branch of the VA. Anatomic variations of the basilar artery are not common, but a common AICA-PICA trunk occurs in 10% of individuals. Basilar artery fenestrations and duplications are associated with intracranial aneurysms (Table 26.7).

**Posterior Cerebral Artery**

The PCA and its branches supply most of the blood flow to the posterior and posterobasal portions of the brain and brainstem (Table 26.15; Figs. 26.15–26.17 and 26.24). The most common classification of the PCA includes four segments (P₁, P₂, P₃, P₄), which provide perforating branches, branches to the choroid plexus and ventricles, and cortical branches to the brain (Table 26.16). Perforating branches usually arise from P₁ and P₂, providing blood flow to the internal capsule, basal ganglia, and midbrain; choroidal branches arise from P₂ and provide blood flow to the choroid plexus and basal ganglia; and cortical branches arise from P₄ (providing blood flow to the temporal lobe) and P₃ (providing blood flow to the temporal, parietal, and occipital lobes) (Table 26.16; Fig. 26.24). Normal variations
of the PCA are quite common, including P1 hypoplasia in 20% of individuals, which is associated with persistent fetal origin of the PCA (Table 26.7; Fig. 26.25). Anomalies of the PCA are quite rare.

Intracranial Aneurysms and Other Conditions

Cardiologists are rarely involved in the angiographic evaluation and treatment of patients with intracranial aneurysms or tumors. However, aneurysms may be identified incidentally during cerebral angiography for other reasons (Fig. 26.20), so cardiologists should have an understanding of the incidence, distribution, and outcomes of intracranial aneurysms (Table 26.17). Other incidental findings might include neovascular tumor blush, an arteriovenous fistula, or an AVM.

ANGIOGRAPHIC TECHNIQUE

Arterial Access

Cerebral angiography and intervention are generally performed from a femoral artery approach, but radial (5), brachial (6), and ulnar (7) approaches have been used when femoral access is difficult. Local anesthesia is achieved with 1% lidocaine, and light conscious sedation may be employed with midazolam (1 mg intravenously). We recommend a 5-Fr sheath and 5-Fr catheters for diagnostic angiography, and intra-arterial heparin (1500–2000 IU) in all patients (Table 26.18).

Pressure Monitoring and Imaging

As is true for left heart catheterization and coronary angiography, we recommend intra-arterial pressure monitoring from the catheter tip, using a standard three- or four-port manifold (Table 26.18). Meticulous attention must be paid to monitoring catheter tip pressure during cannulation of the great vessels. If a dampened pressure waveform is observed the catheter should be repositioned. Catheters that cannot be aspirated should never be flushed in the arch or great vessels, but should be removed and refilled outside the patient. The highest quality images are obtained with digital subtraction angiography (DSA), a power injector, and isosmolar contrast such as ioxitalam. Patient cooperation is essential, so instructions should be provided on breath-hold and avoidance of movement during angiography. Hand injections are useful to verify catheter position and alignment, but generally result in suboptimal vessel opacification, contrast streaming, poor images of the intracranial circulation, and higher radiation doses to the angiographer (Fig. 26.26) (8).

Arch Study

A formal arch aortogram [40° left anterior oblique (LAO)] should be performed in all patients unless the arch type and configuration have been previously defined by noninvasive or invasive imaging (Table 26.18; Figs. 26.1–26.3). For patients who require only left SCA arteriography to evaluate patency of an IMA graft, a formal arch study may not be necessary. Several catheters may be used for arch arteriography, but the ones used most often are the pigtail and tennis racquet catheters (Fig. 26.27). The side-hole arrangement on the tennis racquet catheter minimizes contrast in the ascending aorta and promotes contrast flow from the catheter shaft directly into the great vessels. High-quality DSA images will be obtained by instructing the patient to turn the head to the left, and by injecting 25 to 30 cc contrast over two seconds (600 psi), with a field of view of 34 to 42 cm (Table 26.18).

Selective Cannulation

Several catheters and techniques are available for selective cannulation of the great vessels and it is useful to become familiar with more than one (Tables 26.19 and 26.20). The arch study serves as a roadmap before selective cannulation and minimizes the need for catheter manipulation in the arch. If an arch study is not available, the tracheal air stripe (40° LAO projection) is a useful landmark for the origin of the great vessels: in many patients the IA is just proximal (left), the left CCA is in the middle, and the left SCA is just distal (right) to air stripe (Fig. 26.28). If rapid cannulation cannot be achieved, it is better to perform an arch study than to persist with prolonged catheter manipulation. The most common reasons for failed
selective cannulation of a great vessel are complex arch configurations and anomalous origins; both are readily identified by an arch study.

Catheter selection is largely based on operator preference, arch type, and the presence of anomalous origins (Table 26.19). Catheters for selective angiography are often classified as simple or complex, depending on the primary and secondary curves (Fig. 26.29). Simple catheters include Judkins right (JR), no torque right (NTR), Headhunter, jugular bulb (JB), and vertebral catheters. In general, simple catheters have simple primary and secondary curves, are easier to use, require less contact with the outer curvature of the arch, and are well suited for relatively simple arch configurations. Selective engagement with a simple catheter involves retraction of the catheter and counterclockwise rotation (Fig. 26.30). If the tip is too long, a shorter curve may be used. In contrast, complex catheters, such as Simmons and Vitek (Cook, Inc., Bloomington, Indiana, U.S.), have complex curves, require more manipulation and skill, result in more contact with the outer curvature of the arch, and are suited for many simple and complex arch configurations. Among complex catheters, the Vitek is the easiest to use: selective engagement involves positioning the catheter distal to the left SCA then rotating and advancing it until the tip points superiorly. Each great vessel may be selectively engaged by advancing the Vitek catheter from the left SCA to the left CCA to the IA (Fig. 26.30). The Simmons catheter requires more manipulation, and must be formed first in either the left SCA or the ascending aorta (Fig. 26.30). Most

**Figure 26.13** Schematic illustration of the circle of Willis. (A) A complete circle of Willis is actually a nine-sided polygon plus the basilar artery. (B) A complete circle of Willis with associated major branches. See text for details. Abbreviations: ACOM, anterior communicating artery; A1, precommunicating anterior cerebral artery (ACA); A2, postcommunicating ACA; ICA, internal carotid artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; P1, precommunicating posterior cerebral artery (PCA); P2, postcommunicating PCA; BA, basilar artery; VA, vertebral artery; SCA, superior cerebellar artery; AICA, anterior inferior cerebellar artery; PICA, posterior inferior cerebellar artery.

**Table 26.6** Components of the Complete Circle of Willis

<table>
<thead>
<tr>
<th>Component</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACOM</td>
<td>1(^a)</td>
</tr>
<tr>
<td>A1</td>
<td>2(^a)</td>
</tr>
<tr>
<td>ICA</td>
<td>2(^a)</td>
</tr>
<tr>
<td>PCOM</td>
<td>2(^a)</td>
</tr>
<tr>
<td>P1</td>
<td>2(^a)</td>
</tr>
<tr>
<td>BA</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^a\)Nine-sided polygon plus the BA.

Abbreviations: ACOM, anterior communicating artery; A1, precommunicating anterior cerebral artery; ICA, distal intracranial internal carotid artery; PCOM, posterior communicating artery; P1, precommunicating posterior cerebral artery; BA, basilar artery.
cardiologists will prefer the Vitek catheter, which handles in a fashion that is very similar to a left Amplatz catheter; gentle retraction results in deeper seating, while advancement results in disengagement. In our experience, all great vessels have been successfully engaged with a simple curve catheter and/or a Vitek catheter. For a diagnostic angiogram, the sequence of selective cannulation is generally proximal to distal with a simple curve catheter, and distal to proximal with a Vitek catheter (Fig. 26.30).

Once the great vessel has been selectively engaged and if the catheter provides good coaxial alignment without pressure damping, selective angiography may be performed with the same catheter, preferably using a power injector. If there is pressure damping, suboptimal position, or noncoaxial alignment

Figure 26.14  Schematic illustration of common variations in the circle of Willis. (A) Aplasia or severe hypoplasia of P1 [precommunicating posterior cerebral artery (PCA)]; (B) aplasia or severe hypoplasia of A1 [precommunicating anterior cerebral artery (ACA)]; (C) aplasia or severe hypoplasia of P1 and persistent fetal PCA; (D) isolated cerebral hemisphere, due to aplasia or severe hypoplasia of A1 and P1 (with persistent fetal PCA); (E) aplasia or severe hypoplasia of the anterior communicating artery (ACOM).
### Table 26.7 Normal Variations and Anomalies of the Cerebral Artery Circulation

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Variation</th>
<th>Incidence (%)</th>
<th>Anomaly</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA</td>
<td>Right dominant</td>
<td>25</td>
<td>Aortic origin</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>AICA-PICA trunk</td>
<td>10</td>
<td>Fenestration&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duplication&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;1</td>
</tr>
<tr>
<td>BA</td>
<td></td>
<td></td>
<td>PICA from V&lt;sub&gt;1&lt;/sub&gt;</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fenestration&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duplication&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;1</td>
</tr>
<tr>
<td>PCA</td>
<td>P&lt;sub&gt;1&lt;/sub&gt; hypoplasia/aplasia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20</td>
<td>Accessory MCA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>MCA</td>
<td>Early bifurcation</td>
<td>20</td>
<td>Fenestration&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duplication&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>ACA</td>
<td>A&lt;sub&gt;1&lt;/sub&gt; hypoplasia/aplasia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12</td>
<td>Infracarotid origin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bihemispheric ACA</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Azygous ACA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>PCOM</td>
<td>Hypoplasia/aplasia</td>
<td>5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ACOM</td>
<td>Hypoplasia/aplasia</td>
<td>5</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup>Associated with intracranial aneurysm and AVM.

<sup>b</sup>Associated with persistent fetal origin of PCA.

**Abbreviations:** VA, vertebral artery; BA, basilar artery; PCA, posterior cerebral artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCOM, posterior communicating artery; ACOM, anterior communicating artery; AICA, anterior inferior cerebellar artery; PICA, posterior inferior cerebellar artery; AVM, arteriovenous malformation.

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**Figure 26.15** Schematic illustration of the vascular distributions of the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA), shown in the lateral, medial, superior, and basal views.
that cannot be corrected by gentle catheter manipulation, the catheter may be exchanged over a guidewire for a multipurpose angiographic catheter [or modified tennis racquet (Meditech/Boston Scientific, Watertown, Massachusetts, U.S.)], if necessary (Tables 26.19 and 26.20; Figs. 26.27 and 26.29).

**Selective Angiography of the IA**

The LAO arch study (Figs. 26.1–26.3) provides nice images of the ostia and proximal IA, left CCA, and left SCA, but is less useful for visualizing the IA bifurcation into the right CCA and right SCA (Fig. 26.31). Imaging the IA in the LAO and AP projections may result in overlap of the right VA and right CCA, making selective cannulation of the SCA and CCA more difficult. In contrast, selective angiography of the IA in a 30° right anterior oblique (RAO) projection will clearly demonstrate the IA bifurcation and separate the right VA from the CCA (Table 26.20; Fig. 26.31). This angiogram may be performed by hand injection. The purpose of the IA angiogram is to provide a better roadmap for selective cannulation and angiography of the right SCA and right CCA, and should not be used for images of the right VA, right ICA, and intracranial circulation, due to vessel overlap and poor opacification.

**Selective Angiography of the Right SCA**

Depending on the clinical circumstances, selective right SCA angiography may be performed after advancing the IA catheter into the right SCA (Table 26.20). This may be accomplished by clockwise rotation and advancement of a simple catheter using fluoroscopy, pressure monitoring, and test injections by hand. If necessary, a J-tip guidewire may be positioned in the axillary artery, followed by advancement of any suitable coaxial catheter into the right SCA. To study the right IMA, an IMA or Bartorelli catheter may be used for selective cannulation and angiography. If the purpose is to image the VA and PCA, it is best to perform right SCA with a power injector, or to selectively image the right VA with a vertebral or JR catheter. The best angiographic projections depend on the vessel of interest (Table 26.20); cine angiography rather than DSA is preferred for the images of IMA and coronary artery using a hand injection.
Selective Angiography of the Right CCA

From the IA, selective right CCA angiography may be performed after advancing the IA catheter into the right CCA. This is most easily accomplished in the RAO projection by clockwise rotation (from the IA) and advancement of a simple catheter using fluoroscopy, pressure monitoring, and test injections (Fig. 26.31). If a complex catheter was used to engage the IA, gentle retraction of the catheter and clockwise rotation will point the catheter tip into the right CCA. If these maneuvers do not work, a J-tip guidewire can be advanced into the mid-CCA followed by advancement of any suitable coaxial catheter. For images of the carotid bifurcation and intracranial circulation, hand injections usually result in contrast streaming and suboptimal image quality, so a power injector is preferred (Fig. 26.26). If the catheter position is not ideal or the catheter recoils into the arch, the catheter can be repositioned with a guidewire or exchanged for a more coaxial catheter, such as a modified tennis racquet, multipurpose or glide catheter (Figs. 26.27 and 26.29). In most patients, the best images of the right CCA and cervical ICA are obtained in AP, lateral, and ipsilateral oblique (RAO) projections (Figs. 26.20 and 26.32). Depending on the individual patient, contralateral oblique (LAO) and cranial or caudal angulation may be useful to image highly eccentric stenoses, straighten bends, or eliminate overlapping branches of the ECA. For the intracranial circulation, the best images are AP-cranial and lateral projections (Figs. 26.20, 26.25, and 26.32). In some patients, highly angulated or tortuous sections of the cerebral ICA may appear aneurysmal, in which case an ipsilateral (RAO) caudal projection may prove very useful.

Selective Angiography of the Left CCA

In the presence of simple or complex arch anatomy, the left CCA may be cannulated in a 40° LAO projection with the same
catheter that was used to engage the IA. In some patients, the curve of a simple catheter is too long to engage the left CCA, and a catheter with a more horizontal orientation (shorter) may work better (Tables 26.19 and 26.20). For example, if a JR4 is used to engage the IA but is too long to engage the left CCA, greater success will be achieved with a JR3.5, NTR, or AR-1 catheter. A Vitek catheter will also successfully engage the left CCA in virtually all patients with simple or complex arch
Table 26.8 Classification of the Anterior Cerebral Artery

<table>
<thead>
<tr>
<th>Segment</th>
<th>Region</th>
<th>Branches</th>
<th>Projection</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Horizontal (precommunicating; horizontal segment of ACA between ICA and ACOM)</td>
<td>Perforating</td>
<td>AP-C</td>
</tr>
<tr>
<td>A2</td>
<td>Vertical (postcommunicating; vertical segment of ACA after ACOM)</td>
<td>Perforating and cortical</td>
<td>AP-C, LAT</td>
</tr>
<tr>
<td>A3</td>
<td>Callosal (distal segment of ACA that extends around corpus callosum)</td>
<td>Cortical</td>
<td>LAT</td>
</tr>
</tbody>
</table>

AP-C, anteroposterior with cranial angulation; LAT, lateral; ICA, internal carotid artery; ACOM, anterior communicating artery; ACA, anterior cerebral artery.

Table 26.9 Perforating and Cortical Branches of the Anterior Cerebral Artery

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Perforating branch</th>
<th>Territory</th>
<th>Cortical branch</th>
<th>Territory</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1a</td>
<td>MLSA</td>
<td>Basal ganglia, internal capsule, corpus callosum</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>RAH</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>A2</td>
<td>RAH</td>
<td>Basal ganglia, internal capsule</td>
<td>Orbitofrontalc</td>
<td>Ventral, medial frontal lobe and olfactory bulb</td>
</tr>
<tr>
<td></td>
<td>Callosal RAHb</td>
<td>–</td>
<td>Frontopolarc</td>
<td>Pericallosal</td>
</tr>
<tr>
<td>A3c</td>
<td>–</td>
<td>–</td>
<td>Callosomal marginal</td>
<td>Corpus callosum, 2/3 of medial cerebral hemisphere, strip of cortex over superior convexity</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>Partial</td>
<td>Splenial</td>
</tr>
</tbody>
</table>

aBest seen in AP-C projection.
bRAH originates from A1 in 40% of patients, RAH from A2 in 60% of patients.
cBest seen in LAT projection.

Abbreviations: MLSA, medial lenticulostriate arteries; RAH, recurrent artery of Heubner; AP-C, anteroposterior with cranial angulation; LAT, lateral; ACA, anterior cerebral artery.

Table 26.10 Classification of the Middle Cerebral Artery

<table>
<thead>
<tr>
<th>Segment</th>
<th>Region</th>
<th>Branches</th>
<th>Projection</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Horizontal (ICA bifurcation to genu)</td>
<td>Perforating and cortical</td>
<td>AP-C</td>
</tr>
<tr>
<td>M2a</td>
<td>Insular (superior course after genu)</td>
<td>None</td>
<td>AP-C, LAT</td>
</tr>
<tr>
<td>M3a</td>
<td>Opercular (top of insula to lateral end of Sylvian fissure)</td>
<td>None</td>
<td>AP-C, LAT</td>
</tr>
<tr>
<td>M4</td>
<td>Cortical (lateral surface of Sylvian fissure to cortical surface of cerebral hemisphere)</td>
<td>Cortical</td>
<td>AP-C, LAT</td>
</tr>
</tbody>
</table>

M2 and M3 are conduit vessels between M1 and M4, and do not have major penetrating or cortical branches.

Abbreviations: ICA, internal carotid artery; AP-C, anteroposterior with cranial angulation; LAT, lateral.

Table 26.11 Perforating and Cortical Branches of the Middle Cerebral Artery

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Perforating branch</th>
<th>Territory</th>
<th>Cortical branch</th>
<th>Territory</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>LLSAa</td>
<td>Basal ganglia</td>
<td>ATAab</td>
<td>Anterior, medial, and inferior temporal lobe</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>–</td>
<td>See Table 26.12</td>
<td>See Table 26.12</td>
</tr>
</tbody>
</table>

aBest seen in AP-C projection.
bBest seen in LAT projection.

Abbreviations: LLSA, lateral lenticulostriate arteries; ATA, anterior temporal artery; AP-C, anteroposterior with cranial angulation; LAT, lateral.
anatomy. Advancement of a simple catheter or retraction of a complex catheter and clockwise rotation will usually result in a more stable and deeper position. If the catheter tip is coaxial and there is no pressure clamping, DSA can be performed with a power injector. If the position is not ideal or the catheter recoils into the arch, the catheter can be repositioned with a guidewire or exchanged for a more coaxial catheter, such as a modified tennis racquet, multipurpose, or glide catheter (Figs. 26.27 and 26.29). In most patients, the best images of the left CCA and cervical ICA are observed in the AP, lateral, and ipsilateral oblique (LAO) projections (Figs. 26.12, 26.19, and 26.33). The contralateral oblique (RAO) and cranial and caudal angulation may be useful in selected patients. The best images of the intracranial circulation are AP-cranial and lateral projections (Figs. 26.11, 26.19, 26.26, and 26.33); LAO caudal may be useful to differentiate intracranial aneurysms from tortuous loops of intracranial arteries.

**Table 26.12** Cortical Branches of M4

<table>
<thead>
<tr>
<th>Region</th>
<th>Location</th>
<th>Branch</th>
<th>Territory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>Frontotemporal</td>
<td>Anterior temporal</td>
<td>Anterior, medial, and inferior temporal lobe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temporopolar</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orbitofrontal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prefrontal</td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>Frontoparietal</td>
<td>Precordinal sulcus</td>
<td>Posterior frontal, anterior parietal lobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Central sulcus</td>
<td>Superior parietal lobe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Postcentral sulcus</td>
<td>Mid-parietal lobe</td>
</tr>
<tr>
<td>Posterior</td>
<td>Parieto-occipital-temporal</td>
<td>Posterior parietal</td>
<td>Posterior parietal lobe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angular(^a)</td>
<td>Posterior parietal and occipital lobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temporo-occipital</td>
<td>Posterior temporal and occipital lobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior temporal</td>
<td>Middle temporal lobes</td>
</tr>
</tbody>
</table>

\(^a\) Major terminal branch of the middle cerebral artery.

**Table 26.13** Branches of the Vertebrobasilar System

Vertebral artery\(^a\)
- Cervical branches (originate from V1 segment)
  - Muscular branches
  - Spinal branches
- Meningeal branches (originate from distal V2 and V3 segments)
  - Anterior meningeal artery (small; originate from distal V2 segment)
  - Posterior meningeal artery (large; originate from V3 segment)
- Intracranial branches (originate from V4 segment)
  - Posterior spinal artery
  - Anterior spinal artery
  - Perforating branches
  - Posterior inferior cerebellar artery (PICA)

Basilar artery\(^b\)
- Pontine perforators
- Anterior inferior cerebellar artery (AICA)
- Superior cerebellar artery (SCeA)
- Posterior cerebral artery (PCA)

\(^a\)Supplies blood flow to spinal cord, medulla, inferior cerebellum, and pons.
\(^b\)Supplies blood flow to brainstem, cerebellum, vermis, occipital lobe, temporal lobe, thalamus, midbrain, and internal capsule.

**Table 26.14** Cervical and Intracranial Segments of the Vertebral Artery

<table>
<thead>
<tr>
<th>Region</th>
<th>Segment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraosseus</td>
<td>V(_1)</td>
<td>Subclavian artery to C6 transverse foramina</td>
</tr>
<tr>
<td>Foraminal</td>
<td>V(_2)</td>
<td>C6 to C1 transverse foramina</td>
</tr>
<tr>
<td>Extraspinal</td>
<td>V(_3)</td>
<td>C1 to foramen magnum</td>
</tr>
<tr>
<td>Intradural</td>
<td>V(_4)</td>
<td>Foramen magnum to basilar artery</td>
</tr>
</tbody>
</table>

**Figure 26.22** Schematic illustration of the vertebrobasilar system. The AP projection (left) demonstrates the anatomic relationship to the carotid arterial circulation (left internal carotid artery and right vertebral artery are cut away for clarity). The lateral projection (right) provides nice delineation of the segments of the vertebral artery and their relationship to the cervical transverse foramina and foramen magnum. Abbreviations: AP, anteroposterior; AA, ascending aorta; RSCA, right subclavian artery; RICA, right internal carotid artery; BA, basilar artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; LVA, left vertebral artery; LCCA, left common carotid artery; LSCA, left subclavian artery; V\(_1\), extraosseous segment of VA; V\(_2\), foraminal segment of VA; V\(_3\), extraspinal segment of VA; V\(_4\), intradural segment of VA.
Selective Angiography of the Left SCA

The 40° LAO projection is the best view for selective cannulation of the left SCA (Figs. 26.1 and 26.3), and catheter selection is identical to the IA and left CCA. For complex arch configurations, the Vitek catheter will work for virtually all patients. Hand injections usually suffice for imaging the left SCA, and the 30° RAO projection usually provides ideal separation of the VA, left IMA, and thyrocervical trunk (Figs. 26.4 and 26.5). When it is necessary to image the VA and PCA, a power injector provides the best images when the catheter is in the left SCA; alternatively hand or power injections can be used for selective VA angiography using a JR or vertebral catheter. If the purpose is to image the left IMA graft, the left SCA catheter can be exchanged for an IMA or Bartorelli for selective IMA angiography.

Intracranial Circulation

Angiographic views of the intracranial circulation are an essential part of the cerebral angiogram. AP-cranial (Towne’s) projections are used to characterize the ACA, MCA, PCA, circle of
Figure 26.24 Schematic illustration of posterior cerebral artery (PCA) and its cortical branches in an axial view through brainstem, temporal lobe, and occipital lobe. Note that cortical branches arise from P2 (2) and P4 (4), and supply major portions of the temporal and occipital lobes. 1, Precommunicating (P1) segment of PCA; 2, postcommunicating (P2) segment of PCA; 3, quadrigeminal (P3) segment of PCA; 4, calcarine (P4) segment of PCA; 5, anterior temporal artery; 6, posterior temporal artery; 7, lateral occipital artery; 8, medial occipital artery; 9, splenial artery (cut); 10, parieto-occipital artery; 11, calcarine artery. Abbreviation: BA, basilar artery.

Table 26.16 Branches of the Posterior Cerebral Artery

<table>
<thead>
<tr>
<th>Branch</th>
<th>Segment</th>
<th>Territory</th>
<th>Projection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforating</td>
<td></td>
<td></td>
<td>Lateral</td>
</tr>
<tr>
<td>Thalamic (n = 1–6)</td>
<td>P1</td>
<td>Thalamus, hypothalamus internal capsule, midbrain</td>
<td></td>
</tr>
<tr>
<td>Thalamogeniculate (n = 2–12)</td>
<td>P2 (80%)</td>
<td>Putamen, geniculate, subthalamus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P3 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peduncular (n = 0–6)</td>
<td>P2</td>
<td>Midbrain</td>
<td></td>
</tr>
<tr>
<td>Choroidal plexus/ventricular</td>
<td></td>
<td></td>
<td>Lateral</td>
</tr>
<tr>
<td>Medial PChA</td>
<td>P2</td>
<td>Choroid plexus</td>
<td></td>
</tr>
<tr>
<td>Lateral PChA</td>
<td>P2</td>
<td>Caudate, thalamus</td>
<td></td>
</tr>
<tr>
<td>Cortical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior temporal</td>
<td>P2</td>
<td>Anterior temporal lobe</td>
<td>Anteroposterior, Lateral</td>
</tr>
<tr>
<td>Posterior temporal</td>
<td>P2</td>
<td>Posterior temporal lobe</td>
<td>Anteroposterior, Lateral</td>
</tr>
<tr>
<td>Medial occipital</td>
<td>P4</td>
<td>Parieto-occipital, corpus callosum</td>
<td>Lateral</td>
</tr>
<tr>
<td>Parieto-occipital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcarine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral occipital</td>
<td>P4</td>
<td>Inferior temporal, occipital lobe</td>
<td>Anteroposterior, Lateral</td>
</tr>
</tbody>
</table>

Numbers in parenthesis indicate the usual number of perforating branches. Abbreviations: AP, anteroposterior; LAT, lateral; PChA, posterior choroidal artery.
Willis, and their branches (Table 26.20; Figs. 26.11, 26.19, 26.20, 26.23, 26.25, 26.26, 26.32, and 26.33). It is useful to have an understanding of intracranial collaterals and crossover, particularly in patients with carotid stenosis, and the location of common intracranial aneurysms (Fig 26.34). Ipsilateral caudal views are valuable for differentiating tortuous intracranial vessels from aneurysms. When using a power injector, intra-arterial contrast injection is divided into an early arterial phase

Table 26.17 Intracranial Aneurysms

| Incidence |
| --- | --- |
| General population—1% |
| Cerebral angiogram—7% |

| Location |
| --- | --- |
| Anterior circulation—90% |
| ○ Anterior communicating artery—30% |
| ○ Middle cerebral artery—30% |
| ○ Internal carotid artery/posterior communicating artery—30% |
| Posterior circulation—10% |
| Multiple—20–30% |

| Rupture risk |
| --- | --- |
| ≤6 mm—1% per year |
| ≤7 mm—2.5% per year |
| ≤25 mm (giant)—very high |

Table 26.18 Sequence of Diagnostic Cerebral Angiography

| Patient preparation |
| --- | --- |
| Hydration if eGFR < 60 cc/min/1.73 m² |
| Light sedation if needed |
| 2% Lidocaine for local anesthesia |

| Arterial access |
| --- | --- |
| Retrograde femoral arterial approach |
| 5-Fr sheath |
| 5-Fr catheters |
| Heparin 1500–2000 IU |
| 4-Port manifold |
| Intra-arterial pressure monitoring |

| Arch study |
| --- | --- |
| 40° LAO, pigtail or TR catheter |
| Iodixanol |
| Power injection (25–30 cc over 2 sec; 600 psi) |
| FOV 34–42 cm |

| Selective cannulation |
| --- | --- |
| 40° LAO guided by arch study (or tracheal air stripe) |
| Simple arch: simple catheter (as described in Table 26.19) or Vitek |
| Complex arch: Vitek |
| DMA² |

| Selective angiography |
| --- | --- |
| See Tables 26.19 and 26.20 |

Abbreviations: eGFR, estimated glomerular filtration rate; Fr, French; LAO, left anterior oblique; TR, tennis racquet catheter; FOV, field of view; DMA², don’t monkey around in the arch.
(the artery being injected and its major branches are opacified), a late arterial phase (reveals smaller, more distal arterial branches), a capillary phase (resulting in a “brain blush” or “brainogram”), and a venous phase (filling of the cerebral veins and sinuses). By adjusting the window settings during the capillary phase, it is possible to create a distinct brainogram. Some patients may develop focal neurological impairment after carotid intervention that is not associated with embolic cutoff of a visible intracranial artery. A postintervention brainogram may demonstrate a wedge-shaped cortical perfusion defect consistent with distal embolization.

OTHER ANGIOGRAPHIC TECHNIQUES
Quantitative Angiography
Visual estimates are notoriously unreliable for quantitative assessment of vessel dimensions and stenosis severity. Virtually all angiographic systems have software that allows rapid digital quantitative angiography and can be useful for sizing balloons and other interventional devices. NASCET (North American Symptomatic Carotid Endarterectomy Trial) is the most widely used method for assessment of carotid stenosis severity, using the ICA distal to the carotid bulb as the diameter of the normal reference segment. In contrast, the ECST...
The European Carotid Surgery Trial method uses the carotid bulb as the normal reference diameter, and consistently yields higher percent stenoses than the NASCET method (Fig. 26.35) [9].

### Table 26.19 Catheter Selection for Selective Cerebral Angiography

<table>
<thead>
<tr>
<th>Catheter configuration</th>
<th>Catheter type</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>JR, NTR, AR, VERT, BERN, HN, BEN, JB</td>
<td>Need minimal manipulation for simple arch type, minimal contact with aortic wall</td>
<td>Difficult to use for complex arch type</td>
</tr>
<tr>
<td>Complex</td>
<td>Vitek</td>
<td>Easy to use for simple and complex arch types: no need to form catheter in SCA or aortic root</td>
<td>More contact with aortic wall than simple catheter</td>
</tr>
<tr>
<td>Complex</td>
<td>SIM</td>
<td>Useful for complex arch configurations or if Vitek fails</td>
<td>More contact with aortic wall; need to form catheter in SCA or aortic root</td>
</tr>
<tr>
<td>Multipurpose</td>
<td>MP, Glide, MTR&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Excellent coaxial alignment for virtually all vessel configurations and arch types</td>
<td>Cannot be used to cannulate the great vessels; requires guidewire and catheter exchange</td>
</tr>
</tbody>
</table>

Producer names are given in the text.

<sup>a</sup>Catheter with side holes; all others are end-hole catheters; PSI = 500–550 psi for side-hole catheters, 400–450 psi for end-hole catheters.

<sup>b</sup>MTR is formed by amputating the head of the tennis racquet catheter, leaving 1–2 mm of the radiopaque shaft in place (Fig. 26.27).

**Abbreviations:** JR, Judkins right; NTR, no torque right; AR, Amplatz right; VERT, vertebral; BERN, Bernstein; HN, Headhunter; BEN, Bentson; JB, jugular bulb; SIM, Simmons; MP, multipurpose; MTR, modified tennis racquet; SCA, subclavian artery.

### Table 26.20 Technique of Selective Cerebral Angiography

<table>
<thead>
<tr>
<th>Catheter position</th>
<th>Target vessel</th>
<th>Injection technique</th>
<th>Projection</th>
<th>Catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>IA</td>
<td>Hand</td>
<td>RAO</td>
<td>JR, Vitek</td>
</tr>
<tr>
<td>SCA</td>
<td>R-SCA</td>
<td>Hand</td>
<td>LAO, RAO</td>
<td>JR, Vitek</td>
</tr>
<tr>
<td>R-VA</td>
<td>R-PCA Hand</td>
<td>Power&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AP, LAT</td>
<td>JR, Vitek</td>
</tr>
<tr>
<td></td>
<td>R-VA Power</td>
<td>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AP, RAO,</td>
<td>JR, Vertebral</td>
</tr>
<tr>
<td></td>
<td>R-PCA Hand/</td>
<td>Power&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AP, C, LAT</td>
<td>JR, Vertebral</td>
</tr>
<tr>
<td></td>
<td>R-PCA Power</td>
<td>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-CCA</td>
<td>R-CCA Power</td>
<td>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AP, RAO,</td>
<td>JR, Vitek, MP&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>R-ICA</td>
<td>R-ICA Power</td>
<td>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AP, RAO,</td>
<td>JR, Vitek, MP&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>R-ACA/ MCA</td>
<td>Power&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AP, C, LAT</td>
<td>JR, Vitek, MP&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>L-CCA</td>
<td>L-CCA Power</td>
<td>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AP, LAO,</td>
<td>JR, Vitek, MP&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>L-ICA</td>
<td>L-ICA Power</td>
<td>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AP, LAO,</td>
<td>JR, Vitek, MP&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>L-ACA, MCA</td>
<td>Power&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AP, C, LAT</td>
<td>JR, Vitek, MP&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>L-SCA</td>
<td>L-SCA Hand</td>
<td>Power&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AP, LAO,</td>
<td>JR, Vitek</td>
</tr>
<tr>
<td>L-VA</td>
<td>L-VA Power</td>
<td>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AP, LAO,</td>
<td>JR, Vitek</td>
</tr>
<tr>
<td></td>
<td>L-PCA Hand/</td>
<td>Power&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AP, C, LAT</td>
<td>JR, Vertebral</td>
</tr>
<tr>
<td></td>
<td>L-PCA Power</td>
<td>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>8–10 total volume, 4–6 cc/sec, 450–500 psi.

<sup>b</sup>5–7 cc total volume, 3–5 cc/sec, 450–500 psi.

<sup>c</sup>8–12 cc total volume, 6–9 cc/sec, 450–500 psi (end hole), 500 psi (side hole).

<sup>d</sup>Any multipurpose catheter, such as MP, Glide catheter, or MTR.

**Abbreviations:** IA, innominate artery; SCA, subclavian artery; VA, vertebral artery; PCA, posterior cerebral artery; CCA, common carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; R, right; L, left; RAO, right anterior oblique; LAO, left anterior oblique; LAT, lateral; AP, anteroposterior; AP-C, anteroposterior with cranial angulation; JR, Judkins right; MP, multipurpose; MTR, modified tennis racquet.

Figure 26.28 Relationship of the tracheal air stripe (dotted lines) to the origin of the great vessels. In the 40° LAO projection, the tracheal air stripe is a good landmark for selective cannulation of the innominate artery (proximal to the air stripe), left carotid artery (middle of the air stripe), and left subclavian artery (distal to the air stripe). **Abbreviation:** LAO, left anterior oblique.

(European Carotid Surgery Trial) method uses the carotid bulb as the normal reference diameter, and consistently yields higher percent stenoses than the NASCET method (Fig. 26.35) [9].
Figure 26.29  Catheters commonly employed for selective cannulation and angiography of the great vessels (see text for details). Simple catheters (left) have a simple primary curve and minimal secondary curve (from left to right: Headhunter, JB-1, JR-4, MPA, vertebral). Note that the multipurpose (MPA), glide catheter (not shown), and modified tennis racquet (see Fig. 26.27) are not readily suited for selective cannulation, but are useful for selective angiography when other catheters do not provide coaxial alignment. Complex catheters (right) have more complex relationships between the catheter tip and shaft (left = Simmons, right = Vitek).

Figure 26.30  Schematic illustration of manipulation of simple and complex catheters for selective angiography of great vessels. (A) Simple catheter manipulation involves placement of the catheter in the ascending aorta, followed by retraction and counterclockwise rotation to engage the innominate artery (IA). Retraction and counterclockwise rotation are repeated to engage the left common (CCA) and left subclavian arteries (SCA). (B) Vitek catheter manipulation involves positioning the catheter distal to the left SCA, followed by advancement and counterclockwise rotation into the left SCA. While retaining the curve of the catheter, the Vitek is advanced to the left CCA and IA. (C) Simmons catheter manipulation involves positioning the catheter in the ascending aorta (or left SCA), and forming a curve in the catheter by advancing it over a J-wire. After removing the J-wire, the Simmons can be retracted and rotated counterclockwise to engage the left SCA. While retaining the curve, the Simmons is advanced to the left CCA and IA, similar to the Vitek.
Gradient Assessment and Intravascular Ultrasound

Measurement of translesional pressure gradient is useful for assessing the functional significance of stenoses and may be measured at rest and after intra-arterial nitroglycerin (200–400 mg). A peak-to-peak pressure gradient ≥20 mmHg is considered hemodynamically significant. From a practical standpoint, translesional pressure gradients are useful for assessment of SCA stenoses but are rarely necessary (and may increase the risk of stroke) in patients with ICA stenosis. In addition, the established benefit of carotid revascularization in terms of stroke prevention has been based on stenosis severity and not translesional gradient. Intravascular ultrasound is feasible in the brachiocephalic circulation but has not been widely adopted.

Figure 26.31  Angiography of the innominate artery (IA) and its bifurcation (dotted box) into right subclavian (SCA) and common carotid arteries (CCA). The arch aortogram (40° LAO) demonstrates a type 1 arch with the usual configuration of the great vessels (left). This projection obscures the IA bifurcation into the right SCA and CCA, and results in close overlap of the right vertebral artery (VA) and CCA. Selective angiography of the IA (30° RAO) results in better separation of the right SCA and CCA (right), and no overlap of the right VA and CCA. Note the “string sign” in the right internal carotid artery (arrows). Abbreviations: LAO, left anterior oblique; RAO, right anterior oblique.

Figure 26.32  Selective right carotid artery angiography in a patient with asymptomatic carotid stenosis. Lateral projection demonstrates a focal, ulcerated, severe stenosis at the origin of the internal carotid artery (ICA). The intracranial circulation is normal in the AP (middle) and lateral (right) projections. Note faint filling of the right vertebral artery from reflux of contrast during power injection (arrow).
COMPLICATIONS

In addition to complications associated with other invasive angiographic procedures, cerebral angiography has unique complications related to the central nervous system. Access site complications (hematoma, dissection, AV fistula, pseudoaneurysm, hemorrhage) and systemic complications (contrast reactions, contrast nephropathy, cholesterol embolization) are encountered in <5% of patients undergoing invasive
angiographic procedures, including cerebral angiography. Neurological complications are the most feared complications of cerebral angiography. Causes of neurological events during cerebral angiography include embolism (plaque, thrombus, air) and direct arterial injury (vasospasm, dissection, perforation) (Fig. 26.36). Although older series reported death, stroke, and transient ischemic attacks (TIAs) in 0.06%, 0.14%, and 2% of patients undergoing cerebral angiography respectively (10), the incidence of neurologic complications appears to have decreased substantially. In a recent series from 2001 to 2006, procedure-related TIAs occurred in 0.34%, none resulting in permanent neurologic deficit (11). Factors accounting for the decrease in complications have not been precisely defined, but may include the use of intra-arterial pressure monitoring, heparin anticoagulation, isomolar contrast, and better preformed catheter designs requiring less catheter manipulation.

The potential for complications mandates that neurologic surveillance be performed during and after the procedure. Light conscious sedation is reasonable, but deep sedation should be avoided. Angiography and recovery room staff should be trained to evaluate changes in consciousness, cognitive and language deficits, visual complaints, headache, gait and vestibular symptoms, and focal motor and sensory deficits. Physicians performing cerebral angiography must be competent in performing a thorough neurological examination, be familiar with National Institutes of Health Stroke Scale (NIHSS) (12,13), and recognize criteria for immediate stroke intervention.

Figure 26.35  Methodology for quantitative carotid artery angiography. Calculations for percent diameter stenosis vary depending on the site of the normal reference segment. The NASCET method utilizes the proximal internal carotid artery (C) as the reference segment, whereas the ECST method utilizes the carotid bulb (B) as the reference segment. Abbreviations: NASCET, North American Symptomatic Carotid Endarterectomy Trial; ECST, European Carotid Surgery Trial.

Figure 26.36  Catheter-induced dissection (arrowhead) of the left common carotid artery (55° RAO). Severe asymptomatic eccentric dissection (left) was treated by successful direct carotid stenting using embolic protection (right). Abbreviation: RAO, right anterior oblique.
REFERENCES

Application of intracoronary physiology: use of pressure and flow measurements in clinical practice

Olivier Muller and Bernard De Bruyne

INTRODUCTION
The goal of any treatment is to improve patient prognosis and/or symptoms. Accordingly, the goal of any diagnostic tool is to guide decision making to apply optimal treatment in individual patients. Any diagnostic tool not fulfilling these requirements should not be used in patients. Keeping this in mind, this chapter will briefly review what is often referred to as “invasive coronary physiology.”

As opposed to anatomical (also referred to as “morphological”) approaches, physiological (“functional”) measurements assess the function of the coronary circulation. The function of the coronary arterial circulation is to provide nutrients to the myocardium. Accessorily, the coronary arteries play a role in diastolic function (turgor effect). No other organ is so dependent on the function of the organ it perfuses.

The combination of an accurate anatomic assessment and precise functional information is indispensable to tailor the treatment of patients with suspected or known coronary artery disease.

ANATOMICAL CONSIDERATIONS
Three-Layer Histology of the Coronary Arteries
Normal arteries have a well-developed trilaminar structure—the intima, media and the adventitia. The endothelial cell of the tunica intima constitutes the barrier with blood and plays an important role in the regulation of hemostasis and vascular tone. The strategic location of the endothelium allows it to sense changes in hemodynamic forces and blood-borne signals and to respond by releasing vasoactive substances. A balance between endothelium-derived relaxing (i.e., nitric oxide) and contracting factors (i.e., endothelin) maintains vascular homeostasis. When this balance is disrupted (i.e., atherosclerosis), it predisposes the vasculature to vasoconstriction and thus, to disturbance in coronary blood flow.

The Size of the Arteries Is Proportional to Myocardial Mass
In normal individuals, there is a close correlation between the lumen cross-sectional area of a coronary artery at each point along its length and the corresponding regional myocardial mass. In contrast, in patients with coronary atherosclerosis, measured coronary artery luminal area is diffusely 30% to 50% too small for diastal myocardial bed size compared with normal subjects (2). Figure 27.1 shows the relation between the size of a given artery and the mass of myocardium perfused by this artery. In patients with coronary artery disease, the dimension of a given artery is too small for the mass of myocardium. This relation will be important when considering a stenosis in a large artery (i.e., left anterior descending (LAD)) compared with a smaller one.

Fractal Nature of the Coronary Circulation
The arterial tree is by nature made of arterial bifurcations and follows a stepwise reduction of vascular diameter down to the capillary level. Each bifurcation consists of an asymmetric reduction according to the law of conservation of energy. In fact, the coronary tree has been shown to be governed by fractal geometry, in other words, at whatever level the coronary tree is observed, the morphology of the tree is similar. In fractal models, the quantity to be scaled is related to the power of a fraction. A recent study by Finet et al. proposed a simple and accurate fractal ratio between the diameters of the mother and the two daughter vessels (3). This ratio—diameter of the mother vessel = 0.678 x (diameter of the first daughter + diameter of the second daughter vessel)—confirmed other studies and allows appreciation of the luminal diameter of each daughter vessel.

PHYSIOLOGICAL CONSIDERATIONS

A detailed review of myocardial flow regulation is beyond the scope of this chapter. Yet, a reminder of a number of aspects is useful to understand the basics of the physiological assessment of the coronary circulation.

A Few Basic Concepts
Flow, Pressure, and Resistance
The main parameters of the circulatory function are flow, pressure and resistance.

\[ Q = \frac{\Delta P}{R} \]

Measuring absolute coronary blood flow (in mL/min) and absolute resistance (in mmHg/mL/sec) sounds like the “alpha and omega” of vascular physiology. However, even if absolute flow and resistance were to be measured easily and reliably in patients, it is most likely that their impact on clinical decision making would be rather modest. Flow—and therefore resistance—both depend on the myocardial mass to be perfused. Therefore, there is no unequivocal normal value for coronary flow and resistance. In contrast, under normal conditions, coronary pressure equals central aortic pressure over the entire length of the epicardial arteries, even during hyperemia. This unique characteristic of coronary pressure gives the interventionalist an unequivocal reference value: whatever the myocardial mass, the size of the artery, the systemic
hemodynamics, the age of the patient, the status of the microvasculature, etc., the pressure in the distal part of an epicardial artery should be identical to central aortic pressure. If this is not the case (i.e., in case of a pressure gradient), it necessarily implies that the resistance of the epicardial artery is abnormal.

**Coronary Flow and Myocardial Contractions**

Because of the squeezing effect of the contracting ventricles, coronary blood flow occurs mainly during diastole. This diastolic preeminence of coronary blood flow is most pronounced at rest (as compared with hyperemia) and in the left coronary artery. In case of epicardial stenosis, the pressure gradient will therefore be mainly diastolic ("no flow, no gradient").

**Flow-Function Relationship**

Myocardial blood flow represents approximately 5% of cardiac output. Because of its constant work, resting myocardial oxygen demand is high and the extraction of oxygen by the myocardium is close to its maximum, much higher than in other organs. Oxygen saturation of the coronary sinus venous blood is close to 20% (as a comparison, the oxygen saturation in the renal vein is 85%). Hence, as extraction cannot increase much further, the coronary circulation can only meet oxygen demand by fine tuning myocardial blood flow. In addition, as soon as myocardial flow decreases below 90% of its normal resting levels, myocardial function starts to decrease (Fig. 27.2). It is obvious that the control of myocardial blood flow must be remarkably tight to avoid wall motion abnormalities. Conversely, this also implies that when myocardial wall motion is normal, its resting perfusion must be normal.

**The Control of Myocardial Flow**

The regulation of myocardial blood flow is multifactorial. The neurohumoral, endothelial, endo- and paracrine, metabolic, and physical factors are largely nonlinear, cumulative and interacting. It is therefore very difficult to study these factors individually.

To simplify, the coronary circulation can be considered a two-compartment model. The first compartment consists of epicardial vessels, which are also referred to as "conductance vessels" because they do not oppose any resistance to blood flow. The second compartment consists of arteries <400 µm, or "resistive vessels" (Fig. 27.3). When no stenosis is present, myocardial flow is primarily controlled by resistive vessels (7), as they are able to vasodilate under physiological and pharmacological stress. At coronary angiography they are not...
clearly delineated but appear as a myocardial blush of contrast medium. During exercise or any other form of increased oxygen demand, the resistance of the microvasculature decreases allowing for an increased blood flow. Similarly, when a stenosis is present in the epicardial artery, this increased epicardial resistance is compensated by an equivalent decrease in microvascular resistance. This results in a maintained total resistance to blood flow and a preserved resting flow, with residual—albeit reduced—coronary flow reserve (CFR). When the epicardial stenosis progresses further, its relative contribution to total resistance increases. At the extreme, when the stenosis becomes “critical,” the compensation capacity of the microvascular circulation is exhausted. Any additional increase in epicardial resistance will result in an increase in total resistance and in a decrease in myocardial flow.

PHYSIOLOGICAL INDICES OF THE CORONARY CIRCULATION

Since the seminal work of L.K. Gould (8), several indices of coronary physiology have been proposed to guide clinical decision making. Fractional flow reserve (FFR) is the best validated index. Therefore, we will briefly describe the other indices then we will focus on FFR.

Coronary Flow Reserve

CFR is defined as the ratio of hyperemic blood flow \( Q_{max} \) to resting myocardial blood flow \( Q_{rest} \).

\[
CFR = \frac{Q_{max}}{Q_{rest}}
\]

Normal CFR value is between 4 and 6, which means that microvascular resistance can decrease by a factor of 4 to 6. Since absolute myocardial flow is not easy to determine, surrogates of flow are commonly used: for example, flow velocities assessed by the Doppler Wire (FloWire, Volcano, Inc., Rancho Cordova, California, U.S.) or mean transit time \( T_{mn} \) assessed by the PressureWire \(^{®} \) (St. Jude Medical, St. Paul, Minnesota, U.S./Radi Medical Systems, Uppsala, Sweden). Regardless of technical/practical aspects, the concept of CFR has several limitations: (i) resting flow, which appears as the denominator, is highly variable; (ii) hyperemic flow is directly dependent on systemic blood pressure; (iii) the hyperemic and resting measurements are not performed simultaneously but successively; and (iv) CFR is not specific for the epicardial stenosis. Stated another way, when CFR is too low, it is impossible to tell whether this abnormal value is related to a stenosis in the epicardial artery, to microvascular disease, or to a combination of both. For these reasons, CFR is of limited value for clinical decision making (9).

The Index of Microvascular Resistance

The resistance of a vascular system is given by the ratio of the pressure gradient to the flow across that particular system. Accordingly, the resistance \( R \) of the coronary microvascular compartment is the ratio of

\[
R = \frac{P_d - P_v}{Q}
\]

where \( P_d \) is distal coronary arterial pressure and \( P_v \) coronary venous pressure, or right atrial pressure. In the coronary circulation \( P_v \) is often almost negligible. Fearon et al. introduced the concept of index of microvascular resistance (IMR) considering that the mean transit time during maximal hyperemia is inversely proportional to hyperemic flow. Therefore, during maximal hyperemia:

\[
IMR = \frac{P_a}{T_{mn}} = \frac{P_d}{T_{mn}}
\]

where \( P_a \) is the distal coronary pressure and \( T_{mn} \) is the mean transit time. IMR is specific for the microcirculation and is simple to obtain as \( P_a \) and \( T_{mn} \) can be obtained simultaneously with the PressureWire \(^{®} \) (St. Jude Medical, St. Paul, Minnesota, U.S./Radi Medical Systems, Uppsala, Sweden). It has been well validated in animals (10) and was recently used in the setting of acute coronary syndromes to predict clinical outcomes (11) and assess the effect of treatment (12).

Hyperemic Stenosis Resistance

The resistance of an epicardial stenosis can be given by the ratio of the pressure gradient and the flow across that particular stenosis. Accordingly, Meuwissen et al. introduced the concept of hyperemic stenosis resistance (HSR), which can be calculated as the ratio of transstenotic gradient \( (P_d - P_d) \) to average peak flow velocity \( (Vel) \) during maximal hyperemia.

\[
HSR = \frac{P_d - P_d}{Vel}
\]

This measurement requires both a flow and a pressure sensor (ComboWire, Volcano, Inc., Rancho Cordova, California, U.S.) and is specific for the epicardial stenosis (13,14).

FRACTIONAL FLOW RESERVE

Definition

FFR is the ratio of maximal myocardial blood flow depending on a stenotic artery to maximal myocardial blood flow if that same artery were to be normal. In other words, it is a fraction of the maximal normal flow assuming that these measurements are obtained when the microvasculature resistance is minimal and constant (maximal hyperemia) (15,16).

FFR represents the extent to which maximal myocardial blood flow is limited by the presence of an epicardial stenosis. If FFR is 0.60, it means that maximal myocardial blood flow reaches only 60% of its normal value. Conversely, FFR provides the interventionalist with the exact extent to which optimal stenting of the epicardial stenosis will increase maximal myocardial blood flow. An FFR of 0.60 implies that stenting the focal stenosis responsible for this abnormal FFR should bring FFR to 1.0, which represents an increase in maximal myocardial blood flow of 67%.

Calculation

FFR is a ratio of two flows. It has been shown, however, that this ratio of two flows can be derived from two pressures (distal coronary pressure and aortic pressure), provided they are both measured during maximal hyperemia. The theoretical explanation of this relationship between hyperemic flows and hyperemic pressures is displayed in Figure 27.4.

Equipment

Catheters

The use of diagnostic catheters is technically feasible (17). Yet, because of higher levels of friction hampering wire manipulation,
the smaller internal caliber prejudicing pressure measurements, and the inability to perform ad hoc percutaneous coronary intervention (PCI) using diagnostic catheters, the use of guiding catheters is highly recommended.

Wires
Measuring intracoronary pressure requires the use of a specific solid state sensor mounted on a floppy-tipped guide wire. In mainstream practice two such systems are available at this time, namely the PressureWire® (St. Jude Medical, St. Paul, Minnesota, U.S./Radi Medical Systems, Uppsala, Sweden) and the WaveWire® (Volcano, Inc., Rancho Cordova, California, U.S.). The sensor is located 3 cm from the tip, at the junction between the radio-opaque and the radiolucent portions. The last generations of these 0.014-in wires have similar handling characteristics to most standard angioplasty guide wires.

Hyperemia
To measure FFR, it is absolutely essential to achieve maximal vasodilatation of the two vascular compartments of the coronary circulation, namely the conductance arteries (epicardial) and the resistance arteries (microvasculature). The pharmacological agents most often used to induce hyperemia are listed in Table 27.1 (18–20).
The epicardial arteries  A bolus of 200 mg isosorbide dinitrate (or any other form of intracoronary nitrates) allows the abolition of any form of epicardial vasoconstriction. It is good clinical practice to give intracoronary nitrates when performing coronary angiograms, especially when a wire is manipulated in the coronary tree. In addition, it is important to realize that all the data on FFR and its relation with noninvasive stress modalities or with clinical outcome have been obtained after intracoronary administration of nitrates.

Microvascular circulation  Inducing maximal hyperemia to obtain physiological information about a stenosis might be compared with placing the stenosis in a wind tunnel. From a theoretical point of view, the concept of FFR is based on achieving minimal microvascular resistance (Fig. 27.4). Therefore, expressions like “baseline FFR” or “FFR at rest” are physiological nonsense. This also extends to all other circulations. Even when the resting pressure gradient is large we recommend the induction of hyperemia because it allows us to evaluate what is the residual resistance reserve.

An example of a typical coronary pressure tracing during the administration of intravenous adenosine is shown in Figure 27.5.

Anticoagulation  As soon as a device is advanced into the coronary tree, the use of the same anticoagulation regimens as employed during a PCI procedure is recommended: heparin adjusted to weight, validated by a monitored activated coagulation time (ACT) of at least 250 seconds. Patients are supposed to be under aspirin treatment.

Unique Characteristics of FFR  FFR has a number of unique characteristics that make this index particularly suitable for functional assessment of coronary stenoses and clinical decision making in the catheterization laboratory.

“Universal” Normal Value Is 1  An unequivocally normal value is easy to refer to but is rare in clinical medicine. Since in a normal epicardial artery there is virtually no decline in pressure, not even during maximal hyperemia, it is obvious that \( \frac{P_d}{P_a} \) will equal or be very close to unity. FFR was obtained in 37 arteries in 10 individuals.
without atherosclerosis (group I) and in 106 nonstenotic arteries in 62 patients with arteriographic stenoses in another coronary artery (group II). In group I, the FFR was near unity (0.97 ± 0.02; range 0.92–1), indicating no resistance to flow in truly normal coronary arteries, but it was significantly lower (0.89 ± 0.08; range 0.69–1) in group II, indicating a higher resistance to flow (7).

Thus, it is important to realize that in normal-looking coronary arteries in patients with proven atherosclerosis elsewhere, the epicardial coronary arteries may contribute to total resistance to coronary blood flow even though there is no discrete stenosis visible on the angiogram. In approximately 50% of these arteries, FFR is lower than the lowest value found in strictly normal individuals. In approximately 10% of atherosclerotic arteries, FFR will be lower than the ischemic threshold. Practically speaking, this finding implies that myocardial ischemia might be present in atherosclerotic patients in the absence of discrete stenoses (7,21).

**Has a Well-Defined Cutoff Value**

Cutoff or threshold values are values that distinguish normal from abnormal levels for a given measurement. To enable adequate clinical decision making in individual patients it is paramount that any level of uncertainty is reduced to a minimum. Cutoff value for FFR has been evaluated in several studies and compared with several decision-making modalities, among them radionuclide perfusion was the most used (9). Stenoses with FFR measurement of <0.75 are almost invariably able to induce myocardial ischemia (cutoff with a specificity of 100%, a sensitivity of 88%, a positive predictive value of 100% and an overall accuracy of 93%). Stenoses with an FFR > 0.80 are almost never associated with exercise induced ischemia (Table 27.2). This means that the “grey zone” for FFR (0.75–0.80) spans over 6% to 7% of the entire range of FFR values.

**Is Not Influenced by Systemic Hemodynamics**

In the catheterization laboratory systemic pressure, heart rate and left ventricular contractility are prone to change. In contrast to many other indices measured in the catheterization laboratory, changes in systemic hemodynamics do not influence the value of FFR in a given coronary stenosis (27). This is due not only to the fact that aortic and distal coronary pressures are measured simultaneously, but also to the extraordinary capability of the microvasculature to repeatedly vasodilate to exactly the same extent. In addition, FFR measurements are extremely reproducible. In addition FFR has been shown to be independent of gender and risk factors such as hypertension and diabetes (28). These characteristics contribute to the accuracy of the method and to the trust in its value for decision making.

**Takes into Account the Contribution of Collaterals**

Whether myocardial flow is provided antegrade by the epicardial artery or retrogradely through collaterals does not really matter for the myocardium. Distal coronary pressure during maximal hyperemia reflects both antegrade and retrograde flow according to their respective contribution. This holds for the stenoses supplied by collaterals but also for stenosed arteries providing collaterals to another more critically diseased vessel (Fig. 27.6).

**Specifically Relates Severity of the Stenosis to Mass of Tissue to Be Perfused**

The larger the myocardial mass subtended by a vessel, the larger the hyperemic flow, and in turn, the larger the gradient and the lower the FFR. This explains why a stenosis with a minimal cross-sectional area of 4 mm² has totally different hemodynamic significance in the proximal LAD artery versus the second marginal branch. It also explains FFR measurements of collaterals, where the mass supplied by an artery can change after revascularization of the retrograde supplied vessel.

**Has Unequaled Spatial Resolution**

The exact position of the sensor in the coronary tree can be monitored under fluoroscopy, and documented angiographically. Pulling back the sensor under maximal hyperemia (usually adenosine IV) provides the operator an instantaneous assessment of the abnormal resistance of the arterial segment located between the guide catheter and the sensor. While other functional tests reach a “per patient” accuracy (exercise ECG), or at best a “per vessel” accuracy (myocardial perfusion imaging), FFR reaches a “per segment” accuracy with a spatial resolution of a few millimeters.

**Clinical Applications**

**Angiographically Doubtful Stenoses**

The main general indication for FFR is the precise assessment of the functional consequences of a given coronary stenosis with unclear hemodynamic significance (23). Cardiologists describe angiographic coronary narrowings with uncertain functional consequences as mild-to-moderate stenoses, dubious lesions,
intermediate stenoses, non-flow limiting stenoses, etc. Angiographic assessment of such stenoses produces insufficient information to determine whether a stenosis is hemodynamically significant or not. Moreover, angiographic assessment is often the only decision-making modality to perform an angioplasty. Even if the clinical cardiologist is offered many options and techniques for noninvasive functional evaluation, it has been reported that up to 71% of PCIs are being performed in the absence of any sort of functional evaluation (29). This scenario, often referred to as the “oculostenotic reflex,” is even more worrisome now that safety concerns associated with late stent thrombosis have been identified (30).

Direct translesional pressure measurements correlate well with noninvasive assessment of coronary artery disease. In a study of 45 patients with angiographically dubious stenoses it was shown that FFR has a much larger accuracy in distinguishing hemodynamically significant stenoses than exercise ECG, myocardial perfusion scintigraphy and stress echocardiography taken separately (23). Furthermore, the results of these noninvasive tests are often contradictory, which renders appropriate clinical decision making difficult (Fig. 27.7). In addition, the clinical outcome of patients in whom PCI has been deferred, because the FFR indicated no hemodynamically significant stenosis, is very favorable. In this population the risk of death or myocardial infarction is approximately 1% per year, and this risk is not decreased by PCI (31). These results strongly support the use of FFR measurements as a guide for decision making about the need for revascularization in “intermediate” lesions. Figure 27.8 illustrates how two angiographically similar stenoses may have a completely different hemodynamic severity. One of them should be revascularized, the other not. Based solely on the angiogram, the decision should be identical in both cases, which would lead to an inappropriate interventional decision in one of these patients.

**Left Main Stem Disease**

The presence of a significant stenosis in the left main stem is of critical prognostic importance (32). Conversely, revascularization
of a nonsignificant stenosis in the left main may lead to atresia of the conduits, even when internal mammary arteries are used (33). Furthermore, the left main is among the most difficult segments to assess by angiography (34). Noninvasive testing is often noncontributive in patients with a left main stenosis. Perfusion defects are often seen in only one vascular territory, especially when the right coronary artery (RCA) is significantly diseased (35). In addition, tracer uptake may be reduced in all vascular territories (“balanced ischemia”) giving rise to false-negative studies (36). Several studies have shown that FFR could be used safely in left main stenosis and that the decision not to operate on left main stenosis with an FFR > 0.75 is safe (37–39).

In addition, angiographic assessments of left main lesions with an FFR < 0.75 were no different from those with an FFR > 0.75, further reinforcing the importance of physiological parameters in case of doubt. Therefore, patients with an intermediate left main stenosis deserve physiological assessment before blindly making a decision about the need for revascularization. Two examples shown in Figure 27.9 illustrate how FFR measurements in the left main may drastically influence the type of treatment in these patients. Left main disease is rarely isolated. When tight stenoses are present in the LAD or in the left circumflex artery (LCx) the presence of these lesions will tend to increase the FFR measured across the left main. The influence of an LAD/LCx...
lesion on the FFR value of the left main will depend on the severity of this distal stenosis but, even more, on the vascular territory supplied by this distal stenosis. For example, if the distal stenosis is in the proximal LAD, its presence will notably impact the stenosis in the left main. If the distal stenosis is located in a small second marginal branch, its influence on the left main stenosis will be minimal (Fig. 27.10).

Multivessel Disease
Patients with multivessel disease actually represent a very heterogeneous population. Their anatomical features (number of lesions, their location, and their respective degree of complexity) may vary tremendously and have major implications for the revascularization strategy. Moreover, there is often a large discrepancy between the anatomic description and the actual severity of each stenosis. For example, a patient may have three-vessel disease on the basis of the angiogram, but actually have only two hemodynamically significant stenoses; vice versa, a patient can be considered as having one vessel disease of the RCA but actually have a hemodynamically significant stenosis of the left main. Figure 27.11 shows a typical example of a patient in whom the RCA and the LCx are critically narrowed and in whom the mid-LAD shows a mild stenosis. Myocardial perfusion imaging showed a reversible perfusion defect in the inferolateral segments and a normal flow distribution in the segments supplied by the LAD. In contrast, FFR shows that all three vessels are significantly narrowed but to a different extent. This has a
Figure 27.11  (See color insert) Example of two patients with multivessel disease. (A) A 46-year-old man with stable angina and angiographic three-vessel disease but functional two-vessel disease (LAD, RCA). (B) A 69-year-old man with severe angina. MPI showed a reversible defect in the inferolateral segments. From the angiogram it is obvious that the RCA and the LCx are significantly narrowed (no pressure measurements are needed). However, the mid-LAD stenosis, considered “nonsignificant” on the angiogram, appears to be hemodynamically significant. This LAD stenosis was undetected by MPI because the uptake of tracer is notably worse in the LCx territory than in the LAD territory. 

Abbreviations: LAD, left anterior descending artery; RCA, right coronary artery; MPI, myocardial perfusion imaging; LCx, left circumflex artery; FFR, fractional flow reserve.
major implication as far as revascularization is concerned. Preliminary FFR-guided revascularization strategies in patients with multivessel disease were very encouraging (40–42). Tailoring the revascularization according to the functional significance of the stenoses rather than on their mere angiographic appearance may decrease costs and avoid the need for surgical revascularization. A recent randomized multicenter study (FAME) in 1000 patients showed that routine measurement of FFR during PCI with drug-eluting stent(s) in patients with multivessel disease, when compared with current angiography-guided strategy reduces the rate of the composite end point of death, myocardial infarction, re-PCI, and coronary artery bypass surgery at one year by approximately 30% and reduces mortality and myocardial infarction at one year by approximately 35%. Moreover, the FFR-guided strategy reduces the number of stents used, decreases the amount of contrast agent used, does not prolong the procedure and is cost saving (43,44).

After Myocardial Infarction
After a myocardial infarction, previously viable tissue is partially replaced by scar tissue. Therefore, the total mass of functional myocardium supplied by a given stenosis in an infarct related artery will tend to decrease (45). By definition, hyperemic flow and thus hyperemic gradient will both decrease as well. Assuming that the morphology of the stenosis remains identical, FFR must therefore increase. This does not mean that FFR underestimates lesion severity after myocardial infarction. It simply illustrates the relationship that exists between flow, pressure gradient and myocardial mass and, conversely, illustrates that the mere morphology of a stenotic segment does not necessarily reflect its functional importance. This principle is illustrated in Figure 27.12. Recent data confirm that the hyperemic myocardial resistance in viable myocardium within the infarcted area remains normal (46). This further supports the application of the established FFR cutoff value in the setting of partially infarcted territories. Earlier data had suggested that microvascular function was abnormal in regions remote from a recent myocardial infarction (47,48). However, more recent work taking into account distal coronary pressure indicates that hyperemic resistance is normal in these remote segments (49). These data support the use of FFR to evaluate stenoses remote from a recent myocardial infarction.

Diffuse Disease
Histopathology studies and, more recently, intravascular ultrasound have shown that atherosclerosis is diffuse in nature and that a discrete stenosis in an otherwise normal artery is actually rare. The concept of a focal lesion is a mainly angiographic description but does not reflect pathology. Until recently, it was believed that when no focal narrowing of >50% was seen at the angiogram, no abnormal resistance was present in the epicardial artery. It was therefore assumed that distal pressure was normal and thus that “diffuse mild disease without focal stenosis” could not cause myocardial ischemia. This paradigm has recently been shifted: the presence of diffuse disease is often associated with a progressive decrease in coronary pressure (7) and flow (50), and this cannot be predicted from the angiogram. In contrast this decline in pressure correlates with the total atherosclerotic burden (51). In approximately 10% of patients this abnormal epicardial resistance may be responsible for reversible myocardial ischemia. In these patients chest pain is often considered noncoronary because no single focal stenosis is found, and the myocardial perfusion imaging is wrongly considered false positive (“false false positive”) (52). Such diffuse disease and its hemodynamic impact should always be kept in mind when performing functional measurements. In a large multicenter registry of 750 patients FFR was obtained after technically successful stenting. A post-PCI FFR value <0.9 was still present in almost one-third of patients and was associated with a poor clinical outcome (53). The only way to demonstrate the hemodynamic impact of diffuse disease is to perform a careful pullback maneuver of the pressure sensor under steady-state maximal hyperemia (Fig. 27.13).

Sequential Stenoses
When several stenoses are present in the same artery, the concept and the clinical value of FFR is still valid to assess the effect of all stenoses together. Yet, it is important to realize that when several discrete stenoses are present in the same coronary artery, each of them will influence hyperemic flow and therefore the pressure gradient across the other one. The influence of the distal lesion on the proximal is more important than the reverse. The FFR can theoretically be calculated for each stenosis individually (54,55). However, this is neither practical nor easy to perform and therefore of little use in the catheterization laboratory. Practically, as for diffuse disease, a pullback maneuver under maximal hyperemia is the only way to appreciate the exact location and physiological significance of sequential stenoses.

Bifurcation Lesions
Overlapping of vessel segments as well as radiographic artifacts render bifurcation stenoses particularly difficult to evaluate at angiography, while PCI of bifurcations is often more challenging than for regular stenoses. The principle of FFR-guided PCI applies in bifurcation lesions even though clinical outcome data are currently limited. Two recent studies by Koo et al. (56,57) used FFR in the setting of bifurcation stenting. The results of these studies can be summarized as follows: (i) After stenting, the ostium of the side branch looks often “pinched.” Yet such stenoses are grossly overestimated by angiography—none of these ostial lesions where the diameter stenosis was estimated as 75% were found to have an FFR below 0.75.

### Abbreviations
FFR and myocardial mass before and after myocardial infarction.

**Figure 27.12** Schematic representation of the relationship between FFR and myocardial mass before and after myocardial infarction. **Abbreviations:** DS, diameter stenosis; FFR, fractional flow reserve.
When kissing balloon dilation was performed only in ostial stenoses with an FFR < 0.75, the FFR at six months was >0.75 in 95% of all cases.

**FFR and Coronary Artery Bypass Graft Lesions**

Assessment of stenosis severity in coronary artery bypass grafts by FFR is technically very easy. In addition, all theoretical assumptions underlying the concept of FFR hold in cases of bypasses. There is no reason to believe that another threshold value should be found even though this has not been formally investigated in large series (38). Stated another way, FFR is able to define whether or not a stenosis in a bypass graft is capable of inducing ischemia. In contrast, there are no clinical outcome data obtained in patients in whom decisions regarding revascularization have been based on FFR. It seems common sense to admit that in patients with an FFR < 0.75, the revascularization of this lesion might be beneficial for the patient. However, deferring the revascularization procedure on the basis of an FFR value >0.75 is not proven. Therefore, FFR should be used with caution in bypass grafts.

One important study by Botman et al. has investigated the relationship between stenosis severity in native arteries and graft patency after six months. The authors showed that the rate of occlusion was approximately three times higher when the bypass was placed on a native artery with a hemodynamically nonsignificant stenosis (59). These results corroborate the data reported by Berger et al. who showed that internal mammary arteries placed on mildly diseased native arteries showed a very high attrition rate (33).

**CONCLUSION: TOWARD A NEW DIAGNOSTIC ALGORITHM FOR PATIENTS WITH KNOWN OR SUSPECTED CORONARY ARTERY DISEASE**

Pressure-derived FFR is a theoretically robust and practically simple means of assessing the functional consequences of epicardial coronary atherosclerosis. With minimal experience the technique of FFR measurements is simple, swift and safe. Only a pressure wire and a bolus of hyperemia-inducing medication are required. Its invasive nature is counterbalanced by its unequalled spatial resolution, offering functional information down to the “per centimeter” level, while noninvasive tests operate, at best, at the “per vascular territory” level. Clinical outcome data of patients in whom the revascularization strategy has been based on FFR measurements are very encouraging. Accordingly, FFR can be considered as the interventional cardiologists’ “pocket myocardial perfusion imaging” modality. This is true with some important qualifications: (i) FFR is more accurate in intermediate lesions; (ii) FFR has a better spatial resolution; (iii) combined with the index of myocardial resistance, FFR is able to distinguish epicardial and myocardial resistance (10); and (iv) it is available in the catheterization laboratory, as FFR is performed in conjunction with coronary
angiography. Therefore, it is the only true “all-in-one” approach for patients with suspected or known coronary artery disease as it combines unequalled physiological information, the best possible anatomical information, and the possibility of immediate revascularization if needed.

We believe that the diagnostic work-up of patients with known or suspected coronary artery disease might be drastically shortened. The conventional teaching (60) is that patients with suspected coronary stenosis should first undergo non-invasive functional testing, the so-called “gatekeepers” of the catheterization laboratory. Patients are referred for diagnostic coronary angiography if (and only if) these tests indicate reversible myocardial ischemia. At angiography, a 50% to 70% stenosis is often considered a justification for revascularization. We have seen, however, how often the results of non-invasive functional tests performed sequentially are inaccurate and/or contradictory. In addition, the angiographic degree of stenosis is a battered gold standard, leading to a large number of inappropriate decisions regarding revascularization (30). Finally, non-invasive testing is actually performed in only a minority of patients undergoing angioplasty (29).

In contrast to this conventional approach, we propose to put more emphasis on a careful interrogation of the patients including a precise analysis of his/her risk factors. If, on this basis, an experienced cardiologist comes to the conclusion that “this person might well have significant coronary artery stenoses,” we believe it is more efficacious to send the patient directly to the catheterization laboratory if and only if in the catheterization laboratory, FFR measurements can be obtained, and the revascularization strategy is guided by the integration of clinical, anatomic (angiographic), and functional (FFR) information.

REFERENCES

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Intravascular ultrasound and virtual histology

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INTRODUCTION
Real-time ultrasound imaging originated in the late 1960s and early 1970s when Bom et al. (1) pioneered the development of linear array transducers for visualizing cardiac chambers and valves. The first transluminal images of human arteries were recorded by Yock et al. (2) in 1988, when a miniaturized and single-transducer system was placed within the coronary arteries. Ever since, intravascular ultrasound (IVUS) has become an increasingly important catheter-based imaging technology providing practical guidance for percutaneous coronary intervention (PCI) and numerous clinical and research insights (3,4). For example, IVUS directly images the coronary arterial wall, which contains the major components of atherosclerotic plaque, allowing measurement of plaque size, distribution, and to some extent its composition. Thus, IVUS has become established as the method of choice for the serial assessment of atherosclerotic plaque burden in progression-regression trials. Recently, virtual histology IVUS (VH-IVUS) using spectral analysis of radiofrequency ultrasound backscatter has emerged with the potential to better assess real-time plaque components and vulnerable plaque (5).

This chapter will examine the rationale, technique, and interpretation of IVUS and VH-IVUS imaging in diagnostic and therapeutic applications.

GREYSCALE IVUS
IVUS Imaging: Definitions and Basics
Ultrasound is acoustic energy with a frequency above human hearing. The highest frequency that the human ear can detect is approximately 20 thousand cycles per second (20,000 Hz). For medical diagnostic purposes, ultrasound imaging frequencies are in the range of millions of cycles per second (megahertz, MHz).

The IVUS transducer converts electrical energy into acoustical energy through a piezoelectric (pressure-electric) crystalline material that expands and contracts to produce sound waves when electrically excited. After reflection from tissue, part of the ultrasound energy returns to the transducer; the transducer then generates an electrical impulse that is converted into moving pictures (6). All materials in the body reflect sound waves. Sound waves bounce back at various intervals depending on the type of material and the distance from the transducer. It is the variation in reflective sound waves that creates the ultrasound image on the console.

The intensity of reflected (or backscattered) ultrasound depends on a number of variables including the intensity of the transmitted signal, the attenuation of the signal by the tissue, the distance from the transducer to the target, the angle of the signal relative to the target, and the density of the tissue (3). Several clinically relevant properties of the ultrasound image—such as the resolution, depth of penetration, and attenuation of the acoustic—are dependent on the geometric and frequency properties of the transducer. The higher the center frequency, the better the axial resolution, but the lower the depth of penetration. For coronary imaging because the transducer is close to the vessel wall, high ultrasound frequencies are used that are centered at 20 to 45 MHz (4). Axial resolution is typically 80 to 120 μm, and lateral resolution is typically 100 to 250 μm (3).

Equipment
Two different transducer designs are used: mechanically rotated and electronically-activated phased-array. Mechanical probes use a drive cable to rotate a single-element transducer at the tip of the catheter at 1,800 rpm. At approximately 1° increments, the transducer sends and receives ultrasound signals providing 256 individual radial scan lines for each image. In electronic systems, multiple tiny transducer elements are activated sequentially to generate the cross-sectional image (3,6).

Imaging Artifacts
The recognition of imaging an artifact is critical because it may interfere with image interpretation and measurements. The most common imaging artifacts are (i) ring-down, (ii) nonuniform rotational distortion (NURD), and (iii) reverberations. Ring-down artifacts are usually observed as a series of parallel bands or halos of variable thickness surrounding the catheter and obscuring near-field imaging. Phased-array systems tend to have more ring-down artifacts. NURD is an artifact that arises from frictional forces to the rotating elements in mechanical catheters. NURD creates stretched or compacted portions of the images. Because accurate reconstruction of IVUS two-dimensional images is dependent on uniform rotation of the catheter, NURD may create errors during IVUS measurements (7). NURD artifacts can also occur because of bends in the catheter driveshaft or in the presence of acute bends in the artery. Reverberations are false repetitive echoes of the same structure that give the impression of second or various interfaces at fixed-multiple distances from the transducer. Reverberation artifacts are more common from strong echo reflectors such as stents, guidewires, guiding catheters, and calcium (especially after rotational atherectomy). There are a few other artifacts that can also interfere in IVUS interpretation including side lobes and ghost artifacts also generated from strong echo reflectors such as calcium and stent metal (3). In longitudinal or L-mode display, catheter motion artifacts during the pullback may result in a “saw tooth” appearance.
Catheter position also plays an important role in image quality. Off-axis position of the catheter may alter vessel geometry in an elliptical fashion to mislead the operator to overestimate the lumen and vessel area. Axial (antegrade-retrograde) movement of the IVUS probe during the cardiac cycle scrambles consecutive image slices that may have implications for three-dimensional reconstruction and attempts to assess coronary artery compliance (8).

Image Acquisition and Presentation

Two important consensus documents have been published on image acquisition and reporting of IVUS data: (i) Standards for the Acquisition, Measurement, and Reporting of IVUS Studies: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents (6) and (ii) the Study Group on Intracoronary Imaging of the Working Group of Coronary Circulation and the Subgroup on Intravascular Ultrasound of the Working Group of Echocardiography of the European Society of Cardiology (9).

IVUS supplements angiography by providing a tomographic perspective of lumen geometry and vessel wall structure. A longitudinal view (L-mode or long view) can be also displayed, but this should be done only when using motorized transducer pullback. Longitudinal representation of IVUS images is useful for length measurements, for interpolation of shadowed deep arterial structures (i.e., external elastic membrane (EEM) behind calcium or stent metal) (6).

There are advantages and disadvantages using manual or motorized pullback; however, motorized pullback is usually preferable. Using motorized transducer pullback allows assessment of lesion length, volumetric measurements, consistent and systematic IVUS image acquisition among different operators, and uniform and reproducible image acquisition for multicenter and serial studies.

In standard image acquisition after anticoagulation and intracoronary nitroglycerin administration, the IVUS catheter should be placed distal to the segment of interest (at least 10 mm of distal reference), and a continuous pullback to the aorta should be recorded. The preferred pullback speed is 0.5 mm/sec.

Normal Coronary Artery Morphology

Three layers of the coronary artery are visible by IVUS imaging: intima, media, and adventitia. Normal intima thickness increases with age, from a single endothelial cell at birth to a mean of 60 μm at five years to 220 to 250 μm at 30 to 40 years of age (10). The definition of abnormal intimal thickness by IVUS is still controversial; in general, the threshold of “normal intimal thickness” is <300 μm (0.3 mm). The innermost layer of the intima is relatively echogenic compared with the lumen and media and displayed on the screen as a single bright concentric echo. The lower ultrasound reflectance of the media is due to its homogeneous smooth muscle cells distribution and smaller amounts of collagen, elastic tissue, and proteoglycans. The thickness of media histologically averages 200 μm, but thinning is usually present in the region of atherosclerosis (11). The intima/media border is poorly defined because the intimal layer reflects ultrasound more strongly than the media. Conversely, the media/adventitia border, consistent with the location of the EEM, is accurately defined because a step-up in echo reflectivity occurs without blooming. The outermost layer, the adventitia, is composed of collagen and elastic tissue; it is 300 to 500 μm thick. The outer border of the adventitia is also indistinct due to echo reflectivity similar to the surrounding periadventitial tissues (11). Therefore, the normal coronary artery is either (i) “monolayered” in cases of intimal thickness <100 μm because of IVUS catheter resolution is <100 μm or (ii) “three-layered” to include a bright echo from the intima, a dark zone from the media, and bright surrounding echoes from the adventitia (Fig. 28.1).

Quantitative Analysis

IVUS imaging is not identical to a histologic imaging. In nonstented lesions, two strong acoustic interfaces are well visualized by ultrasound: the leading edge of the intima and the outer border of the media. Therefore, two cross-sectional area (CSA) measurements can be defined: the lumen CSA and the media/adventitia CSA (or EEM CSA). The atheroma or plaque/media (P&M) complex is calculated as EEM minus lumen; the media cannot be measured as a distinct structure. Thus, complete quantification of a nonstented lesion is possible by tracing the EEM and lumen areas of the proximal reference, lesion, and distal reference; calculating derived measures, including minimum and maximum EEM and lumen diameters, P&M area and thickness, and plaque burden (P&M divided by EEM); and measuring lesion length (distance between the proximal and distal reference) (Fig. 28.2).

In stented vessels, the stent forms a third measurable structure (stent CSA). It appears as bright points along the circumference of the vessel. Complete quantification of a stented lesion is possible by tracing the EEM and lumen areas of the proximal and distal reference and the EEM, lumen, and stent areas of the stented lesion; calculating derived measures [minimum and maximum EEM, stent, and lumen diameters; persistent P&M area and thickness; and intrastent intimal hyperplasia (IH, area and %IH)]; and measuring stent length.
Plaque Composition

Atherosclerotic plaques are heterogeneous and contain a mixture of plaque components with different impedance (density). IVUS imaging can categorize lesions into subtypes according to echodensity—typically by using the collagen-rich “bright” adventitia as a reference. Three basic types of lesions are distinguished according to plaque echogenicity: (i) “soft” or hypoechoic plaque does not reflect much ultrasound and appears dark with less echointensity compared to the adventitia, (ii) “hard” or hyperechoic, composed primarily of fibrous tissue with echogenicity equal or greater intensity than the adventitia, and (iii) calcific plaques, characterized by the presence of acoustic shadowing along with the brightest echoes and reverberations (Fig. 28.3).

Intimal hyperplasia due to in-stent restenosis often appears to have low echogenicity depending, in part, on age and adjunct therapies (i.e., brachytherapy). The identification of thrombus is difficult by IVUS. It may appear as lobulated hypoechoic mass within the lumen, scintillating echoes, a distinct interface between the presumed thrombus and underlying plaque, and blood flow through the thrombus (3).

Figure 28.2  IVUS measurements in a nonstented artery. The proximal (Panel A) and distal reference (Panel C) and minimum lumen area (Panel B) of the lesion are shown. The IVUS study is shown in duplicate: 1 unlabeled and 1 highlighted with lines to illustrate quantitative analysis. The dashed line highlights each external elastic membrane cross-sectional area (EEM CSA), and the solid line indicates each lumen interface (lumen CSA). The minimal lumen cross-sectional area (lumen CSA) at the lesion site is 2.1 mm². Between the EEM CSA and lumen CSA, the atheroma or plaque and media (P&M) complex is calculated. Abbreviation: IVUS, intravascular ultrasound.

Figure 28.3  Panel A shows an example of a predominantly soft plaque—a thin fibrous cap (small arrows) and lipid core underlying it; the plaque is less bright than the adventitia (a). In Panel B, fibrous or hyperechoic plaque is as bright as or brighter than the adventitia (a) without shadowing. In this eccentric plaque, the thickness of the media behind the thickest part of the plaque (b) is an artifact caused by attenuation of the beam as it passes through the hyperechoic plaque. In reality, the media becomes thinner with increasing atherosclerosis. Note that the media behind the thinnest part of the plaque is also thinner—without artifacts. The Panel C shows superficial calcium—defined as calcium (a) that is closer to the intima than it is to the adventitia. Calcium shadows the deeper arterial structures; in this case, the arc of calcification is ~180° (dashed line).
Discrepancies Between IVUS and Angiography

Coronary angiography significantly underestimates the presence, severity, and extent of atherosclerosis compared to IVUS (12). Furthermore, IVUS routinely shows significant atherosclerosis in angiographically “normal” segments in patients undergoing PCI (13). This discrepancy may be explained by three major factors: (i) atherosclerosis is often diffusely distributed involving long segments of the vessel containing no truly normal reference segment for comparison, (ii) complex atherosclerotic plaques are not appreciated by the two-dimensional “silhouette,” and (iii) most importantly, the presence of arterial wall remodeling (6).

Arterial Remodeling

Arterial wall remodeling at the site of coronary plaques was originally described by Glagov et al. (14) from necropsy examinations and later validated in vivo by IVUS imaging (15). “Positive,” “outward,” or “expansive” remodeling is defined as an increased in arterial dimensions; and “negative,” “inward,” or “constrictive” remodeling is defined as a smaller arterial dimension. Positive remodeling occurs as a compensatory increase in local vessel size in response to increasing plaque burden, especially during early stages of atherosclerosis (16). An absolute reduction in lumen dimensions typically does not occur until the lesion occupies, on average, an estimated 40% to 50% of the area within the EEM (40–50% plaque burden) (14). Conversely, negative remodeling has been implicated in the development of native significant stenosis in the absence of plaque accumulation (Fig. 28.4) (17).

A number of definitions of remodeling have been proposed (15–20). One definition compares the lesion EEM CSA to the average of the proximal + distal reference EEM CSA; positive remodeling is an index >1.0 and negative remodeling <1.0. A second definition defines positive remodeling as a lesion EEM greater than the proximal reference EEM, intermediate remodeling as a lesion EEM between the proximal and distal reference EEM, and negative remodeling as a lesion EEM less than the distal reference EEM. Using a third definition, arterial remodeling has been calculated by a remodeling index (lesion/reference EEM); positive remodeling is an index >1.05, intermediate remodeling is an index of 0.95 to 1.05, and negative remodeling is an index <0.95 (19). It is important to note that all of these remodeling definitions are based on a comparison of the reference EEM and lesion EEM. Accordingly, because both reference and lesion sites may have undergone quantitative changes in EEM during the atherosclerotic process, the evidence of remodeling derived from this index is relative and indirect (6).

Unstable Lesions

In patients with acute coronary syndromes (ACS), culprit lesions more frequently exhibit positive remodeling and a large plaque area; conversely, patients with a stable clinical presentation more frequently show negative remodeling and a smaller plaque area (19). Echolucent plaques are also more common in unstable than in stable patients. In addition, unstable lesions have less calcium than stable lesions; and when present, calcific deposits in unstable lesions are small, focal, and deep (21). Plaque ruptures can occur with varying clinical presentations although they are more often associated with ACS (22). Multiple ruptured plaques have been reported in patients with ACS; their prevalence, however, is the subject of controversy (23,24).

Intermediate Lesions

Coronary angiography underestimates stenosis severity most markedly in arteries with a 50% to 75% plaque burden and in patients with multivessel disease (25,26). An IVUS-measured

Figure 28.4  These illustrations show an eccentric, calcific, and small plaque accumulation (a) leading to negative remodeling. Panels A and B refer to proximal and distal vessel references and their respective longitudinal views (white arrows). In Panel B, notice how the vessel cross-sectional area (or EEM) is smaller than both the proximal and distal vessels. The longitudinal view depicts clearly the artery shrinkage at the lesion site. Abbreviation: EEM, external elastic membrane.
correlates with MLA significant stenosis because it is the best predictor of FFR minimum luminal area (MLA) of >4.0 mm² in a major (>3.0 mm) proximal epicardial artery excluding the left main coronary artery (LMCA) has been a consensus criterion of a nonsignificant coronary artery stenosis since it correlates well with the findings of other methods including single-photon emission computed tomography (27), Doppler FloWire studies (28), and pressure wire measurements (29). The clinical importance of this criterion has been confirmed by a study of 300 patients showing that deferral of revascularization is safe for patients with an MLA of >4.0 mm² (30).

Left Main Coronary Artery Disease

Several studies have showed that a very high percentage of patients with angiographically normal LMCA have disease by IVUS (31-33). Others have shown that IVUS is helpful in assessing ambiguous LMCA disease (Fig. 28.5) (34,35). The main reasons for the discrepancy between angiography and IVUS are (34)

1. diffuse atherosclerotic plaque involvement may lead to a lack of a normal reference segment,
2. a short LMCA makes identification of a normal reference segment difficult,
3. the presence of arterial remodeling,
4. the correlation between angiography and necropsy or IVUS appears to be better in non-LMCA lesions possibly because of unique geometric issues in the LMCA, and
5. significant inter and intraobserver variability in the angiographic assessment of LMCA disease (36) especially in ostium location (37).

IVUS assessment of lumen dimensions has been shown to correlate with fractional flow reserve (35), and both IVUS and fractional flow reserve predict clinical outcome in patients with LMCA disease (34,38). Jasti et al. reported that an IVUS MLA and MLA of <2.8 mm and <5.9 mm², respectively, strongly predict the physiological significance of LMCA stenosis (35). In general, an LMCA MLA <6.0 mm² has been used as a criteria of significant stenosis because it is the best predictor of FFR <0.75 and correlates with MLA >4.0 mm² in the left anterior descending (LAD) and left circumflex (LCX) using Murray’s Law (39).

Unusual Lesion Morphology

During coronary angiography, it is common to encounter unusual appearing lesions that elude accurate characterization despite thorough examination using multiple radiographic projections. The use of IVUS allows accurate characterization of unusual morphology: filling defects, aneurysms, and spontaneous dissections. While most filling defects are true thrombi, a small percentage is highly calcified plaque (Fig. 28.6) or even calcified nodules, an unusual form of vulnerable plaque.

In an IVUS analysis of 77 angiographically diagnosed aneurysms, 27% were true aneurysms (Fig. 28.7), 4% were pseudoaneurysms (Fig. 28.8), 16% were complex plaques, and 53% were normal arterial segments adjacent to stenoses (40).

By IVUS, a spontaneous dissection appears as a medial dissection with an intramural hematoma occupying some or all of the dissected false lumen without identifiable intimal tears and without a communication between the true and false lumens, typically in a nonatherosclerotic artery.

Percutaneous Coronary Intervention

Stent Sizing

Preinterventional IVUS is performed to assess stenosis severity and plaque composition and distribution, measure reference vessel size, and measure lesion length. As a result stent size can be chosen more accurately than solely by angiography. There are a number of paradigms that can be used. Stent size can be selected by identifying the maximum reference lumen diameter (proximal or distal to the lesion); it results in stent upsizing without an increase in complications. At the other extreme, stents can be sized to the “true vessel,” “media-to-media,” or midwall dimensions to reflect the amount of angiographically silent disease and, in most cases, the extent of positive remodeling, not just vessel size. Typically, this measurement will be larger than lumen reference and, thus, should be used only by experienced operators who understand its limitations.

IVUS measures lesion length more accurately than angiography because IVUS eliminates foreshortening, vessel tortuosity, or bendpoints.

Stent Expansion and Malapposition

IVUS studies have shown that lumen enlargement after stent implantation is a combination of vessel expansion and plaque redistribution/embolization, not plaque compression (41,42). Plaque reduction in patients with ACS is attributed to plaque or thrombus embolization (43). Intrusion or prolapse of plaque through the stent mesh into the lumen is more common in ACS and in saphenous vein graft lesions. Importantly, after
stent implantation, there is a significant residual plaque burden behind the stent struts that almost always measures 50% to 75% at the center of the lesion. Thus, the stent CSA always looks smaller than the EEM even when the stent is fully expanded.

Apposition refers to the contact between the stent struts to the arterial wall (6). Incomplete stent apposition is defined as one or more struts clearly separated from vessel wall with evidence of blood speckles behind the strut (Fig. 28.9). There is no conclusive evidence suggesting that isolated acute incomplete stent apposition (in the absence of concomitant under-expansion) is associated with adverse clinical outcomes.

**IVUS-Guided Stent Implantation**

The two main uses of IVUS are to insure optimal stent expansion (stent CSA) and full coverage of the lesion [especially with drug-eluting stent (DES) implantation]. In the majority of pre-DES studies, IVUS use optimized stent expansion; and the initially larger MSA achieved was associated with a lower restenosis rate (44–54). In the bare metal stent (BMS) era, 10 of 12 studies supported IVUS-guided PCI (Table 28.1).

At the introduction of DES, the importance of optimal stent deployment was initially underestimated. Suboptimal stent expansion with both BMS and DES was a risk factor for restenosis and target vessel revascularization, but also for stent thrombosis (62–64). Recently, Roy et al. reported that IVUS guidance during DES implantation had the potential to reduce both DES thrombosis and the need for repeat revascularization (65). In this study, 884 patients undergoing IVUS-guided DES implantation were compared with 884 propensity-score matched patients undergoing DES implantation with
angiographic guidance alone. At 30 days and at 12 months, a lower rate of definite stent thrombosis using the ARC definition was seen in the IVUS-guided group (0.5% vs. 1.4%; \( P = 0.046 \)) and (0.7% vs. 2.0%; \( P = 0.014 \)), respectively. At one year, target lesion revascularization was also lower in the IVUS-guided group (5.1% vs. 7.2%; \( P = 0.07 \)). A multicenter Korean registry of 805 LMCA interventions showed that the 595 patients treated with IVUS-guided DES implantation had better three-year survival than the 210 patients in whom IVUS was not used to guide LMCA DES implantation (HR = 0.43, \( P = 0.019 \)).

Recognition of Complications

IVUS has a higher sensitivity than angiography in identifying complications that may occur during PCI. Angiography tends to underestimate the presence and extent of dissection. Edge dissections may be more common when the stent ends in a reference segment that contains (i) both plaque and normal vessel wall or (ii) both calcific (or hard) and soft plaque elements. Dissection may not be visible by IVUS if the true lumen is severely stenotic and the ultrasound catheter presses the flap against the arterial wall or if the dissection occurs behind a calcified plaque that prevents accurate morphological definition. In general, the treatment of coronary dissection with stent implantation depends on the combination of angiographic assessment, flow assessment, and signs or symptoms of ischemia, and residual IVUS MLA. Treatment of dissections should be based on IVUS findings when they show evidence (i) reduced lumen dimensions below the threshold for an optimum result, (ii) impingement of the dissection flap on the IVUS catheter, (iii) mobility, and (iv) increased length. In general, minor edge dissections should not be treated unless they result in lumen compromise; the vast majority have healed when imaged at follow-up.

Intramural hematoma is a variant of dissection. Blood accumulates in the medial space; the EEM expands outward and the internal elastic membrane is pushed inward to cause lumen compromise. Intramural hematomas are typically

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**Table 28.1 Angiography Versus IVUS-Guided PCI in BMS Era**

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<th>Study</th>
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<th>IVUS better</th>
<th>IVUS better and cheaper</th>
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<td>Gaster et al. (47, 59)</td>
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**Abbreviations:** IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention; BMS, bare metal stent.

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**Figure 28.8** This patient underwent a previous directional coronary atherectomy of a lesion, in the left anterior descending artery, during which the artery was perforated. Follow-up catheterization showed both restenosis and a large aneurysm on angiography. The IVUS shows the body of the aneurism (Panel A) and the eccentric proximal restenotic lesion (Panel B). Notice that the adventitia stops at the point of transition from the vessel to the aneurism (a), indicating loss of vessel wall integrity and making this, in fact, a pseudoaneurysm. **Abbreviation:** IVUS, intravascular ultrasound. **Source:** From Ref. 3.

**Figure 28.9** The figure illustrates an example of acute stent malapposition. Panel A shows the vessel before stenting implantation; the IVUS study in Panels B and C shows the stent malapposition. In the magnified image in the right, notice the space between the stent strut and the intima and the blood speckle behind the stent struts (a). Five stent struts are malposed (white arrows). Because of stent malapposition, the stent area (9.4 mm\(^2\)) is smaller than the lumen area (14.4 mm\(^2\)). **Abbreviation:** IVUS, intravascular ultrasound.
hyperechoic and crescent shaped, with straightening of the internal elastic membrane (66). In general, an intramural hematoma should be treated because of the propensity for propagation and lumen compromise.

Coronary perforation and rupture usually occurs with over-aggressive and/or oversized balloon dilation although it can occur with a guidewire and stenting as well. In general, there are three distinct IVUS morphologic patterns indicating arterial rupture: (i) free blood speckle outside the EEM (Fig. 28.10), (ii) extramural hematoma—an accumulation of blood outside the EEM, and (iii) less common, a new periadventitial echolucent interface representing contrast extravasation (3). Acute management ranges from a conservative strategy of monitoring to prolonged balloon inflations, covered stents, and surgery.

Serial IVUS Studies

Restenosis

Serial IVUS studies have shown that the main mechanism of restenosis in nonstented arteries is negative arterial remodeling (decrease in EEM area), not intimal hyperplasia (17). Conversely, in-stent restenosis is primarily due to neointimal proliferation, not chronic stent recoil. By IVUS, %IH (IH volume divided by stent volume) has been shown to be consistent for each stent type. DES reduce restenosis by reducing IH from an average of 30% in BMS (67) to 3% to 5% in sirolimus-eluting stents (SESs) (68,69), to 6% in everolimus-eluting stents (70), to 8% to 13% in polymer-based paclitaxel-eluting stents (70,71), and to 16% in zotarolimus-eluting stents (72).

Serial IVUS analysis of the first-in-human ABSORB trial of the bioabsorbable vascular solutions (BVS, Abbott Vascular) fully absorbable DES showed a significant reduction in stent CSA at follow-up (−11.8%), absence of vessel negative remodeling, and IH of 30%. Of concern was the higher incidence of late-acquired incomplete stent apposition of 27% (73).

Acquired Late Stent Malapposition

Late stent malapposition (LSM) is usually caused by regional vessel positive remodeling (Fig. 28.12). LSM has been reported in 4% to 5% after BMS implantation (76). Studies have suggested a higher incidence of LSM after DES (especially after SES) (77–79). Hoffmann et al. studied the impact of LSM after SES implantation on four-year clinical events. This pooled IVUS analysis from three randomized trials comparing SES with BMS showed that LSM at follow-up was more common after SES than after BMS (25% vs. 8.3%; \( P = 0.001 \)); however, major adverse cardiac event-free survival at four years was identical for those with and without LSM (11.1% vs. 16.3%, \( P = 0.48 \)), and LSM was not a predictor for target lesion revascularization, target vessel failure, or late stent thrombosis during the four-year follow-up period in either patient group (80).
Figure 28.11  This patient presented with restenosis at follow-up after Cypher\textsuperscript{TM} sirolimus-eluting stent implantation in the right coronary artery (arrows on angiogram). Note the stent fracture with acquired transection on fluoroscopy. On IVUS, all stent struts have been seen at proximal (Panel A) and distal (Panel C) references, whereas at the fracture site (Panel B; minimal lumen area of 4.8 mm\textsuperscript{2}), only one stent strut has been seen (arrow). \textit{Abbreviation:} IVUS, intravascular ultrasound.

Figure 28.12  This patient underwent Cypher sirolimus-eluting stent implantation in a right coronary stenosis. The final angiogram is shown in Panel A. At follow-up (Panel B), there was a proximal and focal angiographic aneurysm (white arrows). Final (post-stent implantation) IVUS image is shown in Panel C and the follow-up IVUS image is shown in Panel D. Note the late stent malapposition (a and b). At the site of maximum stent malapposition (b), there has been an increase in EEM CSA from 17.8 to 28.9 mm\textsuperscript{2}. The stent CSA (8.8 mm\textsuperscript{2}) and the persistent P&M (8.9 mm\textsuperscript{2}) have not changed. \textit{Abbreviation:} CSA, cross-sectional area. \textit{Source:} From Ref. 75.
Conversely, others have suggested that LSM can contribute to late stent thrombosis (81,82). Cook et al. (82) studied 13 patients presenting with very late stent thrombosis (>1 year) after DES implantation and compared them to 144 control patients who did not experience stent thrombosis. Compared with DES controls, patients with very late stent thrombosis had longer lesions and stents, more stents per lesion, and more stent overlap. Vessel CSA was significantly larger for the in-stent segment (28.6 ± 11.9 mm² vs. 20.1 ± 6.7 mm²; P = 0.03) in very late stent thrombosis patients compared with DES controls, denoting evidence of positive arterial remodeling. Although IVUS was not performed at stent implantation in any patients of either group, incomplete stent apposition was more frequent (77% vs. 12%, P < 0.001) and maximal incomplete stent apposition area was larger (8.3 ± 7.5 mm² vs. 4.0 ± 3.8 mm²; P = 0.03) in patients with very late stent thrombosis compared with controls.

On the basis of these studies with conflicting data, it is still speculative as to how to treat patients with IVUS findings of LSM. However, it appears that there are two populations of LSM: (i) routinely detected LSM that is modest in size and does not appear to cause late events and (ii) large areas of LSM (essentially aneurysms) that are seen in patients with late stent thrombosis.

**VIRTUAL HISTOLOGY IVUS**

Gray scale IVUS is the gold standard for in vivo evaluation of atherosclerotic plaque, as well as lumen and vessel dimensions. However, several studies have suggested that IVUS has limited value for the identification of specific plaque components (5,83,84).

**Basic Principle and Imaging Interpretation**

Virtual histology (VH) is a new imaging modality based on the IVUS technique for quantifying plaque composition. Gray scale IVUS uses the amplitude of the reflected ultrasound signal to generate an image. Different tissues might have similar RF amplitude data, leading to misinterpretation of the gray scale image. Nevertheless, the power and frequency of the RF signal commonly differs between tissues, regardless of eventual similarities in the amplitude (Fig. 28.13) (85). Accordingly, plaque characterization can be explored by analyzing the frequency rather than the amplitude of the IVUS radiofrequency data. VH-IVUS uses the raw RF signal and elaborate automatic calibration technology (known as “blind deconvolution”), which normalizes for catheter-to-catheter and system-to-system variability, allowing standardized image interpretation and tissue characterization (86,87). The RF that underlies the conventional gray scale IVUS image is analyzed using a spectral analysis and compared with a histological database (VH-IVUS, Volcano Corporation, Rancho Cordova, California, U.S.). Eight spectral parameters (maximum power, frequency at maximum power, minimum power, frequency at minimum power, slope, intercept, mid-band fit, and integrated backscatter) are computed and combined in a statistical model to assess plaque composition in terms of four major plaque components: (i) fibrous, (ii) fibrofatty, (iii) necrotic core, and (iv) dense calcified tissue. Fibrous tissue is identified as a dark green group of pixels on the VH-IVUS screen; it is characterized by areas of densely packed collagen with little or no lipid accumulation and no evidence of macrophages indicating inflammatory response. Fibrofatty tissue is identified as a light green group of pixels on the VH-IVUS screen; it is characterized by areas of significant lipid accumulation (mainly extracellular) with no necrotic tissue. Necrotic core (NC) tissue is identified as a red group of pixels on the VH-IVUS screen; it is characterized by areas of significant lipid accumulation (mainly extracellular) with no necrotic tissue. Dense calcium is identified as a white pixel group on the VH-IVUS screen; this tissue is characterized by areas of dense calcium without adjacent necrosis (Fig. 28.14) (5,83,88). The VH-IVUS approach has led to a significant increase in the sensitivity and specificity of IVUS for plaque characterization, particularly lipid deposits. The sensitivity of gray scale IVUS for detecting lipid deposits is reported to be as low as 46%. VH-IVUS, on the other hand, has a combined predictive accuracy >95% for all four VH plaque components, and very high sensitivity (72-96%), and specificity (91-99%), indicating good agreement with histology (88,89).
Data Acquisition
VH-IVUS images are obtained with a commercially available console [IVG (InVision Gold) that has integral pcVH software or S5 that has integral VIAS software, both Volcano Corporation, Rancho Cordova, California, U.S.] Both consoles are interfaced with either a phased-array transducer (Eagle Eye® 20 MHz catheter, Volcano Corporation, Rancho Cordova, California, U.S.) or, in the future, with a developed mechanical transducer (Revolution® 45 MHz, Volcano Corporation, Rancho Cordova, California, U.S.). The integral software allows VH analysis to be performed online in the catheterization laboratory. The IVUS catheter is positioned distally in the coronary artery, and then withdrawn at a speed of 0.5 mm/sec using an automated pullback device. VH-IVUS data are acquired simultaneously with the gray scale IVUS data; however, ECG-gating is used to select frames for VH-IVUS analysis.

Atherosclerotic Lesion Phenotype Classification
On the basis on histopathological studies (90), coronary lesions are classified as (i) fibrotic, (ii) fibrocalcific, (iii) pathological intimal thickening (PIT) (iv) thick cap fibroatheromas (ThCFA), and (v) thin cap fibroatheromas (TCFA). PIT is a mixture of fibrous, fibrofatty, some necrotic core, and some calcified tissue; PIT must have >15% of fibrofatty. Any plaque that contains >10% of confluent NC is classified as fibroatheroma (ThCFA or TCFA). Pathology and autopsy studies indicate that TCFA is the most common type of vulnerable plaque (VP) and is a precursor of plaque rupture (91). The vulnerability of plaque to rupture is typically characterized by the presence of an NC, which is a region of the fibroatheroma that is largely devoid of viable cells and consists of cellular debris and cholesterol clefts, a thin fibrous cap (<65 µm), and macrophage infiltration (92). The threshold for defining the cap as “thin” (and categorize a lesion as a TCFA) has been previously set at <65 µm, based on postmortem studies. However, tissue shrinkage occurs during tissue fixation, and postmortem contraction of arteries is an additional confounding factor (93). Thus, the threshold used to define thin cap in vivo should probably be higher than 65 µm (83). Indeed, some ex vivo studies have used higher (>200 µm) thresholds (94). Because the axial resolution of VH-IVUS is from 100 to 150 µm, some experts maintain that the absence of visible fibrous tissue overlying a necrotic core suggests a cap thickness of below 100 to 150 µm, and use the absence of such tissue to define a thin fibrous cap (83). Hence, by VH-IVUS, TCFA is defined by the following: (i) confluent NC >10% of plaque area in at least three consecutive frames without overlying fibrous tissue and (ii) presence of ≥40% plaque burden (plaque/media divided by EEM) (83). ThCFA is a fibroatheroma with overlying fibrous tissue. Conversely, in vivo VH-IVUS with histopathology also shows a high accuracy. Nasu et al. (88) analyzed 15 stable angina pectoris patients and 15 ACS patients undergoing coronary atherectomy. The results of VH-IVUS data analysis correlated well with histopathologic examination (predictive accuracy: 87.1% for fibrous, 87.1% for fibrofatty, 88.3% for NC, and 96.5% for dense calcium regions). In addition, the authors found that the frequency of NC was significantly higher in the ACS group than in the stable group (in vitro histopathology: 22.6% vs. 12.6%, P = 0.02; in vivo VH-IVUS: 24.5% vs. 10.4%, P = 0.002). Likewise, two different studies reported that vulnerable plaque by VH-IVUS occurred more often in patients with ACS than in patients with stable angina. In one study, Rodriguez-Granillo et al. (95) found that culprit lesions in patients with ACS had greater amounts of NC and smaller amounts of fibrofatty plaque compared with culprit lesions in patients with stable angina.

Arterial Remodeling and Plaque Composition
There are conflicting data regarding the relationship of vessel remodeling to plaque composition by VH-IVUS. In one study, Rodriguez-Granillo et al. (99) showed that plaque composition...
and morphology by VH-IVUS analysis was associated with coronary remodeling. Positive remodeling was found with high-risk lesions such as TCFA or fibroatheromas, whereas negative remodeling was associated with less vulnerable lesions, with 64% characterized by PIT, 29% as fibrocalcific lesions, and only 7% fibroatheromatous lesions ($P < 0.0001$) (99). Surmely et al. (100) and Fuji et al. (101) reported the opposite finding. NC was significantly smaller in lesions with positive remodeling than in lesions with intermediate/negative remodeling. In one study (101), the authors showed a linear relationship between remodeling index and fibrofatty plaque area, demonstrating that positive remodeling occurs in lesions with more fibrofatty plaque. The discrepancy between these studies—including between the two latter studies with pathologic findings (102)—might have resulted from differences in the patient/lesion population, in definition/methods applied or potential VH-IVUS artifacts/limitations. The Figure 28.15 shows two examples of plaque characterization by VH-IVUS.

**VH-IVUS Limitations**

The main limitations of VH-IVUS are as follows: (i) only four plaque components are identifiable. For instance, there are no classifications for thrombus or blood on VH-IVUS. Ruptured plaques filled with blood or thrombus, or even luminal thrombus, are assigned to 1 of the current plaque classifications, usually fibrous. Thus, the lack of ability to identify thrombus limits the recognition of certain high-risk plaques; (ii) ex vivo VH-IVUS validation studies have reported a high accuracy for the classification of plaque components based on selected regions of interest representing homogeneous plaque components on the histology specimen. Validation studies for VH tissue maps of entire plaque cross-sections is reported to be difficult due to the amorphous overlap of the tissue component (89); therefore, VH-IVUS may have a limited accuracy to assess plaque components in highly heterogeneous and complex lesions (103); and finally (iii) there is no consensus about the in vivo definition of TCFA. The VH-IVUS definition is based on the “absence” of visible fibrous tissue overlying a necrotic core; TCFA cannot be directly identified. Thus, vulnerable plaque identification is compromised and might be imprecise by VH-IVUS.

**Potential Clinical Application**

VH-IVUS could potentially aid in the assessment of changes in plaque characteristics induced by lipid-lowering drugs (104), stenting, and could also help predict future coronary events. VH-IVUS is a promising technique to detect vulnerable plaque and to assess its natural history. The lesions that harbor vulnerable plaque are frequently only mildly stenotic on angiographic examination. Because VH-IVUS allows for improved interpretation of coronary disease in the entire artery with volumetric data of the individual VH plaque components, the method shows promise as an approach to identify patients with a high-risk of adverse events. However, there is currently no evidence favoring invasive treatment of a vulnerable plaque. A meta-analysis showed that the restenosis risk after balloon angioplasty or BMS implantation in angiographically determined intermediate lesions corresponded with the restenosis risk in clinically relevant stenosis and was unacceptably high (105). On the other hand, the risk of restenosis in intermediate/nonstenotic lesions treated with DES is reported to be lower when compared with the estimated one-year probability of a nonfatal MI in lesions with a stenosis $<50\%$ (106). Ongoing large-scale, prospective clinical trials will help our understanding of the temporal changes that take place in coronary plaques and how VH-IVUS can be used as a decision-making tool in individual patients. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial is a natural history study designed to analyze the relationship of unexpected ACS with the progression of coronary artery disease. This first prospective trial using serial VH-IVUS analysis may help to identify plaques that are prone to rupture, potentially leading to cardiac events. The results of this study could lead to changes in recommendations regarding how to treat vulnerable plaque and coronary artery disease.

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**Figure 28.15** (See color insert) Examples of conventional IVUS image and VH-IVUS side by side. (Left) Lesion with acute coronary syndrome with positive remodeling. In this segment, notice the presence of thin cap fibroatheromas (i.e., necrotic core representing $>10\%$ of the plaque burden without overlying fibrous tissue). (Right) Lesion with stable angina with negative remodeling. In this segment the plaque is predominantly fibrotic. Abbreviations: IVUS, intravascular ultrasound; VH-IVUS, virtual histology IVUS.
CONCLUSIONS
Gray scale IVUS provides (i) high-quality, tomographic imaging of the lumen, the atheroma, and the vessel wall, (ii) incremental and more detailed qualitative and quantitative information than coronary angiography, (iii) practical guidance during PCI, and (iv) numerous clinical and research insights. More recently, IVUS has become an indispensable part of DES research, as the most effective tool in helping to understand the mechanisms, effects, and complications of this new stent technology.

VH-IVUS provides a reliable representation of plaque composition and morphometry. Thin-capped fibroatheromas can be identified using VH-IVUS. These lesions most often occur in ACS patients, and are associated with positive arterial remodeling. Necrotic core volume may also help identify lesions most at risk for distal embolization during PCI. Prospective clinical trials will provide a better understanding of the temporal changes that occur in coronary plaques and how VH-IVUS can be used as a decision-making tool in individual patients.

REFERENCES


Optical coherence tomography
E. Regar, N. Gonzalo, G. Van Soest, and P. W. Serruys

INTRODUCTION
Optical coherence tomography (OCT) is a light-based imaging modality showing tremendous potential in the coronary circulation. Compared with traditional intravascular ultrasound (IVUS), OCT has a 10-fold higher image resolution resulting from use of light rather than sound. OCT has been successfully applied to the assessment of atherosclerotic plaque, stent apposition, and tissue coverage, introducing a new era in intravascular coronary imaging.

The origins of OCT date back to 1990, when Dr David Huang was in his fourth year of an MD-PhD program at Massachusetts Institute of Technology (MIT). As an offshoot of ongoing femtosecond ranging projects in Prof James Fujimoto’s laboratory, Dr Huang had been studying optical coherence domain reflectometry (OCDR) to perform ranging measurements in the eye. The retinal scans, however, were very hard to interpret. The thought occurred to Dr Huang that adding transverse scanning to OCDR graphs would create an image that would be much easier for a human to interpret than the set of OCDR waveforms. All that was required was to add a translation stage and a software package to convert a data matrix into an image.

The central problem in making tomographic images using light was to develop a technique that would permit reflections from various depths to be measured and recorded in a fashion analogous to ultrasonic imaging. In the case of sound, electronic circuits are fast enough to separate the echoes from structures that are within the resolution cell of the ultrasonic transducer. In the case of light, an interferometer has to be employed to overcome measurement difficulties caused by the speed of light, which is much faster than the speed of sound. By using an interferometer it was, for the first time, possible to record reflections from various depths in a biological tissue.

Since 1990, OCT technology has generated over 5000 articles in academic journals. The first manuscript from MIT, published in 1991, describes the basic concept of an OCT imaging system and discusses its possible applications in both retinal and arterial imaging (1). In 1996, a second manuscript was published that dealt specifically with the possibility of imaging coronary arteries with an OCT device (2).

It became clear early on that OCT could contribute to the diagnosis of ocular diseases. It was believed that the new technology had the potential to serve as an in vivo microscope that could obtain nonexcisional biopsy information from locations at which a conventional biopsy was either impossible or impractical to perform. A second research thrust from the MIT group was to push the resolution of the technology to increasingly higher levels using wider bandwidth optical sources. Sufficiently wide bandwidth sources would enable to resolve subcellular structures and measure the ratio of the nuclear volume to the total cell volume in a manner similar to what a pathologist does when diagnosing cancer. In the days since the initial discussion in Prof Fujimoto’s office, several members of the MIT OCT team have started academic OCT research programs throughout the United States.

Compared with an OCT microscope, used in ophthalmology and in most experimental settings, the application of OCT within the human vascular system, particularly within coronary arteries, represents a challenge, as a number of principal problems need to be overcome. Hence, the intracoronary application of OCT has developed relatively slowly, but steadily, over the last decade, and a commercially available system for clinical use (LightLab Imaging, Inc., Westford, Massachusetts, U.S.) is being approved in Europe and Japan. Today, the technology development from time-domain OCT to Fourier-domain OCT has the potential to dramatically change the research landscape allowing for a widespread clinical intracoronary application in research and patient care. This chapter discusses these technical principles of intracoronary OCT, summarizes the preclinical and clinical research, discusses potential clinical applications, and explains the practical performance of OCT in the catheterization laboratory. Differences in time-domain versus Fourier-domain OCT will be pointed out whenever relevant.

ANATOMIC CONSIDERATIONS
Principally, all epicardial coronary arteries, venous or arterial grafts accessible by a guiding catheter, are eligible for OCT imaging.

Considerations regarding anatomy and patient characteristics arise (i) from the fact that OCT imaging requires a blood-free environment and (ii) from OCT catheter design. As the imaging procedure demands temporary blood removal and flush (e.g., lactated ringers or X-ray catheter design), it should not be performed in patients with severely impaired left ventricular function or those presenting with hemodynamic compromise. Further, OCT should be used with caution in patients with single remaining vessel or those with markedly impaired renal function. Lesions that are ostially or proximally located cannot be adequately imaged using proximal balloon occlusion and, thus, a nonocclusive technique may be preferred in these circumstances. Large caliber vessels or very tortuous vessels often preclude complete circumferential imaging as a result of a noncentral, noncoaxial position of the OCT imaging probe within the vessel.

These anatomic limitations seem to be significantly attenuated in Fourier-domain OCT as the pullback speed is much higher, and as a result, the duration of ischemia and the amount of potentially nephrotoxic flush is much lower.
Increased penetration depth and scanning range allow imaging of the complete circumference of large and tortuous vessels. The design as short monorail catheter enables to negotiate even complex lesions by selecting an appropriate standard guidewire. As there is no proximal balloon occlusion necessary, also ostial lesions, bifurcations and large vessels can be visualized.

**FUNDAMENTALS**

The principle is analogous to pulse-echo ultrasound imaging; however, light is used rather than sound to create the image. Although ultrasound produces images from backscattered sound “echoes,” OCT uses infrared light waves that reflect off the internal microstructure within the biological tissues. The use of light allows for a 10-fold higher image resolution; however, this is at the expense of a reduced penetration depth and the need to create a blood-free environment for imaging. In coronary arteries, blood (namely, red blood cells) represents that nontransparent tissue causing multiple scattering and substantial signal attenuation. As a consequence, blood must be displaced during OCT imaging. This procedure is potentially causing ischemia in the territory of the artery under study. The need for balloon occlusion and intracoronary flush are at the forefront of emerging developments to simplify the OCT image acquisition process. Automated catheter pullbacks at very high speed are currently under development in OCT systems using optical Fourier-domain imaging. Faster pullback speeds offer the potential to scan an entire stent within a matter of five to six seconds.

**OCT Principles**

OCT utilizes a near infrared light source (~1300-nm wavelength) in combination with advanced fiber-optics to create a dataset of the coronary artery. Both the bandwidth of the infrared light used and the wave velocity are orders of magnitude higher than in medical ultrasound. The resulting resolution depends primarily on the ratio of these parameters, and is one order of magnitude higher than that of IVUS: the axial resolution of OCT is about 15 μm. The lateral resolution is mainly determined by the imaging optics in the catheter and is approximately 25 μm. The imaging depth of approximately 1.0 to 1.5 mm within the coronary artery wall is limited by the attenuation of light in the tissue (Table 29.1). Analogous to ultrasound imaging, the echo time delay of the emitted light is used to generate spatial image information, the intensity of the received (reflected or scattered) light is translated into a (false) color scale. As the speed of light is much faster than that of sound, an interferometer is required to measure the backscattered light (3). The interferometer splits the light source into two “arms”—a reference arm and a sample arm, which is directed into the tissue. The light from both arms is recombined at a detector, which registers the so-called interferogram, the sum of reference and sample arm fields. Because of the large source bandwidth, the interferogram is nonzero only if the sample and reference arms are of equal length, within a small window equal to the coherence length of the light source (4,5).

**Time-Domain OCT**

In time-domain OCT, the length of the reference arm is scanned over a distance of typically a few millimeters, by moving a mirror. The point from which intensity is collected from the sample arm is moved through the tissue accordingly, and the amplitude of the recorded interferogram in a scan corresponds to the reflectivity of the tissue along the direction of the sample beam. By scanning the beam along the tissue, in a rotary fashion for intravascular imaging, an image is built up out of neighboring lines. Figure 29.1 shows the currently commercially available time-domain OCT system (LightLab Imaging, Inc.).

**Fourier-Domain OCT**

A new generation of OCT systems operates in the frequency (rather than time) domain, also called Fourier domain. The interferogram is detected as a function of wavelength, either by using a broadband source as in the time domain systems, and spectrally resolved detection, or alternatively by incorporating a novel wavelength-swept laser source (6,7) (Table 29.2). This latter technique is also called “swept-source OCT,” or optical
frequency domain imaging (OFDI), and capitalizes most effectively on the higher sensitivity and signal-to-noise ratio offered by Fourier-domain detection. This development has led to faster image acquisition speeds, with greater penetration depth, without loss of vital detail or resolution, and represents a great advancement on current conventional OCT systems. From the signal received in one wavelength sweep, the depth profile can be constructed by the Fourier transform operation that is performed electronically in the data processing unit. All other components of a Fourier-domain system (the interferometer, the catheter, including the imaging optics, display) are comparable in principle to those in a time-domain OCT system.

The increased sensitivity of Fourier-domain OCT also allows for larger imaging depths. The attenuation of light by the tissue is the same for time-domain and for Fourier-domain OCT, but the lower noise of the latter makes it possible to discern weaker signals that would be indistinguishable from the background in time-domain OCT. The depth range from which useful anatomical information can be extracted is extended by a factor of about 3 (12). Clinically, this advantage enables the assessment of coronary microstructures well beyond the arterial-lumen border.

Fourier-domain OCT systems produce images much faster than standard video-rate, so recorded data has to be replayed for inspection by the operator. Currently, OCT systems scan 200 to 500 angles per revolution (frame), and 5 to 10 images/mm in a pullback. If these parameters are maintained with high-speed systems, 20 mm/sec (or higher) pullback speeds are possible at the same sampling density as conventional OCT data. Figure 29.2
shows different Fourier-domain OCT prototypes as used at the Thoraxcenter in 2008. Figure 29.3 illustrates Fourier-domain OCT images as obtained in vivo in normal porcine coronary arteries.

The high scan speeds have been employed for real-time volumetric imaging of dynamic phenomena including fast pullbacks for intracoronary imaging with minimal ischemia (12), and retinal scans with minimal motion artifacts (13). Imaging of dynamic phenomena in time, or rather removing motion artifacts, is the prime application of high-speed OCT. 3D rendering of volumes becomes possible if motion during the scan is limited. The high data rate of novel OCT technologies could also be used to increase sampling density either in the longitudinal (pullback) or angular direction. A smaller spacing between frames in a pullback would lead to a better sampling of small-scale features in the arterial or stent geometry that would be missed at 100 μm inter-frame distance. Denser sampling in the angular direction would facilitate speckle filtering in OCT images. Speckle is a major obstacle for the development of parametric and quantitative imaging techniques. These possibilities are still largely unexplored.

**Figure 29.2** Different FD-OCT prototypes as used at the Thoraxcenter in 2008. (A) M4 system (LightLab Imaging, Inc., Westford, Massachusetts, U.S.), (B) Terumo OCT, (C) Volcano OCT, (D) MGH OFDI system. Abbreviations: FD-OCT, Fourier-domain optical coherence tomography; OFDI, optical frequency domain imaging; MGH OFDI, Massachusetts general Hospital optical frequency domain imaging. Source: Courtesy of G. Tearney and B. Bouma, Wellman Center for Photomedicine, MGH, Boston, Massachusetts, U.S.A.

**Figure 29.3** FD-OCT images as obtained in vivo in normal porcine coronary arteries. The coronary vessel wall shows a three-layer appearance, and an intimal dissection is visible in the 4 o’clock position. (A) M4 prototype (LightLab Imaging, Inc., Westford, Massachusetts, U.S.), (B) Terumo OCT, (C) MGH OFDI system. Abbreviations: FD-OCT, Fourier-domain optical coherence tomography; OFDI, optical frequency domain imaging; MGH OFDI, Massachusetts general Hospital optical frequency domain imaging.
the proximal reference (F), the lesion site that can be easily identified using anatomical landmarks such as side branches (SB) or calcium nodules. Metallic stent struts appear as bright structures with dorsal shadowing. The distal reference (E) and the lesion site that can be easily identified using anatomical landmarks such as side branches (SB) or calcium nodules. Metallic stent struts appear as bright structures with dorsal shadowing.

**INDICATIONS**

To date, there is no established indication for the clinical use of OCT in patient care. However, there are a variety of research applications where OCT is clearly accepted as the “gold standard.” We summarize the accepted research applications and illustrate the potential clinical implications of OCT findings.

**The Role of OCT in Stent Imaging**

Coronary artery lesions and results following percutaneous coronary intervention (PCI) are usually assessed angiographically. This lumigraphic technique provides a unique overview of the coronary tree, gives information regarding anatomy and topography, and can confirm the presence of atherosclerosis with high specificity. The prognostic relevance for subsequent cardiac events, such as myocardial infarction, however, is limited. Furthermore, stent implantation and optimization undertaken using angiographic guidance alone has been shown to result in more frequent incomplete stent expansion and an increased future risk of target vessel revascularization when compared with guidance with IVUS.

**Assessment of Acute Stent Apposition**

For the past two decades, IVUS has been used to assess the acute result following stenting, giving valuable information on stent expansion, strut apposition, and signs of vessel trauma including dissections and tissue prolapse. IVUS studies suggested that stent strut malapposition is a relatively uncommon finding, observed in approximately 7% of cases, and that strut malapposition does not increase the risk of subsequent major adverse cardiac events. In contrast, OCT can visualize the complex coronary arterial wall structure after stenting in much greater detail (16). As a result, OCT studies in the acute poststent setting (17) have demonstrated a relatively high proportion of stent struts, not completely apposed to the vessel wall contact, even after high-pressure postdilatation with this phenomenon being particularly evident in regions of stent overlap. In an evaluation of OCT findings following stent implantation to complex coronary lesions, Tanigawa et al. (18) examined a total of 6402 struts from 23 patients (25 lesions) and found 9.1 ± 7.4% of all struts in each lesion treated were malapposed. Univariate predictors of malapposition on multilevel logistic regression analysis were the implantation of a sirolimus-eluting stent (SES, likely due to its increased strut thickness and closed-cell design) together with the presence of overlapping stents, a longer stent length, and a type C lesion. Likely mechanical explanations for stent malapposition include strut thickness, closed-cell design, or acute stent recoil (19). Although these findings are impressive and helpful for the improvement of future stent designs, today the clinical relevance and potentially long-term sequelae of malapposed struts as detected by OCT are currently unknown. Figure 29.4 illustrates OCT findings before and immediately after stent implantation in a patient presenting with acute myocardial infarction.

**Assessment of Long-Term Outcome**

**Visualization and quantification of stent strut tissue coverage** OCT can reliably detect early and very thin layers of tissue coverage on stent struts. Figure 29.6 illustrates the typical OCT appearance of neointima in bare-metal stents (BMS) and in drug-eluting stents (DES). Several small studies have recently been published highlighting the application of OCT in the detection of stent tissue coverage at follow-up. Importantly, OCT permits the quantification of tissue coverage with high reliability (20). Matsumoto et al. (21) studied 34 patients following SES implantation. The mean neointima thickness was 52.5 μm, and the prevalence of struts covered by thin neointima undetectable by IVUS was 64%. The average rate of neointima-covered struts in an individual SES was 89%.
Nine SES (16%) showed full coverage by neointima, whereas the remaining stents had partially uncovered struts. Similarly, Takano et al. (22) studied 21 patients (4516 struts) three months following SES implantation. Rates of exposed struts and exposed struts with malapposition were 15% and 6%, respectively. These were more frequent in patients with acute coronary syndrome (ACS) than in those with non-ACS (18% vs. 13%, \( p < 0.001 \); 8% vs. 5%, \( p < 0.005 \), respectively). The same group have recently reported two-year follow-up OCT findings (23), with the thickness of neointimal tissue at two years being greater than that at three months (71 ± 93 \( \mu \)m vs. 29 ± 41 \( \mu \)m, respectively; \( p < 0.001 \)). Frequency of uncovered struts was found to be lower in the two-year group compared with the three-month group (5% vs. 15%, respectively; \( p < 0.001 \)). Conversely, prevalence of patients with uncovered struts did not differ between the three-month and the two-year follow-up study (95% vs. 81%, respectively), highlighting that exposed struts continued to persist at long-term follow-up. Chen et al. (24) recently used OCT to image SES and BMS at different time points following implantation. Of the 10 SES and 13 BMS imaged, the authors identified a significantly higher number of incompletely apposed and uncovered stent struts in patients receiving SES compared with BMS. Figure 29.7 illustrates OCT finding at long-term follow-up after DES implantation.

Assessment of structural details of tissue coverage. OCT also permits the qualitative characterization of neointimal tissue in a qualitative way (25). This is a great advantage as such information has not been available in vivo until now. The limited resolution together with artifacts induced by metallic stent struts do not allow the characterization of such details by IVUS. With OCT, neointimal tissue can show a variety of morphologies ranging from homogenous, bright, uniform tissue to optically heterogeneous tissue or eccentric tissue of various thickness. Furthermore, structural details within the tissue can be observed such as intimal neovascularization (26) or a layered appearance (27), typically observed in restenotic regions. Variations in the appearance of strut coverage can be seen within an individual patient, within an individual stent, or within stents of different design.

OCT findings, such as dark, signal-poor halos around stent struts may reflect fibrin deposition and incomplete healing, as described in pathological and animal experimental series (28). However, there is paucity of data demonstrating directly the OCT appearance of different components in neointimal tissue as defined by histology. Postmortem imaging of DES in human coronaries is difficult and might be limited by the fact that the optical tissue properties show variations with temperature and fixation (29). Long-term animal OCT observations in DES are scarce.

OCT Assessment of Innovative Stent Designs and Materials

OCT is also becoming an integral tool to assess emerging stent technologies that are increasingly becoming more sophisticated (e.g., bioabsorbable polymers and stents, biodegradable magnesium alloy stents) and thus demanding highly detailed assessments both in the initial animal testing phases and in the clinical trial setting. Morphological changes of the
absorbable, polylactic acid stent struts and the vessel wall during follow-up have been recently described and show the unique capabilities of this in vivo imaging modality (30). The ABSORB trial recently published showed the feasibility of implantation of the bioabsorbable everolimus-eluting coronary stent (BVS; Abbott Laboratories, Illinois, U.S.), composed of a poly-L-lactic acid backbone, coated with a degradable polymer-everolimus matrix. OCT allowed not only a precise characterization of the stent apposition and coverage but also demonstrated structural changes in the bioabsorbable DES over time. At present OCT appears as the best available tool for the assessment of the absorption of the stent struts.

Another field of innovation consists in the treatment of bifurcation lesions with a variety of dedicated stents under clinical investigation. Key issues in bifurcation stenting include the ability of a stent to cover different vessel calibers at the proximal lesion site, the carina, and the distal lesion site, and to provide maximal expansion of the carina on both sides, the main vessel and the side branch. OCT can be a very useful tool to study the stent—vessel wall interaction as well as patency of the carina in this more complex anatomy. Clinical and experimental examples of OCT findings in bifurcation stenting are given in Figures 29.8 to 29.11 and Table 29.3.

Atherosclerotic Plaque Assessment

OCT is highly sensitive and specific for the characterization of plaques when compared with histological examination. Recently, pathophysiology and coronary morphology in patients with ACS are getting more and more attention. One reason for this interest is the fact that ACSs caused by the rupture of a coronary plaque are common initial and often fatal manifestations of coronary atherosclerosis in otherwise healthy subjects. The detection of the lesions with high risk of rupture (the so-called “vulnerable plaques”) would be of main importance for the prevention of future ACS. In the last years there has been a growing interest in this field, and a lot of different techniques have been developed to evaluate diverse aspects involved in plaque vulnerability. Among them, OCT has emerged as one of the most promising due to its ability to provide unique information about the plaque composition, the thickness of the fibrous cap, the presence of macrophages and tissue collagen composition.

Plaque Composition

The propensity of atherosclerotic lesions to destabilize and rupture is highly dependent on their composition. In comparison with histology, OCT has demonstrated to be highly sensitive and specific for characterizing different types of atherosclerotic plaques (Figs. 29.12 and 29.13). Yabushita et al. (31) performed an in vitro study of more than 300 human atherosclerotic artery segments. When compared with histological examination, OCT had a sensitivity and specificity of 71% to 79% and 97% to 98% for fibrous plaques, 95% to 96% and 97% for fibrocalcific plaques, and 90% to 94.5% and 90% to 92% for lipid-rich plaques, respectively. Further, the interobserver and intraobserver variability of OCT measurements were high (κ values of 0.88 and 0.91, respectively). Ex vivo validations have also shown that OCT is superior to conventional and
integrated backscatter IVUS for the characterization of coronary atherosclerotic plaque composition (32–35). In vivo, OCT is able to identify most of the architectural features identified by IVUS and may be superior for the identification of lipid pools (36). Several authors have evaluated the OCT appearance of coronary plaques in different groups of patients, reporting higher prevalence of lipid-rich plaques in ACS than in patients with stable angina (37) and no differences in the culprit plaque imaged by OCT between diabetic and nondiabetic patients (38) and men or women with ACS (39). According to histological and IVUS examinations, the percentage of lipid-rich plaque by OCT has been found to be higher in plaques with expansive remodeling (40).

**Thickness of the Fibrous Cap**

Autopsy studies of sudden cardiac death victims have shown that the most frequent cause of the coronary occlusion is rupture of a thin-cap fibroatheroma (TCFA) plaque. Such lesions
are characterized by a large necrotic core with a thin fibrous cap usually <65 μm in thickness. Although conventional intracoronary imaging techniques such as IVUS-VH do not have enough resolution to evaluate in detail the fibrous cap, OCT has demonstrated in correlation with histological examinations that it is able to provide accurate measurements of the thickness of the fibrous cap (41,42). Therefore, it could be useful for the in vivo detection of TCFA. In the study with IVUS, OCT, and angioscopy in acute myocardial infarction patients by Kubo et al., the incidence of TCFA was 83% and only OCT was able to estimate the fibrous cap thickness (mean 49 ± 21 μm). Two studies have reported that the plaque color by angioscopy is related to the thickness of the fibrous cap as measured by OCT with yellow plaques often presenting thin caps (43,44).

Assessment of Collagen Composition
A fibrous cap is predominantly composed of collagen, synthesized by intimal smooth muscle cells, which together impart mechanical integrity. Mechanisms that weaken the cap and potentially lead to plaque instability include collagen proteolysis and impeded collagen synthesis, resulting in a net reduction in collagen content and thinning and disorganization of collagen fiber orientation. Polarization-sensitive (PS) imaging enhances OCT by measuring tissue birefringence, a property that is elevated in biological tissues containing proteins with an ordered structure, such as organized collagen (45–47). PS-OCT imaging can provide both, conventional grayscale OCT as well as PS-OCT images, in one single pullback through the coronary. When light traverses birefringent tissue, light polarized along directions parallel and perpendicular to the fiber orientation of the tissue travels at different velocities, incurring a relative phase retardation. The accumulated phase retardation is then displayed with respect to the tissue surface as a grayscale image with black corresponding to 0° and white to 180°. PS-OFTI birefringence has been demonstrated to be highly

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**Figure 29.10** Bifurcation stent implantation in normal pigs. Serial, in vivo OCT (A) immediately after stenting and (B) at seven-day follow-up. Tissue coverage is visible in various degrees from very thin coverage (C) to more pronounced, irregular coverage (D). Furthermore, a persisted dissection flap can be observed at the proximal reference segment (E) (TD-OCT system, LightLab Imaging, Inc., Westford, Massachusetts, U.S.). **Abbreviations:** OCT, optical coherence tomography; TD-OCT, time domain optical coherence tomography.

**Table 29.3** Qualitative OCT Analysis of the Stent at Different Stent Portions

<table>
<thead>
<tr>
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<th>Proximal</th>
<th>Carina</th>
<th>Distal</th>
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<tr>
<td>Dissection</td>
<td>2 (25.0)</td>
<td>1 (12.5)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Intraluminal tissue</td>
<td>2 (25.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Incomplete apposition</td>
<td>5 (62.5)</td>
<td>4 (50.0)</td>
<td>2 (25.0)</td>
</tr>
</tbody>
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**Figure 29.11** Bifurcation stent implantation in normal pigs (n = 8). Quantitative OCT analysis of the stent area at different stent portion. **Abbreviation:** OCT, optical coherence tomography.
related to total collagen content in atherosclerotic plaques as well as in fibrous plaques in vitro. It has been suggested that the ability of OCT to measure changes in the fibrous cap thickness could be useful to assess the effect of statins in plaque stabilization (48,49). Furthermore, recent data suggest that PS-OCT could be able to assess the collagen content and smooth muscle cell density in the fibrous cap (45). This could provide very valuable information about the mechanical stability of the fibrous cap, enabling the identification of lesions at high risk of rupture.

**Plaque Rupture and Intracoronary Thrombosis**

Plaque rupture with subsequent thrombosis is the most frequent cause of ACS. OCT can identify intracoronary thrombus and plaque rupture with high accuracy (50). Recently, Kubo et al. evaluated the ability of OCT for the assessment of the culprit lesion morphology in acute myocardial infarction in comparison with IVUS and angioscopy. They found an incidence of plaque rupture by OCT of 73%, significantly higher than that detected by both angioscopy (47%, \( p = 0.035 \)) and IVUS (40%, \( p = 0.009 \)). Intracoronary thrombus was observed in all cases by OCT and angioscopy but was identified only in 33% of patients by IVUS (49). Furthermore, Kume et al. demonstrated that OCT might be able to distinguish between white and red thrombus. Red thrombus appears in OCT as high-backscattering structure with signal-free shadowing, while white thrombus appears as a low-backscattering structure (51). OCT could be helpful to identify the culprit lesion in ACS and might provide additional information about the underlying cause that lead to the plaque rupture (Fig. 29.14).
Visualization of Macrophage Accumulation

Intense infiltration by macrophages of the fibrous cap is another feature of the vulnerable plaques. An ex vivo study by Tearney et al. demonstrated OCT could be able to quantify macrophage within the fibrous cap (16). In vivo, it has been demonstrated that unstable patients present a significantly higher macrophage density detected by OCT in the culprit lesion than stable patients. Furthermore, in the same population, the sites of plaque rupture demonstrated a greater macrophage density than nonruptured sites (52). Raffel et al. reported that macrophage density in the fibrous cap detected by OCT correlated with the white blood cell count, and both parameters could be useful to predict the presence of TCFA (53). Figure 29.15 illustrates detailed OCT-based tissue characterization over a long coronary segment including the distribution of macrophages, calcium, and lipid-rich tissue.

EQUIPMENT

The equipment for intracoronary OCT generally consists of an OCT imaging catheter, a motorized pullback device, and an imaging console, which contains the light source, signal processing units, data storage, and display (54). The imaging catheter is part of the sample arm of the interferometer described above. The optical signal is transmitted by a single-mode fiber, which is fitted with an integrated lens microprism assembly to focus the beam and direct it toward the tissue. The focus is approximately 1 mm outside the catheter. To scan the vessel lengthwise, the catheter-imaging tip is pulled back while rotating, usually inside a transparent sheath, allowing to collect a 3D dataset of the coronary artery. Both rotary and pullback motion are driven proximally by a motor outside the patient. We will describe the currently commercially available equipment for time-domain OCT and the imaging procedure in detail.
Terumo, Tokyo, Japan, with inner lumens microcatheter for the nonocclusive technique (e.g., Transit, (for the occlusive technique, see next section) or a simple imaging wire is not torquable, it can be advanced distal to the backscattered light in a cross-sectional plane. Since the permitted real-time data processing and 2D representation of connected at its proximal end to the imaging console that fiber optic core within a translucent sheath. The image wire is 0.014 in. radiolucent coiled tip) and contains a single-mode The imaging probe (ImageWireTM, LightLab Imaging, Inc.) has The ImageWire (55) (Fig. 29.1).

Equipment Time-Domain OCT
The mobile M2/M2x OCT System cart (LightLab Imaging, Inc.) contains the optical imaging engine and the computer. The mouse, keyboard, two monitors, two storage drawers, and the patient interface unit (PIU) are all mounted on top of the cart (55) (Fig. 29.1).

The ImageWireTM
The imaging probe (ImageWireTM, LightLab Imaging, Inc.) has a maximum outer diameter of 0.019 in. (with a standard 0.014 in. radiolucent coiled tip) and contains a single-mode fiber optic core within a translucent sheath. The image wire is connected at its proximal end to the imaging console that permitted real-time data processing and 2D representation of the backscattered light in a cross-sectional plane. Since the imaging wire is not torqueable, it can be advanced distal to the region of interest using the over-the-wire occlusion balloon (for the occlusive technique, see next section) or a simple microcatheter for the nonocclusive technique (e.g., Transit, Cordis, Johnson & Johnson, Miami, Florida, U.S.; or ProGreat, Terumo, Tokyo, Japan, with inner lumens > 0.020 in.; see sect. “Nonocclusive Imaging Technique”). Unlike an IVUS transducer, the optical sensor of the ImageWire is invisible under fluoroscopy and therefore one must estimate the correct position, using the distal 15-mm radiopaque tip of the ImageWire. When fully advanced, the sensor is located 6 to 7 mm proximal to the radiopaque part and is easily confirmed by direct observation of the red light emitted when the wire is handled out of the body. As there are no direct radiopaque markers for the infrared sensor, it is possible to inadvertently miss imaging an area of interest resulting in incomplete distal lesion edge assessment. Imaging after stent implantation facilitates positioning because it is sufficient to advance the proximal end of the radiopaque wire tip at least 1 cm distal to the stent struts to image the entire stented segment. For imaging prior to treatment, it is important to note that the occlusion balloon is too bulky to cross severe stenoses before predilatation and that the imaging wire should be advanced distal to the lesion to ensure that the segment of interest is fully visualized. In such circumstances, the nonocclusive technique is advantageous.

Occlusive Imaging Technique: Proximal Balloon Occlusion and Flush Delivery
The proximal occlusion balloon catheter (Helios, Goodman Co Ltd., Nagoya, Japan) is an over-the-wire 4.4-Fr catheter (inner diameter 0.025 in.), compatible with 6-Fr guiding catheters (inner lumen diameter > 0.071 in.), which is advanced distal to region of interest using a conventional angioplasty guidewire (0.014 in.). The guidewire is then replaced by the OCT ImageWire (0.019 in. maximum diameter), and the occlusion balloon catheter is withdrawn proximal to the segment to be assessed leaving the imaging wire in distal position. During imaging acquisition, coronary blood flow is removed by continuous flush of Ringer’s lactate solution via the end hole of the occlusion balloon catheter at a flow rate of 0.5 to 0.7 mL/sec during simultaneous balloon inflation (0.5-0.7 atm). The vessel occlusion time is limited to a maximum of 30 seconds to avoid hemodynamic instability or arrhythmias. A 1.0 mm/sec pull-back permits the assessment of an up to 30-mm long coronary segment with a frame rate of 15.4 frames/sec (56) (Fig. 29.16).

Nonocclusive Imaging Technique
With improvements in the acquisition speeds of OCT data (currently in the vicinity of 3.0 mm/sec), blood can be evacuated by continuous flush through the guiding catheter, thus doing away with the cumbersome proximal balloon occlusion and thereby simplifying the acquisition process (57). Here, the OCT ImageWire is advanced carefully distal to the region of interest. As the fragile wire does not have the properties of a guidewire, it needs to be directed distally using a single-lumen

Figure 29.15 Longitudinal-cut view of an in vivo FD-OCT pullback through a coronary artery. At the distal end, a coronary stent is visible. Different components of the vessel wall are represented in a color coded way. MGH OFDI system. Abbreviation: MGH OFDI, Massachusetts general hospital optical frequency domain imaging. Source: G. Tearney and B. Bouma, Wellman Center for Photomedicine, MGH, Boston, Massachusetts, U.S.A.

Figure 29.16 TD-OCT imaging (LightLab Imaging, Inc., Westford, Massachusetts, U.S.)—the occlusive image acquisition technique. The imaging catheter directs the infrared light into the tissue and returns the reflected light back to the optical engine. During imaging, blood flow is limited by a dedicated, over the wire, low-pressure (0.4 atm) occlusion balloon catheter (Helios, Goodman, Nagoya, Japan), that is positioned proximally in the artery (A). The central lumen of the balloon occlusion catheter (B) allows for distal flush delivery during imaging of the target segment (C) with automated pullback. The proximal end of the catheter has a chamber the captures the imaging core and allows it to move along the catheter axis to perform an “automated pullback.” The outside of the imaging catheter is stationary with respect to the vessel wall. The imaging core is rotated and translated inside of the external catheter sheath. Abbreviations: TD-OCT, time-domain optical coherence tomography.
thrombus that was compressed during PCI between the stent fracture, late outward vessel remodeling, or the dissolution of in-stent hyperplasia. Other mechanisms of restenosis due to mechanical stent failure have become apparent. Of the two reasons for stent failures, when they do occur.

**Incomplete Strut Apposition**

Stent strut malapposition remains another important consideration. Postulated causes for stent strut malapposition are various and include incomplete stent expansion, stent recoil or fracture, late outward vessel remodeling, or the dissolution of thrombus that was compressed during PCI between the stent strut and the vessel wall. Regardless of the pathophysiological mechanism, the major concern in stent malapposition remains in the assumption that areas of strut malapposition cause nonlaminar and turbulent blood flow characteristics, which in turn can trigger platelet activation and thrombosis. Here, prospective, serial OCT observations immediately and at longer-term follow-up after stenting may improve our understanding of these complex mechanisms and shed light on the likely clinical significance of this phenomenon. The ongoing Optical Coherence Tomography Following Paclitaxel Eluting Stent Implantation in Multivessel Coronary Artery Disease (OCTAXUS) will assess the proportion of uncovered and/or malapposed Taxus Liberté struts at different time points after the implant, as measured by OCT.

**Stent Strut Tissue Coverage and Thrombosis**

Late stent thrombosis is poorly understood. It appears that this condition is multifactorial with premature discontinuation of dual antiplatelet therapy, stent underexpansion, hypersensitivity, and lack of endothelial tissue coverage, all being implicated. The results of small observational OCT studies as described earlier are compatible with evidence from animal and human postmortem series, showing that DES cause impairment in arterial healing, some with suggested incomplete re-endothelialization and persistence of fibrin(oid) possibly triggering late stent thrombosis (59,60). Pathological data in human suggests that neointimal coverage of stent struts could be used as a surrogate marker of endothelialization due to the good correlation between strut coverage and endothelialization. However, OCT observations need to be interpreted with caution. OCT is limited by its resolution of 15 μm, which is greater than the thickness of an individual layer of endothelial cells. Therefore, coverage that is not visible by OCT does not exclude the presence of an endothelial layer. Second, the presence of tissue coverage does not necessarily imply the presence of a functionally intact endothelium. Early experimental stent data showed that endothelial function can vary considerably and show evidence of damage when subjected to the Evan’s blue dye exclusion test, even in the presence of a well-structured neointimal layer (61).

However, OCT is the only imaging modality to date that offers—within the discussed limits—the possibility to understand tissue coverage and neointima formation in DES over time (62). Clearly, larger stent trials with OCT at different time periods are needed to obtain a representative assessment of the true time course of endothelial stent coverage of these stents. Recent improvements in OCT technology, with frequency-domain OCT, will allow for a simple imaging procedure and offer the potential for large-scale, prospective studies, indispensable to address vexing clinical questions such as the relationship of DES deployment, vascular healing, the true time course of endothelial stent coverage, and late stent thrombosis. This may also better guide the optimal duration of dual antiplatelet therapy that currently remains unclear and rather empirical. The ongoing Optical Coherence Tomography Drug Eluting Stent Investigation (OCTDESII) plans to evaluate the completeness of strut coverage and vessel wall response to the new generation JACTAX DES versus Taxus stent in de novo coronary artery lesions at six months post-index procedure. The completeness of the coverage as well as the number of uncovered stent struts per section, high resolution (~10–15 μm axial) will be assessed with intracoronary OCT. The Optical
Coherence Tomography for Drug Eluting Stent Safety (ODESSA) study on the other hand will investigate the number of uncovered and/or malapposed stent struts at overlapping versus nonoverlapping sites in DES versus BMS.

**DES Restenosis**

OCT can be very useful in the evaluation of the causes that contribute to restenosis after DES implantation such as incomplete coverage lesion or gaps between stents.

Stent fracture (with subsequent defect of local drug delivery) has also been related to restenosis in DES and could be visualized with OCT (63). Nonuniform distribution of stent struts can affect the drug concentration within the arterial wall and therefore have an influence in restenosis in DES (64). This has been confirmed in preclinical and IVUS studies. The maximum interstrut angle has been identified in IVUS as predictor of intimal hyperplasia cross-sectional area. OCT allows the assessment of strut distribution in vivo with high accuracy. A study with phantom models showed how the strut distribution of SES and paclitaxel-eluting stents (PES) assessed by OCT were significantly different, suggesting that SES maintained a more regular strut distribution despite expansion (65).

Another field of clinical use for OCT might be the assessment of the performance of DES in complex coronary interventions such as bifurcations. Buellesfeld et al. (66) reported the nine-month OCT follow-up in a case of crush stenting with PES. Crush stenting results in three layers of metal in the segment of the main vessel proximal to the stented side branch. There has been concern that this could release a higher dose of drug locally with the potential adverse effect of delayed endothelialization. In this report, OCT imaging showed the overlapping struts layers in the crushed segment completely covered by tissue. Furthermore, OCT allowed clear visualization of the struts located in the ostium demonstrating a nonuniform distribution and different patterns of tissue coverage. The effect of overlapping stents eluting different drugs in the development of endothelial coverage might also be studied with OCT.

**OCT Safety**

The applied energies in intravascular OCT are relatively low (output power in the range of 5.0–8.0 mW) and are not considered to cause functional or structural damage to the tissue. Safety issues thus seem mainly dependent on the need of blood displacement for image acquisition. One recently published study evaluated the safety and feasibility of OCT in 76 patients in the clinical setting using the occlusive technique. Vessel occlusion time was 48.3 ± 13.5 seconds. The most frequent complication was the presence of transient events, such as chest discomfort, brady- or tachycardia, and ST-T changes on electrocardiogram, all of which resolved immediately after the procedure. There were no major complications, including myocardial infarction, emergency revascularization, or death. The authors reported that acute procedural complications such as acute vessel occlusion, dissection, thrombus formation, embolism, or vasospasm along the procedure-related artery were not observed (67). Comparison of the occlusive versus the nonocclusive imaging method in a small patient cohort (n = 40) did not show major complications and confirmed superiority of the nonocclusive method in ostial lesion assessment (68). In our experience, the introduction of the nonocclusive technique in clinical practice has led to an important reduction in the procedural time and in the incidence of chest pain and ECG changes during image acquisition. These side effects are expected to be further reduced by the introduction of Fourier-domain OCT. In Fourier-domain OCT, high pullback speeds of up to 40 mm/sec allow data acquisition of a long coronary segment within few seconds and thus without introducing relevant ischemia.

**LIMITATIONS**

Generally, the main limitations of intracoronary OCT compared with the established IVUS technology consist first in the fact that light cannot penetrate blood. Thus, OCT requires clearing of the artery from blood as additional step during the imaging procedure. Secondly, the high resolution of OCT is at the expense of penetration depth. More specific issues can impede intracoronary OCT quality and interpretation in clinical intracoronary OCT application. The most important practical limitations originating from coronary anatomy and artifacts are summarized below (56).

**Vessel Tortuosity**

Within the human body, peripheral arteries (the vascular access sites) as well as the coronary arteries (imaging target) represent more or less tortuous structures. This requires high flexibility and steerability from the imaging device. This is not trivial given the fact that light transmission requires easily breakable fiber optics. Another consequence is on the image geometry. In the majority of cases, the imaging device will not be in a coaxial and centered position within the target artery, which may affect penetration depth, brightness, and resolution of the imaged structure (Fig. 29.17).

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**Figure 29.17** In vivo intracoronary OCT of an artery with concentric intimal thickening. The imaging catheter is in a noncoaxial, noncentered position. In consequence, the vessel wall segment close to the OCT catheter in 6 o’clock position appears brighter and shows a finer structure as the opposite vessel wall segment in 12 o’clock position. Abbreviation: OCT, optical coherence tomography.
Coronary Caliber
Coronary arteries represent relatively small structures for in vivo imaging; they are, however, relatively big structures compared with experimental OCT applications that often focus on much smaller sample volumes. Epicardial arteries have a maximal lumen diameter of approximately 4 to 5 mm in their proximal portion, and taper distally. Typically, arteries with a lumen diameter down to approximately 1.0 mm are considered clinically relevant and accessible to standard imaging equipment, such as coronary angiography and IVUS. Ideally, the penetration depth of intravascular OCT should be able to cover the complete caliber range (Fig. 29.18).

Plaque Geometry
Atherosclerotic coronary arteries contain a highly variable degree of plaque deposition within the artery wall. Atherosclerotic plaque can form a concentric ring encroaching the lumen, but will be eccentric with a normal vessel wall sector or with relatively big differences in vessel wall thickness in the majority of cases (69). Intravascular OCT is hampered to penetrate advanced, thick plaque, irrespective of the position of the OCT imaging device within the lumen.

Plaque Composition
The limited penetration depth into the vessel wall can reduce the sensitivity of OCT for different plaque components. An in vitro study comparing OCT to histopathology reported misclassification in 41% of lesions predominantly due to a combination of incomplete penetration depth into the vessel wall and a resulting difficulty to distinguish calcium deposits from lipid pools (70). Calcium deposits as well as lipidic tissues appear signal-poor by OCT. These two tissue types can be discriminated by the tissue borders, calcium typically shows very sharp, well-delineated borders, whereas lipid shows poorly defined borders with diffuse transition to the surrounding tissue.

Motion During Heart Cycle
Epicardial arteries experience significant 3D motion during heart cycle. This affects (i) the vascular dimensions (with a variability of lumen area of ~8% between systole and diastole (71)), (ii) the OCT device position within the artery (transversal and longitudinal motion), and (iii) the image acquisition time (Fig. 29.19).

In coronary stents, typical stent imaging artifacts can be observed (Fig. 29.20).

Shadowing Behind Stent Struts
The light source used for OCT is unable to penetrate metal resulting in dorsal shadowing behind the stent strut. When interpreting OCT images, the thickness of the whole stent strut (including metal and polymer) must be taken into consideration rather than only the visible endoluminal strut surface. Shadowing also limits the interpretation of structures behind the stent strut, and this remains a limitation of OCT, particularly also given its poor tissue penetration (<1.5 mm). Furthermore, the OCT imaging plane rarely intersects the stent struts perpendicularly, thereby resulting in shadows much larger than the actual width of the stent strut.

Bright Reflections Saturating an Entire Line (Spikes)
If the imaging beam hits a strut perpendicularly, it reflects a very large fraction of the beam back toward the catheter. This strong signal may saturate the detector registering the interferogram, producing a readily recognizable artifact of bright radial streaks centered on struts.
Multiple Reflections (Stent-Catheter-Stent)

In a similar geometry, near specular reflection, light may bounce back between catheter and strut more than once. The optical catheter itself reflects part of the received light back into the tissue. Strong reflectors, such as struts, may produce an appreciable signal in the second reflection. The optical path length of light in the secondary reflection is double that of the primary feature. Hence, a double reflection will show up as an apparent second strut appearing behind the first at twice the distance from the catheter.

SPECIAL ISSUES/CONSIDERATIONS/CONTRAINDICATIONS

The unique high-resolution OCT imaging modality permits the analysis of coronary structures in great detail. The sharp contrast between the lumen during flushing and the vessel wall allows for a relatively easy image interpretation. It is noteworthy that indeed OCT has a high accuracy when compared with histomorphometry as discussed earlier, but it also has a remarkably high reproducibility in the clinical setting.

The measurement accuracy of intracoronary OCT has been established in postmortem human coronary arteries and showed good correlation to histomorphometry (72). However, compared to ex vivo imaging, quantitative analysis of in vivo intracoronary imaging is more complicated due to the presence of blood and motion artifacts during cardiac cycle. Furthermore, the OCT dataset acquired during motorized pullback in vivo is much larger than local imaging of selected cross-sections as performed in postmortem studies. A pullback through the region of interest is necessary to visualize the 3D morphology of the coronary artery. We recently reported on standardized automated quantification processes for intracoronary OCT pullback data (20). The interobserver variability for lumen dimensions as measured by computer-assisted quantitative optical coherence tomography was extremely low and in a similar range for both in vitro as well for in vivo studies, despite the occurrence of motion-induced artifacts during the acquisition in vivo. Similarly, interobserver variability in complex vessel anatomy as represented by chronic coronary stents was very low: the absolute and relative difference between lumen area measurements derived from two observers was low (0.02 ± 0.10 mm²; 0.3 ± 0.5%, respectively) with excellent correlation confirmed by linear regression analysis ($R^2$ 0.99; $p < 0.001$). Similarly, in vivo measurements demonstrated a high correlation with the main source of interobserver variation occurring as a result of coronary dissection and motion artifact. The absolute and relative difference between measurements were 0.11 ± 0.33 mm² (1.57 ± 0.05%) for lumen area ($R^2$ 0.98; $p < 0.001$), 0.17 ± 0.68 mm² (1.44 ± 0.08%) for stent area ($R^2$ 0.94; $p < 0.001$), and 0.26 ± 0.72 mm² (14.08 ± 0.37%) for neointimal area ($R^2$ 0.78; $p < 0.001$).

CONCLUSIONS

OCT has caused intense interest in interventional cardiology. Its application to the assessment of coronary stents has been greeted with strong enthusiasm and is now also being incorporated into large multicentre randomized stent trials aimed at complementing angiographic and clinical endpoints. Such applications are currently unique to OCT and, despite the recent progress of noninvasive techniques such as 64 multislice computed tomography (MSCT), conventional stents still represent a challenge to distinguish lumen and intimal hyperplasia within the stent. Reports showing that reconstruction of MSCT images using specific kernels offer good correlation with angiography are encouraging but unlikely to make this technique a reliable alternative at the present time.

The ability to provide high-resolution imaging in vivo is the most significant concept circumventing the limitations of other imaging modalities such as IVUS or the need for multiple animal studies. Refinements in acquisition speeds with OPDI will also make the technique less procedurally demanding and thus able to be applied to many more centers, thereby remaining a key tool in the armamentarium of researchers and interventional cardiologists alike.
REFERENCES


Percutaneous coronary intervention—general principles

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INTRODUCTION
Percutaneous coronary intervention (PCI) was made possible by the pioneering work of Andreas Gruntzig, who in 1977 performed the first coronary angioplasty. That first patient is still doing well more than 30 years later. Over that time span, however, there have been dramatic improvements in the technology available to interventional cardiologists. In addition, advances in the management of thrombotic complications, vascular recoil, acute closure, and restenosis have been dramatic. Currently, more than two million PCI procedures are performed annually, and PCI has significantly eclipsed coronary artery bypass graft surgery (CABG) as the leading revascularization method for coronary artery disease (CAD).

INDICATIONS FOR PCI
In general, elective PCI may be indicated in patients with stable angina or ischemic stress tests, and suitable coronary anatomy. Primary PCI, when performed promptly, improves clinical outcomes compared with fibrinolytic therapy in patients with ST segment elevation myocardial infarction (STEMI). In non-ST elevation myocardial infarction (NSTEMI) and unstable angina, an invasive approach is recommended by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines in patients with high-risk features (1).

The thrombolysis in myocardial infarction (TIMI) risk score is a prognostic tool for acute coronary syndrome (ACS) patients (Table 30.1) (2). Similarly, the Global Registry of Acute Coronary Events (GRACE) risk score includes eight variables: advanced age, Killip class, systolic blood pressure, ST segment deviation, cardiac arrest during presentation, serum creatinine level, elevated cardiac markers, and heart rate (3). A meta-analysis reported an 18% relative risk reduction in the combined end point of death or myocardial infarction (MI) in high-risk non-ST elevation (NSTEMI) ACS patients initially treated with the invasive compared with the conservative strategy, despite a slight increase in early in-hospital mortality (4). Not all studies have confirmed these findings, however. The Invasive Versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) study (5) randomized 1200 NSTEMI patients to an initial invasive versus conservative strategy and found no difference in the composite end point at one year. Nonetheless, the majority of large randomized trials, including Fragmin and Fast Revascularization During Instability in Coronary Artery Disease (FRISC) (6) and Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI 18) (7) support the invasive approach for the high-risk patient cohort.

LESION CLASSIFICATION
The ACC/AHA lesion classification scheme has been used to predict the success rate and risk of balloon angioplasty for specific anatomic subsets (Table 30.2) (8). It incorporates angiographic characteristics including angulation (both proximal to and at the lesion site), location, existence and importance of side branches, length, calcification, and presence of chronic total occlusion. Type B lesions are further subcategorized as B1 or B2 if one or more than one B characteristic is present. Major technical and device advances during the ensuing years have greatly improved the success rate and safety for PCI and thus reduced the predictive accuracy of this classification system. In an analysis from the Society for Cardiovascular Angiography and Interventions (SCAI) registry involving 41,071 single-vascular PCIIs from 1993 to 1996, Krone and colleagues determined that the single most predictive lesion feature was patency (9). Specifically, the success rate of a patent class B lesion was similar to that of any class A lesion; and the success rate of a patent class C lesion surpassed that of an occluded class B lesion. Nonetheless, it is clearly recognized that no anatomic classification scheme can comprehensively assess the complexity of a specific lesion; indeed, the success and risk of PCI is also dependent on the patient’s clinical status, the operator’s expertise, and pharmacologic and device selections.

EQUIPMENT
Guiding Catheters
Most coronary guiding catheters range from 6 to 8 French in diameter, although the former predominates in current practice. While seemingly simplistic in design when compared with other PCI equipment, the guiding catheter may be the most important determinant of procedural success. Stable guiding catheter support is crucial to ensure delivery of the Interventional device to the lesion, especially in the presence of inhospitable anatomy such as severe calcification or tortuosity.

The general principle in guiding catheter selection is to use the smallest diameter and least aggressive design necessary for the specific coronary anatomy. Conservative, atraumatic tip conformations, such as Judkins right and left curves, are generally selected for low complexity cases. Gentle, shallow ostial engagement minimizes potential coronary artery trauma and risk of catheter-induced dissection. When faced with more challenging anatomy, enhanced back-up support is required. The moderate support designs are commonly known as the “extra back-up” group, while even deeper engagement can be achieved with the Amplatz catheters. Meticulous manipulation is required to avoid ostial left main or right coronary dissection, which not infrequently leads to distal spiral dissection.
PERCUTANEOUS CORONARY INTERVENTION—GENERAL PRINCIPLES

Table 30.1 Thrombolysis in Myocardial Infarction Risk Factors for Prognostication in Patients with Acute Coronary Syndrome

- Age 65 or greater
- Three or more coronary artery disease risk factors
- Known coronary stenosis of 50% or greater on previous angiography
- ST segment deviation >0.05 mV on initial ECG
- At least 2 anginal episodes in prior 24 hr
- Aspirin use in prior 7 days
- Elevated cardiac markers

Table 30.2 American College of Cardiology/American Heart Association Lesion Classifications

Type A (high success rate <85%; low risk)
- Discrete (<10 mm in length)
- Concentric
- Easily accessible
- Relatively small (<45°)
- Smooth contour
- Minimal to no calcification
- Nonoccluded
- Nonostial in location
- No major branch involvement
- No thrombus

Type B (moderate success rate <60–85%; moderate risk)
- Tubular (10–20 mm in length)
- Eccentric
- Moderate tortuosity of proximal segment
- Moderate lesion angulation (45–90°)
- Irregular contour
- Moderate to heavy calcification
- Ostial in location
- Bifurcation location, necessitating double wires
- Thrombus present
- Total occlusion (<3 mo)

Type C (low success rate <60%; high risk)
- Diffuse (>20 mm in length)
- Severe tortuosity of proximal segment
- Extreme lesion angulation (>90°)
- Inability to protect major side branch
- Degenerated vein grafts, with friable lesions
- Chronic total occlusion (>3 mo)

Source: From Ref. 8.

Proposition. At the conclusion of the procedure, disengagement of Amplatz catheters should be performed under fluoroscopic observation and may require a slight forward push with rotation, as direct withdrawal may actually result in deep, forceful distal advancement.

Guidewires

Structurally, guidewires are divided into spring-tip and plastic varieties. The former can either be constructed entirely from stainless steel or feature a nitinol tip. The spring-tip wires offer excellent steerability by enhanced torque transmission and are particularly useful in complex lesions such as chronic total occlusions. Plastic wires are hydrophilically coated and offer the advantage of reduced friction, facilitating advancement through tortuous or calcified anatomies. However, this same lubricious coating also promotes wire entry into false channels (10). Short and long guidewires are designed for use with rapid-exchange and over-the-wire devices, respectively.

Varying tip stiffness allows for penetration into hard lesion caps frequently associated with chronic total occlusions. Additionally, tapered tips may further improve penetration. Extreme caution must be exercised with these specialty wires, as coronary dissection or perforation can result (10). Supportive shaft wires are used to straighten tortuous arteries to allow passage of higher profile devices such as atherotomes or stents. Not infrequently, however, “pseudolesions” may result from arterial pleating and may be difficult to angiographically discern from iatrogenic trauma. If intracoronary nitroglycerin fails to resolve this finding, an over-the-wire catheter can be exchanged for the stiff wire. This maneuver will resolve the pleating artifact, while maintaining distal access in case further work is necessary.

Balloon Dilatation Catheters

The original PCI device introduced by Gruentzig in 1977, the balloon catheter, remains the workhorse for the interventionalist. In the modern era, balloons are predominately used for pre- and postdilatation of stents.

Compliant balloons, made of soft materials such as polyolefin copolymers which allow varying diametric expansion without exerting excessive pressure, are useful for predilatation to prepare the intended lesion for stent deployment. Occasionally, small caliber branches may be inappropriate for stent implantation and can be adequately treated with “plain old balloon angioplasty” (POBA). Noncompliant balloons, fashioned from stiff materials such as polyethylene terephthalate, maintain a near-constant diameter in the face of increasing inflation pressures, making them ideal devices for stent postdilatation to ensure full expansion. Additionally, noncompliant balloons can be used to expand hard, calcific or fibro-calcific plaques. Semi-compliant balloons display hybrid features of both their compliant and noncompliant counterparts (10). When inflated to the nominal pressure, the balloon achieves its prespecified diameter.

The monorail or rapid-exchange shaft design features a short wire lumen, with the wire exit opening near the distal tip. This system allows use of a short guidewire, often preferred by operators for simpler cases. Conversely, the wire lumen for the over-the-wire balloon catheter runs the entire shaft length. While the required long guidewire may be more tedious, this system permits catheter exchange as well as distal intracoronary drug administration through the central lumen.

Perfusion Balloon

Although perfusion balloons were initially developed to reduce ischemia during prolonged balloon inflations during the present era, they are now largely relegated to sealing of coronary perforation. Proximal inflow and distal outflow lumens allow distal perfusion during protracted inflation of the perforation site.

Thrombectomy Devices

PCI of thrombotic and/or atherosclerotic lesions can result in plaque fragmentation and distal embolization. This can lead to diminished or absent distal perfusion, known as “slow flow” or “no reflow.” The perfusion adequacy of the distal vasculature...
and subtended myocardium are measured by the TIMI flow and myocardial blush scores, respectively. Pretreatment with certain aspiration devices may decrease the incidence of slow and no reflow and may improve procedural outcome. Recent data suggest that manual thrombus aspiration may improve survival in STEMI patients (11).

A mechanical thrombectomy catheter, the AngioJet (Possis Medical Corporation, Minneapolis, Minnesota, U.S.), utilizes an Archimedes screw mechanism to create a proximally directed high-pressure jet, which generates a vacuum rheolytic action. The captured debris is then removed through the system. The catheter is advanced distal to the thrombus and withdrawn at a rate of 0.5 mm/sec. Not infrequently, there is concomitant bradycardia (especially in the right coronary system) and transient ST segment elevation. Prophylactic temporary right ventricular pacemaker placement has been recommended; recently, intravenous aminophylline infusion has been shown to prevent heart rate disturbances (12,13).

Manual thrombus aspiration can be accomplished with the Export (Medtronic Corporation, Minneapolis, Minnesota, U.S.) or Pronto (Vascular Solutions Incorporated, Minneapolis, Minnesota, U.S.) catheters. These similar rapid-exchange devices feature a second aspiration lumen. Gentle manual aspiration with a syringe is performed by the assistant while the distal tip is advanced through the stenosis. The attraction of these devices is ease of set-up and use, as well as lack of associated bradyarrhythmias. However, their efficacy with large thrombus burden or late patient presentation remains unclear (14,15).

**Distal Protection Devices**

Distal protection devices, including occlusion balloons and filters, trap and retrieve atheroemboli distal to the lesion. The GuardWire system (Medtronic Corporation, Minneapolis, Minnesota, U.S.) catheters, These similar rapid-exchange devices feature a second aspiration lumen. Gentle manual aspiration with a syringe is performed by the assistant while the distal tip is advanced through the stenosis. The attraction of these devices is ease of set-up and use, as well as lack of associated bradyarrhythmias. However, their efficacy with large thrombus burden or late patient presentation remains unclear (14,15).

**Atherectomy Devices**

Atherectomy or atheroablative devices are applicable in specific anatomic subsets such as calcified or thrombotic lesions, either as stand-alone therapy or, more commonly, as pretreatment to facilitate stent deployment. Although quite varied in mechanism and design, these tools may share a slightly higher risk of coronary perforation compared with balloon angioplasty. Additionally, while a few trials have reported modest restenotic advantages, no atherectomy device has clearly demonstrated superior clinical outcomes compared with balloon angioplasty (18).

**Rotational Atherectomy**

The rotational atherectomy (Boston Scientific, Natick, Massachusetts, U.S., Fig. 30.2) system consists of a rapidly rotating oval-shaped burr encrusted with tiny diamond chips. The mechanistic principle is that of differential cutting, whereby hard plaque is selectively ablated while the deflected soft vascular wall is left unharmed. The burr is welded on a drive shaft which is advanced over a proprietary 0.09-in guidewire. The recommended burr-to-artery ratio is 0.7. Through gentle pecking motions of 0.5 mm or less, the operator manipulates the burr with the advancer console at a typical rotational speed.

**Figure 30.1** The GuardWire distal protection device, used in conjunction with the Export aspiration catheter.

**Figure 30.2** Rotational atherectomy burr.
of approximately 140,000 rpm. When encountering decelerations of more than 5000 rpm, indicating extreme lesion resistance, operation should be paused. Further burring in this scenario may result in vascular trauma from dissection, excessive heat buildup, or embolization (18).

“Wire bias” refers to the phenomenon whereby greater cutting force is exerted on the inner curvature of a tortuous vessel. While this occurrence may be advantageous for eccentric lesions in this location, it can lead to excessive coronary trauma. Significant bradycardia may result from microembolization; hence, prophylactic temporary pacemaker placement is recommended, especially for right coronary interventions (13).

The Study to Determine Rotatblator and Transluminal Angioplasty Strategy (STRATAS) (19) evaluated aggressive versus conservative rotational atherectomy strategies using burr-to-artery ratios of 0.7 to 0.9 versus 0.7. While overall success rates were similar, the aggressive arm demonstrated significantly higher restenosis (58% vs. 52%) and MI (11% vs. 7%) rates. In the Angioplasty Versus Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis Trial (ARTIST) (20) the investigators compared rotational atherectomy with balloon angioplasty for treatment of in-stent restenosis (ISR) in 298 patients. Surprisingly, in-hospital complication and restenosis rates were higher with rotational atherectomy, and the six-month event-free survival was lower (79.6% vs. 91.1%). Nonetheless, rotational ablation of calcific, resistant lesions remains a valuable tool in some complex cases.

**Directional Atherectomy**

Since its inception, versions of directional atherectomy devices have progressed through several iterations. Presently, the Flexcut catheter (Abbott Vascular Corporation, Abbott Park, Illinois, U.S.) is approved for coronary use. Diameter sizes are 2.5 to 2.9 mm, 3.0 to 3.4 mm, and 3.5 to 3.9 mm (20). The excised plaque debris is pushed into the distal nose-cone and subsequently retrieved when the compartment is filled. Selection of guiding catheters is crucial, as a gentle curve is necessary to allow smooth vessel entry. Under fluoroscopic visualization, the eccentrically located concave cutting window is directed toward the plaque. A counter-facing compliant balloon is inflated to low pressures to maximize atherotome-to-plaque contact. Early experience, however, revealed that some of the immediate luminal gain was secondary to balloon stretch and failed to result in long-term benefit.

Despite initial enthusiasm, present-day utilization of directional atherectomy has significantly declined. The Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT)-I (21) and Canadian Coronary Atherectomy Trial (CCAT) (22) each reported higher immediate luminal gain after directional atherectomy compared with balloon angioplasty in native coronary lesions. However, no significant differences were observed for follow-up restenosis rates. Similar findings were seen in CAVEAT-II (23), which enrolled patients with saphenous vein graft disease. Additionally, atherectomy-treated patients in this study suffered a higher rate of NSTEMI. Even in the stent era, the Atherectomy Before Multi-link Improves Lumen Gain and Clinical Outcomes (AMIGO) (24) trial failed to demonstrate either angiographic or clinical benefit of directional atherectomy prior to stenting versus stenting alone.

Today, the main “niche” applications of this device appear to be ostial lesions—especially left anterior descending and left circumflex—and bifurcation lesions. In principle, actual plaque excision, rather than dilatation, should reduce the risk of side branch compromise by plaque shift. This technique should be avoided in distal lesions, small branches, degenerated SVGs, and calcified or tortuous vessels (13). Technical difficulties and the need for large caliber guiding catheters have limited the widespread use of directional atherectomy.

**Laser Atherectomy**

The XeCl Excimer utilizes ultraviolet energy with a wavelength of 308 nm to ablate debris through photochemical dissociation. The subsequent photoacoustic effect and heat generation elicits formation of a vapor bubble, which ultimately implodes. Typically, the repetition rate is set at 40 Hz and energy or fluence set up to 60 mJ/mm². Initial issues with arterial dissection were largely attributed to excessive heat generation in the blood- or contrast-filled lumen. The revised technique of constant saline infusion during activation has greatly reduced this complication (25). The recommended catheter-to-artery ratio is 2:3. Technique-wise, the catheter is advanced at a slow rate of 0.5 to 1.0 mm/sec, with simultaneous gentle intracoronary saline infusion at 2 to 3 cc/sec.

The Excimer Laser Rotational Atherectomy Balloon Angioplasty Comparison (ERBAC) trial (26) randomized 685 patients to PCI with three therapeutic modalities. Slightly higher overall MACE and restenosis rates were observed for laser subjects. However, the Amsterdam-Rotterdam (AMRO) trial (27) found no significant differences in six-month MACE between balloon and laser-treated patients. Modern usage of laser atherectomy is aimed at thrombotic, friable saphenous vein graft, bifurcation, and moderately calcific lesions. Even moderately tortuous vessels should be avoided, however, as wire bias can result in perforation from asymmetric arterial wall contact with the vapor bubble.

**Cutting Balloon**

The cutting balloon catheter (Flextome, Boston Scientific Corporation, Fremont, California, U.S.) incorporates longitudinal stainless steel blades affixed to the balloon. When deployed, discrete cuts made in the atheroma may avoid large uncontrolled dissections, resulting in less coronary trauma. Utilizing a similar mechanistic principle, the AngioSculpt catheter (AngioScore Corporation, Fremont, California, U.S.) features helical wires surrounding the balloon, thus enhancing its flexibility to access tortuous anatomy. Both devices have been used to treat ISR, bifurcation lesions, and moderately calcified plaques.

**Bare-Metal Stents**

The advent of bare-metal stents (BMS) has dramatically reduced the significant target vessel revascularization (TVR) rates previously associated with balloon angioplasty. Up to this point, no other nonballoon PCI device had clearly demonstrated a superior impact on restenosis. By scaffolding the dilated segment, BMS eliminated the elastic recoil ubiquitously seen with balloons. Ironically, BMS implantation actually triggers greater neointimal proliferation than balloon angioplasty. However, the significantly larger initial luminal gain, coupled with freedom from elastic recoil, results in a marked restenosis and TVR advantage over balloon angioplasty.

Importantly, BMS have greatly enhanced the procedural safety of PCI. Dissections can often be successfully treated, dramatically decreasing the need for emergent CABG.
Nonetheless, the implantation of an intracoronary prosthesis is not without risk. Nonendothelialized stent struts, as well as gaps between the stent and vascular wall, are potent niduses for thrombosis. To ensure adequate stent expansion, meticulous high-pressure postdilatation is often performed with a non-compliant balloon. A minimum of one month of dual antiplatelet therapy is strongly recommended following BMS deployment (28).

Drug-Eluting Stents
To overcome the enhanced endothelial hyperplasia induced by BMS implantation, drug-eluting stents (DES) were developed by incorporating antiproliferative coatings on stent struts. The seminal Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (RAVEL) (29), Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) (30), and Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent (TAXUS) (31) trials reported superior clinical restenosis rates with sirolimus-eluting stents (SES, Cordis, Miami Lakes, Florida, U.S.) and paclitaxel-eluting stents (PES, Boston Scientific Corporation, Natick, Massachusetts, U.S.) compared with BMS Additionally, zotarolimus-eluting stents (ZES, Medtronic Corporation, Minneapolis, Minnesota, U.S.) and everolimus-eluting stents (EES, Abbott Laboratories, Abbott Park, Illinois, U.S.) are now available for clinical use in the United States.

Indeed, DES may challenge the long-term patency superiority of CABG. The Arterial Revascularization Therapies Study (ARTS)-II investigators compared SES therapy for multivessel disease with historical data from patients assigned to the CABG arm in the preceding ARTS-I trial. The investigators found no differences in MACE, mortality, TVR, or stroke at one year (32).

Concern About Late DES Thrombosis
While initial landmark trials demonstrated equivalent safety to BMS, subsequent follow-up suggested a late stent thrombosis risk. Camenzind reported a significantly higher 6.3% combined death/MI rate for SES compared with 3.9% observed for BMS (33).

The Basel Stent Kosten Effektivitats (Cost-Effectiveness) Trial—Late Thrombotic Events (BASKET-LATE) study followed 544 DES and 281 BMS patients for 18 months. DES patients experienced higher MACE from 6 to 18 months post implantation, including absolute excesses in late mortality (1.2% vs. 0%, p = 0.09) and nonfatal MI (4.1% vs. 1.3%, p = 0.04) compared with BMS (34).

To standardize definitions of stent thrombosis, the Academic Research Consortium (ARC) has classified stent thrombosis according to the relative certainty of the diagnosis. Definite thrombosis includes angiographic target vessel occlusion or intrastent thrombus. Probable thrombosis is defined as acute MI in the target vessel territory, while possible thrombosis represents any unexplained death in a patient with a previously implanted DES (35).

A four-year combined study from Switzerland and the Netherlands evaluated risk factors for stent thrombosis in over 8000 patients receiving SES or PES. The investigators reported that diabetes was an independent risk factor for early stent thrombosis, while PES implantation, younger age, and ACS were associated with late stent thrombosis (36).

ZES, with a more rheologically compatible design, represents the second generation of DES. Its polymer, which mimics an erythrocyte outer layer, is associated with greater endothelialization than seen with either PES or SES. At 24-month follow-up, Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Drive Coronary Stent in De Novo Native Coronary Artery Lesions (ENDEAVOR-II) trial observed that, in addition to the expected superior TVR and MACE rates, the ZES arm actually demonstrated a nonsignificantly lower stent thrombosis rate of 0.5% versus 1.2% for BMS (37).

Overall DES Safety and Efficacy
More recent data indicate that the late stent thrombosis risk with DES is counterbalanced by a reduction in TVR, resulting in equivalent (if not slightly superior) MI, mortality, and overall MACE rates compared with BMS. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) (38) observed equivalent long-term mortality risks for DES and BMS patients, despite a slight increase in late stent thrombosis. This report was particularly noteworthy, given that initial findings from this registry suggested a higher DES death rate, sparking an early firestorm of anti-DES literature.

Recently, three separate analyses have further supported the safety and efficacy of DES during long-term follow-up (39–41). Four-year data from over 5200 patients in the major randomized controlled SES and PES trials (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, and TAXUS I-VI) demonstrated that death and MI rates were similar for both DES and BMS. Furthermore, despite a slight increase in late stent thrombosis with DES, the overall stent thrombosis and MACE rates were similar for all stents. Most strikingly, the expected DES superiority in TVR reduction was reinforced; TVR rates for SES (7.8%) and PES (10.1%) were significantly lower than for BMS (23.6%, p < 0.001) (41). Major contributors to stent thrombosis were male gender, continued tobacco use, overlapping stents, and dual antiplatelet therapy noncompliance.

Another recent large meta-analysis documented persistent and continued TVR benefits by 50% to 70% for up to four years, without notable differences in death or MI (42). Furthermore, the incidences of ARC defined stent thrombosis were similar (HR 1.00, 1.03, and 0.96 for SES vs. BMS, PES vs. BMS, and SES vs. PES, respectively). Additionally, the use of SES was associated with lower risk of MI, compared with PES (HR 0.83, p = 0.045) or BMS (HR 0.81, p = 0.030). Consistent with previous findings, rates of stent thrombosis were higher for BMS within one year and higher for DES beyond one year. Notably, the numbers needed to treat to prevent one MACE event were 7 and 8 for SES and PES versus BMS, respectively. These benefits were similarly observed in diabetic patients.

The safety and efficacy of DES in diabetic patients were further demonstrated in a meta-analysis of nine randomized DES trials involving 1141 diabetic patients (43). DES was associated with lower ISR (8% vs. 41%, OR 0.13, 95% CI, 0.09-0.20, p < 0.000,01) and TVR (8% vs. 27%, OR 0.23, 95% CI, 0.16-0.43, p < 0.000,01). Interestingly, while overall stent thrombosis or death rates were similar between groups, subsequent MI was more frequent in BMS patients (7.2% vs. 3.5%, p = 0.02). The DES advantages prevailed regardless of insulin-dependency status.

It is imperative that all DES patients at low risk of bleeding receive one year of dual antiplatelet therapy (44,45). Additionally, prior to stent implantation, patients should be assessed for financial or clinical challenges (such as upcoming surgery) to prolong dual antiplatelet therapy. Health care providers performing invasive procedures should be well
membrane sandwiched between double-stent layers and is
The covered stent (Jomed International AB, Helsingborg,
demonstrations are further detailed in Table 30.4 (46).
covered stent interruption. They should contact the patient’s cardiologist if unsure about the safety of therapy cessation.
For DES patients undergoing invasive or surgical procedures mandated thienopyridine discontinuation, aspirin should be continued if at all feasible. Thienopyridine should be reinitiated as soon as possible after the procedure.
Health care industry, insurers, U.S. Congress, and pharmaceutical industry should ensure that cost issues do not cause premature thienopyridine discontinuation, as this can result in devastating consequences.

Abbreviations: DES, drug-eluting stents; BMS, bare-metal stents; DAT, dual antiplatelet therapy.
Source: From Ref. 44.

Table 30.3 Recommendations for DAT in Patients with DES

1. DES should only be implanted in patients able to comply with 12 mo of DAT, after economic and clinical considerations.
2. For patients undergoing percutaneous coronary intervention who are likely to undergo invasive or surgical procedures within the next 12 mo, BMS implantation or stand-alone balloon angioplasty should be considered.
3. Health care providers should more thoroughly educate patients regarding the indications of DAT as well as the risks of premature termination.
4. Patients should be advised to contact their cardiologist prior to interruption of DAT, even if instructed to do so by another health care provider.
5. Health care providers who perform invasive or surgical procedures should be aware of the potentially serious sequelae of premature DAT interruption. They should contact the patient’s cardiologist if unsure about the safety of therapy cessation.
6. Elective invasive or surgical procedures associated with significant bleeding risk should be postponed, if possible, until appropriate DAT course is completed (12 mo for DES and 1 mo for BMS).
7. For DES patients undergoing invasive or surgical procedures mandating thienopyridine discontinuation, aspirin should be continued if at all feasible. Thienopyridine should be reinitiated as soon as possible after the procedure.
8. Health care industry, insurers, U.S. Congress, and pharmaceutical industry should ensure that cost issues do not cause premature thienopyridine discontinuation, as this can result in devastating consequences.

Abbreviations: DES, drug-eluting stents; BMS, bare-metal stents; DAT, dual antiplatelet therapy.
Source: From Ref. 44.

Table 30.4 Summary of DES Safety and Recommendations for DES Use

- When compared with BMS, DES are associated with a small but definite increase in risk of late stent thrombosis, predominately manifested 1 yr after implantation.
- When used according to “on-label” indications, DES result in no overall increase in mortality or MI rates compared with BMS. This finding is likely related to the marked decrease in repeat revascularization associated with DES.
- DES and BMS have the similar total mortality rates.
- Larger and longer premarket clinical trials are needed, with longer follow-up durations, more uniform stent thrombosis definitions, and closer attention to DAT therapy.
- At this time, when deployed according to approved indications, the risks of DES do not outweigh their benefits compared with BMS.
- When used in nonapproved patient and anatomic subsets, a higher risk of DES thrombosis, MI, or death may be expected than observed in previous trials.
- Because of limited data for “off-label” DES use (accounting for at least 60% of present-day DES implantation), more studies are needed to determine the safety and efficacy of these devices. DES labeling should state that “off-label” use may not yield the same results as those observed in the clinical trials which led to market approval.
- Studies suggest that prolonged DAT beyond product label recommendations may be beneficial.
- Optimal DAT duration is unknown, and continued DAT does not guarantee freedom from DES thrombosis.
- Patients at low risk of bleeding should continue DAT for 12 mo.

Abbreviations: DES, drug-eluting stents; BMS, bare-metal stents; MI, myocardial infarction; DAT, dual antiplatelet therapy.
Source: From Ref. 44.

versed in indications for dual antiplatelet therapy, and any plans for premature interruption should be discussed with the patient’s cardiologist. These recommendations are summarized in Table 30.3.

An expert panel concluded that DES use is associated with a real, albeit rare, increased incidence of late stent thrombosis that frequently results in MI or death. However, when these devices are used for “on-label” indications, there is no evidence of increased stent thrombosis, MI, or death rates. Furthermore, uninterrupted dual antiplatelet therapy for at least one year is strongly recommended in patients with low bleeding risk. If invasive procedures/surgeries are unavoidable during this time, dual antiplatelet therapy, or at least aspirin alone, should be continued if possible. The complete conclusions and recommendations are further detailed in Table 30.4 (46).

Covered Stent
The covered stent (Jomed International AB, Helsingborg, Sweden) features a circumferential polytetrafluoroethylene membrane sandwiched between double-stent layers and is approved for emergent bail-out treatment of coronary perforation. Given the device’s high profile and relative rigidity, adequate catheter back-up is crucial. As the need for this stent is rare, but invariably emergent, interventionists should familiarize themselves with its deployment technique. Trials involving elective covered stent implantation have uniformly failed to demonstrate a restenosis advantage (46,47).

Intravascular Ultrasound
Intravascular ultrasound (IVUS) interrogation allows for intraluminal cross-sectional assessment of plaque calcification and severity, vessel size, stent apposition, dissection, and thrombus. The device is manufactured by both Boston Scientific Corporation (Natick, Massachusetts, U.S.) and Volcano Corporation (Rancho Cardovo, California, U.S.). When angiographic findings are questionable, IVUS can often provide valuable additional information. Accepted minimal luminal cross-sectional areas of 4 and 5 mm² are used to define critical non-left main and left main narrowings, respectively (48,49). The decision regarding use of rotational atherectomy for an angiographically
calcified lesion may be impacted by superficial versus deep location of calcium. Poststent evaluation of strut apposition, stent-to-vessel sizing, and stent symmetry may indicate the need for further treatment. Finally, IVUS assessment of ISR may elucidate the mechanism of restenosis, such as inadequate stent sizing, plaque prolapse, dissection, or rarely, stent fracture, thereby directing therapeutic strategies.

**Pressure Wire**
The pressure wire features a distal pressure sensor to measure the hemodynamic significance of angiographically borderline stenoses. This device is manufactured by both Radi Medical Systems (Wilmington, Massachusetts, U.S.) and Volcano Corporation. The ratio of pressures distal and proximal to the lesion at maximal hyperemia is known as the fractional flow reserve (FFR). Adenosine, administered by either intravenous infusion or intracoronary bolus, is often used to induce hyperemia. FFR above and below 0.75 have been validated to correlate with functionally benign and significant stenoses, respectively. Additionally, FFR > 0.90 correlates with adequate stent deployment.

The FFR offers comprehensive physiologic assessment and importantly accounts for both the size of the subtended territory and the oxygen demand of the myocardium. The same stenosis may be result in either a normal or abnormal FFR depending on the adequacy of collateral flow in the subtended myocardial territory. Additionally, if the perfusion requirement is low in a predominately scarred region, an anatomically “critical” lesion may be associated with a high FFR, indicating an adequate supply-to-demand relationship. FFR accuracy, however, may be limited in situations of high filling pressures (hypertension or left ventricular hypertrophy), cardiac transplantation, and saphenous vein grafts.

**ADJUNCT PHARMACOLOGY**

**Heparin and GP IIb/IIIa Vs. Bivalirudin**
Whereas unfractionated heparin has been the traditional anticoagulant used during PCI procedures, recent studies involving more modern agents have challenged its role. Bivalirudin, a direct thrombin inhibitor, was assessed in the Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment 3 (ISAR-REACT 3) trial (50). In a double-blind fashion, 4570 patients with either stable or unstable angina were randomized to undergo PCI with unfractionated heparin or bivalirudin after a loading dose of clopidogrel 600 mg. At 30 days, no differences were reported for the composite primary end point of death, MI, urgent TVR, or in-hospital bleeding. However, major bleeding was reduced in the bivalirudin arm (3.1% vs. 4.6%, RR 0.66, 95% CI, 0.49-0.90, p = 0.008).

The Acute Catheterization and Urgent Interventional Triage Strategy (ACUITY) trial compared three strategies for patients presenting with ACS, the majority of whom went to PCI. The anticoagulation arms were unfractionated or low-molecular weight heparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin monotherapy. The composite primary end point included the ischemic end points of death, MI, and unplanned revascularization, plus major bleeding. In the PCI group (7789 patients), the ischemic end point was 8% with heparin plus GP IIb/IIIa and 9% with bivalirudin monotherapy. Major bleeding was reduced from 7% with heparin and GP IIb/IIIa therapy to 4% with bivalirudin.

The net clinical outcome was comparable with 13% of patients reaching the combined ischemic and bleeding end points with heparin plus GP IIb/IIIa and 12% with bivalirudin monotherapy. An interesting substudy showed that patients with major bleeding episodes had higher mortality at 35 days compared with those who did not bleed (51). This observation has led to the inclusion of ischemic events plus bleeding as the primary composite end point in some of the current trials. A similar strategy was tested in the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, which compared heparin plus a GP IIb/IIIa inhibitor with bivalirudin monotherapy in patients with STEMI. The 30-day outcome showed a net benefit with bivalirudin for ischemic and bleeding end points (9.2% vs. 12.1%). Ischemic MACE was equivalent, but there was less bleeding with bivalirudin (4.9% vs. 8.3%). These two trials have resulted in a significant reduction in the use of GP IIb/IIIa therapy in both ACS and AMI in favor of bivalirudin therapy.

**Fondaparinux**
The Organization for Assessment of Strategies for Ischemic Syndromes (OASIS)-6 (52) trial reported an increased incidence of guiding catheter thrombosis in cases of stand-alone fondaparinux therapy. Hence, concomitant heparin administration with either unfractionated heparin or low-molecular-weight heparin is recommended during PCI.

**Dual Antiplatelet Therapy**
Dual antiplatelet therapy with aspirin and clopidogrel is indicated for a minimum of one year and one month after DES and BMS implantation, respectively. High-dose aspirin (162-325 mg) is recommended for the initial postprocedural period. Additionally, while the recommended clopidogrel loading dose is 300 mg, higher doses (600 or 900 mg) may be associated with reduced platelet resistance (53). In one trial, 119 patients undergoing DES implantation were randomized to a loading dose of clopidogrel 600 mg followed by 75 mg twice daily for one month versus a loading dose of 300 mg followed by 75 mg daily. There were no differences in bleeding complications, but high-dose subjects demonstrated greater platelet inhibition (41% vs. 27%, p = 0.046 at four hours, 19% vs. 10%, p = 0.047 at 30 days) and a lower composite end point of cardiovascular death, MI, and TVR (10.3% vs. 23.8%, p = 0.04) (54).

Although aspirin resistance has been linked to a clear increase in overall MACE, the role of aspirin or clopidogrel resistance in stent thrombosis remains less certain. Part of the challenge relates to the lack of definition uniformity for platelet resistance. Additionally, accompanying confounders such as lesion complexity, stent deployment techniques, and patient clinical characteristics have made analyses difficult in the absence of large randomized trials. Nevertheless, Duzenli and colleagues found that, in diabetic subjects with demonstrated resistance to aspirin 100 mg daily, increased platelet inhibition occurred with both higher aspirin dose (300 mg daily) and dual antiplatelet therapy (clopidogrel 75 mg and aspirin 100 mg daily) (54).

Clinically significant aspirin resistance has been estimated to range from 5% to 60% of treated patients, and in vitro laboratory evidence of such resistance may be associated with increased cardiovascular event rates (55). Clopidogrel resistance appears dose-dependent; one study reported incidences of 28% and 8% for 300- and 600-mg loading doses,
respectively (56). Furthermore, Buonamici and coauthors found clopidogrel resistance to result in a fourfold increased risk of DES thrombosis over four-year follow-up (57). A recent evaluation of point-of-care platelet inhibition measurement in PCI patients reported a sixfold increase in 30-day MACE for subjects with platelet activity in the highest quartile compared with the lowest quartile (\( p = 0.016 \)) (58). The ongoing Gauging Responsiveness with a VerifyNow Assay—Impact on Thrombosis and Safety (GRAVITAS) trial will evaluate tailored clopidogrel dosing on the basis of a new bedside platelet assay system.

**SPECIAL CLINICAL SCENARIOS**

**STEMI**

Coronary thrombosis accounts for approximately 70% of cardiovascular morbidity and mortality. Plaque rupture, or less frequently plaque erosion, is the substrate for superimposed thrombosis. Other, less common causes of MI include coronary spasm, spontaneous coronary dissection, coronary embolism, coronary vasculitis, and anomalous coronary arteries (59). Primary PCI for STEMI remains the only clinical scenario in which survival benefit from PCI has been unequivocally demonstrated.

Pathology/Pathophysiology of STEMI

Over two centuries ago, Virchow first described arterial plaque rupture and analogized the necrotic core to that of an abscess. Rupture of thin-cap fibroatheromas is the most acute pathophysiology of STEMI (59). In their sudden death autopsy series, Virmani et al. found that 65% to 70% of atherothrombi involved plaque rupture, whereas 25% to 30% arose from plaque erosion (60). These etiologies are gender-specific; plaque erosion occurs with twice the frequency in women versus men (61). However, this phenomenon is rarely observed in premenopausal women (62).

Pharmacology

The enhanced thrombotic milieu necessitates potent antithrombotic and antiplatelet therapy; thus, STEMI patients are at increased risk for bleeding. Significant bleeding, as well as the need for transfusion, has been found to predict one-year mortality (63). The HORIZONS-AMI trial (64) demonstrated lower composite end points and major bleeding for bivalirudin compared with heparin plus a GP IIb/IIIa inhibitor. Additionally, while overall MACE was equivalent, 30-day mortality was significantly less with bivalirudin (2.1% vs. 3.1%, \( p = 0.047 \)). Of note, the rate of acute thrombosis (<24 hours, ARC definite or probable thrombosis) was higher with bivalirudin, although the overall 30-day stent thrombosis rates were similar. The ACC/AHA have accordingly assigned class IIa status to concomitant clopidogrel administration with upstream bivalirudin (65).

Technical Considerations

Multiple randomized trials have demonstrated the superiority of primary angioplasty over fibrinolytic therapy in STEMI (66-68). The door-to-balloon time should be within 90 minutes. A triage system with immediate notification of the on-call interventionalist and catheterization laboratory staff by the emergency department facilitates this process. Nonetheless, many eligible patients still fail to receive optimal care. A recent analysis of 20,279 STEMI patients found that patients presenting during off-hours were less likely to receive PCI (OR 0.93, 95% CI, 0.89-0.98), had longer door-to-balloon times (median 110 vs. 85 minutes, \( p < 0.0001 \)), and had lower rates of under 90-minute door-to-balloon times (adjusted OR 0.34, 95% CI, 0.29-0.39) (69).

Primary PCI should only be directed at the infarct artery; treatment of concomitant lesions in other arteries should be staged. Results of the Primary Angioplasty in Myocardial Infarction (PAMI) trial (70) demonstrated the superiority of stenting over balloon angioplasty acutely and up to five years. Furthermore, the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) trial (40) found that SES implantation was safe during STEMI and resulted in significantly reduced rates of recurrent MI and TVR compared with BMS. However, the Paclitaxel-Eluting Stent Versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION) (71) investigators reported no difference in the primary end point of cardiac death, recurrent MI, or TVR when SES was compared with BMS.

Although previously controversial, DES implantation during AMI appears to be safe and efficacious. Mauri and co-investigators reviewed 7217 PCI cases, 4016 with DES and 3201 with BMS. Utilizing propensity-score matching, they found superior two-year risk-adjusted mortality rates for patients treated with DES versus BMS (10.7% vs. 12.8%, \( p = 0.02 \)). The DES advantage was present for STEMI (8.5% vs. 11.6%, \( p = 0.008 \)) and non-STEMI (12.8% vs. 15.6%, \( p = 0.04 \)) subgroups. Moreover, recurrent MI rates were reduced for non-STEMI patients treated with DES; and repeat revascularization rates were superior for DES patients in all groups. The authors concluded that DES implantation resulted in superior two-year mortality and TVR compared with BMS (13). Although these results are encouraging, they may be influenced by selection bias and use of prolonged dual antiplatelet therapy (72). This is supported by the HORIZONS-AMI trial that showed no difference in death, MI or stroke rates between DES and BMS (73).

Fragmentation of a friable thrombus can lead to distal microembolization during primary PCI. Angiographic slow flow or no reflow represents microembolization of fibrin and platelets into the arteriolar bed. Selection of slightly longer stent length may help “trap” much of the extruded material.

Various distal protection devices have been designed to trap and subsequently remove debris after stent placement. Aspiration devices physically extract the friable components of the plaque. Pretreatment of these high-risk lesions with manual catheter aspiration has recently been demonstrated in the Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) (13) to confer acute and one-year benefit. At one year, cardiac death (3.6% vs. 6.7%, \( p = 0.020 \)) and cardiac death or nonfatal reinfarction (5.6% vs. 9.9%, \( p = 0.009 \)) rates were lower with thrombus aspiration compared with PCI only.

When no reflow is encountered, intracoronary administration of vasodilators such as nitroprusside, adenosine, or calcium-channel blockers through the central lumen of an over-the-wire balloon catheter into the distal vascular bed frequently provides prompt resolution. It is important to bear in mind that surgical revascularization offers no benefit in cases of refractory no reflow. The over-the-wire system is further useful in distal visualization of a totally occluded artery. After initial guidewire lesion penetration, the balloon can be advanced distally then retracted, without inflation. The slightly
higher balloon profile often results in a sufficient channel to allow visualization of the distal coronary artery. If distal flow is still not achieved at this point, the balloon is then advanced distally followed by removal of the guidewire. Contrast medium is subsequently injected through the central balloon lumen to opacify the distal artery, confirming intraluminal position.

In most cases of STEMI, direct stenting (without balloon before dilatation) may be preferable, as aggressive balloon inflations can result in lesion fragmentation. Use of smaller diameter balloons (2.0 or 2.5 mm) sufficient to allow stent passage is recommended. Additionally, a single high-pressure stent inflation may minimize the “cheese-grating” extrusion and subsequent downstream embolization of friable thrombus.

Cardiogenic Shock

The occurrence of cardiogenic shock has notably declined in recent years, coincident with the increasingly widespread practice of primary PCI for STEMI. This dreaded complication of AMI occurs in 5% to 8% and 2.5% of all patients with STEMI and non-STEMI, respectively. In-hospital mortality is approximately 50%. Clinical risk factors for development of cardiogenic shock include anterior STEMI, left bundle-branch block, older age, multivessel CAD, and history of heart failure, diabetes, hypertension, prior MI or angina (74). Although commonly diagnosed clinically by symptoms or signs of left ventricular or biventricular failure, formal criteria for cardiogenic shock include marked hypotension (systolic pressure < 80 mmHg) and reduction of baseline mean arterial pressure by 30 mmHg) and pump failure (cardiac index < 1.8 L/min × m²) in the presence of adequate filling pressures (LV end-diastolic pressure > 18 mmHg) (74).

Mechanical complications occur infrequently, but usually have dramatic presentations. Acute mitral regurgitation results from papillary muscle ischemia or rupture, and acute ventricular septal rupture can result in a large left-to-right shunt. These two entities have clinically similar presentations of marked pulmonary congestion, hypotension, and holosystolic murmurs. The harsh and turbulent flow across the interventricular septum may be associated with a palpable thrill along the sternal border, whereas most mitral regurgitant murmurs are not. Echocardiography and/or sequential blood oxygen saturations obtained from the right atrium and pulmonary artery (“sat run”) can frequently distinguish these etiologies. Additionally, while free ventricular wall rupture, resulting in immediate tamponade, is almost universally fatal, a contained rupture may allow time for urgent diagnosis and intervention. For all mechanical causes of cardiogenic shock, emergent surgical repair is crucial and potentially life-saving.

Most commonly, however, cardiogenic shock results from significant left ventricular dysfunction. While takotsubo cardiomyopathy (also known as the “broken heart” or “apical ballooning” syndrome) (75) has become an increasingly recognized etiology of STEMI and cardiogenic shock, the vast majority of cardiogenic shock occurs in the setting of coronary artery occlusion and STEMI. Of note, the degree of left ventricular dysfunction may not be predictive of clinical presentation. In the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial (76), Hochman and associates reported a mean left ventricular ejection fraction of almost 30%. Nonetheless, left ventricular ejection fraction remains a strong predictor of long-term prognosis (74).

Right heart catheterization is invaluable in diagnosing and monitoring these patients. Constant pulmonary arterial pressure and frequent cardiac index assessments guide titration of inotropic and pressor agents. Aside from aggressive pharmacologic and ventilatory support measures, emergent angiography and revascularization, as well as mechanical circulatory devices, are warranted. The intra-aortic balloon pump provides augmentation of diastolic coronary perfusion, cardiac index, and mean arterial blood pressure. Data from the National Registry of Myocardial Infarction revealed significant survival advantage associated with intra-aortic balloon counterpulsation (77). Intra-aortic counterpulsation is contraindicated in cases of significant aortic insufficiency and aortic dissection.

Total circulatory support may be needed in refractory cases. Left ventricular assist devices drain blood from the left heart and pump it back into the systemic arterial circulation. The TandemHeart device (Cardiac Assist, Inc., Pittsburgh, Pennsylvania, U.S.) is a percutaneously inserted device consisting of a transeptal left atrial inflow catheter and a femoral artery outflow catheter. The Impella device (Abiomed, Inc., Danvers, Massachusetts, U.S.) operates on a similar principle, but is inserted across the aortic valve. Extracorporeal circulatory devices additionally pass the venous blood through a membrane oxygenator, thereby incorporating oxygenation with perfusion support. Although left ventricular assist devices offer superior hemodynamic support over intra-aortic balloon counterpulsation, current data fail to demonstrate a survival difference (78).

Urgent revascularization was shown to impart a 13% absolute increase in survival for patients in the SHOCK trial (NNT < 8) (76). The ACC/AHA guidelines assign class I and class II indications to urgent revascularization for cardiogenic shock in patients younger and older than 75 years, respectively. Adherence to the 90-minute door-to-balloon time is less important in the setting of shock, with survival benefit demonstrated up to 48 hours after AMI and 18 hours after shock onset (74). If significant delay to primary PCI is anticipated, fibrinolytic therapy can be administered, although the scope of benefit is clearly diminished. Multivessel disease can be treated with either CABG or PCI. Two-thirds of the patients who underwent PCI in the SHOCK trial had multivessel disease (76). A recent follow-up study of the SHOCK registry reported promising three- and six-year survival rates of 41.4% and 32.8% for patients receiving early PCI (79). Primary PCI for cardiogenic shock is further a separate chapter.

Isolated or predominant right ventricular infarction accounts for 5% of cardiogenic shock. The mainstay of initial therapy consists of volume resuscitation and inotropic support. Not infrequently, left ventricular function may also be compromised by impaired filling due to leftward shift of the interventricular septum as well as decreased preload (80).

BIFURCATION LESIONS

Despite dramatic improvements in PCI techniques and equipment, bifurcation lesions remain a serious challenge for the modern interventionalist. Turbulent flow dynamics and high shear stress likely predispose to plaque formation in such locations. These lesions comprise 15% to 20% of PCI. Compared with other interventions, bifurcation PCI is associated with lower procedural success rates, higher procedural costs, longer hospitalizations, and higher clinical and angiographic restenosis rates. Some studies have reported bifurcation lesions as an...
independent risk factor for subacute and late stent thrombosis (81,82). Compared with BMS, DES are associated with less TVR and main branch restenosis in this anatomic subset (1).

**Lesion Classification**

The presence of atheromatous plaque causing >50% stenosis in both the main and side branches is considered the definition of a true bifurcation lesion. Several classification schema of varying complexity have been proposed. The Duke classification (83) is ordered A through F according to main branch and side branch plaque location (Fig. 30.3).

Lefevre et al. (84) have proposed an alternate classification based on the side branch to main branch angle and lesion morphology; bifurcation lesions are classified as Y-shaped or T-shaped (side branch to main branch angle less than or greater than 70°, respectively). In most cases, Y-shaped lesions allow easier side branch access but may be associated with greater plaque shift. The converse is generally true for T-shaped lesions. By this scheme, type 1 lesions are defined as true bifurcation lesions involving the main branch, proximal and distal to the bifurcation, as well as the side branch ostium. Type 2 lesions involve only the main branch at the bifurcation, sparing the side branch ostium. Type 3 lesions are located in the main branch proximal to the bifurcation. Type 4 lesions involve only the bifurcation, without proximal or distal disease in either branch. The latter is further divided into subtypes 4A and 4B, isolated to the main branch and side branch, respectively (Fig. 30.4).

The Medina classification (85) is a simplified, practical system involving binary allocation of “1” or “0” based on the respective presence or absence of significant plaque burden in the proximal main branch, distal main branch, or side branch. A “1,1,0” bifurcation lesion, for instance, would indicate proximal and distal main branch involvement, with sparing of the side branch (Fig. 30.5). The location of the bifurcation lesion relative to the carina is a crucial determinant in the decision regarding a single- or double-stent strategy.

**Techniques**

**Debulking Techniques**

Plaque shift or “snow-plowing” can occur in 4.5% to 26% of bifurcation lesion PCI (86,87) and is more frequent with smaller side branch reference diameter, side branch origination from the main branch lesion, and ACS presentation (87). Occlusion of the side branch often results in periprocedural biomarker elevation, which may negatively impact long-term MACE, including TVR (86). Fortunately, more than 75% of side branch occlusions are patent at angiographic follow-up (88).

Prestent debulking strategies utilizing rotational, directional, or laser atherectomy have been proposed to minimize potential plaque shift. The FLEXI-CUT (89) study evaluated directional coronary atherectomy-assisted single-vessel stenting of left main bifurcation lesions. The procedural success rate was 96.7%, with 10.3% TVR and 6.9% overall MACE rates. Interestingly, Karvouni and colleagues found that prestent directional atherectomy resulted in a lower procedural success.
rate (87.1% vs. 100%, \( p = 0.03 \)), due to higher non-Q wave MI rates (12.9% vs. 0%, \( p = 0.03 \)). However, directional atherectomy-stenting was associated with greater acute gain, as well as a trend toward reduced MACE at follow-up (\( p = \text{NS} \)) (17). Nonetheless, because of the relative technical complexity of these approaches, single- or double-vessel stent strategies remain preferred in the majority of cases.

Stent Techniques

While expert opinion varies regarding the preferred technique for treating bifurcation lesions, employment of at least one DES is recommended in most cases. When the risk for compromising a large side branch is low, main branch stenting with provisional side branch stenting frequently offers the simplest and most practical solution. The Nordic Bifurcation Study (90) was a DES study comparing the results of two-vessel stenting versus main branch stenting with provisional side branch stenting. At six months, there was no difference in MACE; however, two-vessel stenting was associated with significantly greater procedural and fluoroscopic times, contrast volumes, and rates of postprocedural biomarker elevation.

In cases requiring double-stent implantation, many techniques have been proposed. The T-stent technique (91) involves stenting the side branch ostium after initial stent deployment in the main branch. A second wire is initially left in the side branch and jailed by the main branch stent. The favorable side branch angle modification and angiographic reference offered by the jailed wire facilitates subsequent side branch access through the deployed stent using the main branch wire. After dilating the stent struts, a second stent is meticulously implanted at the side branch ostium with a final kissing balloon dilatation. The technique is best suited to bifurcation lesions with an angle close to or equal to 90°. Nonetheless, incomplete coverage of the side branch ostium remains a major limitation.

In the modified T-stenting technique, the side branch stent is advanced into position followed by main branch stent positioning without deployment. The former is then carefully positioned at the ostium and deployed first with only the proximal stent marker protruding into the main branch. Following removal of delivery catheter and guidewire from the side branch, the main branch stent is then deployed across the

Figure 30.4 The Lefevre bifurcation lesion classification. Source: From Ref. 84.

Figure 30.5 The Medina bifurcation lesion classification. Source: From Ref. 85.
ostium of the side branch. The side branch is then rewired for performance of a final kissing balloon dilatation.

The crush technique (92) ensures complete lesion coverage of the side branch ostium. As in the modified T-stenting technique, the side branch stent is positioned and deployed first. However, in this case, the proximal side branch stent marker is placed 2 to 3 mm proximal to the bifurcation within the main branch. After withdrawal of the side branch wire and stent delivery catheter, the main branch stent is subsequently inflated, crushing the proximal segment of side branch stent. Three layers of stent struts are thus compressed against the ipsilateral main branch wall. Finally, kissing balloon dilatation is undertaken (through the triple layer of stent struts at the bifurcation). This last step is essential to ensure adequate carinal and side branch ostial patency and to reduce long-term TVR of either branch.

In their IVUS follow-up of DES crush technique in 40 subjects, Costa and colleagues (93) found that main branch stent minimum luminal diameter measured <4 and <5 mm² in 8% and 20% of lesions, respectively. For the side branch ostium, minimal stent areas of <4 and <5 mm² were seen in 44% and 76%, respectively. Incomplete apposition of side branch or main branch stent struts against the precarinal main branch wall was seen in the majority (>60%) of non-left main lesions. Consistent with other reports, the minimal side branch area was observed at the ostium, suggesting this as a likely contributor to the higher restenosis rate at this location.

The culotte (or “pant-leg”) technique (94) ensures complete bifurcation carinal coverage. In its original description, after double-wire insertion, the first stent is deployed in the more sharply angulated artery (usually the side branch) at high pressure (12–14 atm). The main branch wire is thus trapped, and a third wire is introduced to recross the struts of the initial stent into the other branch. After removal of the jailed wire, balloon predilatation through the stent struts facilitates passage of a second stent into the other vessel. The procedure ends with a final kissing inflation. Technical complexity and high rates of postprocedural events and restenosis in registry reports have limited the popularity of this strategy.

The simultaneous kissing stent (94) technique is usually employed for bifurcation lesions with similar-sized branches and large proximal vessel reference diameter. The procedure involves wiring the main and side branches and allows maintenance of access to both during the entire procedure. Both stents are positioned side by side and sequentially inflated, followed by a final kissing inflation. A “double-barrel” configuration results, and the carina is thus extended proximally. The simultaneous stent deployment minimizes plaque shift. The advantage of this technique lies in its ease and predictability. Kim and colleagues (95) reported a procedural success rate of 100%. At 26-month follow-up, there were no deaths, MI, or stent thromboses. TVR occurred in five patients (14%), with four (13%) in the main branch and three (10%) in the side branch. Of note, in 14 patients (47%), a membranous film coating the double-layered carina was noted both angiographically and by IVUS. However, no clinical sequelae were associated with this membrane.

The V-stent variant involves proximal alignment of both stents at the carina. While this strategy minimizes proximal main branch dissection, carinal coverage may not be assured. Y-stenting is performed by additional deployment of a proximal main branch stent juxtaposed against the proximal edges of both V stents. This technique was developed to allow complete lesion coverage but is limited by its procedural complexity and the need for three stents.

LIMITATIONS OF PCI

PCI Vs. Medical Therapy

Despite widespread popularity, PCI has not been shown to decrease mortality in patients with stable CAD. Conversely, primary PCI provides a survival advantage compared with fibrinolytic therapy in patients with STEMI.

In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (96) over 35,000 patients with chronic stable angina and angiographically documented CAD were screened for randomization to optimal medical therapy with or without PCI. Inclusion criteria included >70% stenosis in a proximal major epicardial artery, CCS class I to III angina, and precateterization objective evidence of ischemia. Patients with uncontrolled angina, complicated post-MI course, EF < 30%, or cardiogenic shock were excluded. Only 2287 patients (<10%) were enrolled (1149 optimal medical therapy and 1138 PCI). Few patients received DES in this trial. No difference was observed for the primary composite end point of death or MI at a median of 4.6-year follow-up (96). Subsequent revascularization for ischemia was required in 21% PCI and 32.6% medical patients.

The 314-patient nuclear stress test substudy reported significantly greater ischemic burden reductions with PCI versus optimal medical therapy alone (78% vs. 52%, p = 0.007). Additionally, those patients deriving significant ischemia improvement also demonstrated lower unadjusted mortality or MI rates (p = 0.037). The unadjusted primary endpoint reduction was especially pronounced in those individuals with moderate to severe baseline ischemia (p = 0.001). While DES use would not likely have impacted mortality results, it probably would have decreased TVR and recurrent angina rates. It would thus seem reasonable that patients with CAD and moderate to severe ischemia should be considered for PCI as an adjunct to optimal medical therapy.

The Medicine, Angioplasty, or Surgery Study (MASS) II compared medical therapy, PCI, and CABG in patients with stable multivessel CAD (97). At five years, no significant differences were observed in subsequent revascularization and overall MACE rates between medical and PCI patients.

Conversely, the Japanese Stable Angina Pectoris (JSAP) study reported possible benefit for PCI/optimal medical therapy versus optimal medical therapy alone in 384 low-risk patients with stable angina and single- or double-vessel CAD (98). Over a 3.3-year follow-up, the PCI group demonstrated a significantly reduced combined death and ACS risk (7.9% vs. 14.9%, p = 0.018). Similarly, combined death, ACS, and stroke (8.5% vs. 16.4%, p = 0.044) and combined death, ACS, stroke, and emergency hospitalization (22% vs. 33.2%, p = 0.04) rates were decreased for PCI patients.

Left Main and Multivessel CAD

While CABG has traditionally been recommended for patients with triple-vessel and left main CAD, the enhanced safety and restenosis benefits of PCI due to technical and device improvements have prompted randomized trials comparing PCI and CABG. No significant mortality or MI differences have been demonstrated, although TVR was greater in PCI patients (99).

The recent Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial...
randomized patients with left main or triple-vessel CAD to multivessel PCI or CABG (100). The study protocol was reflective of modern PCI strategies using DES and optimal CABG techniques, with overall and bilateral mammary arterial conduit rates of 97% and 27.6%, respectively. Additionally, coronary anatomy was complex with 84% bifurcation or trifurcation lesions, 22% chronic total occlusions, and 39% significant left main disease. A mean of 4.6 DES were implanted per patient with a mean total stent length of 86 mm (one-third of patients >100 mm).

There was a higher MACCE (major adverse cardiovascular or cerebrovascular event) rate for PCI (17.8% vs. 12.1% for CABG, p = 0.0015). Hence, the noninferiority primary end point for PCI was not achieved. Consistent with prior findings, combined rates for all-cause mortality, MI, and stroke were equivalent between groups (7.6% for PCI and 7.7% CABG, p = 0.98); and TVR after PCI exceeded that of CABG by 7.8%. However, a significantly higher stroke risk was observed with CABG (2.2% vs. 0.6%, p = 0.003). Despite challenging coronary anatomy, t-PA with PCI was much less than that observed in previous PCI versus CABG trials. Interestingly, rates of symptomatic bypass graft occlusion and stent thrombosis were equivalent.

CONCLUSION

Despite recent advances in treating structural heart disease, PCI remains the cornerstone of interventional cardiology; and technical improvements have dramatically improved outcomes. A continuing challenge will be appropriate use of PCI (101). In addition, optimal medical therapy must be applied to achieve optimal long-term outcomes for PCI patients.

REFERENCES


100. Nishigaki K, Yamazaki T, Kitabatake A, et al. Percutaneous coronary intervention plus medical therapy reduces the


Guiding catheters and wires

David W. M. Muller

GUIDING CATHETERS
Introduction
Selection of an appropriate guiding catheter is fundamental to the success of every coronary interventional procedure. The catheter should provide coaxial access to the coronary artery to facilitate passage of a guidewire, stability for delivery of balloons and bulky devices, and sufficient contrast flow to adequately visualize the coronary anatomy. It should have a soft atraumatic tip to minimize the risk of injury to the coronary ostium. Changes in procedural complexity over the past two decades have had important influences in guide catheter selection. Bulky inflexible devices such as the directional atherectomy catheter and early generation coronary stents required considerable support from the guide and gentle deflectable curves distally. A progressive decrease in the bulk of devices, an increase in their flexibility, and technical improvements in guiding catheter design have permitted a gradual reduction in visualization of the coronary ostium. The benefit of the side holes incorporated close to the catheter tip, particularly in large caliber catheters, to limit the hypoperfusion caused by partial occlusion of the coronary ostium. Changes in procedural complexity over the past two decades have had important influences in guide catheter selection. Bulky inflexible devices such as the directional atherectomy catheter and early generation coronary stents required considerable support from the guide and gentle deflectable curves distally. A progressive decrease in the bulk of devices, an increase in their flexibility, and technical improvements in guiding catheter design have permitted a gradual reduction in visualization of the coronary ostium. The benefit of the side holes incorporated close to the catheter tip, particularly in large caliber catheters, to limit the hypoperfusion caused by partial occlusion of the coronary ostium. The benefit of the side holes may, however, be offset by a reduction in visualization of the distal coronary artery, an increase in the volume of contrast used, and loss of pressure damping, an important indicator of coronary flow limitation.

Catheters are constructed in a variety of shapes to cater for differences in coronary anatomy. They all have a primary curve close to the tip and a secondary curve that varies according to the catheter size and shape. Subtle differences in construction along the length of the catheter give more support and torquability to the catheter shaft, and greater flexibility to segments closer to the tip (Fig. 31.2A, B). Variation in characteristics of these zones or segments can greatly influence catheter performance.

Active Vs. Passive Guide Support
Depending on the design characteristics of the catheter, a guide may be best used passively or actively. Passive guide support relies on the inherent properties of the catheter and its interaction with the walls of the aortic root. Passive support can be increased by increasing the caliber of the guide (e.g., 8 Fr vs. 6 Fr), by selecting a shape that provides greater contact with the contralateral aortic wall, or by selecting a catheter with a stiffer shaft and power zone. A guide that is used actively is manipulated, for example, by deep seating into the proximal coronary artery (or beyond), to maximize back up support. This requires a soft atraumatic catheter tip and a flexible primary curve. Some guides such as the Vista Brite Tip (Cordis Corporation, Miami Lakes, Florida, U.S.), Launcher (Medtronic, Santa Rosa, California, U.S.), and Runway (Boston Scientific, Natick, Massachusetts, U.S.) are better suited to provide passive support, whereas others such as the Mach1 (BSC), Zuma2 (Medtronic), and Viking (Abbott Vascular, Redwood City, California, U.S.) catheters can be manipulated actively.

Catheter Shape and Variations in Coronary Anatomy
The left main coronary and the right coronary artery usually arise horizontally from the left and right coronary cusps, respectively. It is not uncommon, however, for their position to be anterior or posterior to the usual position and for their takeoff to be superior or inferior to the horizontal (1) (Fig. 31.3). The left main coronary artery may be long or short, or the left anterior descending artery (LAD) and circumflex may arise from separate ostia (1,2). The right coronary artery often arises high and anterior to its usual position. It may arise from the left coronary cusp adjacent to the left main coronary artery. The circumflex can take origin from the proximal right coronary artery (2). In this position, it can be difficult to cannulate using a guiding catheter that seats deeply in the proximal right
coronary artery. Changes in the size and shape of the aortic root and ascending aorta, and whether access is obtained from the femoral or radial artery, also have an important influence on the optimal size and shape of the guiding catheter.

**Normal Anatomy**

Traditional curves such as the left Judkins (JL or FL) catheter provide adequate backup for many left coronary interventions (Fig. 31.4). More supportive shapes such as the EBU, XB, Voda, and DC curves provide better support for complex interventions and, in some catheter laboratories, have become the standard choice for all left coronary procedures. These shapes have the added advantage of less angulated primary and secondary curves that facilitate the passage of bulky devices. Gentle advancement with clockwise rotation can be used to selectively engage the LAD. Counterclockwise rotation can be used to selectively engage the circumflex coronary artery. Other curves that provide excellent backup in the left coronary artery include the Amplatz curve (AL1 or AL2), the CLS (contralateral support) curve, and the Q curve (Fig. 31.5A).

The right coronary artery is most commonly cannulated using a right Judkins curve but, unless actively deep-seated, this provides relatively little support for complex anatomy. If greater support is required, alternative curves include the Hockey stick, Amplatz (AL1), XB or Voda right, allRight, and Kiesz Right (Fig. 31.5A). On occasions, the right coronary has a very superior take-off (Shepherd’s crook). If the artery is calcified or severely diseased, instrumentation of these arteries requires excellent backup using Shepherd’s crook, Amplatz (AL1), and Hockey stick curves. In this, and other circumstances in which the guide is deep seated, great care must be taken to avoid guide catheter-related dissection of the proximal artery.

**Radial Approach**

Judkins curves can be used for procedures performed using a left or right radial approach, but curves specifically designed for transradial interventions are often used. These include the Kimny, MUTA, and Radial catheters, the RB catheter, and the MAC catheter (Fig. 31.5B).

**Bypass Grafts**

Saphenous vein grafts to the right coronary artery are best approached with a multipurpose catheter if the takeoff is vertical, or a right Judkins or right coronary bypass (RCB) catheter if it is more horizontal. Vein grafts to the left coronary artery can be cannulated with a right Judkins, an IMA, a left
coronary bypass (LCB), or an AL1 curve though none of these provides contralateral wall support. An IMA curve is used for interventions performed through an internal mammary artery graft.

**Anomalous Origins**

Right coronary arteries arising high and anteriorly, or low in the right coronary cusp, can usually be cannulated with an Amplatz left catheter. Circumflex arteries arising from the proximal right coronary artery are best approached with a short-tipped JR catheter, and AL1 or an AR1.

**GUIDEWIRES**

**Introduction**

As originally conceived and developed by Gruntzig (3), balloon dilatation catheters had a closed end attached to a short, fixed, nonsteerable, and relatively atraumatic guidewire. The inability to direct the wire to, and through, stenotic coronary lesions was a major limitation of the technique. As a consequence, the primary technical success rate reported in the NHLBI PTCA Registry in 1982 was only 59% (4). In the same year, Simpson and colleagues reported the use of an over-the-wire system that allowed a central guidewire to be advanced independently of the dilatation catheter (5). This adjustment improved the success and safety of the procedure by allowing the operator to exchange or reshape the wire without removing the balloon catheter, to minimize ischemia time by wiring the distal vessel before attempting to cross with the balloon catheter, and to exchange the balloon catheter without having to also remove the guidewire. Soon thereafter, technical success rates approaching 90% were reported (6).

Technical advances in guidewire technology followed. In the mid 1980s, 0.018 and 0.016 in. wires were constructed from a stainless steel core shaft that tapered distally and was covered by a flexible stainless steel coil spring (Fig. 31.6A). The shaping ribbon was added to the tip to improve shaping and steerability of the wire. Visibility of the tip was enhanced by adding a platinum alloy spring coil segment, and tip flexibility and steerability were manipulated by varying the length and diameter of the central core taper. Trackability was enhanced by coating the distal coil with hydrophilic or hydrophobic materials (e.g., Teflon, silicone). This spring coil construction has remained dominant as the workhorse wire design in the two decades since then, but other refinements have been introduced to improve wire performance in specific situations. In addition, several manufacturers have developed wires with polymer coatings covering part of or the entire distal segment to facilitate passage of the wire through complex lesions and chronic total occlusions. The wire may or may not have an underlying spring coil supporting the polymer.

**Wire Characteristics**

Contemporary wires can vary considerably in a variety of important performance characteristics. The torque response of a wire refers to the extent of wire tip rotation in response to rotation of the wire shaft. Wires with high torque respond to very fine movements of the wire shaft and are therefore more steerable than less torqueable wires. Wire support relates to the stiffness of the working length of the wire. Stiffer more supportive wires more readily allow passage of a balloon catheter.
or stent through noncompliant arteries. **Wire trackability** refers to the ease with which a wire can be advanced through a tortuous artery without buckling, kinking, or prolapsing. **Pushability** relates to the extent to which pressure applied to the shaft is transmitted to the wire tip. **Durability and shape retention** describe the impact of repeated use of the wire on the integrity of the shaft and shape of the distal tip. **Tip flexibility** refers to the ease with which a wire tip is deflected from an object. Very flexible, floppy-tipped wires are less likely to cause plaque disruption, dissection, or perforation than less flexible wires, but are also less likely to cross complex lesions and subtotal or total occlusions. **Tip malleability** refers to the ease with which the wire tip can be shaped. **Tactile sense** is the ease with which the operator can recognize changes in movement of the wire tip. **Tip load** refers to the force required to buckle the distal tip (10 mm) of a wire. This is typically measured in grams. The higher the tip load, the greater the ease with which a wire will penetrate fibrous or calcified occlusions and the greater the risk of arterial injury (dissection or perforation). **Penetration power** is derived from the tip load and the area of the tip [tip load/tip area (kg/in²)].

**WORKHORSE WIRES**

**Coiled Tip Wires**

The most frequently used workhorse wires are still stainless steel coiled spring wires. These wires have a 0.014 in. stainless steel shaft that tapers distally to a 30- to 40-cm long stainless steel core (Table 31.2). The core typically tapers segmentally and terminates before the end of the overlying coils (Fig. 31.6A) with a shaping ribbon between the end of the core and the tip weld. This wire construction provides good torque control, good pushability, and light support. Examples of this include the Hi-Torque Floppy II wire (Abbott Vascular), the Asahi Light (Asahi Intec Co. Ltd., Nagoya-shi, Aichi, Japan), and the Boston Scientific Forte. The performance of this type of wire can be
modified by increasing the diameter of the core to increase wire support and torquability. This may require shortening or elimination of the intermediate coils between the shaft and the floppy tip. Greater trackability and flexibility can be achieved by reducing the diameter of the core, by reducing the abruptness of the taper (transitionless core), by increasing the length of the taper to extend to the wire tip (core-to-tip), or by changing the shape of the taper (parabolic taper).

Other modifications to this original design and construction were introduced to further enhance wire performance. Changing the core material to nitinol (e.g., Hi-Torque Balance Middleweight, IQ wire, Cougar), a highly elastic alloy of nickel and titanium, improved the durability (kink resistance) and flexibility of the wire while maintaining a moderate degree of support (Fig. 31.6B). The price paid for this improvement may be a reduction in torque control of the tip. Changing the core material to a high tensile strength stainless steel (e.g., Hi-Torque Advance, Asahi Provater/Rinato) also improved wire durability, shape retention, and torque control. Particularly good torque control is evident in the Asahi family of wires that are based on a unique method of processing the shaft and core as a single piece with a transitionless, core-to-tip taper (Tru-Torque) and eliminating the joint between the stainless steel and the platinum coil segments at the tip.

**Polymer-Coated Wires**

To maximize trackability, wires have been developed with polymer sleeves coating the distal tip (Fig. 31.6C). These include wires with polymer-coated coils (e.g., Hi-Torque Whisper, Advance, Fielder, and Pilot wires), those with polymer-coated core wires (e.g., PT2, PT Graphix, and ChoICE PT wires), and hybrid combinations of both (BMW Universal, Hi-Torque All Star) (Tables 31.1–31.4). The polymer is typically impregnated with a material such as tungsten to add radiopacity to the tip. The reduced friction attributable to the polymer sleeve enhances passage of the guidewire through tortuous, severely diseased arterial segments, and through the microchannels of chronic total coronary occlusions. The major disadvantages of the coating are a loss of tactile sense and an increased risk of arterial perforation. Wires without underlying...
tip coils may be difficult to shape and may have a reduced torque response. Some of these limitations have been addressed with the Hi-Torque Progress family of wires (Abbott Vascular).

These have a polymer sleeve coating all but the distal 5 mm of coils that are left bare to improve the tactile feel of the wire and to reduce the risk of perforation (Fig. 31.6C).

### SPECIFIC PURPOSE WIRES

#### Angulated Lesions

Highly angulated lesions require wires that have exceptional torque control to allow fine movements of the tip. The tip should also be malleable with excellent shape retention. Polymer-coated wires may provide an advantage in very

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**Table 31.1** Wires Suitable for Standard Anatomy

<table>
<thead>
<tr>
<th>Wire</th>
<th>Manufacturer</th>
<th>Core</th>
<th>Tip</th>
<th>Tip coating</th>
<th>Tip stiffness</th>
<th>Rail support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hi-Torque Floppy</td>
<td>Abbott Vascular</td>
<td>SS</td>
<td>Coil</td>
<td>Silicone</td>
<td>Floppy</td>
<td>Light</td>
</tr>
<tr>
<td>BMW</td>
<td>Abbott Vascular</td>
<td>SE nitinol</td>
<td>Coil</td>
<td>Silicone</td>
<td>Floppy</td>
<td>Light</td>
</tr>
<tr>
<td>Light/Softh</td>
<td>Asahi</td>
<td>SS</td>
<td>Coil</td>
<td>Hybrid</td>
<td>Floppy</td>
<td>Light</td>
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<td>Choice Floppy</td>
<td>Boston</td>
<td>SS</td>
<td>Coil</td>
<td>Hydrophilic</td>
<td>Floppy</td>
<td>Light</td>
</tr>
<tr>
<td>Forte</td>
<td>Boston</td>
<td>SS</td>
<td>Coil</td>
<td>Hydrophilic</td>
<td>Floppy</td>
<td>Light</td>
</tr>
<tr>
<td>Zinger</td>
<td>Medtronic</td>
<td>SS</td>
<td>Coil</td>
<td>Hydrophilic</td>
<td>Floppy</td>
<td>Light/Mod</td>
</tr>
</tbody>
</table>

**Abbreviations:** Boston, Boston Scientific Corporation; SS, stainless steel; SE, super elastic.

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**Table 31.2** Wires Suitable for Tortuous Arteries

<table>
<thead>
<tr>
<th>Wire</th>
<th>Manufacturer</th>
<th>Core</th>
<th>Tip</th>
<th>Tip coating</th>
<th>Tip stiffness</th>
<th>Rail support</th>
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<tr>
<td>IQ</td>
<td>Boston</td>
<td>LE nitinol</td>
<td>Coil</td>
<td>Silicone</td>
<td>Floppy</td>
<td>Light</td>
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<tr>
<td>Luge</td>
<td>Boston</td>
<td>SS</td>
<td>PCC</td>
<td>Silicone</td>
<td>Floppy</td>
<td>Moderate</td>
</tr>
<tr>
<td>PT²</td>
<td>Boston</td>
<td>LE nitinol</td>
<td>Polymer</td>
<td>Hydrophilic</td>
<td>Floppy</td>
<td>Intermediate</td>
</tr>
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<td>Prowater (Rinato)</td>
<td>Asahi</td>
<td>HTSS</td>
<td>Coil</td>
<td>Hydrophilic</td>
<td>Floppy</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fielder</td>
<td>Asahi</td>
<td>SS</td>
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<td>Light</td>
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<td>Whisper</td>
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<td>Advance</td>
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<td>PCC</td>
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<td>Wizdom</td>
<td>Cordis</td>
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<td>Cougar</td>
<td>Medtronic</td>
<td>LE nitinol</td>
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<td>Floppy</td>
<td>Light/Mod</td>
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**Abbreviations:** Boston, Boston Scientific Corporation; LE, linear elastic; PCC, polymer-covered coils; SS, stainless steel; HTSS, high tensile stainless steel.

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**Table 31.3** Wires Providing Extra Support

<table>
<thead>
<tr>
<th>Wire</th>
<th>Manufacturer</th>
<th>Core</th>
<th>Tip</th>
<th>Tip coating</th>
<th>Tip stiffness</th>
<th>Rail support</th>
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<td>Extra S'Port</td>
<td>Abbott Vascular</td>
<td>SS</td>
<td>Coil</td>
<td>Silicone</td>
<td>Floppy</td>
<td>Extra</td>
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<td>Stabilizer Plus</td>
<td>Cordis Corporation</td>
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<td>Extra</td>
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<td>Thunder</td>
<td>Medtronic</td>
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<td>Floppy</td>
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<td>Super</td>
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<td>Mailman</td>
<td>Boston</td>
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<td>Hydrophilic</td>
<td>Silicone</td>
<td>Floppy</td>
<td>Super</td>
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<td>Grand Slam</td>
<td>Asahi</td>
<td>SS</td>
<td>Silicone</td>
<td>Floppy</td>
<td>Extra</td>
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</tbody>
</table>

**Abbreviations:** Boston, Boston Scientific Corporation; SS, stainless steel.

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**Table 31.4** Chronic Total Occlusion Wires

<table>
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<tr>
<th>Wire</th>
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<th>Core</th>
<th>Tip</th>
<th>Tip coating</th>
<th>Tip stiffness</th>
<th>Rail support</th>
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<tr>
<td>Miracle 3–12</td>
<td>Asahi</td>
<td>SS</td>
<td>Coil</td>
<td>Silicone</td>
<td>3–12 g</td>
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</tr>
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<td>Conflanza/Conquest</td>
<td>Asahi</td>
<td>SS</td>
<td>Coil</td>
<td>Silicone</td>
<td>9–20 g</td>
<td>Extra</td>
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<td>Pilot 50–200</td>
<td>Abbott Vascular</td>
<td>SS</td>
<td>PCC</td>
<td>Hydrophilic</td>
<td>2–5 g</td>
<td>Moderate</td>
</tr>
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<td>Cross-it 100–400 XT</td>
<td>Abbott Vascular</td>
<td>SS</td>
<td>Coil</td>
<td>Hydrophilic</td>
<td>2–9 g</td>
<td>Moderate</td>
</tr>
<tr>
<td>Progress 40–200T</td>
<td>Abbott Vascular</td>
<td>HTSS</td>
<td>Hybrid</td>
<td>Hydrophilic</td>
<td>5–13 g</td>
<td>Moderate</td>
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<td>Persuader</td>
<td>Medtronic</td>
<td>SS</td>
<td>PCC</td>
<td>Silicone</td>
<td>3–9 g</td>
<td>Moderate</td>
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<td>Shinobi</td>
<td>Cordis</td>
<td>SS</td>
<td>PCC</td>
<td>Hydrophilic</td>
<td>7–8 g</td>
<td>Moderate</td>
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<td>Terumo</td>
<td>Nitinol</td>
<td>PCC</td>
<td>Hydrophilic</td>
<td>Moderate</td>
<td></td>
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**Abbreviations:** HTSS, high tensile stainless steel; LE, linear elastic; PCC, polymer-covered coils; SS, stainless steel.

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diseased arterial segments but only if torque control and shape retention are not compromised. Wires such as the Fielder and Fielder XT (Asahi) and the Whisper wire (Abbott Vascular) combine the benefits of excellent tip control with a polymer coating and work well in this situation.

Angled Bifurcations/Tortuous Arteries
When the target vessel arises at a considerable angle from an adjacent artery (e.g., retroflexed circumflex, acutely angle OM branch, or stented artery side branch), many wires prolapse into the larger adjacent vessel rather than track around the acute bend. This is particularly true of wires that have an abrupt transition zone or rapidly tapering core. Wires with a transitionless core or long taper are most effective in negotiating bends without prolapse of the wire tip. Suitable wires for this situation include the Luge and IQ wires (BSC), the Advance and Whisper wires (Abbott Vascular), and the Fielder wire (Asahi) (Table 31.2). The major downside to these wires is a reduction in support for delivery of bulky devices.

Calcified Tortuous Arteries
When strong support is required to deliver a device to a distal lesion in an artery that is calcified or very tortuous, extra support wires are valuable. These typically have a large diameter inner core with a short taper at the tip. The PT2 Moderate Support (Boston Scientific), for example, has a core diameter of 0.097 in. compared with 0.075 in. in the PT2 Light Support. Other examples of support wires are shown in Table 31.4 and include the Balance Heavyweight (Abbott Vascular), the Stabilizer (Cordis), and the ChoICE PT Extra Support wire (Boston Scientific). Even greater support can be obtained using the Ironman (Boston Scientific), Grand Slam (Asahi), or Mailman (Boston Scientific) wires (Table 31.3). The downside to these very rigid, heavily supportive wires is a tendency to distort angulated segments of the artery causing pleating and potentially even transient closure of the artery. An alternative strategy, if additional support is required, is to place a second wire (buddy wire) alongside the first wire to help straighten curves in the artery and to increase the stability of the guiding catheter.

Subtotal Occlusions/Short or Recent Total Occlusions
A major stimulus for the development of the plethora of wires currently available was recognition that traditional wires do not adequately address the needs of operators treating chronic total occlusions. Considerable effort has been expended in improving our understanding of the pathology of chronic occlusions. For example, the presence of microchannels and partial recanalization has implications for wire selection. For subtotal chronic occlusions, and those with visible microchannels, polymer-coated wires with excellent tip control are very effective. Occlusions due to recent myocardial infarction can usually be crossed readily with a soft or floppy tipped wire. Care does need to be taken to avoid dissection due to passage of the wire into the base of an ulcerated or aneurysmal lesion.

Chronic Total Occlusions
Chronic total occlusions vary considerably in the duration of occlusion, in the extent of calcification, angulation, and proximal tortuosity, and in the presence of adjacent side branches. As a result, there is no single wire design that is best suited to this subset of lesions. It is commonly necessary to use an array of wires to deal with the specific characteristics of individual lesions. Most chronic occlusions that are more than six months old have a proximal fibrous cap that is difficult to penetrate with conventional wires. Several families of stiffer wires have been developed with greater capacity to penetrate hard lesions (Table 31.4). However, use of these wires in tortuous proximal segments increases the risk of dissection or perforation of the less diseased proximal artery. It is, therefore, recommended that softer wires are used to negotiate proximal bends. These can then be exchanged using an over-the-wire balloon or microcatheter for an appropriate total occlusion guidewire (7).

Wires that are specifically designed to penetrate the proximal fibrous cap have a larger core diameter and short core taper and are consequently stiffer and less flexible than conventional wires (Table 31.4). Tip loads of these wires range from 3 to 20 g compared with 0.5 to 1 g for most soft wires. Some wires taper distally to a diameter of 0.009 to 0.010 in. to further increase tip penetration power. Examples of the latter include the Confianza (Conquest) Pro (Asahi), the Cross It XT (Abbott Vascular), and Hi-Torque Progress (Abbott Vascular) wires. It is important to recognize that the stiffer the wire, the greater the risk of subintimal dissection and perforation. Once the proximal fibrous cap has been penetrated with a stiff wire, more flexible wires, such as the Miracle 3 or a polymer-coated wire, can be used particularly in long chronic total occlusions. It may then be necessary to exchange this wire for another stiff wire to penetrate the distal fibrous cap and enter the true lumen of the distal vessel (7).

Retrograde Approach
An increasingly popular strategy for treating chronic total occlusions is the retrograde approach (8). This requires the operator to pass a wire through the contralateral artery into the distal segment of the occluded vessel via septal or epicardial collaterals. Wires specifically designed for this approach, such as the Fielder XT and Fielder FC, have excellent torque control to facilitate negotiation of very fine and often tortuous (cork-screw) collateral arteries. Most are also polymer coated to increase their trackability through these channels. Once the distal vessel is entered, the wire can be exchanged for a stiffer, more penetrating wire using a microcatheter.

OTHER SPECIALTY WIRES
Wiggle Wire
This has a series of corrugations in the distal wire to promote passage of the wire and balloon catheter through heavily calcified or previously stented lesions (Fig. 31.6D). The angulated segment of the wire displaces it from the wall or the stent struts allowing free movement of the wire and balloon.

RotaWire
This dedicated rotational atherectomy wire has a 0.009 in. shaft that tapers to 0.005 in. distally. Attached to the tip is a 2.2 or 2.8 cm long, 0.014 in. diameter spring coil tip. Floppy and Extra Support versions of the wire are available.

Distal Protection Wires
Balloon dilatation and stenting of coronary or peripheral stenoses may liberate embolic material causing ischemic injury to the distal bed. Numerous guiding wires designed to collect and
retrieve embolic debris are now available (Fig. 31.7) (9). The shaft of the wires is usually sufficiently robust to allow stenting in most situations. If greater support is required, a buddy wire system can be used.

CONCLUSIONS

Although a vast and potentially daunting array of guiding catheter and guidewire designs is currently available, most coronary interventions can be performed with a small number of safe and reliable workhorse guides and wires. Specialty wires and guides should be used less frequently to treat the specific lesions for which they were designed.

REFERENCES


INTRODUCTION
The safety and efficacy of percutaneous coronary intervention (PCI) has continuously improved since its inception more than 30 years ago. The breathtaking growth of PCI reflects its widespread acceptance as the preferred revascularization strategy compared with coronary artery bypass graft surgery (CABG). Stents have remarkably improved the safety of PCI by reducing periprocedural acute closure due to coronary dissection (1) and the need for emergent CABG (2).

The basic principles underlying short-term efficacy are common to all coronary stents and include the following:
1. Increasing the arterial lumen by scaffolding the arterial wall
2. Trapping intimal flaps between the stent surface and arterial wall
3. Sealing medial dissections

Historical Perspective
The word “stent” was coined in 1916 by Jan F. Esser, a Dutch plastic surgeon, and referred to a dental impression compound developed formerly by Charles Thomas Stent. The first vascular stent was developed and implanted in 1968 by Charles Dotter in a canine popliteal artery (3).

The first coronary stent resulted from discussions between two Swedish expatriates in Switzerland: Hans Wallsten, a paper engineer, and Ake Senning, the chief cardiac surgeon collaborating with Andreas Grünzig during the first coronary angioplasties in Zurich. The first coronary stent (Wallstent) was self-expanding and was developed by Medinvent in cooperation with Ulrich Sigwart. It was first implanted in March 1986 by Jacques Puel (Toulouse, France) in a 63-year-old male suffering from restenosis after balloon angioplasty of the left anterior descending (LAD) artery. The first bailout stenting was performed by Ulrich Sigwart during a live course (Lausanne, Switzerland) in June 1986 in a 50-year-old female suffering from occlusive dissection of the LAD artery after balloon angioplasty (Fig. 32.1). Shortly after these successful procedures, an unanticipated bane of stent implantation emerged: stent thrombosis. To limit this serious complication, aggressive anticoagulant regimens were introduced.

Gianturco-Roubin Stent
The Gianturco-Roubin stent, a balloon-expandable stent, had a coil design manufactured from a single strand of stainless steel wire (4). The stent was approved in the United States in 1993 for the treatment of coronary dissection during balloon angioplasty. Similar to the Wallstent, the Gianturco-Roubin stent had a great degree of flexibility but poor radial strength resulting in increased rates of restenosis and stent thrombosis.

Palmaz-Schatz Stent
In the late 1980s, Julio Palmaz, an Argentine radiologist, designed a vascular stent from a model taken from a piece of lathed metal. Together with Richard Schatz, a cardiologist from San Antonio, Texas, he modified the initial version of this prototype into the first tubular slotted balloon-expandable stent. In October 1987, the first peripheral Palmaz stent was implanted in Freiburg, Germany, and in December of the same year the first Palmaz-Schatz coronary stent was implanted in Sao Paulo, Brazil. The stents were cramped on the coronary angioplasty balloon by the interventional cardiologists, a method which was prone to stent loss.

Drug-Eluting Stents
More recently, drug-eluting stents (DES) have been introduced. DES deliver site-specific, controlled release of therapeutic agents. Heparin has been used as a stent coating in an attempt to reduce the thrombogenic potential and risk of acute/subacute stent thrombosis (8). When used in the setting of acute myocardial infarction (AMI), one study showed a reduced rate of stent thrombosis and recurrent myocardial infarction (MI) at 30 days with a heparin-coated stent (9). However, although heparin has anti-inflammatory effects, no effect was observed on restenosis. Sirolimus-eluting stents (SES) were first implanted in 2001 and subsequently became the first DES that significantly reduced the risk of restenosis inherent with bare-metal stents (BMS). This was followed by paclitaxel-eluting stents (PES), which also consistently reduced the rate of restenosis and the need for repeat revascularization procedures compared with BMS.
TECHNICAL CONSIDERATIONS

Bare-Metal Stents

The key prerequisites for a modern coronary artery stent are:

1. deliverability with favorable flexibility and low profile,
2. radial strength to prevent elastic recoil (usually <4%) and limit foreshortening (usually <3%),
3. sufficient plaque coverage (usually 10–25%) to avoid tissue prolapse, and
4. access to side branches with limited stent deformation when opening struts for stent deployment in bifurcation lesions.

The available stents may vary in their metallic composition, strut design and thickness, delivery system, and coating. These different parameters play an important role in deliverability, visibility, scaffolding performance, and procedural success. Some of the parameters can also influence the occurrence of adverse events during the hospital stay (periprocedural myocardial necrosis, stent thrombosis) and long-term follow-up (restenosis) (10).

The importance of stent design on acute vascular injury and the subsequent proliferative response is well established. In animal models, changes in stent design lead to diverse degrees of vascular injury, thrombosis, and neointimal hyperplasia (11). Furthermore, stents that allow a circular rather than angular vessel lumen lessen neointimal proliferation (12). Figure 32.2 illustrates the impact of stent design on restenosis and stent thrombosis. However, only a few randomized trials have addressed the role of stent design on clinical outcome. Compared with the Palmaz-Schatz stent, the Gianturco-Roubin II stent was shown to be inferior for the prevention of restenosis (13). Several second-generation BMS have been directly compared with the Palmaz-Schatz stent in noncomplex lesions without showing differences in terms of stent thrombosis, restenosis, or major adverse cardiac events (MACE) (14–16).

Metallic Composition

Although nitinol, tantalum, cobalt chromium, and platinum alloys have all been tested in the coronary circulation, 316L stainless steel remains the most frequently used component of coronary stents. Cobalt chromium (L605 CoCr) alloy has become a more recent alternative. L605 CoCr is stronger, more radiopaque, and contains less nickel than 316L stainless steel. Stents manufactured from L605 CoCr feature thinner struts without compromising radial strength or radiographic visibility and provide improved deliverability compared with 316L stainless steel stents.

Strut Design and Thickness

Basic stent characteristics—coil versus slotted tube versus modular, percent metal coverage, number of struts, strut thickness, and strut morphology—are summarized in Figure 32.3. Currently, most stents have a slotted tube design, which can be further categorized into closed-cell and open-cell design. The closed-cell design provides better coverage of the luminal surface and conveys greater radial strength. Cell size is minimally affected with a closed-cell stent design deployed in a tortuous site. However, it is less flexible and may be more difficult to deliver in tortuous and calcified arteries. In addition, side branch access may be more challenging. The open-cell design allows for a greater flexibility of the stent and easier access to side branches. The drawbacks are a weaker radial strength, changes in cell size in tortuous anatomy, and less coverage of the lumen, particularly on the outer curvature of the artery. To further improve flexibility, the number of crowns has been increased accompanied by a decrease in strut length and strut thickness. Finally, the geometry of the cross-section of the strut has been improved and most of the struts are rounded to limit edge dissections and perforation.
Delivery System
Many balloon-expandable and a few self-expanding coronary stents have been developed for clinical use over the past several years. None of the self-expanding stents has found broad application in the coronary circulation.

Surface Coatings
Stent surface material importantly affects neointimal hyperplasia. Various biological inert coatings (barrier coating), such as carbon, gold, platinum, and phosphorylcholine, have been developed to limit both restenosis and the risk of stent
Four components of a drug-eluting coronary stent.

**Covered Stents**

The use of polytetrafluoroethylene-covered stents has been evaluated in saphenous vein graft interventions. The rationale is that a covered stent may be able to entrap friable degenerated material, decrease the probability of distal embolization, and reduce neointimal hyperplasia. However, a randomized trial of 400 patients undergoing PCI of saphenous vein grafts yielded disappointing results, showing no benefit in terms of restenosis or MACE over BMS (22). In the coronary circulation, the use of covered stents is confined to the emergency treatment of coronary perforations and to exclusion of coronary aneurysms (23).

**Drug-Eluting Stents**

Apart from the delivery system and the platform, which are basically the same as for a BMS, DES contain two specific parts: the polymer coating and the drug. The four components of a DES are summarized in Figure 32.4. With respect to drug elution, the geometric configuration of the platform is critical to accommodate the required dose of the agent on the drug-carrying units (the struts) and to allow adequate diffusion to ensure optimal tissue drug levels. Strut-based drug delivery has shown to be highly spacing-dependent. Accordingly, an increased strut number has been associated with higher mean arterial wall drug concentrations, and inhomogeneous strut placement has been shown to significantly affect local concentrations (24).

**Coating**

The stent coating consists of one to three layers (Table 32.1). The most important layer is the polymer, which contains the drug and allows for drug elution into the arterial wall by contact transfer. Supplemental layers are found in most DES and consist of either top coatings to delay drug release (e.g., PBMA) or base coatings to increase polymer adhesion to the stent struts (e.g., Parylene C). Most polymers are durable (nonbioabsorbable), but newer generation stents use bioabsorbable polymer carriers. Coatings are typically sprayed or dip coated.

Polymers have been pivotal for the development of local drug delivery, and in particular DES. Polymeric materials act as a drug reservoir and allow for controlled drug release over time. The drug may be dissolved either in a reservoir surrounded by a polymer film or within a polymeric matrix. Controlled drug release can occur by diffusion, chemical reaction, or solvent activation. Biodegradable polymers allow drug release by both drug diffusion and matrix degradation, whereas nondegradable polymers enable drug release by particle dissolution (25). Early efforts to identify suitable polymers for stent coating were characterized by exuberant inflammatory and thrombotic responses resulting in excessive neointimal hyperplasia and arterial occlusion (26). These adverse effects have been attributed in part to inappropriate polymer degradation and the molecular weight of the compounds. More recently, a wide variety of biocompatible polymers, some of which trigger no or minimal inflammatory response, have been developed as carriers for DES. Furthermore, some stents have only an abluminal polymer coating (asymmetric coating) (Fig. 32.5). In the investigation of new drugs for local delivery, it is therefore mandatory to address not only the drug itself but also the biocompatibility of the polymeric carrier.

**Figure 32.4** Four components of a drug-eluting coronary stent.

**Drug**

The drug aims to limit neointimal proliferation, and the drug’s ideal profile should be characterized by:

1. wide therapeutic window,
2. low inflammatory potential,
3. selectivity for smooth muscle cell proliferation without toxicity to the medial and adventitial cell layers, and
4. promotion of re-endothelialization.

The efficacy of candidate drugs is not only dependent on biological activity in vitro but is also determined by local pharmacokinetics and physicochemical drug properties. Drug distribution is mediated by strut strut configuration and the balance between convective and diffusive forces (24). Hydrophilic drugs such as heparin readily permeate into tissue but are also rapidly cleared. In contrast, lipophilic agents such as paclitaxel or limus analogues are water-insoluble and bind to hydrophobic sites in the arterial wall. Although both hydrophilic and hydrophobic drugs show large spatial concentration gradients in the arterial wall, lipophilic agents distribute better
and more homogenously into the arterial wall than hydrophilic drugs. To date, immunosuppressive (limus family) and anti-proliferative (paclitaxel) drugs are used.

Most DES use drugs that are analogues of sirolimus (limus family). The principal therapeutic agents of the limus family include sirolimus, tacrolimus, zotarolimus, everolimus, biolimus, and myolimus. These agents bind to the intracellular receptor FKBP-12 and inhibit a phosphoinositide 3-kinase mammalian target of rapamycin, thereby reversibly inhibiting the growth factor– and cytokine-stimulated cell proliferation in the G1 phase of the cell cycle (27) (Fig. 32.6). Vascular smooth muscle cells are usually quiescent, proliferate at low indices (<0.05%), and remain in the G0 phase of the cell cycle. However, stimulated by vascular injury or growth factors, vascular smooth muscle cells reenter the cell cycle at G1 and advance into S phase.

**Sirolimus** Sirolimus, a highly lipophilic drug, was the first member of the limus family to be used for prevention of restenosis following PCI. Following experimental studies showing potent suppression of vascular smooth muscle cell proliferation, local delivery of sirolimus from stents also effectively inhibited neointimal proliferation (28). The kinetics of drug release from SES was investigated in vivo and showed that tissue levels were maximal at 14 days and remain substantial up to 28 days.

The FDA-approved sirolimus-eluting Cypher stent (SES) (Cordis Corporation, Warren, New Jersey, U.S.) is based on the BX Velocity stent (Cordis Corporation) made of stainless steel with a strut thickness of 140 μm. Sirolimus is immersed in a 10 to 15 μm thick durable polymer matrix (1:1 mixture of the polymers polyethylenevinylacetate and polybutylmethacrylate) at a 30% drug-to-polymer weight ratio, with a sirolimus concentration of approximately 140 mcg/cm² stent surface area. Drug release occurs by passive diffusion. A slow release formulation has been derived by application of a diffusion barrier topcoat over the basecoat.

The principal studies evaluating SES were the first-in-man studies (29,30) (45 patients with focal lesions), the RAVEL (31) trial (238 patients with single lesion, SES vs. BMS) and the SIRIUS trial (32) (1058 patients, SES vs. BMS). The sirolimus-eluting Cypher stent received CE mark approval in Europe in
April 2002 and was approved by the FDA in the United States in May 2003. In a pooled analysis of individual patient data on 4,958 patients enrolled in 14 randomized trials (mean follow-up ranging between 1 and 5 years) comparing SES with BMS, there was a significant 57% reduction in the combined risk of death, MI, or reintervention in favor of the DES (33). Therapeutic benefit was largely driven by a pronounced reduction in the need for repeat revascularization (Fig. 32.7).

Mural release of sirolimus from the bioresorbable polymer polylactide-co-glycolide embedded in large nondeforming reservoirs (Conor Medsystems, LLC, Menlo Park, California, U.S.) is currently being investigated as a novel DES platform. In vitro drug release mimics the elution curve of the sirolimus-eluting Cypher stent with approximately 80% of drug released during the first month after stent implantation, and preclinical studies indicate that coronary artery tissue levels of sirolimus closely match those achieved with the sirolimus-eluting Cypher stent.

**Everolimus**

Everolimus is a sirolimus derivative, whose binding activity to the FKBP-12 domain is threefold lower and

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**Figure 32.6** Mechanism of action of SES versus PES stents. **Abbreviations**: SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents.

**Figure 32.7** Kaplan–Meier curve showing a pronounced reduction in the need for repeat revascularization with SES versus BMS. **Abbreviations**: SES, sirolimus-eluting stents; BMS, bare-metal stents. **Source**: Adapted from Ref. 54.
immunosuppressive activity in vitro is two- to fivefold lower than sirolimus. Nevertheless, the in vivo efficacy of everolimus is as potent as sirolimus (34) and potentially associated with less inflammation than SES or PES (35).

The FDA-approved everolimus-eluting XIENCE V stent (EES) is based on the Multilink Vision stent (Abbott Laboratories, Abbott Park, California, U.S.), a cobalt chromium stent with a strut thickness of 81 μm. A combination of acrylic and fluoro polymers allow for an everolimus concentration of approximately 100 mcg/cm² stent surface in the absence of a topcoat polymer. The stent is designed to release approximately 80% of the drug within 30 days after implantation. So far the stent platform has been evaluated in the SPIRIT I, II and III trials. SPIRIT I (36) (60 patients) demonstrated the superiority of EES over the otherwise identical BMS with respect to in-stent late loss (0.10 ± 0.21 mm vs. 0.87 ± 0.37 mm, P < 0.001) and repeat interventions (3.8% vs. 17.9%). In both SPIRIT II (37) and III (38) (300 and 1002 patients, respectively), EES proved not only noninferior but superior to PES regarding in-stent late loss (SPIRIT II: 0.11 ± 0.27 mm vs. 0.36 ± 0.39 mm; P < 0.001, SPIRIT II: 0.16 ± 0.41 mm vs. 0.30 ± 0.53 mm; P = 0.002). Binary restenosis tended to be lower in EES- than PES-treated patients in each trial, a difference which became significant in a pooled analysis of both studies (in-stent restenosis EES 1.9%, PES 4.9%, P_{superiority} = 0.02; in-segment restenosis EES 4.1%, PES 7.8%, P_{superiority} = 0.039). Finally, MACE was significantly reduced in favor of EES in SPIRIT III (4.6% vs. 8.1%; RR = 0.56; 95% CI, 0.34–0.94; P = 0.03). Of note, the rate of MI tended to be lower with EES than PES at 30 days, presumably related to fewer side branch occlusions (EES 1.0% vs. PES 2.7%; HR = 0.38; 95% CI, 0.14–1.02; P = 0.06).

Zotarolimus Zotarolimus is an equipotent analogue of sirolimus in vitro and in vivo. Two stents eluting zotarolimus are currently available. Both stents are based on the Driver stent platform (Medtronic, Inc., Minneapolis, Minnesota, U.S.) with a strut thickness of 91 μm, made of cobalt chromium alloy, and have coatings with both hydrophilic and hydrophobic moieties.

The FDA-approved zotarolimus-eluting Endeavor stent (ZES) has a 5-μm thick phosphorylcholine layer with a zotarolimus concentration of approximately 1.6 mcg/mm² stent surface area. In contrast to the sirolimus-eluting Cypher stent, which elutes approximately 80% of its drug during the first 30 days, the Endeavor stent releases the same proportion of zotarolimus within 10 days only. This stent platform has been evaluated in the ENDEAVOR I (39), II (40), III (41), and IV (42) trials.

The ENDEAVOR I trial (39) (100 patients) was a non-randomized, single-arm study and showed an in-stent late loss of 0.33 ± 0.26 mm at four months and of 0.61 ± 0.44 mm at 12 months. In the ENDEAVOR II trial (40) (1197 patients), ZES proved superior to the otherwise identical BMS regarding the primary endpoint of target vessel failure (7.9% vs. 15.1%; P < 0.001) as well as in-stent late loss (0.61 ± 0.46 mm vs. 1.03 ± 0.58 mm; P < 0.001) and in-segment binary restenosis (13.2% vs. 35%; P < 0.001). ENDEAVOR III (41) compared ZES with SES. ZES was found inferior regarding late loss (in-stent: ZES 0.60 ± 0.48 mm; SES: 0.15 ± 0.34 mm, P < 0.001) and binary restenosis, but superior regarding late acquired stent malapposition (ZES 0.5% vs. SES 5.9%; P = 0.02) and rate of MI (SES 3.5% vs. ZES 0.6%; RR = 0.18; 95% CI, 0.03–0.46; P = 0.04). There were no significant differences in rates of death, cardiac death, stent thrombosis, repeat revascularization, MACE, or target vessel failure. ENDEAVOR IV (42) compared ZES with SES in 1548 patients. ZES did not achieve the prespecified secondary endpoint, in-segment late loss (ZES 0.36 ± 0.47 mm vs. PES 0.23 ± 0.45 mm; P = 0.023). Similarly, in-stent late loss was significantly higher with ZES (0.67 ± 0.49 mm) than PES (0.42 ± 0.50 mm; P < 0.001) with a nonsignificant trend in in-stent binary restenosis (ZES 13.3%; SES: 6.7%; P < 0.08). ZES achieved its primary endpoint of noninferiority regarding target vessel failure at nine months (ZES 6.6% vs. PES 7.2%; P = 0.685). Although the rate of MI was lower at 30 days (ZES 0.8% vs. PES 2.3%; P = 0.02), largely related to fewer side branch occlusions, there were no significant differences in rates of death, cardiac death, or MI at 9 and 12 months (43). Stent thrombosis occurred in 0.8% of ZES-treated and 0.1% of PES-treated patients.

The CE-approved zotarolimus-eluting Endeavor Resolute stent (Medtronic Vascular, Santa Rosa, California, U.S.) is a modified stent platform, which uses the Biolinx™ polymer system for release of zotarolimus from the Driver stent surface. Biolinx consists of three polymers, a hydrophilic C19 polymer (a mixture of hydrophobic hexyl methacrylate and hydrophilic vinyl pyrrolidinone and vinyl acetate), water soluble polypyrrolidinone, and a hydrophobic C10 polymer (hydrophobic butyl methacrylate to provide adequate lipophilicity for zotarolimus) and allows for a more delayed release of the same zotarolimus concentration as on the original Endeavor Sprint stent (1.6 mcg/mm² stent surface area) with approximately 50% of drug released during the first 7 days, and 85% of drug released at 60 days after stent implantation. In vitro assays showed low levels of monocyte adhesion, inflammatory reaction, and tissue factor expression suggesting a high degree of biocompatibility comparable to the original Endeavor platform (44).

The RESOLUTE FM trial (45) (139 patients) showed an in-stent late loss of 0.22 ± 0.27 mm and in-segment binary restenosis of 2.1% at nine months. Intravascular ultrasound (IVUS) follow-up at nine months revealed a percent volume obstruction of 3.7 ± 4.0% and late acquired stent malapposition in 6.8% of cases. At 12 months, the rate of target lesion revascularization (TLR) was 0.8% and target vessel failure 7.0%. This platform is currently being compared against the EES in a large-scale clinical trial (RESOLUTE III).

Biolimus-A9 Biolimus-A9 is a highly lipophilic, semi-synthetic sirolimus analogue. The drug is immersed at a concentration of 15.6 mcg/cm² into a biodegradable polymer, polylactic acid, which is applied solely to the abluminal surface of a flexible stainless steel stent. On the basis of in vivo studies, polylactic acid is fully converted to lactic acid at six months and the polymer is resorbed within nine months.

The device utilized for the clinical evaluation of the biolimus-A9-eluting stent (BES; Biosensors International Group, Ltd., Newport Beach, California, U.S.) is the S-stent, which features a strut thickness of 112 μm and is made of laser-cut stainless steel (46). Whereas the BioMatrix I and II platforms share a parylene primer on the stent surface to allow for binding of the biodegradable polymer-drug layer to the stent surface, the more recent BioMatrix III platform is free of the parylene primer. Since the drug is co-released from the biodegradable polylactic acid polymer by means of hydrolysis, a lower proportion of biolimus-A9 (50%) is released at 30 days compared with the sirolimus-eluting Cypher stent, followed by complete drug release at approximately 180 days.

The STEALTH I trial (120 patients, 2:1 randomization) demonstrated the superiority of the biolimus-A9-eluting BioMatrix I stent over the otherwise identical BMS with respect to in-stent late loss (0.26 vs. 0.74; P < 0.001) and in-stent
restenosis (3.9% vs. 7.7%, respectively; \( P = NS \)) (47). BES was compared with SES in a large-scale randomized trial (LEADER-S) with a primary clinical endpoint in 1707 patients with 2472 lesions when used in routine clinical practice. The primary endpoint, a composite of cardiac death, MI, or clinically indicated target vessel revascularization (TVR) within nine months, occurred in 9.2% of patients treated with BES and 10.5% of patients treated with SES, thus establishing noninferiority \( (P_{\text{noninferiority}} = 0.003; \text{RR} = 0.88; 95\% \text{ CI}, 0.64–1.19; P_{\text{superiority}} = 0.39) \). Rates of cardiac death (1.6% vs. 2.5%; \( P = 0.22 \)), MI (5.7% vs. 4.6%; \( P = 0.30 \)), and clinically indicated TVR (4.4% vs. 5.5%; \( P = 0.29 \)) were similar for both stent types. BES were also noninferior to SES in in-stent percent diameter stenosis (20.9% vs. 23.3%; \( P_{\text{noninferiority}} = 0.001; P_{\text{superiority}} = 0.26 \)), the principal angiographic endpoint of the study (48).

A BES using the NOBORI stent platform has been directly compared against SES in two studies, NOBORI I phase 1 (85 patients, \( 2:1 \) randomization) and phase 2 (243 patients, 153 BES, 90 SES) (49,50). Both studies found BES to be noninferior and superior to SES regarding in-stent late loss (phase 1: 0.15 ± 0.27 mm vs. 0.32 ± 0.33 mm; \( P_{\text{superiority}} = 0.006 \)), neointimal volume assessed by IVUS (phase 1: 3.8 ± 10.9 mm\(^3\) vs. 14.6 ± 15.0 mm\(^3\); \( P = 0.006 \)) (49), and binary restenosis (phase 2: BES 0.7% vs. SES 5.4%; \( P = 0.049 \)). When compared with SES, the biolimus-eluting NOBORI stent (54 patients) was similar at nine months for the primary endpoint of in-stent late loss (BES 0.10 ± 0.26 mm vs. SES 0.13 ± 0.44 mm; \( P = 0.66 \)) and in-segment restenosis (BES 3.3% vs. SES 6.3%; \( P = 0.65 \)) (50). Moreover, the same investigators assessed endothelium-dependent coronary vasomotion proximal and distal to the implanted stents using right atrial pacing at increasing heart rates. While SES showed significant vasoconstriction both proximal (2.3 ± 10%) and distal (5.4 ± 9%) to the stented segment, BES showed more physiological vasodilatation proximal (7.9 ± 10%) and distal (6.1 ± 8.0%) to the stented segment comparable with BMS (51).

**Paclitaxel**

Paclitaxel stabilizes polymerized microtubules and enhances microtubule assembly, forming numerous unorganized and decentralized microtubules inside the cytoplasm. As a result, cell replication is inhibited and this effect is seen predominantly in the G0/G1 and G2/M phases of the cell cycle. Paclitaxel was shown to effectively inhibit vascular smooth muscle cell migration and proliferation (52). In addition, it has several favorable characteristics for stent-based local drug delivery, such as a high degree of lipophilicity and a long-lasting antiproliferative effect following a single-dose application at low concentrations. In the porcine restenosis model, implantation of stents dip-coated with paclitaxel at increasing doses resulted in a dose-dependent inhibition of neointimal formation at 28 days. However, the beneficial effects of paclitaxel on neointimal formation were complicated by local cytotoxic effects manifested as a decrease in medial wall thickness, focal neointimal and medial wall hemorrhage, and cell necrosis (53).

The FDA-approved device currently used for stent-based paclitaxel delivery is the Express stent (Boston Scientific Corporation, Natick, Massachusetts, U.S.) made of stainless steel with a strut thickness of 132 μm. Paclitaxel is immersed into a nonbiodegradable polymer matrix to control release of the drug (Fig. 32.6). Most studies have been performed with a slow-release formulation, from which paclitaxel at a dose density of 1 mcg/mm\(^2\) is released with an initial burst phase over 2 days, followed by a slow release of paclitaxel for 10 days. Of note, more than 90% of the drug remains sequestered in the polymer indefinitely. This paclitaxel-eluting Taxus stent platform gained FDA approval in 2004. It has undergone extensive clinical investigation and proved highly effective at reducing the risk of angiographic restenosis by approximately 75% and the risk of TLR by approximately 60% compared with BMS across nearly all studied lesion and patient subsets (54).

In contrast to the TAXUS experience, nonpolymeric release of paclitaxel from the V-Flex stent (Cook, Inc., Bloomington, Indiana, U.S.) failed to prove superiority over BMS. Paclitaxel embedded into the bioreosorbable polyactide-co-glycolide and eluted from large reservoirs (COSTAR stent platform, Conor Medsystems) appeared promising in the 1 mcg/30 day abluminal release formulation. However, results of the randomized COSTAR II trial (1700 patients) comparing the paclitaxel-eluting COSTAR stent with the paclitaxel-eluting TAXUS stent showed significantly higher in-stent late loss (COSTAR 0.64 mm vs. TAXUS 0.26 mm; \( P < 0.0001 \)) and in-segment restenosis (18.7% vs. 6.7%; \( P = 0.0007 \)). At eight months and prior to angiography, the clinical outcome with COSTAR was inferior to TAXUS for MACE (11.0% vs. 6.9%; \( P = 0.005 \)) and clinically driven TVR (8.1% vs. 4.3%), leading to the withdrawal of the device for commercial use (55). Of note, following burst release of 1 mcg of paclitaxel, only very little drug was released during the first 60 days, whereas the bulk of paclitaxel (80%) was released thereafter. It has been suggested that drug release was insufficient during the early period after arterial injury at the time of maximal smooth muscle cell replication, which underlines the importance of dose and timing of drug release for effective reduction of restenosis.

The principal studies evaluating the clinical use of PES are TAXUS I (61 patients, simple lesions, SES vs. BMS) (56), TAXUS II (538 patients, simple lesions, slow- or moderate-release SES vs. BMS) (57), TAXUS IV (1314 patients, complex lesions, SES vs. BMS) (58), TAXUS V (1156 patients, complex lesions, SES vs. BMS) (59), and TAXUS VI (448 patients, long lesions, SES vs. BMS) (60). In the pooled analysis of these randomized trials including 3513 patients, patients randomized to PES had significantly lower rates of TLR (HR = 0.46; \( P < 0.001 \)) and TVR (HR = 0.62; \( P < 0.001 \)), while no difference was observed with respect to death or MI compared with BMS (Fig. 32.8) (54).

Two dedicated TAXUS studies focused on in-stent restenosis following BMS implantation. Patients were randomly assigned to undergo angioplasty followed by brachytherapy or PES implantation. The results of both TAXUS III (28 patients) (61) and TAXUS V–ISR trials (396 patients) (62) were favorable for PES. For instance, in TAXUS V–ISR, the cumulative MACE rate was higher in patients treated with brachytherapy compared with PES (20.1% vs. 11.5%; \( P = 0.02 \)).

**Drugs and Stents Under Investigation**

Several other antiproliferative drugs (i.e., novolimus, myolimus) are under investigation, and aim to widen the therapeutic window and increase the safety profile while lowering the dose. Some investigators advocate combination therapy of two or more different drugs. Moreover, polymer-free DES platforms are under evaluation. These stents (Translumina porous stent, BioMatrix Freedom, MIV three core technology) use surface porosity rather than polymers as the drug reservoir.

In parallel, various biodegradable stents are under scrutiny. The concept of biodegradable stents as a temporary scaffolding and drug delivery unit during the vascular healing process following stenting is particularly appealing and several polymers have been tested for this purpose. An important
limitation in the past has been the polymer-mediated occurrence of severe local inflammation (26). A magnesium alloy-based stent has undergone clinical evaluation, but results were disappointing due to early recoil as well as restenosis. A more promising concept is the biodegradable BVS stent platform introduced by Abbott. It consists of a crystalline poly-L-lactide backbone on top of which everolimus is applied in a form of poly-L-lactide acid. Although the initial version also showed some recoil, a revised platform has been shown to provide satisfactory long-term patency in porcine coronary arteries with little inflammation (63), and no early stent recoil or thrombosis in the first human trial (64).

Finally, an alternative to current DES is a stent surface modification that facilitates cell growth and limits neointimal proliferation. One such platform is the Genous bioengineered stent, with iridium oxide coating, EPC capture technology, nano-textured surfaces, or cell-specific peptide linkers (Affinergy, Inc., Durham, North Carolina, U.S.).

**BASIC CONSIDERATIONS**

**Benefits of Bare-Metal Stents**

Routine implantation of BMS has virtually abolished the risk of abrupt closure and emergency CABG. Moreover, BMS moderately lower the rates of restenosis (4–6,65–67).

The STRESS (6) and the BENESTENT (5) trials compared elective stenting with angioplasty alone in native coronary arteries with short (<15 mm in length) de novo lesions and showed a 25% to 30% reduction in restenosis rate. Subsequent stent trials confirmed reduced rates of restenosis and TLR.

**Clinical Importance of Restenosis**

The clinical consequences of restenosis depend on the degree of restenosis, area at risk subtended by the restenosed target lesion, amount of recruitable collaterals, and lesion location. Restenosis impacts clinical outcome in several ways. First, repeat revascularization procedures influence patients’ quality of life and well being. In the Optimal Angioplasty versus Primary Stenting (OPUS) I trial, a randomized comparison of routine and provisional BMS implantation that prospectively assessed quality-of-life parameters, patients without restenosis had less frequent angina (17% vs. 22%; \( P = 0.03 \)), fewer limitations in physical activities (21% vs. 27%; \( P < 0.004 \)), and better quality of life (25% vs. 21%; \( P = 0.003 \)) (68). Secondly, restenosis is associated with a low risk of MI. Thus, several studies reported a 2% to 19% rate of restenosis-related MI (69–71). In addition, the treatment of restenosis itself also is associated with a small but finite procedural risk of mortality or MI (72). Finally, some observational studies suggest a potential negative impact of restenosis on prognosis. The outcome of 3363 patients treated with balloon angioplasty and repeat angiography was analyzed according to the presence (1570 patients) or absence (1793 patients) of restenosis (73). Although survival at six years was similar in both groups (95% vs. 93%; \( P = 0.16 \)), patients with restenosis had an increased rate of MI (15% vs. 12%; \( P = 0.0001 \)). A study of 603 patients with diabetes who underwent balloon angioplasty observed a higher 10-year mortality in patients with restenosis (24% without restenosis, 35% with nonocclusive restenosis, and 59% with occlusive restenosis). Notably, occlusive restenosis was an independent predictor of mortality in multivariable analysis (74). Another series of 2272 consecutive patients treated with BMS between 1992 and 1996 reported a mortality rate of 6.0% at four years in patients without and 8.8% in patients with restenosis (\( P = 0.02 \)) (75). Multivariable analysis identified restenosis and age as the only independent predictors of mortality. These studies are limited because of their retrospective design, small sample size, lack of predefined outcome variables, and potential ascertainment bias. An association of restenosis with prognosis has not been observed in prospective randomized clinical trials.

**Benefits of Drug-Eluting Stents**

Numerous randomized clinical trials and meta-analysis attest that DES reduce rates of restenosis and repeat TLR by 40% to 70% compared with BMS (31,59,76–78). In a collaborative network meta-analysis of 38 randomized trials involving 18,023 patients, the rate of TLR was reduced by 70% with SES and by 58% with PES compared with BMS at four years (Fig. 32.9) (79). For the comparison of SES versus BMS, this benefit translated into a need to treat seven patients to prevent one revascularization event; for PES versus BMS the number needed to treat was eight patients. Although the greatest benefits of DES over BMS regarding TLR reduction are seen during the first year.
after implantation, all long-term analyses indicate that the benefit is sustained at four years.

The data of randomized trials were corroborated in large-scale registries comparing BMS and DES without protocol-mandated angiographic follow-up. TVR amounted to 7.4% for DES and 10.7% for BMS ($P < 0.0001$) at two years in a propensity score matched study from Ontario (80), and to 4.0% and 7.5%, respectively ($P < 0.001$), at three-year follow-up in the one-stent cohort of the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) (81). In the Western Denmark Heart Registry, rates of TVR at 15 months were 4.6% and 7.1%, respectively (adjusted RR $= 0.57$; 95% CI, 0.48–0.67; $P < 0.001$) (82).

**Risks of Drug-Eluting Stents**

DES delay healing and impair endothelialization as documented in necropsy studies (83,84) and clinical investigations (85-87). IVUS studies show a higher incidence of incomplete stent apposition with DES than BMS, and evidence of vessel remodeling following DES implantation is evident in patients with very late stent thrombosis (88-90). In addition, the drugs released from the polymer might have thrombogenic effects themselves; paclitaxel and sirolimus enhance endothelial tissue factor expression, the principal activator of the coagulation cascade that activates factors IX and X (91,92). DES could therefore predispose to thrombotic stent occlusion.

**Early and Late Stent Thrombosis**

Definitions of early, late, and very late stent thrombosis are summarized in Figure 32.10. A meta-analysis of six studies comparing SES with BMS in 2963 patients and of five trials comparing PES with BMS in 3513 patients demonstrated similar rates of early stent thrombosis for both types of DES and BMS (0.5–0.6%). The same holds true for late stent thrombosis: a meta-analysis of 5023 patients showed no difference in the incidence of late stent thrombosis between DES and BMS (0.2% vs. 0.3%; $P = 1.00$) (93). A network meta-analysis of 18,023 patients also showed no difference in the rate of early and late stent thrombosis between SES, PES, and BMS (79), although the average length of dual antiplatelet therapy was longer in patients treated with DES than BMS.

**Very Late Stent Thrombosis**

Conversely, case reports, observational studies, extended follow-up of trials comparing DES with BMS, and meta-analysis of randomized trials indicate that very late stent thrombosis is more common with DES than BMS. Pooled analysis of four randomized trials (1748 patients) comparing SES and BMS and of five randomized trials (3513 patients) comparing PES with BMS revealed significantly higher rates of very late stent thrombosis with DES (0.6% SES vs. 0% BMS, $P = 0.03$; 0.7% PES vs. 0.2% BMS, $P = 0.03$) (54). Similarly, a systematic review of 14 trials comparing SES with BMS revealed that very late stent thrombosis was more frequent with SES (0.3% vs. 0.04%; $P = 0.02$) (33).

It should be noted, however, that these analyses were based on primary stent thrombosis events (without intercurrent revascularization). Secondary stent thrombosis events following intercurrent revascularization procedures were censored and, therefore, could have disadvantaged devices with low reintervention rates (DES) compared with high reintervention rates (BMS). One study reanalyzed stent thrombosis events according to each of the newly proposed Academic Research Consortium (ARC) categories. The overall incidence of stent thrombosis did not differ between DES and BMS, and differences in the incidence of very late stent thrombosis diminished...
resulting from more events following intercurrent revascularization in the BMS group (94).

**Net Safety Outcome of Drug-Eluting Stents**

In balancing the risks and benefits of DES compared with BMS from a patient’s perspective, the assessment of safety endpoints such as overall mortality and MI are most important. The safety of DES compared with BMS has been analyzed in several observational studies and meta-analysis of randomized controlled trials. It must be noted, however, that observational studies cannot reliably determine small-to-moderate risks or benefits of a therapeutic intervention (95). Factors associated with the selection of stent type and confounded by indication are uncontrollable. In light of these limitations, the results of registries do not provide a definitive answer and should be interpreted with caution.

Stone and colleagues observed no difference between PES and BMS regarding death (6.1% vs. 6.6%; \( P = 0.68 \)) and MI (7.0% vs. 6.3%; \( P = 0.66 \)) at four years in a patient-level meta-analysis of five trials comprising 3513 patients (54). Similarly, Kastrati and colleagues observed similar rates of death (6.0% vs. 5.9%) and death or MI (9.7% vs. 10.2%) for SES and BMS in a meta-analysis of 14 trials with 4958 patients at five-year follow-up (33). In addition, a collaborative network meta-analysis of 38 randomized trials involving 18,023 patients compared first-generation DES with BMS showed similar rates of death and cardiac death at four-year follow-up (79). The apparent paradox between increased rates of very late stent thrombosis and lack of increased rates of mortality and MI with first-generation DES has been explained by the very low incidence of stent thrombosis, the offsetting effect of reduced rates of restenosis and increased rates of stent thrombosis, and the potential of secondary stent thrombosis following intercurrent revascularization for BMS restenosis.

INDICATIONS

**Bare-Metal Stents**

*Treatment of Abrupt or Threatened Closure After Balloon Angioplasty*

Coronary stents effectively scaffold coronary dissections complicating balloon angioplasty, and the availability of stents has nearly eliminated the need for emergency CABG (<1% of all PCI procedures). The initial approval of coronary stents for this “bailout” indication was based on a multicenter registry of patients with angioplasty complications who were treated with the Gianturco-Roubin II stent (4).

*Reduction of Restenosis and the Need of Repeat Revascularization Procedures*

Randomized clinical trials have shown that coronary artery stent implantation in de novo lesions of native coronary arteries with a diameter \( >3.0 \) mm improves short- and long-term outcomes compared with balloon angioplasty. The principal studies in support of these findings are the STRESS (6) (410 patients; restenosis, stent vs. balloon angioplasty: 32% vs. 42%; \( P = 0.046 \)), BENESTENT (5) (520 patients; 22% vs. 33%; \( P = 0.02 \)), BENESTENT II (8) (827 patients; heparin-eluting stent vs. balloon angioplasty: 16% vs. 33%; \( P = 0.0008 \)), LAD stenting versus angioplasty (96) (120 patients with isolated stenosis of the proximal LAD; 19 vs. 40%; \( P = 0.02 \)), and START (97) (452 patients; 22% vs. 37%; \( P < 0.002 \)) trials. The REST (98) trial was a randomized study of 383 patients with prior restenosis after angioplasty who were assigned to Palmaz-Schatz stent implantation or repeat angioplasty. Angiographic restenosis was lower among stent-treated patients (18% vs. 32%).

*Stenting in Selected Subsets of Patients/Procedures*

**Saphenous vein grafts** Two studies (SAVED (99), 220 patients; VENESTENT (100), 150 patients) randomly assigned patients with de novo stenosis in saphenous vein grafts to
treatment with Palmaz-Schatz stent implantation or balloon angioplasty. In both studies, restenosis was not different between patients treated with BMS and balloon angioplasty (SAVED: 37% vs. 46%; VENESTENT: 19% vs. 36%), while the incidence of MACE was lower at 6 and 12 months in the BMS group.

**Total coronary occlusions** Three studies [SICCO (101), 119 patients; TOSCA (102), 410 patients; GISSOC (103), 110 patients] compared the outcome of patients treated with angioplasty alone or implantation of a Palmaz-Schatz stent (TOSCA: heparin-eluting). In the SICCO study, 119 patients with successful recanalization followed by angioplasty of a chronic total occlusion were assigned to no further intervention or to Palmaz-Schatz stent placement. Stent implantation was associated with a 30% to 50% lower incidence of restenosis in all studies.

**ST-elevation myocardial infarction** The CADILLAC (104) trial evaluated the use of abciximab and stents in a 2 x 2 factorial design in 2082 patients with ST-elevation myocardial infarction (STEMI). At six months, angiographic restenosis occurred in 41% treated with angioplasty compared with 22% of those undergoing stent implantation (P < 0.001). The PAMI stent (105) trial randomly assigned 900 STEMI patients to treatment with balloon angioplasty or implantation of a Palmaz-Schatz heparin-coated stent. After six months, angiographic restenosis was less frequent among patients treated with BMS than balloon angioplasty (20% vs. 33%; P < 0.001). In the FRESCO (106) trial, 150 STEMI patients who underwent successful balloon angioplasty were randomly assigned to stent implantation or no further intervention. At six months, the incidence of restenosis or reocclusion was 17% in the stent group compared with 43% in the angioplasty group (P = 0.001).

**Drug-Eluting Stents**
The therapeutic benefit of DES is largely related to the powerful inhibition of neointimal hyperplasia, which is particularly important in patients suffering from diabetes mellitus or in smaller vessels less able to accommodate neointimal tissue.

**Patients with Diabetes**
PCI in patients with diabetes is associated with an increased risk of restenosis, repeat revascularization procedures, stent thrombosis, and mortality. Although a recent meta-analysis of four trials suggested that SES conferred an increased risk of death in patients with diabetes compared with BMS (107), this finding was not confirmed in a larger analysis of 14 trials (33). Results from a 30-trial network meta-analysis of 3762 patients with diabetes failed to show any difference regarding the combined endpoint of death or MI between DES and BMS (79). In an updated analysis focusing on diabetic patients, the risk of TLR was reduced by 62% with PES and 71% with SES compared with BMS, a benefit similar to that observed with nondiabetic patients. In 3751 pairs of patients treated with either DES or BMS in the Ontario study, TVR was significantly reduced with DES in all subsets of individuals with diabetes, with the exception of those with large vessels (>3 mm) and short lesions (<20 mm) (80). As a result of the higher baseline risk of restenosis, the absolute reduction in repeat revascularization is more pronounced in diabetic than nondiabetic populations, and DES should be recommended in this patient subgroup.

**Small Vessels, Long Lesions**
A small, randomized trial (300 patients) comparing SES with thin-strut BMS showed significantly lower angiographic restenosis (8.3% vs. 25.5%; RR = 0.33; 95% CI, 0.19-0.56; P < 0.001) and TVR (7.2% vs. 18.8%; RR = 0.38; 95% CI, 0.22-0.66; P < 0.001) with SES (52). The benefit was, however, largely restricted to patients with small-vessel disease (reference vessel diameter <2.8 mm; restenosis 7.0% SES vs. 34.2% BMS; P < 0.001). In contrast, binary restenosis was similar in arteries with a reference diameter of 2.8 mm or more (mean RVD 3.1 mm; 10% SES vs. 13% BMS; P = 0.52) (108). Another randomized trial comparing newer generation DES with BMS in 826 patients without routine angiographic follow-up observed lower rates of TVR at 18 months (7.5% vs. 11.6%; P = 0.05). A stratified subgroup analysis of this trial indicated that the benefit was limited to patients who received at least one small stent (<3.0 mm diameter; TVR HR 0.44 in favor of DES; P = 0.02), whereas no difference was observed in patients who received only large stents (≥3 mm) (109). The Ontario propensity score matched comparison of DES and BMS showed that DES were particularly beneficial in patients with small vessels (<3 mm) and long lesions (>20 mm) (80). The number needed to treat in patients with small vessels ranged from 0 to 12 in patients with diabetes to 27 to 83 in nondiabetic patients. Similarly, the number needed to treat in patients with long lesions ranged from 10 to 23 in patients with diabetes, to 27 to 53 in nondiabetic patients. Accordingly, DES seem particularly useful in arteries with a reference diameter ≤3 mm and long lesions, whereas BMS remain a valuable alternative for larger arteries with discrete lesions.

**CLINICAL ASPECTS**

**Procedure-Related Factors**
Better angiographic results correlate with improved clinical outcome. Uncovered dissections and intramural hematomas are associated with abrupt closure. Stent underexpansion is associated with both restenosis and stent thrombosis after BMS and DES implantation. Therefore, an adequate minimal luminal diameter following stent implantation should be reached. Along with improvements in stent design, observations made by IVUS led to changes in deployment strategy, emphasizing the importance of complete apposition of stent struts to the arterial wall. However, routine use of IVUS to guide stent implantation has not been shown to improve clinical outcomes. A minimal stent area of >5 mm² is usually considered satisfactory. Avoidance of long stented segments and stent overlap should be considered. For bifurcation lesions, the strategy of provisional side branch stenting is preferred, and techniques using two stents with excessive stent overlap like the “crush” or “culotte” techniques should be avoided (110,111).

**Antiplatelet Therapy**
An important prerequisite for the widespread use of coronary artery stents was the modification of the antithrombotic regimen, replacing the combination of aspirin and warfarin with dual antiplatelet therapy consisting of aspirin and a thienopyridine. In conjunction with improved deployment techniques, dual antiplatelet therapy has led to a significant reduction of acute and subacute stent thrombosis from 3% to 5% to currently <1% in elective patients. Most of the BMS studies used a two-to four-week regimen of thienopyridine therapy. However, prolonged use of thienopyridine (9–12 months) therapy had been shown beneficial in patients undergoing PCI with BMS (CREDO study) (112) as well as in patients with acute coronary syndromes.
In patients treated with DES, most studies with SES used a two- to three-month regimen, whereas studies with PES prescribed a six-month regimen of thienopyridine therapy. However, the optimal duration of dual antiplatelet therapy following DES implantation is not well established. The BASKET-LATE study observed more ischemic adverse events in DES-treated than in BMS-treated patients during the observation period between months 7 and 18, when clopidogrel treatment had been discontinued (113). The impact of thienopyridine treatment on long-term outcome following DES implantation has been examined in a single-center observational study of 4666 patients (3165 BMS patients, 1501 DES patients) (114). Using landmark analyses of patients event-free at 6 and 12 months, the investigators assessed the risk of death and MI at two years stratified according to stent type and self-reported thienopyridine intake. Although thienopyridine use offered no advantage in patients treated with BMS who were event-free at six months, it was a significant predictor of lower adjusted mortality (2.0% with thienopyridine therapy vs. 5.3% without; \( P = 0.03 \)), and death or MI (3.1% vs. 7.2%, respectively; \( P = 0.02 \)) in patients treated with DES. More recently, Airoldi and colleagues investigated the impact of thienopyridine discontinuation on the risk of stent thrombosis following DES implantation at various time points (115). Discontinuation of the thienopyridine within the first six months of DES implantation conferred an increased risk of stent thrombosis (HR = 13.7; 95% CI, 4.0–47; \( P < 0.001 \)); however, beyond six months the increased risk was no longer apparent (HR = 0.94; 95% CI, 0.30–3.0; \( P = 0.92 \)). Of note, 23% of patients with late stent thrombosis in a large, two-center cohort were on dual antiplatelet therapy, indicating that prolonged therapy may not be a panacea for late stent thrombosis (116).

Newer antiplatelet agents such as the thienopyridine prasugrel might have a beneficial effect in further reducing early stent thrombosis by means of a more rapid and consistent inhibition of platelet aggregation. The incidence of stent thrombosis was more than halved in the TRITON-TIMI 38 study comparing prasugrel and clopidogrel, with most of the benefit emerging during the early period after stent implantation (stent thrombosis with prasugrel 1.1% vs. clopidogrel 2.4% \( \text{HR} = 0.48 \); 95% CI, 0.36–0.64; \( P < 0.001 \)) (117). With the currently available evidence, it seems reasonable to maintain dual antiplatelet therapy for a duration of 6 to 12 months or even indefinitely in patients treated with first-generation DES if they are at low risk of bleeding. The adherence to a 12-month regimen of dual antiplatelet therapy after DES implantation has been endorsed by a recent science advisory report (118) as well as by a clinical alert issued by the Society of Cardiac Angiography and Interventions DES Task Force (119).

**LIMITATIONS AND CONTRAINDICATIONS**

**Patient-Related Restrictions**

The indication for stent implantation versus an alternative treatment should be carefully weighed against the risk of bleeding and thrombosis in any patient. Of special interest are patients at increased risk of bleeding, those scheduled for elective major surgery, patients with gastrointestinal disorders preventing full absorption of thienopyridines, and those requiring oral anticoagulation due to atrial fibrillation, pulmonary embolism, left ventricular aneurysms, or prosthetic heart valves. In these patients, when a coronary stent is mandatory, BMS should be preferred. Furthermore, DES are contraindicated in individuals with unexplained thrombocytopenia or established allergy to thienopyridines, and all those in whom compliance with extended dual antiplatelet therapy cannot be ensured.

**Lesion-Related Restrictions**

Severe calcification preventing sufficient stent expansion should be considered as a relative contraindication to stenting. Several studies have identified acute coronary syndrome at the time of DES implantation as a predictor of stent thrombosis (116,120). Potential explanations for this observation include the large thrombus burden encountered during PCI for STEMI, which seems to predispose to early and late stent thrombosis (121). IVUS studies revealed a high incidence of incomplete stent apposition in patients with very late stent thrombosis, which could be related to thrombus resolution or positive arterial remodeling in patients with STEMI (88). Although a recent meta-analysis found DES to reduce TVR without excess risk when implanted in the setting of STEMI compared with BMS (122), the clinical outcome of DES in this setting requires further study.

**SPECIAL ISSUES**

**Noncardiac Surgery After Drug-Eluting Stent Implantation**

Surgery poses a risk to patients with coronary artery disease, particularly those after stent implantation due to antiplatelet therapy withdrawal, increased platelet aggregation (123), and decreased fibrinolysis during the perioperative period. A recent study of 103 stent patients undergoing noncardiac surgery found a 5% mortality and 45% complication rate (124). It is, therefore, essential to determine whether the procedure can be postponed by 1 to 3 months after BMS and 12 months after DES implantation, and whether dual antiplatelet therapy can be maintained throughout the perioperative period. If the risk of bleeding is judged unacceptably high, clopidogrel should be discontinued no longer than 5 days before the procedure and resumed within 48 hours; aspirin (80–100 mg daily) should not be interrupted (125). Whether the addition of heparin (unfractionated or low molecular weight) or glycoprotein IIb/IIIa inhibitors is useful for prevention of ischemic events in the perioperative period is not known.

**CONCLUSIONS**

The introduction of coronary stenting successfully addressed the risk of abrupt closure after PCI. Moreover, systematic stent implantation has importantly reduced the risk of restenosis and therefore the need of repeat revascularizations compared with balloon angioplasty. More recently, the introduction of DES has further decreased the risk of restenosis. This benefit appears particularly pronounced in patients at increased risk of restenosis such as diabetic patients and those with small vessels and long lesions. While early and late stent thrombosis occur with similar frequency with DES and BMS, very late stent thrombosis is more frequently encountered following DES implantation, potentially related to delayed healing and re-endothelialization. Notwithstanding, long-term follow-up to four years indicates no difference between DES and BMS regarding overall mortality, and the combined endpoint of death or MI. The increased risk of very late stent thrombosis with DES may be too small to have a measurable impact on clinical outcome, may be offset partly by the reduction in repeat revascularizations, and be...
balanced by secondary stent thrombosis events following intercurrent revascularization of BMS.

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Primary PCI in ST elevation myocardial infarction

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INTRODUCTION
Perspectives
Every year, millions of individuals throughout the world sustain an acute myocardial infarction (AMI). The vast majority of these events are initiated by disruption or erosion of the thin fibrous cap of a vulnerable atherosclerotic plaque, which results in the exposure of subendothelial constituents of the arterial wall and the consequent triggering of the thrombosis cascade (1–4). Appreciation of this pathophysiological construct, accompanied by the recognition that coronary artery occlusion could generally be identified by ST segment elevation on the electrocardiogram (5), were the key insights prompting the exploration of reperfusion strategies. Further evolution of our understanding of the spectrum of disease now encompassed by the term acute coronary syndrome (ACS) (6) resulted in abandoning the terms “non-Q wave” and “Q-wave” myocardial infarction in favor of the current lexicon of “unstable angina/non-ST elevation myocardial infarction (UA/NSTEMI)” and “ST elevation myocardial infarction (STEMI).” The focus of this chapter is primary percutaneous coronary intervention (PCI), including the processes of emergency referral for diagnostic cardiac catheterization and infarct-related artery PCI as the preferred approach to managing the patient with STEMI (7).

The description by Rentrop and colleagues that the fibrinolytic agent streptokinase could restore coronary perfusion in STEMI was the seminal event that ushered in the reperfusion therapy era (8). The benefits of fibrinolytic therapy are well documented in the randomized clinical trials literature (9–18). Overall, it has been shown that 30 deaths are prevented for every 1000 patients treated with fibrinolysis (19). The greatest benefit of fibrinolytic therapy is seen in the first six hours of symptom onset and is comparable to primary PCI when given within two to three hours of symptom onset. Efficacy increases with patient risk, with patients with new (or presumed new) left bundle branch block deriving the greatest benefit, followed by those with anterior wall myocardial infarction; conversely, the least benefit is seen in those with an uncomplicated inferior wall MI, with only eight lives saved per 1000 patients treated.

However, treatment with fibrinolytic therapy is not without limitations. A prominent hazard is the increased risk of hemorrhagic stroke, with most of the hazard appearing on the day of treatment (9). The rate of intracranial hemorrhage approaches 1% and is associated with a 60% fatality rate (20–23). Other types of major, life-threatening bleeding occur in up to 4% to 13% of patients (21,22,24). Were these the only issues, fibrinolysis might still be preeminent; however, complete reperfusion, the actual goal of therapy, is achieved in perhaps only 25% of patients treated with fibrinolysis, termed the “illusion of reperfusion” (25). These issues contributed to the search for alternative rapid, complete, and sustained approaches to reperfusion in STEMI.

Angioplasty Awakenings
Contemporaneous with the initial explorations of fibrinolytic therapy in STEMI, Andreas Gruentzig was introducing the world to coronary balloon angioplasty (26,27). In the early days, the potential applications were not just uncertain—they were undiscovered. The ability to mechanically reperfuse an acutely occluded coronary artery was demonstrated by Peter Rentrop in 1979; he reestablished flow in a right coronary artery that abruptly occluded during diagnostic angiography by passing a coronary guidewire through the occlusion (28). The first primary PCI is generally attributed to Geoffrey Hartzler for a balloon angioplasty procedure performed in 1980 on a patient sustaining an acute inferior STEMI due to occlusion of a high-grade right coronary lesion that had been documented by diagnostic angiography the day before (29). The first published account appeared shortly thereafter, not as a scientific report, but as a first person account in a local newspaper, of a primary PCI performed by Robert “Jess” Peter at Duke University Medical Center on a columnist for the Durham Morning Herald (30). Anecdotally, others began performing primary PCI on the occasional patient brought to the catheterization suite presenting with STEMI, not necessarily as an intentional treatment but more as one of opportunity.

Fibrinolysis Vs. Primary PCI
These early successes led to the design and conduct of three landmark trials of primary PCI versus fibrinolysis published as adjoining articles in the March 11, 1993 edition of the New England Journal of Medicine (31–33). The principal findings of these pioneering studies—reliable acute restoration of myocardial perfusion in over 80% of patients, with the near elimination of intracerebral hemorrhage, resulting in improved clinical outcomes—have proven remarkably durable. Since then, over 20 comparative randomized trials of primary PCI versus fibrinolysis have been published. A 2003 meta-analysis of these trials provides a fairly reliable estimate of the improvement in outcomes seen with primary PCI compared with fibrinolysis, including an approximate 2% absolute (25% relative) reduction in short-term mortality (7.4% vs. 5.3%, p = 0.0003; Fig. 33.1) (34). Interestingly, these salutary effects approximate the relative mortality reduction of fibrinolysis compared with placebo; in the nine large randomized clinical trials of fibrinolysis versus placebo, mortality at 35 days was also reduced by approximately 2% (11.5% vs. 9.6%, p < 0.0001) (Fig. 33.2) (9,34).
Abbreviation
myocardial infarction.

right primary PCI versus fibrinolytic therapy (a significant reduction in mortality with revascularization seen in both cohorts. However, the six-month results revealed a striking finding of the SHOCK trial was the high 30-day mortality rate in the early revascularization group was higher in the elderly (75%) than in those less than 75 (41.4%). However, there were significant imbalances between the emergency revascularization elderly cohort and the initial medical stabilization elderly cohort; specifically, there were greater proportions of women and those with an anterior myocardial infarction, and the baseline ejection fraction was lower in the emergency revascularization group. Furthermore, the 30-day mortality was 53.1% in the elderly managed medically versus 56.8% in younger patients. Also, the number of patients in the elderly subgroup (56 patients) was small. The authors argued that since there was a numerically lower mortality in patients older than 75 years in the immediate medical stabilization arm, differences in baseline characteristics (and the small sample size) were more likely to be responsible for the possible hazard of early revascularization in the elderly than an attributable effect of treatment.

Results of the Senior Primary Angioplasty in Acute Myocardial Infarction (SENIOR PAMI) trial directly addressed the issue of primary PCI in the elderly (41). In the SENIOR PAMI trial, 481 patients greater than 70 years old were randomized to primary PCI or fibrinolytic therapy, with the primary end point being death or disabling stroke. At 30 days, while there was no significant difference in mortality (10% vs. 13%, p = 0.48) or in the combined end point of death or disabling stroke (11.3% vs. 13%, p = 0.57), there was a reduction in the composite end point of death, cerebrovascular accident, and reinfarction (11.6% vs. 18%, p = 0.05). Perhaps more importantly, there was no suggestion of harm in the elderly with primary PCI.

Transfer for Primary PCI
The first decade of primary PCI versus fibrinolysis investigation was conducted primarily at tertiary centers capable of performing on-site primary PCI. Following the demonstration of efficacy and safety of primary PCI in this setting, the concept of transferring patients with STEMI for primary PCI became the next logical step. Two seminal trials heralded the now common approach of transferring patients acutely for primary PCI when PCI can be accomplished promptly. The Danish Trial in Acute Myocardial Infarction 2 (DANAMI 2) (42) and the Primary Angioplasty in Patients Transferred from General Community Hospitals to Specialized PTCA Units.

INDICATIONS
Updated Lessons from Clinical Trials
Generically, primary PCI has proven as good as or better than fibrinolysis (35,36). In an updated meta-analysis of the randomized trials comparing fibrinolysis with primary PCI conducted from 1990 to 2006, there remained highly statistically significant relative risk reductions in mortality (28%), recurrent MI (63%), and stroke (50%) (37). With this continuing experience, sufficient numbers accrued to address subgroups where there remained the question of harm with primary PCI: patients presenting in cardiogenic shock and the elderly.

In the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, 302 patients presenting in cardiogenic shock were randomized to emergency revascularization or initial medical stabilization (38). The unsettling finding of the SHOCK trial was the high 30-day mortality seen in both cohorts. However, the six-month results revealed a significant reduction in mortality with revascularization (50% vs. 63%, p = 0.03) even though the enrollment goal was not met. The survival advantage was most pronounced in patients treated within 6 hours of symptom onset, although the median time to treatment was approximately 12 hours. At six years, there was a 13.2% absolute increase in survival with early revascularization compared with initial medical stabilization (32.8 vs. 19.6%, p = 0.03) (39). Among hospital survivors (n = 143), there was also a sustained mortality benefit with early revascularization compared with immediate medical stabilization (62.4 vs. 44.4%, p = 0.03).

Despite the overall salutary benefit, there was a trend toward a mortality hazard with early revascularization in those older than 75 years of age (75.0% with primary PCI vs. 53.1% with medical management, p = NS). This contributed to the 2004 ACC/AHA guidelines class IIa recommendation for primary PCI in the elderly versus a class I indication for those younger than 75 years (19). Subsequently, a possible explanation for the divergent results regarding age has been published (40). As might be anticipated, in the SHOCK trial, the 30-day mortality rate in the early revascularization group was higher in the elderly (75%) than in those less than 75 (41.4%). However, there were significant imbalances between the emergency revascularization elderly cohort and the initial medical stabilization elderly cohort; specifically, there were greater proportions of women and those with an anterior myocardial infarction, and the baseline ejection fraction was lower in the emergency revascularization group. Furthermore, the 30-day mortality was 53.1% in the elderly managed medically versus 56.8% in younger patients. Also, the number of patients in the elderly subgroup (56 patients) was small. The authors argued that since there was a numerically lower mortality in patients older than 75 years in the immediate medical stabilization arm, differences in baseline characteristics (and the small sample size) were more likely to be responsible for the possible hazard of early revascularization in the elderly than an attributable effect of treatment.

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Emergency Thrombolysis 2 (PRAGUE 2) (43) trials compared the outcomes of STEMI patients undergoing primary PCI at a tertiary hospital (including those transferred from an initial hospital without primary PCI capabilities) with those receiving fibrinolysis and managed more electively. In the DANAMI 2 trial, of the 1572 patients enrolled, 567 were randomized to transfer for primary PCI while 562 received fibrinolysis at the initial referring hospital; another 220 patients were randomized to fibrinolysis at the tertiary center and 223 were referred for emergency primary PCI. The primary end point was the composite of death, reinfection, or stroke at 30 days, and occurred less frequently in the primary PCI group than in the fibrinolysis group (8.5% vs. 14.2%, p = 0.002). Although trends favoring primary PCI were seen in mortality and stroke, the observed efficacy was primarily due to a reduction in reinfection (1.6% vs. 6.3%, p < 0.001). It should be noted that in DANAMI 2, transfer times were quite short, contributing to rapid door-to-balloon (DB) times in the transfer for primary PCI group, and rescue or elective PCI were discouraged. In this group, the median time from initial presentation to treatment start time was 117 minutes. In the referring hospital fibrinolysis arm, the median time from admission to initiation of fibrinolysis was 64 minutes. The difference between the median time for primary PCI treatment and time to fibrinolysis administration was thus only 53 minutes, highlighting the importance of well-organized and rapid systems to facilitate transfer of STEMI patients for primary PCI.

In the PRAGUE 2 trial, 850 patients were randomized to either immediate fibrinolysis at a referring hospital (n = 421) or transfer for primary PCI (n = 429) (43). In the transfer for PCI group, the median time from randomization to balloon activation was 97 ± 27 minutes, and in the fibrinolysis arm, the median time from randomization to needle time was 12 ± 10 minutes. The primary end point in this trial was 30-day mortality, with the trend favoring the primary PCI group (6.8% vs. 10.0%, p = 0.12). The authors performed a nonprespecified mortality analysis of the 380 patients who actually underwent primary PCI versus the 419 patients who received fibrinolysis (five of whom were assigned to the PCI group) and found a statistically significant reduction in 30-day mortality (6.0% vs. 10.4%, p < 0.05). Among the 299 patients randomized greater than three hours after the onset of symptoms, the mortality even more strongly favored primary PCI (6.0% with primary PCI vs. 15.3% with fibrinolysis, p < 0.02). Conversely, in patients presenting within three hours of symptom onset (n = 551), there was no difference in mortality in the two treatment arms (7.3% with primary PCI vs. 7.4% with fibrinolysis).

Important considerations when evaluating the DANAMI 2 and PRAGUE 2 trials include the use of tissue plasminogen activator (tPA) as the fibrinolytic agent in DANAMI 2 and the use of streptokinase in PRAGUE 2. In addition, the rate of stent implantation in DANAMI 2 was 93%, whereas in PRAGUE 2 it was only 63%. Both trials had very low rates of complications during transfer, with two deaths and three cases of successfully resuscitated ventricular fibrillation in PRAGUE 2 and no deaths and eight cases of successfully resuscitated ventricular fibrillation in DANAMI 2. Both trials, while demonstrating the feasibility and efficacy of transferring patients for primary PCI, were performed in small countries with experienced catheterization laboratories. The time for transfer was on average 32 minutes in DANAMI 2 and 48 minutes in PRAGUE 2, with DB times at the receiving hospitals averaging 26 minutes in both studies. Whether these results can be extended to environments with longer transfer times and/or DB times remains to be demonstrated. Of note, in the National Registry of Myocardial Infarction (NRF) 3/4 registry in the United States, patients undergoing transfer for STEMI average DB times of 53 minutes at the receiving hospital and have a median interval from initial hospital arrival to balloon inflation of approximately 180 minutes (44).

In 2003, Dalby and colleagues performed a meta-analysis of the six published randomized trials of 3750 patients evaluating transfer for primary PCI versus immediate fibrinolysis (45). The primary end point was the composite of death, reinfection and stroke. The time from randomization to primary PCI was between 80 and 122 minutes. The authors found a 42% relative risk reduction in the primary end point (p < 0.001) in the group transferred for primary PCI compared with the group receiving on-site fibrinolysis. When the individual components of the composite end points were evaluated, reinfection was significantly reduced by 68% (p < 0.001) and stroke by 56% (p = 0.015). There was a trend toward reduction in all-cause mortality of 19% (p = 0.086) with primary PCI. The authors concluded that even when transfer for primary PCI is required, primary PCI remained superior to a strategy of immediate fibrinolysis, provided that ambulance systems, prehospital management, and appropriate primary PCI capabilities are in place to rapidly and effectively accomplish the transfer and perform emergency PCI. An updated analysis of an expanded data set (n = 4135) has provided similar results (Fig. 33.3) (46).

**Door-to-Balloon Time Vs. Door-to-Needle Time**

Given the extensive body of evidence, primary PCI has become the standard of care for the patient presenting with STEMI. However, constrained primarily by accessibility, primary PCI is not universally available, contributing to a continuing debate regarding transfer for primary PCI versus immediate fibrinolysis. For primary PCI, the current ACC/AHA STEMI guidelines identify a target time of less than 90 minutes from presentation to first treatment device activation; for fibrinolysis, the target for time from presentation to administration of thrombolytic therapy...
is less than 30 minutes (19,35,36). At an institutional level, when the difference between DB and door-to-needle (DN) time can be expected to exceed 60 minutes, immediate fibrinolysis is therefore suggested as the preferred strategy.

In an analysis conducted in 2003 by Nallamothu and Bates of data compiled from the 23 trials included in the quantitative review by Keeley, Boura and Grines (34), the authors evaluated the four- to six-week incidence of death, reinfarction, and stroke, assessing the effects of PCI-related time delays on outcomes, where PCI-related time delay was defined as the difference between DB and DN times (47). The analysis, conducted utilizing a variance-weighted linear regression model, evaluated mortality in 21 of the studies, and the combined end point of death, reinfarction, or stroke in the 13 studies reporting these respective end points. As the PCI-related time delay increased, the mortality reduction favoring primary PCI decreased significantly (0.94% decrease for every additional 10-minute delay, p = 0.006). Overall, the two reperfusion strategies appeared to reach equipoise (where fibrinolysis outcomes become equal to primary PCI) with regard to mortality once the PCI-related time delay reached 62 minutes or more. Similarly, the impact of the PCI-related time delay on the composite end point of death, reinfarction, or stroke was also significant (1.17% decrease for every 10-minute delay, p = 0.016, time to equipoise of 93 minutes).

There has subsequently been refinement of the analyses of Nallamothu and Bates. A 2005 reanalysis of the same data by Betriu and Masotti utilized a different statistical model to assess the relationship between PCI-related delay and treatment benefit (48). Magnitude and statistical significance of the relationship were estimated using weighted least-squares regression, in which results from each trial were weighted by the square root of the number of patients in each trial. Linear regression analysis was used to estimate the decrease in benefit for each additional minute of PCI-related delay and the delay duration predicted to nullify the benefit of a primary PCI approach. The key finding remained that the survival benefit of primary PCI over fibrinolysis decreased as the PCI-related time delay increased, specifically 0.24% for every additional 10-minute delay. The overall point of equipoise was calculated to be 110 minutes, with shorter times to equipoise associated with fibrin-specific fibrinolytic agents, shorter duration of symptoms, younger age, and other variables.

These findings have been confirmed in an expanded analysis of the NRMI database by Pinto and colleagues (49). In this analysis, relationships between PCI-related delay and in-hospital mortality of 192,509 STEMI patients were evaluated using a hierarchical model to simultaneously adjust for patient-level risk factors and hospital covariates. These investigators identified a DB minus DN equipoise time of 114 minutes (Fig. 33.4), a value remarkably similar to the finding of 110 minutes by Betriu and Masotti described above. In addition, this analysis also recognized that the point of equipoise varied depending on baseline characteristics. Specifically, it increased with age (71 minutes for age <65 vs. 155 minutes for age ≥65) and duration of symptoms (94 minutes for symptom duration of ≤120 minutes vs. 190 minutes for symptom duration of >120 minutes). In summary, these analyses have informed the guidelines regarding the optimal approach an institution should follow with STEMI patients. Where primary PCI is available, systems should focus on strategies to reduce delays such as prehospital assessment with 12-lead electrocardiography, activation of interventional cardiology services from the field, and transportation of patients directly to facilities capable of primary PCI (bypassing facilities that do not provide 24/7 coverage) (50–53). Where primary PCI cannot be delivered, the focus should be on reducing delays to fibrinolysis (53). The balance of these systems-based approaches to reducing DB and DN time will thus influence the optimal strategy of a given institution. Regardless, the message is that delays should be reduced to the absolute minimum given the uniform improvements in outcomes associated with decreasing time to treatment.

### PHARMACOLOGY

#### Antithrombotic Therapies

As STEMI is primarily a thrombosis-mediated event, (non-fibrinolytic) antithrombotic agents have logically been the subject of extensive evaluations as adjuncts to reperfusion strategies (7). Studies have included agents directed at mitigating platelet activity (aspirin, the thienopyridines clopidogrel and prasugrel, and the glycoprotein IIb/IIIa inhibitors abciximab, eptifibatide, and tirofiban), and inhibiting the coagulation cascade (heparin, enoxaparin, bivalirudin, and fondaparinux). What has been consistently demonstrated is that antithrombotic therapies effectively and efficaciously improve outcomes in the acute STEMI setting; what remains less well-defined is whether there is an optimal approach or a series of approaches that best balance efficacy and safety in primary PCI. Reflecting the central import of both pharmacotherapy and primary PCI in the management of STEMI, in 2009 the ACC/AHA Task Force on Practice Guidelines authored a joint update combining recommendations for STEMI management and primary PCI into one document (36). A summary of the resulting joint guidelines regarding antithrombotic therapies relevant to primary PCI is provided in Table 33.1.

#### Thienopyridines

There are no pivotal trials explicitly examining the efficacy and safety of clopidogrel (and in particular, a 600-mg loading dose...
ever, the median number of days from randomization to PCI to death and myocardial infarction (3.3 vs. 5.4%, \( p < 0.001 \)), and an independent reduction in cardiovascular death and myocardial infarction (3.3 vs. 5.4%, \( p = 0.03 \)). However, the median number of days from randomization to PCI was 3.2 days in the clopidogrel arm and 2.9 days in the placebo arm; these results are thus of only modest relevance to the primary PCI context. Nonetheless, the current STEMI guidelines for primary PCI recommend a 300- to 600-mg dose of clopidogrel before or at the time of primary PCI (Table 33.2) (36).

Of perhaps greater relevance are the results observed in the STEMI subgroup of patients from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON TIMI-38) trial (58). In the TRITON TIMI-38 study, 13,608 patients were randomized to prasugrel or clopidogrel therapy as an adjunct to PCI. Of these, 3534 (26%) were in the STEMI cohort, with a large majority of these managed with primary PCI (59). Prasugrel was administered as a 60-mg loading dose followed by a 10-mg/day maintenance dose, while clopidogrel was given as a 300-mg loading dose followed by 75 mg/day. Treatment could be initiated before, during, or immediately following PCI. In the STEMI subgroup,
a 21% relative risk reduction (2.4% absolute risk reduction) in the primary composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at 14.5 months favoring prasugrel was observed (Kaplan-Meier estimate of 12.4% vs. 10.0%, p = 0.02). The efficiency improvement was largely related to a reduction in nonfatal myocardial infarction in the prasugrel arm (6.7% vs. 8.8%, p < 0.02) with a trend favoring mortality (2.4% vs. 3.3%, p = NS). Of note, efficacy was greater than had been projected; the trial had not been independently powered to demonstrate efficacy in the STEMI cohort (60). Furthermore, prasugrel has a more rapid onset of action than clopidogrel (61) and thus may be better suited to the emergency primary PCI context, particularly when given prior to arrival in the cardiac catheterization suite. On the basis of TRITON TIMI-38, prasugrel treatment is now listed as a IB recommendation to clopidogrel as an adjunct to primary PCI in STEMI, unless contraindicated (Table 33.2) (36).

**Glycoprotein IIb/IIIa Receptor Blockade**

The platelet glycoprotein IIb/IIIa inhibitors have been the subject of extensive clinical trials evaluating their efficacy and safety in ACS, including a number of randomized controlled studies specific to the STEMI indication. In STEMI, these agents have been shown to decrease ischemic complications (62,63). Specifically, a meta-analysis of the 27,115 patients in 11 randomized controlled trials of the glycoprotein IIb/IIIa receptor antagonist abciximab in STEMI demonstrated a significant reduction in short-term (30-day) mortality (2.4% vs. 3.4%, p = 0.047) (63). This improvement in mortality was sustained at the 6- to 12-month time frame (4.4% vs. 6.2%, p = 0.01) in the patients treated with primary PCI; in contradistinction, there was no mortality benefit when abciximab was used to facilitate fibrinolysis. Furthermore, when used to facilitate fibrinolysis, abciximab treatment was associated with an increase in major bleeding (5.2% with abciximab vs. 3.1% in controls, p < 0.001); conversely, there were no differences in rates of major bleeding in the primary PCI context (4.7% with abciximab vs. 4.1% in controls, p = 0.36). It should be acknowledged, however, that most of these trials were conducted before dual antiplatelet therapy (aspirin plus a thienopyridine) had become a standard of care in stent PCI.

More recently, several trials have evaluated platelet glycoprotein IIb/IIIa blockade with concomitant dual antiplatelet (aspirin plus clopidogrel) therapy in the primary PCI setting. In the second Ongoing Tirofiban in Myocardial Infarction Evaluation (ONTIME) 2 trial, 984 acute STEMI patients were randomized to higher dose tirofiban (25-mcg/kg bolus with a 0.15-mcg/kg-min infusion) or placebo at first medical contact in the ambulance or other prehospital setting (64). All patients were given aspirin and a 600-mg loading dose of clopidogrel. The primary end point, mean residual ST segment deviation 60 minutes following primary PCI, was improved in the tirofiban arm (3.6-mm residual deviation with tirofiban vs. 4.8 mm with placebo, p = 0.003). Clinically, the key secondary end point of the composite of death, recurrent myocardial infarction, urgent target vessel revascularization, or blinded bailout use of tirofiban at 30 days also favored the tirofiban group (26.0% vs. 32.9%, p = 0.020), with longer transfer times being associated with a greater efficacy advantage. Importantly, tirofiban treatment did not result in a significant increase in major bleeding (4.0% with tirofiban vs. 2.9% with placebo, p = 0.363).

These findings stand in contrast to the results of the Harmonizing Outcomes with Revascularization and Stents in AMI (HORIZONS-AMI) trial (65). The HORIZONS-AMI trial was an open-label, randomized trial of 3602 patients presenting with an acute STEMI managed with primary PCI. Patients were given aspirin and a 600-mg loading dose of clopidogrel, and then randomized to either unfractionated heparin with a glycoprotein IIb/IIIa antagonist or bivalirudin alone (provisional glycoprotein IIb/IIIa receptor antagonist treatment was allowed). The primary end point was a net composite of efficacy and safety, including cardiovascular death, reinfarction, target vessel revascularization for ischemia, stroke, and major bleeding within 30 days. The primary end point favored the bivalirudin arm, with a 24% relative improvement in net events.
at 30 days (9.2% vs. 12.1%, p = 0.005). The difference was derived almost entirely from a decrease in major bleeding events in the bivalirudin arm (4.9% vs. 8.3%, p = 0.001). However, there was a statistically significant 1% absolute increase in stent thrombosis within 24 hours in the bivalirudin group (1.3% vs. 0.3%, p = 0.001), and 66% of patients treated with bivalirudin also received heparin before randomization. At one year, while composite rates of ischemic cardiac events were essentially the same between the two arms, mortality favored the bivalirudin group (3.4% vs. 4.8%, p = 0.03).

Given the available evidence, the ACC/AHA guidelines list platelet glycoprotein IIb/IIIa receptor blockade as a reasonable (class IIa) therapeutic adjunct, particularly in patients with a high thrombus burden on angiography (Table 33.2) (36). While a stronger level of evidence exists for abciximab therapy, the small molecule antagonists (tiroliban and epitilabidite) are also recognized as equivalent options. Finally, even with ONTIME-2, the limited evidence supporting use of this class of agents as a preparatory strategy to facilitate reperfusion or improve outcomes when given upstream prior to PCI.

Parenteral Anticoagulants

Despite the plethora of commercially available and investigational anticoagulants, there have curiously been few studies in primary PCI evaluating anticoagulants in a direct comparative fashion. The ACC/AHA guidelines from 2004, 2007, and 2009 (19,35,36) largely reflect the pharmacological and pharmacodynamic findings of the elective PCI and ACS literature (Table 33.2). Even HORIZONS-AMI (described above) did not compare the anticoagulant bivalirudin with another anticoagulant directly, but instead permitted heparin treatment prior to bivalirudin administration and had a comparator arm comprised of unfractionated heparin plus a platelet glycoprotein IIb/IIIa receptor blocker. Given the remarkably low overall event rates in both arms of HORIZONS-AMI, the critical finding may be the overall excellent efficacy and safety of a primary PCI strategy using an approach of aspirin, clopidogrel, and an anticoagulant, along with the recognition that bivalirudin can be given safely after an initial bolus of heparin. What does appear clear is that anticoagulants, while requisite for PCI, should be titrated to the degree sufficient to prevent the generation and propagation of thrombus while minimizing their adverse potential to accentuate bleeding.

CLINICAL ASPECTS STEMI Networks

Successful best practice management of the STEMI patient is presaged by both cooperative regional planning and local implementation (7,51,52,66). A political that must frequently be addressed is the coordination of ambulance service coverage areas and transportation patterns since catchment areas for primary PCI centers frequently overlap. As ambulance transport times of up to 45 to 60 minutes can still result in initial medical contact-to-balloon times of <120 minutes, discussions of service coverage areas and referral patterns must include not only the immediate community but also the extended coverage region. Emergency medical services should be outfitted with 12-lead electrocardiography systems with computerized analysis and telemetry; a single vendor for all of the ambulance services of a given triage area increases the chance for coordinated communication. Bypassing nonprimary PCI hospitals to transport the patient directly from home to the cardiac catheterization suite will dramatically reduce first medical contact-to-balloon time. As a proportion of patients are emergency department “walk-ins,” all hospitals should develop protocols for the rapid recognition and triage of the chest pain patient. Prehospital emergency medical services, referring hospital emergency departments, and primary PCI emergency departments should be enabled to directly activate the catheterization laboratory without requiring the input of a cardiologist. An equitable on-call rotation of the interventional cardiologists in a community should be created that emphasizes coverage of the laboratory by a single physician (regardless of practice alignment) rather than patient “ownership.” Once primary PCI has been completed, responsibility for the patient should then be transitioned promptly from the interventional operator to the patient’s identified cardiologist.

A key role of the STEMI network is to enable the administration of an antithrombotic “cocktail” early in the course of management, preferably by emergency medical services and/or the emergency department. This regimen should include antiplatelet and anticoagulant therapies (see the previous section “Pharmacology”). A suggested regimen includes 325 mg of chewable aspirin, a thienopyridine loading dose (600 mg of clopidogrel or 60 mg of prasugrel), and an unfractionated heparin bolus (50-70 units/kg, to a maximum of 5000 units).

Assessment and Preparation

The initial evaluation of the STEMI patient should mirror the evaluation of the acute trauma patient. An abbreviated Allergies, Medications, Past Medical History, Last Meal, and Current Events (AMPLE) history should be obtained. Specific key points should include questions about previous contrast reactions, chronic antithrombotic therapy, comorbidities (particularly renal dysfunction, cerebrovascular disease, and peripheral vascular disease), and coronary disease and the details thereof. An attempt should be made to assess the ability of the patient to take and tolerate dual antiplatelet therapy for a minimum of one year.

The key anatomic consideration is to identify the infarct territory from the 12-lead electrocardiogram (67), information useful for clinical risk determination and the selection of catheters (and sequencing of angiographic imaging) during the primary PCI procedure. Particular attention should be directed at evaluating clues of left main or three vessel disease (68). Evidence of diffuse ischemia should also prompt an evaluation for aortic dissection. Computerized interpretations, while generally reliable, may miss an acute STEMI, so questionable electrocardiograms should promptly be over-read by a physician and placed in the context of the clinical presentation. In some cases of posterolateral branch occlusion, the electrocardiogram may show prominent ST depression and tall R-waves in the anterior precordial leads rather than classic ST segment elevation. Also, 25% of patients with a NSTEMI will have an occluded artery at the time of angiography, with 66% of these being in the posterolateral distribution (69). This argues for a low threshold for referral for cardiac catheterization in the patient with the appropriate presentation but nondiagnostic changes on the electrocardiogram.

The physical examination should focus on signs and symptoms of both right-sided and left-sided cardiac compromise. This includes an assessment of vital signs (particularly pulse rate, blood pressure, and respiratory rate), oxygenation,
and adventitial pulmonary and cardiac sounds. The tachycardic and hypotensive patient is at highest risk, especially with an anterior myocardial infarction. Patients presenting with an inferior myocardial infarction and hypotension or who develop profound hypotension after administration of nitroglycerin should be aggressively resuscitated with crystalloid fluid expansion. Right ventricular involvement may substantially impair forward cardiac output, resulting in profound hypotension even with relatively clear lungs. Left ventricular cardiogenic shock, on the other hand, frequently presents with hypotension and pulmonary edema. A rapid assessment should be made as to whether an intra-aortic balloon pump (or other form of circulatory support), transvenous pacemaker, and/or intubation are immediately needed to manage hypotension, bradyarrhythmias, and/or ventilatory compromise, respectively. It is recommended that these procedures be completed prior to the initiation of coronary arteriography, even if this prolongs the ultimate DB time, as contrast injection and PCI may result in further hemodynamic decompensation.

TECHNICAL FUNDAMENTALS

Procedure and Technique

Upon arrival in the laboratory, monitoring and/or defibrillation patches should be placed on the patient and both groins prepared. Once the patient has been prepped and draped, the first technical task is establishing vascular access. By this point, the patient should have been treated with the antithrombotic cocktail (or variant, depending on local protocol) described above. When using the femoral approach, fluoroscopy (rather than the inguinal crease) should be employed to identify anatomic landmarks, particularly the location of the head of the femur. The femoral artery should be accessed with a single anterior wall puncture, with the target zone being between the lower margin and mid portion of the femoral head. Transradial access has been used quite successfully in primary PCI (70); however, the operator should first become facile with this approach via a series of elective cases before attempting to perform primary PCI via the radial artery.

Before the first coronary arteriogram, a quick reassessment should be performed to evaluate the cardiopulmonary status of the patient. Placement of an intra-aortic balloon at this juncture should be considered if the systolic blood pressure is 90 mm or less or if the patient has developed pulmonary edema (Killip class III or IV). It should be anticipated that coronary arteriography and intervention will transiently impair cardiac performance, and the contrast load can further compromise oxygenation. Even though placement of an intra-aortic balloon pump necessitates access via a second vascular access site, stability of the patient through the procedure and beyond should be the paramount concern.

The initial set of coronary arteriograms should evaluate the (anticipated) noninfarct coronary artery. Typically, a standard Judkins diagnostic catheter serves this purpose well. The caution is that the noninfarct artery may supply substantial collateral supply, with angiography precipitating ischemia. A brief delay of a few additional seconds relative to the normal pace of coronary injections will allow time for myocardial recovery from contrast-induced ischemia. Once angiography of the noninfarct related has been completed, a guide catheter (rather than diagnostic catheter) should be advanced to the contralateral coronary artery to perform diagnostic arteriography and obtain diagnostic images of the infarct-related lesion.

While the vast majority of coronary interventions in the primary PCI setting can be performed with six-French systems, exchange for a seven- or eight-French guide catheter should be considered in the unusual circumstance that diagnostic angiography identifies a true bifurcation culprit lesion.

For the intervention itself, a basic set of interventional tools should be prepared by the scrub assistant at the same time the diagnostic images are being obtained. These include a soft-tipped 0.014-in coronary guidewire, a thrombus aspiration catheter, and a 2.0- to 2.5-mm coronary balloon sized to be at least 0.25 to 0.5 mm smaller than the nominal vessel diameter. If a platelet glycoprotein IIb/IIIa receptor antagonist is to be administered, the bolus and infusion should also be initiated at the same time. A coil-tipped coronary guidewire (rather than a polymer-coated hydrophilic guidewire) is generally preferred to decrease the potential for coronary dissection and perforation. Should a hydrophilic guidewire ultimately be required, successful placement of the wire in the distal lumen should be confirmed before intervention is performed, even if this requires removal of the guidewire and injection of contrast through a (nonrapid exchange) balloon catheter or an end-hole infusion catheter. Our preference is to start with a 300-cm guidewire as this allows the balloon to be preloaded, provides increased support for advancing interventional devices across the infarct lesion, and facilitates the injection of contrast and medications through the balloon lumen into the distal artery.

Crossing the lesion with a guidewire may at least partially restore epicardial blood flow. In STEMI involving a right coronary or dominant left circumflex artery, reperfusion may precipitate the vagally mediated Bezold-Jarisch reflex (71). Administration of 0.5 mg of atropine before the reestabilishment of flow, especially when a narrow pulse pressure or relative bradycardia are present, should at least partially mitigate this reflex. The reflex nominally lasts 5 to 10 minutes; if longer than 15 minutes, other etiologies of hypotension should be considered. If significant disease exists in the noninfarct related arteries, the development of the Bezold-Jarisch reflex with severe hypotension can precipitate cardiogenic shock or closure of a noninfarct artery.

The obvious goal of primary PCI is to restore normal epicardial coronary blood flow and myocardial microvascular perfusion. Table 33.2 lists the most commonly used grading scales related to these concepts: thrombolysis in myocardial infarction (TIMI) flow and TIMI myocardial perfusion grade (56,57). Another measure, the corrected TIMI frame count, has the advantage of being a continuous, quantifiable, and reproducible measure of coronary perfusion (72). Achievement of TIMI 3 flow remains a most powerful predictor of mortality at 30 days and one year, with restoration of normal myocardial perfusion having perhaps an even stronger predictive value.

Once the coronary guidewire has been advanced into the distal true lumen, the first mode of intervention must be selected. The principal choices are balloon angioplasty, direct stenting (without predilation with a balloon catheter), or aspiration thrombectomy. The Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS), which randomized 1071 primary PCI patients to either thrombus aspiration with the Export Aspiration Catheter (Medtronic, Minneapolis, Minnesota, U.S.) or conventional treatment, documented a 46% relative reduction in cardiac mortality at one year with aspiration (6.7% vs. 3.6% with aspiration, p = 0.020) and a 43% reduction in death or nonfatal myocardial infarction (9.9% vs. 3.6% with aspiration, p = 0.009).
(73). After primary PCI, microvascular perfusion improved to final TIMI myocardial blush grade 2 or 3 in 73.7% in the conventional treatment group and 82.9% in the aspiration group ($p < 0.001$), with histopathological examination documenting successful thrombus aspiration in 72.9% of patients (74). A meta-analysis of 21 trials of a variety of thrombectomy devices available before 2007 (preceding the TAPAS trial) had previously demonstrated an improvement in myocardial blush scores (but no mortality benefit); (75) an updated analysis has subsequently demonstrated an all-cause mortality benefit at a median of 365 days in 11 randomized trials of thrombectomy versus PCI without thrombectomy ($p = 0.049$), with the benefit confined to patients treated in the manual (aspiration) thrombectomy trials of the Export, Pronto (Vascular Solutions, Minneapolis, Minnesota, U.S.), and Diver CE (Invatec, Roncadelle, Brescia, Italy) catheters (Fig. 33.5) (76). In aggregate, these data suggest that manual aspiration thrombectomy should be considered the first interventional option where technically feasible.

If balloon angioplasty is chosen as the initial intervention, the goal should generally not be to achieve a definitive result with balloon angioplasty alone, unless a stent cannot be delivered to the infarct lesion or a clinical consideration (such as impending surgery) dictates otherwise. Compression of soft thrombus can elaborate vasoactive substances and cause distal embolization of thromboembolic particulate material, and aggressive balloon dilation can produce arterial dissection. Instead, the goals of balloon angioplasty should be to restore epicardial flow and to prepare the artery for stent implantation.
The current primary PCI approach anticipates the implantation of a coronary stent as the definitive intervention. Interestingly, this approach was still the topic of debate into the early 2000s (27). In the five-year follow-up of the Primary Angioplasty in Myocardial Infarction (PAMI) trial (n = 2087, stents in 692), patients who underwent stent implantation (not as a randomized treatment) experienced a lower mortality than those treated solely with balloon angioplasty (78). However, randomized comparisons, notably the Stent Primary Angioplasty in Myocardial Infarction (Stent PAMI) study initially were inconsistent with this finding. In Stent PAMI, 900 patients were randomized to balloon angioplasty or implantation of the first generation Palmaz-Schatz (Cordis Corporation, Miami Lakes, Florida, U.S.) stent (79). While patients assigned to balloon angioplasty had higher rates of restenosis, target vessel revascularization, and more angina at six months compared with the stent arm, stent implantation was associated with a strong trend toward increased mortality, raising concerns about stent implantation in STEMI. These issues informed the design and execution of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) study, a trial with a 2 × 2 factorial design that evaluated both a second generation (Multi-Link, Guidant Corporation, Mountain View, California, U.S.) stent versus balloon angioplasty and treatment with the platelet glycoprotein IIb/IIIa receptor blocker abciximab versus no treatment (62,80). The key findings of CADILLAC were a reduction in restenosis at one year with stent implantation compared with balloon angioplasty (without a difference in mortality) and a reduction in recurrent myocardial infarction and infarct-related artery thrombosis with abciximab treatment. A number of additional trials have since been conducted with stent implantation in primary PCI, confirming the value of this strategy in maintaining arterial patency and improving short- and long-term outcomes (46,53).

In STEMI, some degree of vasoconstriction is more often the rule than the exception. This can lead to an underestimation of the nominal reference vessel diameter. Small amounts of intracoronary vasodilators (nitroglycerin or nitroprusside) as tolerated by the patient’s blood pressure should therefore be given prior to stent implantation to aid in sizing the stent. A general rule of thumb is to undersize the diameter of the initial dilatation balloon by 0.25 to 0.5 mm, while the opposite is true for stent selection. A slightly longer (5–10 mm) and larger (0.25–0.5 mm) stent should be selected for implantation in the infarct target lesion. Mastery of the compliance curves of stent systems is thus a prerequisite for the primary PCI operator. The goal should be to deploy the stent at a high pressure without further postdilatation, or a “one and done” philosophy. Additional dilations of an implanted stent can precipitate microembolization and potentiate the no-reflow phenomenon. Once epicardial flow has been reestablished, the primary determinant of myocardial recovery will be myocardial perfusion, not epicardial flow. The failure of at least 50% ST segment elevation resolution from the initial ECG after reperfusion is a strong predictor of one year mortality (81). Every effort should therefore be made to avoid further compromise of the microcirculation. Direct stenting, while having the potential to reduce distal embolization, remains to be rigorously evaluated as an independent variable in primary PCI. Because of the potential for size and length mismatch of the stent to the lesion and the nominal vessel diameter, particularly when there is TIMI 0 or 1 flow, we generally discourage direct stenting as the first intervention in primary PCI.

Support of the Critically Ill Patient
In the hemodynamically unstable STEMI patient, changes to the above procedural sequence may need to be considered. While ventriculography can usually be deferred until after PCI has been completed (to reduce DB time), ventriculography should be performed prior to PCI in the unstable patient. This is to exclude mechanical complications of STEMI such as flail mitral leaflet, ventricular septal rupture, pseudoaneurysm, and free wall rupture. An ascending aorta aortogram should be performed in the patient with diffuse ST segment depression (or diffuse elevation) on the electrocardiogram to evaluate for aortic dissection. The presence of any of these conditions should be considered a contraindication to PCI and should prompt emergency cardiothoracic surgical consultation.

Equipment in the catheterization laboratory must anticipate the need to provide cardiopulmonary support in the critically ill patient. Supplies that must be immediately available include a cardiopulmonary resuscitation cart, intra-aortic balloon system, and external and transvenous temporary pacemaker supplies. The threshold for intubation should be quite low, not only for obvious pulmonary embarrassment, but also in the delirious or otherwise uncooperative patient; an inability to cooperate or follow instructions is often an early sign of respiratory embarrassment.

As highlighted above, patients in frank cardiogenic shock should undergo immediate intra-aortic balloon pump implantation before the initiation of coronary arteriography. Placement of an intra-aortic balloon pump in this setting has been demonstrated to improve short-term outcomes (82) and should not require more than three to five minutes in experienced hands. Of note, however, the prospective randomized PAMI-II trial of intra-aortic balloon counterpulsation in 437 high-risk patients, (out of a cohort of 1100 acute STEMI patients), prophylactic placement of an intra-aortic balloon pump did not improve in-hospital outcomes (83).

Multivessel disease identified at the time of STEMI remains a challenging scenario. In the absence of cardiogenic shock, identification and treatment of the culprit lesion with deferral of additional (nonculprit) PCI remains the guideline (19,35,36). Unsuccessful or otherwise compromised nonculprit vessel PCI can have unpredictable and even disastrous consequences in the acute STEMI patient. Multivessel PCI at the time of the initial primary PCI remains to be systematically evaluated in large-scale trials.

Complications
In the STEMI setting, the optimal management of thrombus includes dissolution and/or aspiration. However, even with optimal pharmacotherapy and thrombus aspiration, embolization may occur and lead to compromise of the distal coronary bed (84). Large emboli in the distal epicardial coronary can often be disrupted sufficiently to restore flow by advancing an interventional device (e.g., guidewire, balloon, aspiration catheter) through the thrombus. Selective intracoronary infusion of platelet glycoprotein IIb/IIIa receptor inhibitors can also restore perfusion.

At the microvascular level, the no-reflow phenomenon can complicate otherwise successful reperfusion of the epicardial artery. This phenomenon is characterized angiographically by a poor myocardial blush and reflects inadequate myocyte perfusion. It occurs in 10% to 40% of acute STEMI patients, frequently complicating primary PCI (84–87). The key to
management is prevention; to reduce the probability of no-reflow, “light-touch” techniques similar to those used in saphenous vein graft PCI should be employed in the treatment of infarct lesions. When it does occur, no-reflow can produce myocardial ischemia, worsen myocardial necrosis, extend myocardial infarction, cause ventricular arrhythmias, and result in rapid hemodynamic deterioration. The occurrence of no-reflow demands a rapid response. Intracoronary administration of a calcium channel blocker, adenosine, or sodium nitroprusside through an end-hole infusion catheter positioned beyond the target lesion may help resolve no-reflow. Patients who develop persistent ST elevation have a significantly higher mortality. Fortunately, even without demonstrable improvement in left ventricular contractile function, reversal of no-reflow can have favorable effects on remodeling of the left ventricle (88). The most important element of the differential is major coronary artery dissection. If further stent implantation is elected, it is absolutely critical to confirm that the coronary guidewire is in the true lumen distally. Finally, although it has become routine to administer vasodilators to help resolve no-reflow, large prospective randomized trials are lacking.

**PCI AFTER FIBRINOLYSIS**

While the focus of this chapter has been to develop, describe and delineate the primary PCI strategy in acute STEMI, there nonetheless remain a substantial proportion of patients who will be initially managed with fibrinolytic therapy. Several constructs therefore deserve mention in the context of an intervention-based approach to the patient with STEMI.

**Rescue PCI**

Failure of fibrinolysis to restore perfusion within 60 to 90 minutes of administration is associated with reduced left ventricular function and increased rates of mechanical complications and mortality compared with successful reperfusion (89–91). The clinical markers of reperfusion, such as chest pain diminution, partial resolution of ST segments (>50–70%) and the occurrence of reperfusion arrhythmias unfortunately are of limited predictive value (92). Califf and colleagues studied 386 patients undergoing angiography 90 minutes after the initiation of tPA for STEMI and found that while 96% of patients who had complete resolution of ST segment elevation had coronary patency, this finding was relatively rare as it was seen in only 6% of patients (93). Among patients with partial improvement in ST segment elevation, 84% had coronary patency, but even this finding occurred in only 38% of patients. Unchanged ST segment elevation was associated with a 60% patency rate. The presence or absence of arrhythmias also did not appear to be closely associated with coronary patency. Of the patients without either ST segment or symptom resolution, 56% were still found to have a patent infarct artery at 90 minutes.

Given these uncertainties, the approach of urgent transfer following fibrinolysis for immediate catheterization and rescue PCI has been espoused as a strategy to increase reperfusion, prevent further myocardial dysfunction, and improve outcomes. There are currently five published randomized trials that have enrolled 920 patients evaluating this approach. In a meta-analysis of these trials performed by Collet and colleagues, the immediate catheterization with rescue PCI approach was associated with a 35% relative risk reduction \( (p = 0.04) \) in mortality and a 36% relative risk reduction \( (p = 0.009) \) in the combined endpoint of death or reinfarction compared with a conservative approach (Fig. 33.6) (94,95).

Rescue PCI (rather than repeat fibrinolysis or conservative management) has thus emerged as the preferred strategy for patients without evidence of successful reperfusion 60 to 90 minutes after fibrinolytic administration. This is especially true for patients with a large amount of myocardium at risk and hemodynamic or electrical instability. Bleeding risk should be taken into consideration as the pooled analysis did demonstrate a significant increase in the combined end point of major and minor bleeding (11.9%) in the rescue PCI arm compared with the conservative arm (1.3%, \( p < 0.001 \)). In particular, bleeding events were associated with concomitant abciximab therapy and were typically associated with the arterial access site.

**Routine Early PCI After Fibrinolysis**

A variant of rescue PCI for failed fibrinolysis is routine early catheterization following (presumably successful) fibrinolysis (94,95). In the Collet meta-analysis described above, this approach was also analyzed, specifically differentiating “balloon era” from “stent era” trials. Studies included in the analysis employed a strategy of systematic and early (<24 hours) PCI versus delayed or ischemia-guided PCI. The authors found that the three stent era studies of early catheterization with PCI demonstrated a strong trend toward reduction in mortality compared with a delayed or ischemia-guided PCI approach (3.8% vs. 6.7%) (OR 0.56, 95% CI 0.33–0.83, \( p = 0.07 \)) and a twofold reduction in the rate of death or reinfarction (7.5% vs. 13.2%) (OR 0.53, 95% CI 0.33–0.83, \( p = 0.0067 \)). Since then, the large-scale 1059-patient Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) has confirmed the advantage of early referral for cardiac catheterization and PCI following fibrinolysis (Table 33.3) (96). Of note, while the ACC/AHA guidelines list routine cardiac catheterization after fibrinolysis as class IIa in high risk patients and IIb in low risk...
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>n</th>
<th>Symptom onset</th>
<th>Fibrinolytic</th>
<th>End point event rate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southwest German Interventional Study in Acute Myocardial Infarction III (SIAM III)</td>
<td>2003</td>
<td>197</td>
<td>&lt;12 hr</td>
<td>rPA</td>
<td>Routine (%)</td>
<td>Early PCI (%)</td>
</tr>
<tr>
<td>Grupo de Análisis de la Cardiopatía Isquémica Aguda 1 (GRACIA-1)</td>
<td>2004</td>
<td>500</td>
<td>&lt;12 hr</td>
<td>Tissue plasminogen activator</td>
<td>D/RI/TVR</td>
<td>20.3</td>
</tr>
<tr>
<td>Combined Angioplasty and Pharmacological Intervention Versus Thrombolysis Alone in Acute Myocardial Infarction (CAPITAL AMI)</td>
<td>2005</td>
<td>170</td>
<td>&lt;6 hr</td>
<td>TNK</td>
<td>D/RI/ischemia/stroke</td>
<td>24.4</td>
</tr>
<tr>
<td>Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI)</td>
<td>2009</td>
<td>600</td>
<td>&lt;12 hr</td>
<td>Half-dose rPA</td>
<td>D/RI/ischemia</td>
<td>10.7</td>
</tr>
<tr>
<td>Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI)</td>
<td>2009</td>
<td>1059</td>
<td>&lt;12 hr</td>
<td>TNK</td>
<td>D/RI/ischemia/congestive heart failure/cardiacogenic shock</td>
<td>17.2</td>
</tr>
</tbody>
</table>

*Abbreviations: PCI, percutaneous coronary intervention; TNK, tenecteplase; rPA, reteplase; D, death; RI, reinfarction; TVR, target vessel revascularization.

*Source: From Refs. 96–100.*
patients, the European Society of Cardiology guidelines assign this a class I status (101,102). While outcomes in the balloon era were indeed worse with coronary intervention, improvements in technique and technologies of the stent era have dramatically reversed this finding in favor of early and systematic cardiac catheterization with immediate percutaneous revascularization.

In summary, a percutaneous revascularization strategy focused on restoring (and maintaining) patency has indeed become the recommended approach for managing the patient presenting with STEMI, whether via primary PCI or as an adjunct to augment fibrinolysis. Finally, regardless of initial strategy, the need for advanced PCI capabilities including cardiopulmonary support also argues for the transfer of all STEMI patients to tertiary centers of excellence as we collectively strive to improve clinical outcomes.

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PRIMARY PCI IN ST ELEVATION MYOCARDIAL INFARCTION


INTRODUCTION
Circulatory shock is characterized by inadequate systemic tissue perfusion due to altered physiology and reduced blood supply. Hypotension is differentiated from shock by the ability to meet the tissue’s metabolic demands by maintaining tissue perfusion. Tissue perfusion, a function of systemic vascular resistance (SVR) and cardiac output, is significantly reduced in instances where SVR is low and cardiac output is elevated (vasodilatory shock) or where SVR is elevated and cardiac output is reduced. When the latter is accompanied by inadequate intravascular volume, hypovolemic shock is present. Depressed cardiac output with elevated SVR in the presence of adequate intravascular volume defines cardiogenic shock (CS) (Table 34.1).

FUNDAMENTALS OF CS
The pathophysiology of CS due to pump failure usually begins with profound depression of myocardial contractility. Resultant reduction in cardiac output leads to hypotension, coronary insufficiency, further reduction in contractility, and compensatory systemic vasoconstriction. Without intervention, further declines in tissue perfusion, organ failure, and death may ensue. Left ventricular (LV) pump failure is often due to large ST-segment elevation myocardial infarction (STEMI) but can also be caused by smaller infarction in the presence of preexisting LV dysfunction, right ventricular involvement, or mechanical complications (papillary muscle, ventricular septal, or free wall rupture).

In clinical practice, two other scenarios are often encountered: preshock and mixed shock. Patients may develop a state of preshock where hypoperfusion is present but compensatory increases in heart rate and peripheral vasoconstriction allow for the maintenance of cardiac output and systemic blood pressure. Preshock can be present at the time of hospital admission for STEMI in patients who ultimately develop CS. Indeed, most patients with CS complicating acute MI develop shock after initial presentation to the hospital (1). In the GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial, five times the number of patients developed shock after admission than they had it on presentation (2). In CS complicating non-STEMI, the delay may be even more pronounced (3,4). The preshock state may provide a window of opportunity for aggressive reperfusion and supportive strategies. In the case of mixed shock, evidence for vasodilatation or underfilling confuses the classic paradigm of CS. In fact, the average SVR of patients in the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial was not elevated with wide variability between patients (5). Normal SVR, therefore, even in the presence of vasopressor therapy, does not preclude the presence of CS. Together, these two frequently encountered clinical scenarios of preshock and mixed shock raise the possibility of alternate mechanisms of hypotension in CS (such as systemic inflammation and vasodilatation) and iatrogenic contributions to the disorder (vasodilation with angiotensin-converting enzyme inhibitors, excessive diuresis and preload reduction, and intravenous β-blocker therapy).

ETIOLOGIES
The focus of the remainder of this chapter will be CS complicating acute MI. Over 90% of cases fit into one of five etiologic categories with approximately 80% of these due to pump failure (left or right ventricular) and the remainder due to myocardial rupture.

LV Pump Failure
LV pump failure is the dominant category of CS (Fig. 34.1) (6). The vast majority of CS resulting from LV pump failure is due to large, often anterior, infarction; a minority of cases is due to smaller infarctions in patients with preexisting LV dysfunction resulting in cumulative loss of >40% of LV mass (4,7). Triple vessel or left main disease is present in 80% (8) and CS may be present despite only moderate degrees of LV systolic dysfunction (5). Data from the National Registry of Myocardial Infarction (NRMI) database and others suggest that the incidence of CS due to LV failure after MI is consistently 6% to 9% (9). However, data conflict regarding whether the incidence has decreased over the past few decades (10,11). The anecdotal impression of many clinicians that CS incidence is declining is supported by observations published in 2008 analyzing data from 70% of the acute care hospitals in Switzerland. The observed downward trend was explained by decreases in CS not evident on presentation but developing during hospitalization (Fig. 34.2) (11).

Clinical Manifestations
The typical clinical criteria and bedside findings of CS due to LV pump failure are shown in Table 34.2. Physical examination, while helping rule out other causes for hypotension and shock, typically reveals ashen skin, cool extremities, altered sensorium, tachycardia, narrow pulse pressure, low pulse volume, distant heart sounds, and an audible and palpable left S3 gallop. Distended neck veins may or may not be present; pulmonary congestion often is present. Urgent 12-lead electrocardiography usually shows STEMI or evidence for prior infarction with new ST-segment depression, or left bundle branch block. Tachy- and bradyarrhythmias are common.
Management

Addressing metabolic perturbations, respiratory insufficiency, arrhythmias, and supportive care in general take on special urgency with CS. If initial assessment suggests hypovolemia as a possible etiology (i.e., no obvious pulmonary congestion), small boluses of normal saline (100 cc at a time) may be used with careful assessment of its effects on systemic blood pressure, heart rate, and urine output. When CS (or preshock) is suspected, quickly establishing the diagnosis and ruling out mechanical complications with immediate echocardiographic, hemodynamic, and angiographic evaluations is necessary. Because LV failure CS is directly related to the degree of myocardial tissue loss, strategies that limit infarct size are paramount. The benefits of early revascularization for CS due to LV failure complicating MI has been well described in the SHOCK trial (12). Comparing early revascularization—either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)—with initial medical stabilization with fibrinolysis, inotropes, and vasopressor support when indicated, this landmark study demonstrated numerical, albeit not statistically different, improvement in 30-day survival with early revascularization (12) that became statistically significant by six months and persisted for at least six years (Fig. 34.3) (13). Intra-aortic balloon pump (IABP) counterpulsation was used in 86% of patients. Those randomized within six hours of MI onset and those younger than 75 years had particular benefit with early revascularization. Equally beneficial effects were seen with PCI (64%) and CABG (36%). While unselected patients age >75 years in the SHOCK trial appeared to have worse outcomes with early revascularization (13),

Table 34.1 Shock Physiology

<table>
<thead>
<tr>
<th>Contractility</th>
<th>Afterload</th>
<th>Preload</th>
<th>Mixed venous saturation</th>
<th>Type of shock</th>
</tr>
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<tbody>
<tr>
<td>↑</td>
<td>↓</td>
<td>↑ or ↔</td>
<td>↑</td>
<td>Vasodilatory</td>
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<td>↓</td>
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<td>Hypovolemic</td>
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<td></td>
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<td>Cardiogenic</td>
</tr>
</tbody>
</table>

Figure 34.1 Etiologies of cardiogenic shock. Abbreviations: LVF, predominant left ventricular failure; RVF, isolated right ventricular shock; MR, acute severe mitral regurgitation; VSR, ventricular septal rupture; FWR, free-wall rupture and cardiac tamponade. Between groups, comparisons were based on hierarchical groups. Source: From Ref. 6.

Figure 34.2 Temporal trends in the incidence of cardiogenic shock. Source: From Ref. 11.
nonrandomized data from the SHOCK Registry (14) and a subsequent study in 2009 (15) suggest that patients >75 years of age who are otherwise good candidates for early revascularization may also benefit (Fig. 34.4) and should be considered for revascularization (16).

Although relatively ineffective as a stand-alone therapy, IABP counterpulsation is useful in stabilizing and temporizing patients before more definitive therapy is instituted and during the revascularization procedure. For patients with STEMI complicated by CS who present to hospitals without primary angioplasty capabilities, early fibrinolytic therapy and IABP counterpulsation followed by immediate transfer for PCI or CABG is recommended (Fig. 34.5) (17). Critics may argue that a lack of randomized controlled mortality data supporting IABP use exists. This lack of evidence is principally due to the early acceptance into practice of this device for CS and the difficulty of performing a meaningful trial testing its efficacy. A 2009 meta-analysis of over 10,000 patients with CS after acute MI demonstrated some of the limitations of nonrandomized trials (18). It showed that patients receiving fibrinolysis treated with IABP had decreased 30-day mortality and those undergoing primary PCI treated with IABP had increased mortality. Despite attempts to account for confounders like younger age and high PCI rates in the fibrinolytic/IABP group and attempts to minimize selection bias, these data are not definitive. Many would agree with the opinion that “as long as we do not have any other evidence from randomized controlled clinical trials we should not change our current practice because the beneficial hemodynamic effects of the IABP should overweigh any potential hazard” (19). In fact, the current guidelines from both the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) give a class I recommendation for IABP in the setting of CS (20,21). Despite this, only approximately one in four patients with CS receive an IABP (9,22,23).

Although more complicated and costly, percutaneous cardiopulmonary bypass has also been used for CS. By providing up to 5 L/min of flow, percutaneous cardiopulmonary bypass may improve survival but can be used for only several hours because of hemolysis (24). Percutaneously placed extracorporeal life support (ECLS) has also shown promise in select centers despite the grave of clinical circumstances (25). Although burdened by high complication rates, LV assist devices provide better hemodynamic support than IABP but have not been shown to improve survival in a small randomized trial (26). Presently, LV assist devices are best used as a
bridge to transplantation, and early transfer to centers providing such cardiopulmonary support and transplantation services is encouraged for appropriate candidates. In 2008, a much more simply applied percutaneous LV assist device, the Impella 2.5, was shown to offer superior hemodynamic support for CS compared with IABP (27). The use of percutaneous assist devices has not significantly displaced IABP use for CS outside of a few select centers, and data suggesting more than just hemodynamic supremacy over IABP are still lacking. While anecdotal experience is very encouraging, it is tempered by the historical fact that improved hemodynamics do not necessarily translate into outcome advantages. A more comprehensive review of assist devices is covered elsewhere in this text.

While controversy exists regarding the use of invasive hemodynamic monitoring in the critical care setting in general (28,29), in expert hands the use of pulmonary artery catheterization for CS can be very helpful. The 2007 Focused Update of the 2004 ACC/AHA guidelines for the management of STEMI states that pulmonary artery catheterization should be performed, or is considered useful, in the majority of cases of CS or suspected shock (Table 34.3) (20).

Vasopressors and inotropes should be used to treat hypotension. The agents to be considered include dopamine (5–15 mcg/kg/min intravenously), dobutamine (2–20 mcg/kg/min intravenously), and norepinephrine (0.5–30 mcg/min intravenously); the latter when a significant vasodilatory component is present (5). Pure α-adrenergic agents such as phenylephrine should be reserved for the rare cases where vasodilation predominates. The overzealous use of intravenous β-blockers at the time of presentation for patients with acute coronary syndromes (ACS) and STEMI should be avoided. As noted, many CS patients initially present with preshock and can easily deteriorate to CS by limiting both stroke volume and heart rate with acute β-blockade.

Prognosis

The in-hospital mortality rate for CS complicating MI remains unacceptably high. During the 1970s and 1980s, mortality was >80% (30) and was only slightly better (70–75%) by the 1990s (31). The second NRMI analysis from hospitals with revascularization capability documented decreasing CS mortality rates from 60% in 1995 to 48% in 2004 (9). The fall in mortality was associated with an increase in revascularization rates, specifically PCI, suggesting a possible causal relationship. The Swiss MI registry published in 2008 had similar findings; overall CS in-hospital mortality decreased from 63% to 48% and rates of PCI and IABP increased, whereas rates of fibrinolytic therapy decreased and rates of CABG surgery remained stable (Fig. 34.6) (11). Predictors of mortality from CS due to LV pump failure vary in the literature (6,32) probably due to

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**Table 34.3** Indications for Pulmonary Artery Catheterization in Cardiogenic Shock

<table>
<thead>
<tr>
<th>Should be performed (class I recommendation) if</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Progressive hypotension unresponsive to fluid or when fluid may be contraindicated</td>
</tr>
<tr>
<td>• Suspected mechanical complications of STEMI if echocardiogram not yet performed</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Considered useful (class IIa recommendation) if</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypotension without pulmonary congestion not responsive to initial trial of fluid</td>
</tr>
<tr>
<td>• Cardiogenic shock</td>
</tr>
<tr>
<td>• Severe or progressive heart failure or pulmonary edema not responding to therapy</td>
</tr>
<tr>
<td>• Persistent signs of hypoperfusion without hypotension or pulmonary congestion</td>
</tr>
<tr>
<td>• During administration of vasopressor and/or inotropic agents</td>
</tr>
</tbody>
</table>

**Abbreviation**: ST-segment elevation myocardial infarction.

**Source**: Adapted from Ref. 20.
differing patient populations studied, therapies used, and the era during which the analyses were performed. Despite this, advanced age and concomitant multiorgan failure adversely affect survival, whereas the etiology of ACS does not (4).

Right Ventricular Pump Failure

Although some degree of right ventricular (RV) infarction is seen in up to 50% of inferior wall MI (33), resultant severe RV dysfunction leading to CS is less common. Isolated RV infarction and shock is rare (6).

Clinical Manifestations

The classic presentation of RV shock is that of CS without pulmonary congestion, elevated right-sided filling pressures (manifest by elevated jugular venous distention, Kussmaul’s sign, pulsus paradoxus, and pressure waveforms with steep right atrial y descent and RV dip and plateau), ST-segment elevation in the right precordial ECG leads, and RV chamber enlargement and dysfunction. Marked depression in cardiac output is present. On occasion, elevated right-sided filling pressures can lead to right-to-left shunting through a patent foramen ovale and manifest as unexpected degrees of hypoxemia. The clinical presentation of RV shock can include components of LV dysfunction depending on the relative involvement of the inferior LV. Patients with predominant RV shock are more likely to have single- or double-vessel disease and less likely to have triple-vessel disease than patients with LV shock, and as expected, RV shock is rare with acute left anterior descending occlusion (34). RV shock need not occur due to occlusion of the proximal right coronary artery (RCA) leading to cessation of blood flow to the RV marginal artery. It can be seen in conjunction with posterior LV infarction and distal RCA or distal dominant circumflex occlusion (35,36).

Management

Immediate reperfusion therapy, either with fibrinolysis or PCI, is the goal of therapy. Avoidance of medications that decrease preload (nitroglycerin or morphine) or depress cardiac output (β-blockers) is mandatory. Maintaining or augmenting RV preload with volume expansion constitutes initial therapy for predominant RV shock. If hypotension is not reversed after 1 to 2 L of fluid, cardiac output augmentation with dobutamine may be necessary, especially if there is a delay to reperfusion therapy or while awaiting recovery of RV function after reperfusion. The loss of atrioventricular synchrony can result in marked reduction in RV filling and systemic hypotension. Atrial or atrioventricular pacing or cardioversion may provide benefit in such circumstances (37). Typically, however, when patients are promptly diagnosed, adequately supported, and treated with immediate reperfusion therapy, return of sinus rhythm and improved RV filling often is forthcoming and pacing unnecessary.

Prognosis

Somewhat surprisingly, predominant RV and LV shock resulted in similar mortality in the SHOCK registry, despite younger age, less LV wall injury, and less multivessel disease in RV shock patients (34). Anecdotal experience and single center studies of patients undergoing primary PCI for predominant RV shock, however, suggest they do better than their LV shock counterparts (38), often recover quickly, and represent a particularly gratifying subgroup of shock patients to treat. In patients who do survive, return of RV function to normal is common (39).

Papillary Muscle Rupture

The three categories of myocardial rupture following MI have unique presentations (Table 34.4) and require mechanical intervention for survival. Acute mitral regurgitation (MR) due to papillary muscle rupture and dysfunction was responsible for 7% of CS in the SHOCK Registry of CS complicating acute MI (6).

Clinical Manifestations

The posteromedial papillary muscle is supplied by a single source—the right or left circumflex coronary artery. Inferior MI due to thrombosis of either of these arteries can therefore lead to posteromedial papillary necrosis and rupture. Because the dual sourced anterolateral papillary muscle is relatively protected from necrosis after thrombotic coronary occlusion, anterior wall MI less commonly leads to acute MR. Acute MR shock typically presents with profound hypotension and pulmonary edema. The lack of an audible murmur is not uncommon and does not rule out acute MR due to papillary rupture. Immediate echocardiography for suspected acute MR is diagnostic. Dislocation of the tip of the papillary muscle or chordal rupture is often seen. As expected, LV ejection fraction may be better preserved than those with CS due to LV failure. The pulmonary capillary wedge tracing may show tall V waves.

### Table 34.4 Cardiogenic Shock due to Myocardial Rupture

<table>
<thead>
<tr>
<th></th>
<th>PMR</th>
<th>VSR</th>
<th>FWR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>3/4 inferior</td>
<td>2/3 anterior</td>
<td>1/2 anterior</td>
</tr>
<tr>
<td><strong>Exam</strong></td>
<td>Murmur in 50%</td>
<td>Murmur in 90%</td>
<td>JVD, PEA</td>
</tr>
<tr>
<td><strong>Thrill</strong></td>
<td>Rare</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td><strong>Echocardiography</strong></td>
<td>Regurgitant jet</td>
<td>Shunt</td>
<td>Effusion</td>
</tr>
<tr>
<td><strong>PA catheterization</strong></td>
<td>C-V wave in wedge tracing</td>
<td>O₂ step-up</td>
<td>Diastolic equalization</td>
</tr>
</tbody>
</table>

Abbreviations: JVD, jugular venous distention; PEA, pulsus electrical activity; PMR, VSR, ventricular septal rupture; FWR, free-wall rupture.
Management
Immediate mitral valve surgery (repair or replacement) with revascularization is the only currently established treatment. All other efforts should be aimed at stabilizing the patient prior to surgery. IABP counterpulsation should be used and, if the augmented systemic blood pressure allows, afterload reduction with intravenous sodium nitroprusside should be started. Patients with papillary muscle necrosis and rupture (and not simply ischemia) would not be expected to benefit from revascularization alone, and primary PCI does not appear to benefit the degree of MR in the setting of severe acute papillary rupture complicating STEMI (40).

Prognosis
Like all cases of myocardial rupture complicating MI, survival with or without aggressive surgical intervention is poor. In the nonrandomized SHOCK registry, patients undergoing mitral valve surgery for acute MR fared poorly, albeit significantly better than those managed medically (Fig. 34.7) (41).

Ventricular Septal Rupture
Ventricular septal rupture (VSR) complicating MI was responsible for 3% of CS in the SHOCK Registry of CS complicating acute MI (6) and represents a particularly challenging group because of the difficulties of operative management and very poor prognosis.

Clinical Manifestations
Patients with VSR complicating MI often fit the classic rupture dictum “first MI in an older hypertensive patient presenting late” (42,43). In the SHOCK registry, VSR patients were less likely to have had prior MI compared to those with LV failure CS, and the average age was 72 years (43). Unlike acute MR, VSR is almost always accompanied by a murmur (harsh holosystolic) and thrill. Doppler echocardiography visualizes the shunt, and oxygen saturation step up in the RV is present. Both anterior and inferior infarction can lead to VSR.

Management
CS due to VSR is a nearly uniformly fatal ailment requiring immediate surgery. Delaying surgery in patients who do not have overt CS is appealing in concept as it may allow for healing of the defect margins. Unfortunately, waiting risks the development of shock, which is unpredictable and significantly worsens surgical survival. Because of the high mortality of immediate surgical repair, some have experimented with less invasive acute percutaneous VSR closure using septal occlusion devices. While still in its infancy, this less invasive approach to treating acute VSR does not appear to offer an advantage over surgery, especially when CS is present (44).

Prognosis
VSR with CS carries with it one of the worst survival rates of all cardiac conditions (Fig. 34.8) (6). Despite high operative mortality, surgical repair offers an improved chance of survival (Fig. 34.9) (43). Although not all surgical series agree (45), VSR complicating inferior MI can be particularly challenging for two reasons. First, because RV involvement is more likely with inferior infarction, the hemodynamics are more foreboding.
Second, proximal RCA occlusion leading to basal septal VSR is more difficult to repair than the apical defects often seen with anterior MI (46). In making decisions about whether to proceed to surgery in patients with many comorbidities and advanced age, the location of the VSD may help determine the usefulness or futility of going forward with surgery.

**Free-Wall Rupture and Hemorrhagic Tamponade**

The most devastating complication of MI, free-wall rupture (FWR), was responsible for 1% of CS in the SHOCK Registry of CS complicating acute MI (6).

**Clinical Manifestations**

Like other forms of myocardial rupture complicating MI, FWR often presents with a first MI and may be more common in hypertensive women (42,47). Typically, the infarct is large and anterior (47,48). Because acute FWR and hemopericardium can lead to abrupt hemodynamic collapse, electromechanical dissociation, and near instant death, many of the clinical manifestations of FWR reported in the literature may represent a subacute variety of FWR in which the rupture is contained. A spectrum exists from catastrophic to subacute, with clinical presentation varying from immediate death to hypotension with pericarditic chest pain. Whether fibrinolytic therapy increases the likelihood of rupture is in dispute and was not found to be the case in the SHOCK trial registry (48,49). Echocardiography has obvious utility in diagnosis and is very specific for FWR when the pericardial effusion is large (50). Because small effusions and tamponade physiology may be missed, up to 25% of patients with FWR may have no significant pericardial effusion by echocardiography (49,50).

**Management**

Early recognition and swift operative repair are the keys to management. Contained ruptures may allow for the institution of supportive measures like IABP counterpulsation and vasopressor therapy in preparation for surgery. Some patients can be temporized with pericardiocentesis. Long-term survival without surgery has been reported (using pericardiocentesis, bed rest, and blood pressure control with β-blocker therapy) for patients surviving initial FWR and tamponade (51); however, prompt surgical repair is recommended.

**Prognosis**

Many patients succumb almost instantly with rapid and irreversible electromechanical dissociation. Patients presenting with subacute FWR and hemopericardium appear to have survival rates similar to CS due to LV pump failure (48,49). Survival requires prompt recognition of tamponade, aggressive stabilization, and prompt surgery.

**CONCLUSIONS**

The high lethality of CS in conjunction with the importance of establishing the correct etiology makes the management of CS challenging and fascinating. While the two types of pump failure CS are best treated with urgent (usually percutaneous) revascularization, stabilizing medical therapies differ significantly and require early detection of LV versus RV failure. Conversely, the three types of myocardial rupture CS share similar supportive therapies but usually require very specialized and complex surgical interventions; urgent percutaneous revascularization is rarely indicated and may squander valuable time best used to establish a diagnosis and prepare for surgery.

**REFERENCES**


**Figure 34.9** In-hospital mortality for cardiogenic shock due to ventricular septal rupture. Source: From Ref. 43.


A clinical rationale and strategy for chronic total coronary occlusion revascularization: innovative solutions to an old problem

Colin M. Barker and David E. Kandzari

INTRODUCTION
Despite remarkable advances in the procedural and clinical outcomes of percutaneous coronary intervention (PCI), chronically occluded coronary arteries remain a formidable challenge and unresolved dilemma in interventional cardiology. Although a total coronary occlusion is identified in approximately one-third of diagnostic cardiac catheterizations, an attempted revascularization accounts for less than 8% of all PCIs (1). In the Emory Angioplasty versus Surgery Trial (EAST), for example, the presence of a chronic total occlusion (CTO) was the most common reason for physician referral to coronary artery bypass graft surgery (CABG) (2). Such a disparity between their frequency and treatment not only underscores the technical and procedural frustrations associated with these complex lesions, but also the clinical uncertainties regarding which patients may benefit from CTO revascularization. CTOs remain the single most important reason not to attempt PCI in favor of CABG or medical treatment. Illustrating this, in the multivessel PCI versus CABG SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) study, the prevalence of CTO in the randomized arm was 27% compared with 59% in the CABG registry cohort (3).

Unlike PCI of nonocclusive coronary disease, much of our understanding regarding CTOs has been further challenged by relatively few studies describing the procedural and clinical outcomes among patients undergoing attempted revascularization. Moreover, these investigations are limited by their retrospective, observational design, variability in operator skills, and inconsistencies regarding the definition of CTO and patient selection. Since the duration of an occluded artery is an independent predictor of procedural outcome (4,5), an inability to date these lesions, in addition to their heterogeneous composition, has restricted the evaluation of novel revascularization technologies. Until recently, many of the technologies promoted for the treatment of CTOs were simply modeled after devices applied to nonocclusive disease, erroneously assuming that the pathophysiology between these lesion subsets were similar.

ANATOMIC CONSIDERATIONS
The definition of a coronary CTO is reflective of the degree of lumen stenosis, the amount of antegrade blood flow, and the age of the occlusion. The degree of stenosis can range from complete occlusion (Thrombolysis in Myocardial Infarction [TIMI] grade 0 flow), frequently called a “true” CTO, to 99% occlusion with minimal contrast penetration through the lesion (TIMI grade 1 flow), referred to as a “functional” total occlusion. Without serial angiograms, the duration of coronary occlusion is difficult to specify with any certainty and must be estimated from available clinical information related to the timing of the event that caused the occlusion, for example, clinical history of myocardial infarction (MI) or sudden change in angina pattern with electrocardiographic changes consistent with the location of the occlusion. In most patients, the age of the CTO cannot be determined with precision. Furthermore, the temporal criterion used to define a CTO has varied among registries, trials, and databases, ranging from >2 weeks (6–8) to >3 months (9), which in part explains interstudy differences in lesion characteristics and procedural success. In general, a total occlusion of duration >3 months may be considered “chronic.”

CTO Histopathology
CTOs most often arise from thrombotic occlusion followed by thrombus organization and tissue aging (10,11). Particularly relevant to PCI strategies for CTO recanalization is the histological finding that approximately half of all CTOs are ≤99% stenotic when observed by histopathology, despite the angiographic appearance of total occlusion with TIMI grade 0 antegrade flow. Moreover, little to no relationship exists between the severity of the histopathological lumen stenosis and either plaque composition or lesion age.

The typical atherosclerotic plaque of a CTO consists of intracellular and extracellular lipids, smooth muscle cells, extracellular matrix, and calcium. Collagens are the major structural components of the extracellular matrix (8,12), with predominance of types I and III (and minor amounts of IV, V, and VI) in the fibrous stroma of atherosclerotic plaques (13). The concentration of collagen-rich fibrous tissue is particularly dense at the proximal and distal ends of the lesion, contributing to a column-like lesion of calcified, resistant fibrous tissue surrounding a softer core of organized thrombus and lipids. Key histopathological attributes of CTOs are calcification extent, inflammation, and neovascularization. The typical CTO may be classified as “soft,” “hard,” or a mixture of both (Figs. 35.1 and 35.2). Soft plaque consists of cholesterol-laden cells and foam cells with loose fibrous tissue and neovascular channels, and is more frequent in younger occlusions (<1-year-old). Soft plaque is more likely to allow guidewire passage either directly through tissue planes or via neovascular channels into the distal lumen. Conversely, hard plaques are characterized by dense fibrous tissue and often contain large fibrocalcific regions without neovascular channels. During PCI, these occlusions are
thus more likely to deflect coronary guidewires into the subintimal area, creating dissection planes. Hard plaques are more prevalent with increasing CTO age (>1-year-old). Of note, however, areas of calcification frequently occur even in CTOs <3 months of age, although the extent and severity of calcification increase with occlusion duration. This age-related increase in calcium and collagen content of CTOs in part underlies the progressive difficulty during PCI in crossing older occlusions.

Inflammatory cell infiltrates in CTOs consist of macrophages, foam cells, and lymphocytes. Inflammation may exist in the intima, media, and adventitia of CTOs, although it is most predominant in the intima. As fibrotic CTO lesions age, the vessels typically undergo negative remodeling with decreasing dimension of the external elastic membrane, a phenomenon due to adventitial vascular responses. Occasionally, plaque hemorrhage and inflammation may result in positive remodeling (14).

Another hallmark of CTOs is extensive neovascularization, which occurs throughout the extent of the vessel wall. Capillary density and angiogenesis increase with advancing occlusion age. In CTOs <1-year-old, new capillary formation is greatest in the adventitia. In CTOs >1-year-old, the number and size of capillaries in the intima have increased to a similar or greater extent than those present in the adventitia. Relatively large (>250 μm) capillaries are frequently (47–67%) present throughout the CTO vessel wall, even in young occlusions, suggesting that angiogenesis within the CTO is an early event. Frequent colocalization of inflammation and neovascularization within the intimal plaque and adventitia suggests that

Figure 35.1 (See color insert) (A) CTO, soft plaque (hematoxylin-eosin stain; magnification 1×). (B) Magnified view of A, showing cholesterol clefts and loose fibrous tissue (hematoxylin-eosin stain; magnification 10×). (C) CTO, hard plaque, dense fibrous tissue, and calcium (elastic van Gieson stain; magnification 1×). Abbreviation: CTO, chronic total occlusion. Source: From Ref. 8.

Figure 35.2 (See color insert) (A) A single large channel is seen in this CTO (elastic van Gieson stain; magnification 1×). (B) Traversing capillaries connect with the small recanalization channels in the center of this CTO (elastic van Gieson stain; magnification 1×). (C) Small recanalization vascular channels are seen in the center of this CTO (elastic van Gieson stain; magnification 1×). (D) Inflammation is found adjacent to vascular channels of the adventitia in this vessel (hematoxylin-eosin stain; magnification 25×). (E) Adventitial capillaries have grown to large size in this CTO (hematoxylin-eosin stain; magnification 40×). Abbreviation: CTO, chronic total occlusion. Source: From Ref. 8.
these findings are closely related, although it is unclear whether inflammation is a cause or an effect of neovascularization in CTOs. Lymphocytes and monocytes/macrophages may play an active role in both angiogenesis and atherosclerotic lesion progression by producing a variety of mitogenic and angiogenic factors (15).

A rich neovascularity network often traverses the CTO vessel wall, arising from the adventitial vasa vasorum across the media and into the lesion intima, suggesting that vessel ingrowth proceeds from the adventitia in younger lesions. An autopsy study of subtotal atherosclerotic lesions demonstrated that new intimal vessels originate in the adventitial vasa vasorum of lesions with >70% stenosis, but rarely from the coronary lumen (16). Such microchannels, which can recanalize the distal lumen, may result from thrombus-derived angiogenic stimuli (17) and are suggested on an angiogram of an old CTO without a well-defined proximal cap or stump. In this regard, the distinction should be made between ipsilateral epicardial angiographic “bridging” collateral vessels and true microvascular collaterals. Neochannels may also develop with organization of thrombus, connecting the proximal and distal lumens; this is suggested by a tapered CTO proximal cap on an angiogram. Such channels may serve as a route for a guidewire to reach the distal vessel and hence may have therapeutic value.

Collaterals and CTOs
Collaterals preserve myocardial function and avoid cell death in the distribution of the occluded artery. A CTO that is well collateralized is functionally equivalent to a 90% stenosis (18) (Fig. 35.3). The myocardium remains viable but produces ischemia during periods of increased oxygen demand, and thus patients with these lesions are likely to have exertional angina. The risk of unstable angina or an acute coronary syndrome due to the lesion is unlikely as it is totally occluded. The myocardium supplied by the CTO can result in an acute coronary syndrome if the arteries supplying the collaterals become compromised in any way.

Recovery of impaired left ventricular function after revascularization of a CTO is not directly related to the quality of collateral function, as collateral development does not appear to require the presence of viable myocardium. However, those patients with recovery had a lower peripheral resistance measured by intracoronary Doppler and pressure wires as an indicator of preserved microvascular integrity (19).

Clinical Impact Relative to Target Vessel
Very little data exist regarding the potential for differential benefit of CTO recanalization depending on the target vessel, for example, left anterior descending (LAD), left circumflex (LCX), or right coronary artery (RCA). A recent, large, single-center registry suggests that PCI for CTO of the LAD, but not LCX or RCA, is associated with improved long-term survival (20). This study included 2608 patients and the LAD was the target vessel in 936 (36%), the LCX in 682 (26%), and the RCA in 990 (38%) patients. Angiographic success rates were 77%, 76%, and 72%, respectively. Procedural success compared with failure was associated with improved five-year survival in the LAD cohort (88.9% vs. 80.2%, P < 0.001), but not in the LCX (86.1% vs. 82.1%, P = 0.21) and RCA groups (87.7% vs. 84.9%, P = 0.23). In multivariable analysis, CTO PCI success in the LAD group remained associated with decreased mortality risk [HR 0.61; 95% confidence interval (CI), 0.42–0.89]. In addition to other clinical characteristics, this information may assist in selecting patients for attempted CTO PCI.

INDICATIONS FOR REVASCULARIZATION
In general, when the CTO represents the only significant lesion in the coronary tree, PCI is warranted when the following three conditions are all present (8):

1. The occluded artery is responsible for the patient’s symptoms of chest pain or heart failure despite maximal medical therapy (PCI may also be considered in selected cases of silent ischemia if a large myocardial territory at risk is demonstrable).
2. The CTO territory is associated with significant left ventricular dysfunction and viability is demonstrated within the myocardial territory supplanted by the occluded artery.
3. The likelihood of success is moderate to high (>60%), with an anticipated major complication rate of death <1% and MI <5%.

If the PCI attempt is unsuccessful, further management will depend on the symptomatic status and the extent of jeopardized ischemic myocardium. Repeated PCI following initial failure (typically with an allowance of several weeks for vessel healing in the case of dissection) or CABG may be warranted if a large myocardial territory is ischemic or the patient is very symptomatic. Alternatively, conservative therapy may be appropriate if repeated PCI is unlikely to be successful and the patient’s symptoms can be managed with antianginal medications.

In patients with multivessel disease and one or more CTOs, the relative risks and benefits of CABG compared with PCI should be considered. The presence of any of the following may favor CABG (8):

1. Left main artery disease
2. Complex triple-vessel disease, especially in the patient with insulin-requiring diabetes, severe left ventricular dysfunction, or chronic kidney disease
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3. An occluded proximal LAD (supplying a viable anterior wall), which is not favorable for PCI.
4. Multiple CTOs with a relatively low anticipated success rate.

Other patients with multivessel disease, including a CTO, may be appropriately managed by PCI, with the goal being complete revascularization whenever possible. Typically, in patients presenting with an acute coronary syndrome or with stable angina in whom the nonoccluded vessels can be reliably stented with a low rate of complication, angioplasty of the CTO should be performed after PCI of nonoccluded lesions. The one exception to this rule would be in patients in whom failed PCI of the CTO would result in referral for CABG, in which case the CTO should be approached first unless conditions dictate otherwise.

Patients with medically refractory angina or a moderate to large ischemic burden deserve consideration for PCI, particularly if the symptoms or jeopardized myocardial territory are enough to warrant CABG as an option. In several large databases, only 11% to 15% of patients undergoing PCI for CTO were asymptomatic (21,22). Conversely, the proportion of patients presenting with unstable angina due to a CTO is also fairly low (9–18%) (8,23). Thus, the majority of patients undergoing PCI for CTO have stable or progressive angina, whereas many asymptomatic patients with CTO are managed medically.

A history of prior MI has been reported in 42% to 68% of patients with CTO (21). One study identified reversible perfusion defects using stress myocardial single-photon emission computed tomography (SPECT) in 83% of 71 patients without history of prior MI and with single-vessel disease involving a CTO (24). Similarly, another study documented severe and extensive stress perfusion defects in 56 patients with no prior MI and single-vessel CTO with the presence of collaterals (25). Adenosine SPECT imaging may be even more sensitive than exercise-induced stress imaging to detect perfusion defects in patients with CTO.

The temporal changes in contractility and hyperemic and resting myocardial blood flow (MBF) in dependent and remote myocardium after PCI of CTOs were investigated using cardiovascular magnetic resonance (CMR) imaging (26). Three groups were prospectively studied: 17 patients scheduled for CTO PCI, 17 scheduled for PCI of a nonocclusive coronary artery stenosis (non-CTO), and 6 patients with CTO who were not scheduled for revascularization. Contractility in treated segments was improved at 24 hours and 6 months after CTO PCI but only at 6 months after non-CTO PCI. In both PCI groups, treated segments no longer had reduced MBF or contractility compared with remote segments. In patients with untreated CTO segments, however, MBF and wall thickening did not improve at follow-up.

Debate and conflicting data exist regarding the optimal timing for revascularization of a total coronary occlusion resulting from a recent infarction. In the OAT (Occluded Artery Trial) (27), PCI of infarct arteries 3 to 28 days after MI did not reduce death, recurrent MI, or congestive heart failure over 4 years. Notably, exclusion criteria included multivessel coronary disease, rest angina, or demonstration of at least moderate ischemia by noninvasive stress testing. The TOSCA-2 (Total Occlusion Study of Canada) substudy (28) of this trial also reported no improvement in left ventricular function at one year with revascularization. Given these findings, it may be best to allow recovery from acute MI for patients similar to those included in this trial who present to the interventional suite within this time period. Conversely, a more recent meta-analysis of randomized control trials demonstrated that PCI of the infarct artery performed late (12 hours to 60 days) after MI is associated with significant improvements in cardiac function and survival (29). Angiographic documentation of total occlusion was required as an inclusion criterion in 5 of the 10 studies, and 3 additional studies required either a total occlusion or significant stenosis. The analysis included 3560 patients with median time from MI to randomization of 12 days (range 1–26 days) and follow-up of 2.8 years (42 days to 10 years). Randomization allocated 1779 subjects to PCI and 1781 to medical treatment. There were 112 (6.3%) PCI and 149 (8.4%) medical therapy deaths, yielding significantly improved survival in the PCI group (OR 0.49; 95% CI, 0.26–0.94; P = 0.030). These benefits were associated with similarly favorable effects on cardiac remodeling, including improved left ventricular ejection fraction in the PCI group (+4.4% change; 95% CI, 1.1–7.6; P = 0.009).

PROCEDURAL FUNDAMENTALS

The technical and procedural success rates of PCI in CTOs have modestly increased over the last 20 years because of greater operator experience and improvements in equipment and procedural techniques (30). Despite this observation, CTOs remain the lesion subtype in which PCI is most likely to fail. In recent contemporary series, procedural success rates have ranged from 55% to 80%, with the variability reflecting differences in operator technique and experience, availability of advanced guidewires, CTO definition, and case selection. The most common PCI failure mode for CTOs is inability to successfully pass a guidewire across the lesion into the true lumen of the distal vessel.

Most studies have consistently reported that increasing age of the occlusion, greater lesion length, presence of a non-tapered stump, origin of a side branch at the occlusion site, excessive vessel and lesion tortuosity, calcification, ostial occlusion, and lack of visibility of the distal vessel course negatively affect the ability to successfully cross a CTO (30). In the past, the presence of bridging collaterals was also consistently identified as a determinant of failed CTO PCI, but in more recent experiences, success rates may no longer be inversely correlated with the presence of bridging collaterals and other angiographic characteristics. Bridging collaterals may reflect the chronicity of the lesion and signify the requirement for stiffer and/or tapered tip wires to penetrate the occlusion. The availability of enhanced force wires with greater torque response has clearly increased the success rates in occlusions with bridging collaterals and similar angiographic complexities to the point where CTOs should no longer be avoided for these reasons alone.

A recent multicenter CTO registry identified predictors of unsuccessful recanalization (31). This study documented experiences with 1362 patients at three centers from 2000 to 2007. Both angiographic and clinical outcomes were measured over long-term follow-up, presently out to three years for the majority of patients. Recanalization was successful in 65.5% of native vessels and 76.6% of in-stent restenosis cases. In the overall cohort, a longer lesion, blunt appearance of the proximal...
oclusion, vessel calcification, and prior CABG were all associated with procedural failure.

**CLINICAL AND PROCEDURAL CONSIDERATIONS FOR CTO REVASCULARIZATION**

**Imaging: Invasive Angiography, CT Angiography, and IVUS**

Once a decision has been made to attempt recanalization of a CTO, characterization of the plaque (e.g., extent of calcification, CTO origin) and visualization of the distal vessel must be optimized. In most instances, this may be achieved with invasive angiography utilizing contralateral injection of contrast into the artery supplying collaterals to the distal vessel (Fig. 35.4). If there is any doubt regarding the location of the true lumen or the anatomical course of the occluded vessel segment, a coronary CT angiogram with 3D reconstruction may be particularly useful (Fig. 35.5). Furthermore, in selected cases, coronary CT angiography may improve patient selection for CTO recanalization, decrease the time and contrast needed for the procedure, decrease complications, and ultimately improve procedural outcome (32).

To increase the likelihood of success, an 8-Fr guiding catheter is recommended. Extended length sheaths (≥35 cm) will provide additional support. Larger guide catheters provide excellent support for guidewire penetration but may also be associated with increased contrast utilization. Larger diameter guiding catheters also enable delivery of covered stent grafts in uncommon instances of coronary perforation after successful recanalization. If a second angiographic catheter is used for contralateral injection, a 5- or 6-Fr catheter may be inserted into the contralateral femoral artery or either brachial or radial artery. For RCA CTOs, an Amplatz guide will provide maximal support, while any supportive catheter with extra backup can be used for the left coronary system. One exception is in instances using the retrograde approach (described below), in which a short guide (≤85 cm) is required in the “donor” artery that supplies the collateral flow.

Intravascular ultrasound (IVUS) has become a routine imaging modality in interventional cardiology and can be very useful in the evaluation and treatment of CTOs. Using an antegrade approach to the lesion, IVUS can be used to

1. identify the proximal cap location using the IVUS catheter in the side branch,
2. confirm the wire penetration into the proximal cap,
3. redirect the wire into the true lumen after penetrating the subintimal space, and
4. optimize stent placement, expansion, and apposition.

When performing a retrograde approach, IVUS can be used to help guide the retrograde wire into the proximal lumen of the CTO (Fig. 35.6).

**Antithrombotic Therapy**

Unfractionated heparin (UFH) is the preferred antithrombin therapy during percutaneous CTO revascularization. In the case of coronary perforation, unlike presently available direct thrombin inhibitors, UFH can be readily reversed with administration of protamine (10 mg reverses 1000 U of UFH). In most instances, a reduced initial bolus dose is administered to achieve an activated clotting time (ACT) of approximately 200 to 250 seconds until the guidewire has successfully crossed the CTO, after which additional UFH may be required before angioplasty and stent placement to achieve an ACT of approximately 300 seconds.

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**Figure 35.4** Angiogram with dual injections showing a chronic total occlusion (CTO) of the left anterior descending artery (LAD).

**Figure 35.5** CT angiogram of a known chronic total occlusion (CTO) of the right coronary artery (RCA) demonstrating heavy calcification at the site of occlusion and a significant bend in the RCA within the occluded segment.
Guidewire Technology and Selection

Crossing the CTO with a guidewire is the most important and challenging step of the procedure and is the most frequent cause for failed PCI of a CTO. There are three separate steps to crossing a CTO: penetrating the proximal fibrous cap; traversing the body of the CTO to reach the distal fibrous cap; and penetrating the distal fibrous cap to enter the true lumen. Wires designed particularly for treating CTOs can be broadly divided into two major groups: polymer-jacketed and/or hydrophilic guidewires, and stiffer, nonpolymer (nonhydrophilic or hydrophilic) guidewires. Both wire categories may be available in standard (0.014-in. diameter) or tapered (0.009- to 0.010-in. diameter) tip configurations. The stiffer, nonhydrophilic guidewires are typically more controllable, provide better tactile feel, and are less likely to cause vessel dissection. Techniques differ, but depending on operator experience, it is generally recommended to initially attempt CTO penetration with a less stiff guidewire and progress to graduated tip-load wires if resistance to penetration is encountered.

Hydrophilic wires advance with minimal resistance and tactile feel, even down minute branches and false channels, contributing to an increased risk of coronary perforation. These guidewires offer maneuverability in tortuous vessels and may be steered more easily in a true lumen immediately after sharp bends. However, they are more likely than noncoated wires to penetrate beneath plaque and cause subintimal dissections. Furthermore, they less commonly maintain their tip shape compared with nonpolymer coated wires and do not offer precise tip control. A hydrophilic wire may be passed for long distances in a false channel without resistance. The course of hydrophilic wires must be assessed in at least two orthogonal views to confirm the wire is in the true lumen. The most commonly used polymer-coated wires are the Asahi Fielder (Regular, FC, and XT), the Abbott Whisper, the Guidant Pilot (ranging in support from 50 to 200), and the Boston Scientific Choice and Graphix series. Once a CTO-specific guidewire has crossed the occlusion and passed into the distal lumen, the wire should be exchanged with a soft, floppy-tipped wire to minimize the risk of distal wire perforation or dissection.

A microcatheter or an over-the-wire (OTW) 1.5-mm balloon catheter can be used for support as well as access for ease of exchanging wires. The current 1.5-mm compliant balloons are very low profile and are able to cross lesions in a majority of cases. Smaller-diameter (≤1.25 mm) balloons are presently under investigation and are available outside the United States. A balloon catheter also offers the option of treatment with dilation of the vessel as well as added support by using it as an anchoring device within the vessel for greater guidewire support.

Inability to cross a CTO with a balloon catheter despite successful guidewire recanalization is an infrequent event. Assuming adequate guiding catheter support, one method is to use a second angioplasty balloon in a side branch vessel proximal to the CTO (“anchoring balloon” technique). In some instances, incremental inflations with a small diameter (≤1.5 mm) balloon within the proximal segment of a CTO may facilitate eventual crossing. Other treatment options include laser atherectomy using a 0.9-mm laser catheter, rotational atherectomy (which requires passage of specialized rotablator guidewire), or the Tornus (Asahi Intec, Aichi, Japan) support catheter. In the latter example, the Tornus catheter is a braided stainless steel support catheter that is advanced in a counterclockwise fashion over the guidewire to create a passage in highly stenosed lesions and facilitate subsequent balloon catheter delivery.

Guidewire Techniques: Antegrade, Retrograde, Controlled Dissection

The antegrade approach is the most common initial strategy for attempting to recanalize a CTO. Starting equipment may vary depending on lesion characteristics and anatomy. A support catheter (OTW balloon or microcatheter) with either a stiff nonhydrophilic guidewire (e.g., Miracle Bros 3 g, Asahi Intec/Abbott Vascular, Redwood City, California, U.S.) or a tapered hydrophilic wire (e.g., Fielder XT, Abbott Vascular) is used to probe the lesion initially. If the proximal cap cannot be penetrated or the wire is unable to be advanced within the lesion, progressively stiffer wires may be substituted. For some experienced CTO interventionists, high penetrating force wires (e.g., 9- to 12-g tip load) are often selected as an initial guidewire. With the use of the stiffer (and hydrophilic) guidewires, however, the operator must be aware of the increased risk of complications (e.g., coronary perforation or major dissection). Wire shaping for the antegrade approach of CTOs is markedly different than for nonocclusive disease. In general,
the initial wire should have a bend with an angle < 30° approximately 1 mm from the tip. If more angulated bends are required to access the CTO, this should be done with a soft, floppy wire and then exchanged for a dedicated CTO wire.

Two specialized techniques for CTO recanalization using an antegrade approach have evolved for failure after initial wire entry in the lesion. The parallel wire technique is a common method to approach CTO PCI (Fig. 35.7). Occasionally a guidewire may exit the true lumen of the occluded vessel and enter a subintimal dissection plane. In this instance, the wire is left in place as a visual landmark to avoid further vessel trauma and to obstruct entry into the false lumen. A second wire (stiff or hydrophilic, depending on the lesion characteristics) is advanced to the point of the first wire's exit and then redirected toward the true lumen. A twin-pass dual access exchange catheter (Vascular Solutions, Inc., Minneapolis, Minnesota, U.S.) can be very useful when introducing the second wire.

An alternative method is the subintimal tracking and reentry (STAR) technique (33) (Fig. 35.8). This is a method of intentional subintimal dissection using a hydrophilic wire typically shaped with a prolapsed tip. The wire is advanced beyond the occlusion adjacent to the distal lumen and may spontaneously reenter the true lumen in the main vessel, or more commonly at the confluence of bifurcating side branches. Ultimately, an extensive dissection is created, which typically requires

Figure 35.7 Angiogram of a CTO of the right coronary artery using a parallel wire technique. The first guidewire entered the subintimal space and was left in place. A second guidewire was passed adjacent to the first one and directed toward the true lumen. Abbreviation: CTO, chronic total occlusion.

Figure 35.8 Angiogram showing the subintimal tracking and reentry (STAR) technique for treatment of a right coronary artery CTO (A). This is a method of intentional subintimal dissection using a hydrophilic wire with a prolapsed tip. The wire is advanced beyond the occlusion adjacent to the distal lumen (B). It may spontaneously reenter the true lumen in the main vessel, or more commonly in side branches. Ultimately, an extensive dissection is created, which needs to be treated with several stents (C, D). Abbreviation: CTO, chronic total occlusion.
treatment with several stents. Notably, this technique may not only be associated with a higher risk of coronary perforation but can also result in shearing and occlusion of side branches and should be reserved as a bailout technique for highly symptomatic patients refractory to medical therapy.

More complex techniques for difficult CTOs include the retrograde approach as well as the controlled antegrade and retrograde subintimal tracking (CART) and reverse CART methods (34,35) (Fig. 35.9). These advanced techniques are generally reserved for passing wires in a retrograde course through septal or occasionally epicardial collaterals, although manipulations in epicardial collaterals are extremely high risk for perforation. Because the collaterals often originate from the contralateral coronary artery, dual arterial catheter access is required, and shortened guiding catheters (85-90 cm) are essential (at least for the retrograde donor catheter) to enable appropriate working length. Selective angiography of the collaterals is essential to define the location, size, and tortuosity of the vessels. Once localized, the collateral can be crossed with a supportive hydrophilic wire such as a Fielder FC (Asahi) and microcatheter. To deliver support catheters or angioplasty balloons to the target vessel, the septal collateral often requires dilatation. This can be accomplished with either a dedicated septal dilator catheter (Corsair, Asahi), or a 1.25- to 1.5-mm diameter compliant balloon at very low atmospheres. A stiff wire, such as a Miracle Bros 3 g or Conflanza, is then used to penetrate the proximal cap via a retrograde approach followed by balloon dilatation and then antegrade crossing. Alternatively, in cases of successful retrograde crossing but inability to deliver balloon catheters, the retrograde wire (300 cm in length) may be externalized through the antegrade guiding catheter and then exchanged and followed by antegrade PCI. IVUS from the proximal portion of the CTO may also assist in guiding the wire into the true lumen.

Figure 35.9 Angiogram showing a retrograde approach for treatment of a CTO of the left anterior descending artery (A). After selecting a septal collateral, a polymer-coated wire is advanced to the distal edge of the occlusion (B). The proximal lumen is accessed and treated with angioplasty. Next, guidewires are introduced in from an antegrade approach (C), and the vessel is treated definitively (D). Abbreviation: CTO, chronic total occlusion.
A CLINICAL RATIONALE AND STRATEGY FOR CTO REVASCULARIZATION

Table 35.1  Randomized Clinical Trials of Angioplasty Versus Stenting for Chronic Total Coronary Occlusions

<table>
<thead>
<tr>
<th>Trial</th>
<th>PTCA (%)</th>
<th>Stent (%)</th>
<th>P</th>
<th>PTCA (%)</th>
<th>Stent (%)</th>
<th>P</th>
<th>PTCA (%)</th>
<th>Stent (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenting in Chronic Coronary Occlusion (SICCO) (36)</td>
<td>26</td>
<td>16</td>
<td>0.058</td>
<td>74</td>
<td>32</td>
<td>&lt;0.001</td>
<td>42</td>
<td>22</td>
<td>0.025</td>
</tr>
<tr>
<td>Gruppo Italiano di Studi sulla Stent nelle Occlusioni coronariche (GISSOC) (37)</td>
<td>34</td>
<td>8</td>
<td>0.004</td>
<td>68</td>
<td>32</td>
<td>0.0008</td>
<td>22</td>
<td>5</td>
<td>0.04</td>
</tr>
<tr>
<td>Mori et al. (38)</td>
<td>96</td>
<td>11</td>
<td>0.04</td>
<td>57</td>
<td>28</td>
<td>0.005</td>
<td>49</td>
<td>28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stent vs Percutaneous Angioplasty in Chronic Total Occlusion (SPACTO) (39)</td>
<td>24</td>
<td>3</td>
<td>0.01</td>
<td>64</td>
<td>32</td>
<td>0.01</td>
<td>40</td>
<td>25</td>
<td>NS</td>
</tr>
<tr>
<td>Total Occlusion Study of Canada (TOSCA) (40)</td>
<td>20</td>
<td>11</td>
<td>0.02</td>
<td>70</td>
<td>55</td>
<td>&lt;0.01</td>
<td>15</td>
<td>8</td>
<td>0.03</td>
</tr>
<tr>
<td>Stents in Total Occlusion for Restenosis Prevention (STOP) (41)</td>
<td>17</td>
<td>8</td>
<td>NS</td>
<td>71</td>
<td>42</td>
<td>0.032</td>
<td>42</td>
<td>25</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not significant; PTCA, percutaneous transluminal coronary angioplasty.

In cases of primary retrograde crossing failure, variations on the retrograde approach include controlled dissection techniques termed CART and reverse CART. With CART, a balloon is inflated in the distal portion of the CTO over the retrograde wire that is located in the false lumen. A second antegrade wire is introduced distal to the proximal cap and into the subintimal space. When the retrograde balloon is inflated, expanding the subintimal space, the antegrade wire is then directed toward the retrograde balloon as it is deflated. Once the antegrade wire enters the space occupied by the balloon, it may then be advanced distally into the true lumen parallel to the path taken by the retrograde wire and balloon. The reverse CART is the same concept, although the roles are reversed; specifically, a balloon is inflated in the proximal portion of the CTO on the antegrade wire, and the retrograde wire is advanced into the subintimal space. These techniques are highly specialized and carry a significant risk. They require dedicated equipment and unique skills learned from extensive training, separate from most other interventional procedures.

CORONARY STENT OUTCOMES IN CTO REVASCULARIZATION

Six randomized trials of bare-metal stent (BMS) placement compared with balloon angioplasty alone have been reported (Table 35.1). Collectively, these trials have shown that BMS implantation achieves statistically significant and clinically meaningful reductions in angiographic restenosis and reocclusion. Compared with angioplasty alone, BMS also confer a long-term benefit with fewer repeat revascularization procedures (23,42). Despite these results, outcomes with BMS in CTOs are more similar to outcomes with balloon angioplasty in less complex, nonocclusive disease (43,44). In the TOSCA trial (40), for example, rates of restenosis and reocclusion in complex lesions exceeded 50% and 10%, respectively. At three-year follow-up, the occurrence of reocclusion was associated with a trend toward higher mortality and significant increase in the need for repeat revascularization (45).

Although these trials have varied considerably regarding enrollment criteria, antithrombotic regimen, and trial design, their results are remarkably concordant, demonstrating significant reductions in restenosis and reocclusion associated with BMS. Additional studies have demonstrated statistically significant yet modest improvement in left ventricular function and regional wall motion with CTO revascularization (37,46–48). Importantly, an increase in left ventricular function may be conditional on vessel patency at follow-up and revascularization of total occlusions of shorter duration (<6 weeks) (49).

Except for lesion length (49), exactly which features predict late target lesion failure remain elusive (50). While the lesion complexity of CTOs cannot be altered, the potential for new stent designs to improve rates of restenosis and reocclusion is considerable. Two observations mandate the need for systematic evaluation of drug-eluting stents (DES) in CTO revascularization: (i) advances in CTO technical and procedural success have been disproportionate to the increasing number of PCI procedures that involve nonacute occlusions and (ii) outcomes with stenting in CTOs are more similar to balloon angioplasty than to stenting in nonocclusive lesions.

Drug-Eluting Stents

Sirolimus-Eluting Stents

Against the background of several nonrandomized, observational studies demonstrating improved angiographic and clinical outcomes with DES, only one randomized trial comparing DES with BMS has been performed. In the Primary Stenting of Occluded Native Coronary Arteries (PRISON) II trial, 200 CTO patients were randomized in a single-blinded fashion at two centers in The Netherlands to treatment with either sirolimus-eluting stents (SES; Cypher, Cordis Corporation, Bridgewater, New Jersey, U.S.) or the bare-metal BX Velocity stent (Cordis Corporation) (51). Patients enrolled in this study underwent six-month angiographic follow-up to assess the primary endpoint of in-segment binary restenosis (>50% reduction in minimal lumen diameter). Overall, diabetes mellitus was present in 13% of patients, 55% of patients had a total occlusion <3 months old, and the average lesion and stent lengths were approximately 16 mm and 30 mm, respectively. At six months, treatment with SES was associated with statistically significant reductions in both in-stent (7% vs. 36%; P < 0.0001) and in-segment (11% vs. 41%; P < 0.001) angiographic restenosis (Fig. 35.10). Reocclusion was also significantly reduced with SES (4% vs. 13%; P < 0.04), despite treatment in both groups.
with aspirin and clopidogrel for a minimum duration of six months. The clinical benefit with SES also paralleled the relative benefit observed with angiographic measures. Specifically, target lesion revascularization (TLR) at 12 months occurred in 21% and 5% of BMS and SES patients, respectively ($P = 0.001$).

In addition to this randomized trial, several recent modest-sized observational studies examining clinical outcomes among patients treated with DES in CTO revascularization have supported the notion that DES may achieve similar reductions in the need for target vessel revascularization (TVR), as observed in less complex lesions (Table 35.2). In a retrospective study of 122 patients with CTOs treated with SES ($N = 144$ lesions), clinical and angiographic outcomes were compared with a historical control of 259 patients treated with BMS ($N = 286$ lesions) (54). At six months, overall major adverse cardiac events (MACE) were significantly lower with SES (16.4% vs. 35.1%; $P < 0.001$), principally due to a significantly lower rate of TLR (7.4% vs. 26.3%; $P < 0.001$). Restenosis was identified in 9.2% of patients in the SES group and 33.3% in the BMS group ($P < 0.001$). In multivariate analysis, significant predictors of six-month MACE were the use of BMS (HR 2.97; 95% CI, 1.80–4.89), lesion length ($P < 0.001$), and the left ventricular ejection fraction also significantly improved among the SES patients (51.8% baseline vs. 57.0% at 6 months; $P < 0.001$). This latter finding implies that maintenance of vessel patency with DES may be an important predictor of the improvement in left ventricular function.

Most recently, the Approaches to Chronic Occlusions with Sirolimus-Eluting Stents/Total Occlusion Study of Coronary Arteries-4 (ACROSS)/TOSCA-4 trial prospectively enrolled 200 patients undergoing CTO revascularization with SES using contemporary techniques and crossing technologies (Fig. 35.11) (61). In this nonrandomized study, clinical and six-month angiographic outcomes were compared with a historical control of patients receiving BMS in the prior TOSCA-I trial. Compared with the BMS group, patients treated with SES had significantly older age, more CTOs (i.e., $>6$ weeks), smaller caliber vessels, a higher proportion of diabetes, and longer lesion and stent lengths. However, despite higher complexity in the SES cohort, treatment with SES was associated with an unadjusted 66% relative reduction in the primary endpoint of angiographic binary restenosis within the treated segment.

### Table 35.2  Clinical Trials Evaluating Drug-Eluting Stents in Total Coronary Occlusions

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>6 mo</th>
<th></th>
<th>1 yr</th>
<th></th>
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<tr>
<td></td>
<td></td>
<td>Angiographic</td>
<td>TVR (%)</td>
<td>MACE (%)</td>
<td>TVR (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>restenosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SICTO (52)</td>
<td>25</td>
<td>0</td>
<td>8.0</td>
<td>12.0</td>
<td>12.0</td>
</tr>
<tr>
<td>e-Cypher Registry (53)</td>
<td>360</td>
<td>–</td>
<td>1.4*</td>
<td>3.1</td>
<td>–</td>
</tr>
<tr>
<td>RESEARCH Registry (54)</td>
<td>56</td>
<td>9.1</td>
<td>3.6</td>
<td>3.6</td>
<td>–</td>
</tr>
<tr>
<td>Werner et al. (55)</td>
<td>48</td>
<td>8.3</td>
<td>–</td>
<td>–</td>
<td>6.3</td>
</tr>
<tr>
<td>Nakamura et al. (56)</td>
<td>60</td>
<td>2.0</td>
<td>3.0</td>
<td>–</td>
<td>3.0</td>
</tr>
<tr>
<td>Ge et al. (57)</td>
<td>122</td>
<td>9.2</td>
<td>9.0</td>
<td>16.4</td>
<td>–</td>
</tr>
<tr>
<td>WISDOM Registry (58)</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>6.7</td>
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<tr>
<td>TRUE Registry (59)</td>
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<td>17.0</td>
<td>16.9</td>
<td>17.1</td>
<td>–</td>
</tr>
<tr>
<td>Buuellesfeld et al. (60)</td>
<td>45</td>
<td>13.2</td>
<td>13.2</td>
<td>15.6</td>
<td>–</td>
</tr>
<tr>
<td>ACROSS/TOSCA-4 (61)</td>
<td>200</td>
<td>7.5</td>
<td>6.0</td>
<td>6.5</td>
<td>–</td>
</tr>
</tbody>
</table>

*Denotes target lesion revascularization.

**Abbreviations:** TVR, target vessel revascularization; MACE, major adverse cardiac events.

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![Figure 35.10](6m 1y r 6 w e eks 2.8 mm (HR 0.62; 95% CI, 0.42–0.92). In a related study of 226 patients undergoing CTO revascularization (SES 106, BMS 120), treatment with SES was associated with a sustained, significant reduction in MACE through four-year follow-up (7.5% vs. 33.8%; $P < 0.001$) (56).

In the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry, among 56 patients treated with SES following CTO revascularization, the one-year occurrence of TVR was 3.6%, compared with 17.9% among a historical control group of patients receiving BMS (54). Similarly, the six-month rate of TLR was only 1.4% for 360 patients with CTOs who were included in the prospective e-Cypher registry (53). Among 180 patients undergoing SES implantation for CTO revascularization in Asia, the six-month occurrences of angiographic binary restenosis and TVR were 1.5% and 2.3%, respectively (62).

As part of a multicenter Asian registry evaluating DES, clinical and angiographic outcomes among 60 patients who underwent SES implantation during CTO revascularization were compared with a matched control of 120 CTO patients treated with BMS (62). At six-month angiographic follow-up, treatment with SES was associated with significant reductions in in-stent late loss, restenosis, and reocclusion. TLR was significantly lower at six months (23.0% vs. 2.0%; $P = 0.001$), and the left ventricular ejection fraction also significantly improved among the SES patients (51.8% baseline vs. 57.0% at 6 months; $P < 0.001$). This latter finding implies that maintenance of vessel patency with DES may be an important predictor of the improvement in left ventricular function.

At one year, treatment with SES was associated with sustained reductions in hierarchal MACE (3.0% vs. 42.0%; $P = 0.001$) and TLR (43.0% vs. 3.0%; $P = 0.001$). In a related study of 226 patients undergoing CTO revascularization (SES 106, BMS 120), treatment with SES was associated with a sustained, significant reduction in MACE through four-year follow-up (7.5% vs. 33.8%; $P < 0.001$) (62).
(19% vs. 55%; P < 0.001), defined as the length of contiguous target segment exposed to balloon dilation prior to stent placement. Following adjustment for baseline characteristics predictive of restenosis, the treatment effect increased to an 84% relative reduction in treated segment restenosis. Rates of in-segment and in-stent restenosis were 11.5% and 6.5%, respectively. At six-month clinical follow-up, rates of MI and TLR were 1% and 6%, respectively, contributing to a 6% occurrence of the composite endpoint of target vessel failure (cardiovascular death, MI, or TVR).

Paclitaxel-Eluting Stents

Compared with studies evaluating SES, relatively limited evidence exists to support the use of paclitaxel-eluting stents (PES) in CTO revascularization. One study examined treatment with PES (Taxus, Boston Scientific Corporation, Natick, Massachusetts, U.S.) in 48 patients undergoing CTO PCI and compared these patients with a historical control group with similar clinical and angiographic characteristics (55). At six months, both restenosis (8.3% vs. 51.1%; P < 0.001) and reocclusion (2.1% vs. 23.4%; P < 0.005) were significantly reduced among patients treated with PES. Because of significantly decreased rates of repeat PCI or CABG, MACE was also significantly lower in the PES group. One year following the index revascularization, repeat revascularization occurred in 3 patients in the PES group and 21 patients in the BMS group (6.3% vs. 43.8%; P < 0.001).

In the European TRUE Registry among 183 patients with CTOs who were treated with PES, seven-month rates of restenosis and TVR were 17.0% and 16.9%, respectively (59). It is noteworthy that the mean (±standard deviation) number of stents per patient (2.2 ± 1.2) and total stent length (58 ± 33 mm) were considerably greater than previous DES trials involving treatment of less complex lesion subsets. Other studies evaluating PES in CTO PCI have included fewer patients. One study examined clinical and angiographic outcomes among 45 CTO patients treated with PES (60). At six months, the rates of angiographic restenosis and TVR were 13.2%. Among 65 patients with CTOs in the international WISDOM registry, treatment with PES resulted in freedom from MACE and TVR at one year in 93.3% and 98.3% of patients, respectively (58).

More recently, analyses related to the subgroup of CTO patients included in the SYNTAX trial have been reported (52). Conducted at 62 European sites and 23 sites in the United States, the SYNTAX trial randomized 1800 patients to either CABG (N = 897) or PCI (N = 903) with PES to examine a primary endpoint of 12-month MACE and cerebrovascular events (MACCE), defined as all-cause death, cerebrovascular event, MI, and any repeat revascularization (PCI and/or CABG). Altogether, 479 patients had CTOs (CABG 235, PCI 244) that contributed to a higher SYNTAX lesion complexity score. Overall, less than 50% of the CTOs were successfully treated with PCI, but if any revascularization attempt was made, the success rate was 78%. Interestingly, despite randomization to CABG, more than 30% of vessels involving a CTO were not surgically revascularized. Safety outcomes (all death, stroke, MI) for patients with CTOs were similar between PCI- or CABG-treated patients, although CTO lesions treated with PCI had a higher rate of revascularization compared with CABG.

Comparative DES Trials in CTO Revascularization

Whether safety, clinical efficacy, and angiographic outcomes are similar between differing DES has only been recently examined (63,64). Despite more predictable variance in measures of neointimal hyperplasia by angiography and IVUS, demonstration of differences in clinical outcome across individual trials has been less consistent (65–74). However, whether disparities in angiographic and clinical outcome emerge in more complex lesion morphologies is an issue of ongoing study and is particularly relevant to CTOs.

At present, four comparative trials of SES and PES have been performed (Table 35.3). In general, these studies have been limited by their small study populations that limit statistical comparisons, variability in trial design, and limited clinical and angiographic follow-up. In the single-center Rotterdam registry (RESEARCH and T-SEARCH) comparing clinical
outcomes among CTO patients treated with BMS (N = 26), SES (N = 76) and PES (N = 57), one-year freedom from repeat TVR was significantly greater with DES compared with BMS (97.4% with SES; 96.4% with PES; 80.8% with BMS; P = 0.01 for comparison), despite significantly greater stent number and length per patient with DES (79). Similarly, the open-label, multicenter Asian CTO registry reported no significant differences in one-year TVR rates of 3.6% and 6.7% for SES (N = 396) and PES (N = 526) (76). In a subgroup of patients with three-year follow-up, MACE was significantly lower in the SES group (10.9% SES vs. 16.3% PES; P = 0.03), although rates of TLR were statistically similar (7.7% SES vs. 9.5% PES) (79). Recently, these same investigators reported results from a prospective registry of 1149 CTO patients treated with SES (N = 365), PES (N = 482), zotarolimus-eluting stents (ZES) (N = 154), tacrolimus-eluting stents (TES) (N = 109), or endothelial progenitor cell (EPC) capture stents (N = 39) (76). At nine months, TLR was significantly lower with SES compared with ZES, TES, and EPC stents, but did not statistically differ from PES. In another nonrandomized comparison of CTO patients treated with SES (N = 107) and PES (N = 29), statistically significant differences were observed regarding angiographic restenosis (9.4% with SES vs. 28.6% with PES; P < 0.05), although rates of TVR did not statistically vary (3.7% with SES vs. 6.9% with PES) (78). Finally, a modest-sized randomized trial comparing SES (N = 60) and PES (N = 58) in CTO PCI also demonstrated no significant difference in the eight-month TVR rates of 3.3% and 7.0% in the SES and PES cohorts, respectively (77).

The ongoing PRISON III trial is intended to compare clinical and angiographic outcomes among 300 CTO patients randomized in a 1:1, open-label fashion to treatment with either SES or ZES (Medtronic Corp., Santa Rosa, California, U.S.) (80). The primary endpoint is in-segment late lumen loss at eight-month angiographic follow-up, and secondary clinical endpoints include TLR, target vessel failure, and stent thrombosis.

CTO COMPLICATIONS

CTO PCI has traditionally been considered benign, with the presupposition that because the artery is already occluded with collateral circulation, no harm can be done. However, observational studies demonstrate that CTO PCI carries much the same risk as conventional PCI (81). Coronary perforation is the most feared complication of CTO intervention. Perforation often may not occur at the occluded segment or be related to the guide-wire itself rather than to adjunctive devices including balloon inflation, stent implantation, or atherectomy. Coronary perforation may also occur in epicardial or septal collateral branches related to catheter delivery during retrograde procedures. Further, perforation is not always manifest during the procedure; in one case series study, 45% of 31 tamponade events were diagnosed after the patient had left the catheterization laboratory (82). Although infrequent, coronary perforation and the development of cardiac tamponade may have severe clinical consequences. Among patients developing cardiac tamponade, rates of death, emergency surgery, MI, and transfusion occurred in 42%, 39%, 29%, 65% of patients, respectively (82). Aside from early recognition, management of coronary perforation requires simultaneous action on behalf of multiple catheterization laboratory personnel, including (i) prolonged inflation across the perforation with an occluding balloon or perfusion balloon catheter, (ii) reversal of anticoagulation, (iii) covered stent placement, emergency surgery or embolization, and/or (iv) pericardiocentesis. In the absence of clinically evident perforation, an operator nevertheless should be vigilant if a perforation is suspected. Angiography of the contralateral vessel must be performed to exclude the possibility of extravasation via the collaterals. Close monitoring with a pulmonary artery catheter and serial echocardiograms may also be necessary. Finally, aside from coronary perforation, additional procedural-related complications that may result in MI, include thrombus formation, coronary dissection, and side-branch or collateral occlusion.

INNOVATIVE CTO TECHNOLOGIES

In spite of the enthusiasm for DES to substantially reduce restenosis and repeat revascularization, CTOs remain the last great barrier to initial technical and procedural success. Although the complexity of lesions treated with DES is likely to increase, interventionalists must first be able to recanalize CTOs before even considering which type of stent to implant. Accordingly, several novel technologies have been proposed to facilitate CTO PCI, with variable success.

Extending the platform of wire-based technology further is the Safe-Cross system (Spectranetics, Colorado Springs, Colorado, U.S.) that employs forward-looking optical coherence reflectometry coupled with a radiofrequency energy source at
the distal end of the guidewire. In addition to direct visualization, optical coherence reflectometry enables guidance within the CTO, informing and/or alerting the operator when the wire engages the intraluminal CTO segment or the vessel wall, respectively. This mechanism of indirect imaging within the CTO may then facilitate guidewire advancement using the energy source to ablate fibrous or calcified tissue. Recent evaluations in both coronary and peripheral interventions have demonstrated the potential of this technology, particularly following guidewire failures. Among 116 patients enrolled in the Guided Radiofrequency Energy Ablation of Total Occlusions (GREAT) registry, technical success (defined as guidewire placement in the true lumen distal to the CTO) was achieved in 56% of patients following conventional guidewire failure (83). One device-related clinical perforation was reported. A similar success rate was observed in peripheral arterial occlusions in the Guided Radiofrequency in Peripheral Total Occlusion (GRIP) trial, in which the Safe-Cross system was capable of traversing 76% of CTOs (75 lesions) after failure with standard guidewires (75).

An alternative to wire-based technologies is the Frontrunner catheter (Cordis Corporation, Warren, New Jersey, U.S.). Intended to cross through fibrous, resistant CTOs, the Frontrunner catheter performs blunt microdissection of tissue within the CTO to facilitate guidewire placement in the distal true lumen. Specifically, the actuation of jaws on the distal end of a 0.039-in. diameter catheter creates a 2.3-mm excursion that separates tissue planes within the occluded segment. The catheter is approved for use in both coronary and peripheral arterial interventions and may also be used with a support catheter intended for greater stability at the proximal occlusion. Among 105 patients with CTOs, a previous design of the Frontrunner catheter successfully crossed 56% of CTOs otherwise impenetrable to conventional guidewires (84).

Innovative technologies presently under investigation include true lumen crossing and intraluminal reentry devices. Using the facilitated antegrade steering technique (FAST), both the CrossBoss CTO catheter and the Stingray CTO reentry system (Bridgepoint Technologies, Minneapolis, Minnesota, U.S.) may provide increased success rates and safety compared with guidewires alone. The CrossBoss CTO catheter tracks over a wire via a FAST spin technique. Specifically, the catheter has a highly torqueable coiled-wire shaft, and the spin technique reduces the amount of forward force required to cross the CTO. The Stingray system is a balloon catheter with a flat shape and opposing exit ports for selective guidewire reentry when positioned within a dissection plane but adjacent to the vessel true lumen. The first-in-human experience reported a technical success of 88% (36/41) with no in-hospital or 30-day MACE (85). The ongoing FAST-CTO clinical trial will ultimately address the feasibility and effectiveness of this new technology.

For many CTO-specific device therapies, clinical success has not exceeded expectations compared with historical standards. In the Total Occlusion Trial with Angioplasty by Laser Guidewire (TOTAL) trial, no significant differences were observed between patients treated with standard guidewires or the excimer laser guidewire (76% vs. 75% conventional guidewire, P = 0.33) (22). Limited evaluations with catheter-based delivery of high-frequency mechanical ultrasound have also reported lower procedural success compared with guidewires (86,87), although investigation with a revised catheter platform is planned. Further, pharmacological approaches to CTO dissolution have been developed with extended intracoronary infusions of fibrinolytic agents and collagenase. Recent preclinical investigation with the local administration of collagenase has suggested that this matrix metalloproteinase may effectively degrade occlusive fibrotic plaque to facilitate crossing with standard guidewires (88).

Finally, for patients with CTOs that are not amenable to revascularization, performance of transmyocardial laser revascularization does not appear to improve survival or general health status (89).

FUTURE DIRECTIONS
Although the angiographic results of intended revascularization are unmistakable (i.e., either failed or successful epicardial recanalization), the effects of total occlusion and reperfusion at the level of the myocardium are less apparent. To identify which patients might benefit from revascularization, delayed-enhancement contrast magnetic resonance imaging (MRI) may be useful for the identification of viable and ischemic myocardium subtended by a CTO. Recent clinical experience has been useful in identifying viable myocardial tissue in spite of matched, regional wall motion abnormalities by other imaging methods (90). Among 44 patients with 58 CTO segments, 37 patients (64%) had ≤50% transmural infarction, with 12 patients (21%) having no evidence of infarction. Further, the presence of collateral flow did not predict either myocardial viability or improvement following revascularization. Territories without extensive infarction at baseline demonstrated significant regional wall motion improvement following revascularization, and more recent evaluations with adenosine stress MRI following percutaneous revascularization have demonstrated resolution of ischemia. Thus, application of noninvasive imaging with coronary CT angiography and MRI may inform patient selection by assisting in prediction of both procedural success (coronary CT angiography) and clinical improvement (MRI).

Novel methods for CTO revascularization may also look beyond the occluded vessel segment as an alternative to guidewire-based techniques. Although still a developing technology, percutaneous in situ coronary artery bypass (PICAB) may provide an alternative method of revascularization for patients in whom conventional revascularization has either failed or is not feasible (91). Specifically, percutaneous in situ coronary venous arterIALIZATION (PICVA) utilizes the native coronary vein as a bypass conduit. Using IVUS guidance, an adjacent coronary vein is accessed with a nitinol needle that permits passage of a 0.014-in. wire followed by placement of venous occluder devices proximal and distal to the bypass segment. Feasibility studies are ongoing to overcome challenges in venous anatomy, variable quality of imaging with IVUS, and accurate sizing of venous occluder devices. Aside from venous arterIALIZATION, the transvascular access catheter may also be effective in facilitating guidewire reentry from a dissection plane distal to an occluded segment.

CONCLUSIONS
The implications of improving early procedural and long-term clinical outcomes among patients with CTOs are considerable. However, our current knowledge of procedural, angiographic, and clinical outcomes following PCI for CTOs is limited by the systematic or preferential exclusion of patients with CTO target lesions from major interventional cardiology clinical trials. Further, no technology is presently available to reliably predict
procedural success in patients considered for CTO revascularization. Even following successful guidewire crossing, compared with revascularization in nonocclusive lesions, the unfavorable results with coronary stenting reflect the complexity of CTOs with regard to lesion length, plaque burden, negative vascular remodeling, thrombus, and calcification.

While the challenges associated with CTOs may seem formidable, it is equally clear that our evolving understanding of the benefits of revascularization has contributed to increasing interest in CTOs, reflected in an increasing number of CTO procedures, the development of novel technologies, and the design of trials dedicated to CTO revascularization. Over the past five years alone, a number of alternative technologies to guidewires have been advanced, including mechanical techniques, ablation, microdissection, and transvascular reentry. Further clinical trials with DES and drug-eluting balloons are also underway. Recent evaluations with MRI in patients with CTOs provide further mechanistic support toward improvement in left ventricular function and how these findings may translate into observations of favorable clinical outcomes associated with successful CTO revascularization. Thus, while CTOs reflect the current inadequacies in PCI methods for achieving initial procedural success and for sustaining restenosis-free patency following initial success, they also represent a very unique opportunity to conquer perhaps the most difficult and yet one of the most common lesion subsets in interventional cardiology.

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Saphenous vein grafts
Claudia P. Hochberg and Joseph P. Carrozza

INTRODUCTION
In 1969, Favaloro described the first use of coronary artery bypass surgery (CABG) for the treatment of myocardial ischemia due to coronary artery disease (1). Subsequent advances in myocardial preservation and surgical techniques led to improvements in outcomes and the widespread use of CABG. Whereas CABG improves long-term prognosis in high-risk subsets, such as patients with significant left main and three-vessel disease with decreased left ventricular function, for most patients CABG is a palliative, rather than a curative procedure. The use of the internal mammary artery (IMA) and other arterial conduits revolutionized CABG because of the relative resistance of arterial conduits to accelerated atherosclerosis compared with saphenous vein bypass grafts (SVG) (2,3). Recurrent ischemic events occur in a time-dependent manner and may result from progression of disease in the native coronary arteries. However, the most common cause of adverse cardiac events in the post-CABG patient is atherosclerosis and attrition of SVG (4).

ANATOMIC CONSIDERATIONS
SVG Patency and Predictors of SVG Failure
Ischemia in myocardial territories supplied by SVG is often highly dependent on the time from implantation. Historically, the peroperative SVG occlusion rate was 10% and the 10-year occlusion rate was 50% (Fig. 36.1) (5). A more recent assessment reported improved 10-year SVG patency rates, but lower IMA patency rates than had previously been reported (6). At 7 to 10 days, 95% of SVG were patent by angiography. One week patency was associated with a 76% 6-year patency rate and 68% 10-year patency (Fig. 36.2). The overall 10-year SVG patency rate was 61%. IMA patency at one week was 99% and was associated with 90% 6-year and 88% 10-year patency rates. The overall 10-year IMA patency rate was 85% (6).

Early SVG failure may result from any process that contributes to flow reduction and thrombosis such as prothrombotic states, surgical misadventure (e.g., constrictive sutures), nonlaminar flow patterns secondary to SVG-coronary artery size mismatch, compromised outflow from distal coronary artery disease, and venous varicosities. Predictors of SVG patency include the location of the SVG, with left anterior descending artery SVG having a 69% 10-year patency rate compared with 56% for right coronary artery SVG, and 58% for left circumflex artery SVG. The diameter of the recipient artery by angiography was also highly predictive. Grafting of arteries >2.0 mm in diameter had an 88% 10-year patency rate compared with arteries ≤2.0 mm, which had a 55% 10-year patency rate (p < 0.001) (6). Clinical presentations of early SVG failure can be protean and include exertional chest pain, acute coronary syndromes, ventricular arrhythmias, hemodynamic compromise, or may be clinically silent, especially if the grafted artery subtends a minimal amount of viable myocardium.

Pathology of SVG Failure
Within one year following CABG, most SVG have developed some degree of concentric intimal proliferation similar to the smooth muscle cell proliferative response observed after vascular injury induced by percutaneous coronary intervention (PCI). The development of intimal hyperplasia in "arterialized" veins is a ubiquitous process commencing approximately four weeks after implantation. While this proliferative response often results in mild luminal narrowing throughout the SVG, it may be of sufficient magnitude to obstruct blood flow. The etiology of this pathologic response probably involves endothelial cell damage or denudation occurring during harvesting, vascular ischemia when vasa vasorum are severed, and barotrauma resulting from exposure of the vein to arterial pressure. This proliferative response is often most exuberant at anastomotic sites suggesting greater injury at these loci. Even if intimal hyperplasia does not result in ischemia within the first year following CABG, its presence may provide the substrate for accelerated SVG atherosclerosis (5). Caños et al. compared the clinical, angiographic, and intravascular ultrasound (IVUS) characteristics of early (mean SVG age 6 months) and late (mean SVG age 105 months) SVG failure. Early SVG failures were more likely to be ostial (37.5% vs. 17.5%, p < 0.001), and had smaller pretreatment reference diameters (2.47 ± 0.86 vs. 3.26 ± 0.83, p < 0.001), smaller minimum lumen diameters (MLD) (0.80 ± 0.64 vs. 1.08 ± 0.64, p < 0.001), and greater pretreatment diameter stenosis (71.6 ± 19% vs. 66.7 ± 17.7%, p < 0.017). Additionally, early SVG failure was associated with lower thrombolysis in myocardial infarction (TIMI) flow rates and SVG that failed late were more likely to have degenerated, diffuse atheroma. IVUS analysis suggested that SVG that fail early are diffusely diseased conduits without positive remodeling, resulting in smaller lumen size (7). While it is controversial as to whether SVG undergo positive remodeling, the lack of positive remodeling may contribute to early graft failure.

Premature atherosclerosis is the major factor contributing to the SVG attrition and accounts for the majority of acute ischemic syndromes in the post-CABG patient. While the pathophysiologic of atherosclerosis in SVG generally resembles that of native coronary arteries, there are important differences. Compared with native arteries, SVG atherosclerosis is often rapidly progressive, more diffuse, associated with greater numbers of foam and inflammatory cells, lacks a fibrous cap, and is generally more friable (Fig. 36.3). Furthermore, since SVG lack side branches, any process resulting in decreased flow may precipitate secondary thrombosis. Arterial bypass conduits are relatively resistant to
There has recently been a greater likelihood of long-term freedom from ischemic events (8). However, focal stenoses may develop within the first year, especially at anastomotic sites. Repeat CABG is technically more challenging than the first operation and is associated with increased procedural morbidity and mortality (9).

SVG Stenting: Early Experience

The favorable angiographic and clinical outcomes observed after stenting native coronary arteries provided a rationale for investigation into the use of stents for the treatment of SVG disease. Several single and multicenter observational studies reported on the use of the Palmaz-Schatz coronary stent (15–17). The multicenter Palmaz-Schatz Stent Registry enrolled 589 patients with 624 focal SVG lesions. Procedural success was high (>98%) and major adverse cardiac events such as myocardial infarction (MI), urgent CABG, and death occurred in only 2.9%. Stent thrombosis within the first month was diagnosed in only 1.4% of patients. However, there was a high incidence of hemorrhagic complications (14.3%) secondary to the mandated use of aspirin, heparin, dextran, dipyridamole, and warfarin. Quantitative angiographic analysis of a subset of patients in the registry revealed an overall
restenosis rate of 34% (15), with significantly higher restenosis rates observed for previously treated (51% vs. 22%) and aorto-ostial (61% vs. 28%) lesions. Debubbling of ostial SVG lesions before stent placement did not appear to confer improved long-term outcomes compared with stenting alone (18). This relatively high incidence of restenosis may have been due in part to the absence of stents designed to optimally treat vessels larger than 4 mm in diameter.

The SAVED Trial
The first multicenter, prospective randomized trial of SVG stenting was the Saphenous Vein in De Novo (SAVED) trial, in which 220 patients were randomized to Palmaz-Schatz stenting or balloon angioplasty for the treatment of relatively focal, de novo lesions in 3- to 5-mm SVG (19). The primary endpoint of the trial was angiographic restenosis at six months. Procedural success (defined as a reduction in diameter stenosis <50%, in the absence of major cardiac complications) was significantly higher with stenting compared with balloon angioplasty (92% vs. 69%), although the incidence of major hemorraghic complications was also higher in the stent cohort. The posttreatment minimal lumen diameter was significantly larger in the stent group (2.81 vs. 2.16 mm) and at six months, despite a greater late loss (1.06 vs. 0.66 mm), stenting conferred both a significantly greater net gain (0.85 vs. 0.54 mm) and larger minimal lumen diameter (1.73 vs. 1.49 mm). Whereas the angiographic restenosis rates were not statistically different (37% vs. 46%, p = 0.11) because of inadequate sample size, freedom from major adverse cardiac events [MACE defined as freedom from death, MI, repeat CABG, or target lesion revascularization (TLR)] was significantly improved in the stent group (73% vs. 58%, p = 0.03) (Fig. 36.4). Although the SAVED trial did not conclusively demonstrate a reduction in angiographic restenosis with stenting, the favorable clinical results from the trial as well as the limitations of other devices, has established stenting as the predominant percutaneous treatment modality for SVG disease. While stand-alone balloon angioplasty can be performed with similar safety and efficacy as stenting at the distal anastomosis of SVG, adjunctive stenting improves long-term outcome by reducing the need for repeat revascularization (20).

Bare-Metal Vs. Drug-Eluting Stents in SVG Disease
On the basis of the findings of the SAVED trial and the more recent VENESTENT trial, the implantation of stents in diseased SVG has become the standard of care for the endovascular treatment of SVG lesions (21). Despite improved angiographic results and clinical outcomes after bare-metal stent (BMS) implantation, the rate of BMS restenosis in SVG is higher than in the native coronary arteries, with restenosis rates over 30% (19). The introduction of drug-eluting stents (DES) has conclusively decreased the rates of angiographic and clinical restenosis, as well as target vessel revascularization (TVR) in native coronary arteries compared with BMS. Whether there is comparable benefit to DES implantation in SVG is unknown. Several registries and one small randomized trial evaluating both the short- and the long-term outcomes of DES and BMS in the treatment of SVG disease have been completed (22–26). The Reduction of Restenosis in Saphenous Vein Grafts with Sirolimus-Eluting Stents (RRISC) trial randomized 75 patients with SVG lesions (distal graft anastomotic lesions were excluded) to receive BMS or sirolimus DES (22). In-stent late loss was significantly lower in DES (0.38 ± 0.51 vs. 0.79 ± 0.66 mm) compared with BMS, and both binary in-stent and in-segment restenosis were reduced (11.3% vs. 30.6% and 13.6% vs. 32.6%, respectively). Additionally, both TLR and TVR were significantly reduced with DES compared with BMS, but there were no significant differences in rates of death or MI between the two groups. However, intermediate term follow-up (median 32 months) reported an excess mortality in the cohort randomized to DES with 11 deaths in the DES group compared with 0 deaths in the BMS group (p < 0.00) (Fig. 36.5A). A post hoc analysis of the RRISC trial suggests that the reduction in repeat revascularization in the DES group seen at six months is lost at later follow-up (Fig. 36.5B) (27). One possible mechanism of DES failure in SVG was the potential for stent-SVG size mismatch. Many SVG are >4.0 mm in diameter and DES are not currently manufactured larger than 3.5 mm. This potential size mismatch may lead to stent undersizing and increased rates of restenosis. Another possibility is that although DES implantation in SVG is associated with a lower early risk of restenosis, there may be a significant “catch-up phenomenon” (similar to that seen with brachytherapy) resulting in later events.

Recent results from the Registro Regionale Angiologiche (REAL) Emilia-Romagna Registry from Italy also suggested similar long-term clinical outcomes of DES compared with BMS in the treatment of SVG disease (25). The registry contained 288 BMS patients and 72 DES patients. The incidence of MACE at 12 months was similar in the two groups (17.8% with DES and 20.3% with BMS, p = 0.460). Nor was there a difference in the individual components of the primary endpoint. Additionally the TLR was not significantly different between the two groups, although there was a two-fold increase in TLR in the BMS group compared with the DES group (8.1% vs. 4.3%) (25). In contrast, a single center study with 61 DES and 89 BMS showed cumulative MACE rates at six months to be 11.5% in the DES group compared with 28.1% in BMS group, (p = 0.02) and TLR rates of 3.3% vs. 19.8%, respectively (24). Similarly, Lee et al. looked at 139 patients undergoing SVG PCI and
found that DES was associated with a lower incidence of MI (4.3% vs. 20%, \( p = 0.04 \)), and TVR (1.01% vs. 36.9%, \( p = 0.035 \)) at a mean follow-up of 9.1 months (23). There are even fewer data available on late stent restenosis in DES-treated patients. A large randomized trial with long-term follow-up is needed to better delineate the outcomes of DES compared with BMS in the treatment of SVG disease.

**COMPLICATIONS OF SVG STENTING**

**Distal Embolization and No-Reflow**

The major limitation of SVG stenting is the occurrence of acute ischemic events secondary to distal embolization and no-reflow. When serial cardiac biomarkers are measured routinely following SVG stenting, the incidence of periprocedural CK-MB elevation may be as high as 50%, with an incidence of large (>5 times normal) CK-MB release of 15% (28). The pathophysiology of distal embolization following SVG stenting is multifactorial. Compared with native coronary arteries, diseased SVG are on average 0.3 mm in diameter larger and more diffusely diseased, and thus contain a greater plaque burden (29). Furthermore, the friable nature of a SVG atheroma, with its abundance of cholesterol-laden foam cells and thin fibrous caps renders it prone to embolization following high-pressure dilatation commonly employed to optimize stent expansion. Aspirates from stented SVG are enriched with atheromatous elements, that is, foam cells, inflammatory cells, fibrous caps, and necrotic cores (30). Older, degenerated SVG often contain abundant fresh and organized thrombus, which develop in SVG with reduced or nonlaminar flow resulting from vascular ectasia, flow-limiting atheroma, poor distal outflow, and systemic prothrombotic states associated with comorbidities such as diabetes mellitus (31). Disruption of fresh thrombus may lead to no-reflow from the embolization of platelet aggregates or intense microvascular constriction following the release of soluble mediators of vasoconstriction such as serotonin or thromboxane A2 (32). Risk factors for distal embolization include angiographically visible thrombus, intervention for acute coronary syndromes, plaque ulceration, and SVG degeneration (33).

The inability to restore TIMI 3 flow is associated with a 32% incidence of Q-wave, or large (CK-MB > 50 IU/L) non-Q wave MI, and an 8% in-hospital mortality, underscoring the link between reduced postintervention TIMI flow and clinical outcome (34). Rates of periprocedural MI in one study were 41.7% with postprocedure TIMI 1 or 2 flow, and only 5.6% with TIMI 3 flow (26). However, it is important to remember that even in the absence of angiographic complications or impaired flow, patients who undergo successful SVG stenting are at risk for periprocedural myonecrosis. The incidence and consequences of distal embolization following SVG stenting are best illustrated by a retrospective analysis of 1056 patients by Hong et al. (28). Seventy percent of the patients did not experience an angiographic complication, however posttreatment CK-MB elevation was still an important determinant of mortality at 12 months indicating that angiography is inadequate to completely evaluate downstream microperfusion. Postprocedural enzyme elevation and diabetes mellitus were the strongest independent predictors of long-term mortality. This strong association between periprocedural myonecrosis and poor prognosis in post-CABG patients (compared with patients undergoing stenting of native arteries) is best explained by the observation that this population is older, and has a greater incidence of comorbidities such as congestive heart failure, diabetes mellitus, and reduced ejection fraction (29). A more recent pooled analysis of five randomized control trials and one registry study conducted by Coolong et al. evaluating embolic protection devices (EPDs) in SVG PCI evaluated determinants of MACE at 30 days. The univariate predictors of increased risk were current smoking, history of MI, glycoprotein (GP) IIb/IIIa inhibitor use, the angiographic presence of thrombus and two novel angiographic determinants, the SVG degeneration score and the estimated plaque volume (35). The SVG degeneration score is determined by estimating the degree of luminal irregularities or ectasia making up >20% of the reference normal segment. Multivariate analysis found that the strongest...
independent predictors of MACE were the SVG degeneration score (p < 0.0001) and the estimated plaque volume (p < 0.001). However, the presence of thrombus, increasing patient age, the use of a GP IIb/IIIa inhibitor and current smoking still carried lesser independent risk. The use of GP IIb/IIIa inhibitors was not randomized in these studies, therefore a detrimental effect could not be determined. The finding that GP IIb/IIIa inhibitor use was associated with a higher risk of MACE independent of the angiographic predictors may reflect that these medications are chosen for use in patients with a perceived higher procedural risk (35). Likewise, in a post hoc analysis of the PRIDE study, Kirtane found that lesion length was an independent predictor of both CK-MB release and adverse events in patients undergoing SVG PCI with EPDs (36). These studies underscore the unequivocal link between SVG atheroma, procedural events, and clinical outcome. The use of an EPD offers a 25% to 40% reduction in 30-day MACE, however the lack of other effective treatments or strategies to prevent distal embolization is the impetus for a large body of research focusing on adjunctive pharmacologic and mechanical treatments to render SVG stenting safer and more predictable.

There is some evidence that direct stenting of SVG (i.e., without predilation) may be associated with a reduction in the volume of atheroembolic debris (30). Another strategy to reduce distal embolization during SVG stenting is to deploy a self-expanding stent such as the Wallstent, without predilation. It was hypothesized that primary stenting with these self-expanding endovascular prostheses might reduce the likelihood of distal embolization by trapping friable atheroma before high-pressure balloon dilatation. However, thus far this strategy has not been validated in a prospective clinical trial.

**ADJUNCTIVE THERAPY AND EQUIPMENT**

**Pretreatment with Vasodilators**

An important mediator of no-reflow is downstream microvascular vasoconstriction. The intragraft administration of a variety of microvascular vasodilators such as verapamil, diltiazem, adenosine, nicardipine, and nitroprusside have been shown to improve flow in no-reflow events (37-39). Prophylactic treatment of SVG before the intervention with verapamil, and more recently with nicardipine, has been shown to decrease the occurrence rates of no-reflow. One study reported no cases of no-reflow in the verapamil treated population compared with 33.3% in the placebo group (39). Among patients pretreated with intragraft nicardipine, only 4.4% had a CK-MB >3 times normal and the total MACE at 30 days was 4.4%, with no deaths, MI or repeat TVR from hospital discharge to 30 days (39). Prophylactic intragraft administration of a vasodilator can decrease the rates of no-reflow and periprocedural elevations of CK-MB in patients treated without EPDs, however the role of medical pretreatment in conjunction with EPDs has not been studied. Combined mechanical and medical therapy may offer an additive benefit for reducing MACE and long-term mortality after SVG PCI. Clearly, adjunctive therapies in addition to EPD are needed to further reduce the high adverse event rates after SVG PCI.

**Antithrombotic and Thrombolytic Therapy**

Given the consistent demonstration that GP IIb/IIIa receptor antagonists improve procedural safety in native coronary arteries, many operators routinely administer a GP IIb/IIIa receptor antagonist before SVG PCI. As discussed above, administration of these agents in nonrandomized trials has been associated with increased MACE risk, potentially because of biased patient selection (35). Moreover, a meta-analysis of five randomized trials of GP IIb/IIIa receptor antagonists also failed to demonstrate improved outcomes in 627 patients undergoing SVG PCI (40). At 30 days, death, MI, or TVR occurred in 16.5% of patients treated with GP IIb/IIIa receptor antagonists versus 12.6% in the placebo group. One small series demonstrated that local delivery of abciximab significantly reduced the lesion percent diameter stenosis and TIMI thrombus grade (41).

Thrombolytic agents such as urokinase are moderately effective in recanalizing occluded SVG, but are associated with a high incidence (>10%) of hemorrhagic complications (42). There has been recent interest in the intracoronary administration of fibrinolytic agents to help dissolve thrombus in an effort to improve microvascular dysfunction post-PCI without requiring systemic doses of fibrinolytics. Intragraft administration of fibrinolytics has not been studied, but may offer an alternative approach to treating SVG with large thrombus burden. One approach to reducing the thrombus burden before SVG stenting, without exposing the patient to the risk of systemic fibrinolysis, is mechanical thrombectomy. The Angiojet™ (Possis Medical, Inc., Minneapolis, Minnesota, U.S.) utilizes the Venturi principle to create a low-pressure vortex around the catheter tip, macerating fresh thrombus before aspiration (Fig. 36.6). In the VEGAS trial, 351 patients with thrombotic lesions, the majority of which were SVG, were randomized to prolonged urokinase infusion or thrombectomy with the Angiojet (43). Randomization to Angiojet treatment was associated with greater procedural success, reduced incidence of major adverse events, shorter length of hospitalization, and reduction in in-hospital cost. However, despite a significant reduction in angiographic thrombus, 11% of patients still had periprocedural MI, affirming the growing understanding that factors beyond thrombosis, for example, atheroembolism and soluble mediators are major contributors to adverse events after SVG stenting. Thrombus aspiration using hollow-lumen catheters such as the Export™ (Medtronic, Inc., Santa Rosa, California, U.S.) have also been used to remove thrombus in SVG prior to stenting.

Bivalirudin, a direct thrombin inhibitor, is increasingly administered instead of unfractionated heparin as an anticoagulant during PCI of native coronary arteries. It has been associated with lower rates of bleeding without increased ischemic complications. Bivalirudin has been compared with heparin in SVG PCI with adjunctive EPDs. The use of bivalirudin was safe and was associated with a trend toward fewer in-hospital non-Q wave MI, TVR, and vascular complications and a significantly lower rate of periprocedural CK-MB increases >5 times normal (44).

**Debunking Prior to SVG Stenting**

Mechanical approaches to plaque removal before stenting include directional atherectomy, excimer laser angioplasty, and extraction atherectomy (12,14,45). The CAVEAT II trial randomized patients with SVG lesions to treatment with directional atherectomy vs. PTCA. Directional atherectomy was associated with an increased incidence of distal embolization (13.4% vs. 5.1%) and non-Q wave MI (10.1% vs. 5.8%) (12). These disappointing results dampened any enthusiasm for the use of directional atherectomy in the treatment of SVG disease. The transluminal extraction catheter combines both atherectomy and thrombectomy features and has been used in diffusely diseased, thrombus-laden SVG, with the aim of minimizing distal embolization. Safian analyzed the results of extraction...
atherectomy in 146 patients with SVG disease and reported a 21% incidence of acute angiographic complication including distal embolization (11.3%), no-reflow (4.4%), and abrupt closure (5%) (19). Results from the X-SIZER™ (EV3, Inc., Plymouth, Minnesota, U.S.) for Treatment of Thrombus and Atherosclerosis in Coronary Interventions Trial (X-TRACT) comparing short-term outcomes in patients with SVG disease randomized to stenting alone or pretreatment with the X-Sizer showed a benefit of this atherothrombectomy device (46). Thirty-day events included one death (2.0%), Q- or non–Q wave MI in 4.0%, TVR in 6.0%, and any MACE in 6.0%. Pretreatment with the X-Sizer was associated with a lower incidence of large MI and need for bailout GP IIb/IIIa receptor blockade.

Adjunctive excimer laser before balloon angioplasty of SVG has been evaluated in retrospective studies, however, its use has been plagued by a high rate of restenosis and total occlusion (14,46). Ahmed compared debulking with excimer laser prior to stand-alone stenting for treatment of aorto-ostial SVG lesions and found no difference in procedural safety or efficacy (18). The ATLAS study randomized patients with acute coronary syndromes undergoing SVG PCI to acolysis (ultrasound thrombolysis) or abciximab. The acolysis probe delivers a therapeutic level of ultrasound which leads to a cavitation effect resulting in a vortex that pulls thrombus toward the catheter tip. The study was terminated prematurely because of a significantly higher number of adverse clinical outcomes in the acolysis arm, with a 25% 30-day incidence of MACE with acolysis compared with 12% with abciximab ($p = 0.036$) (47).

**Embolic Protection**

As the widespread use of stents has consistently improved acute angiographic outcome, considerable attention has been focused on reducing the high rate of no-reflow and...
death, MI, emergency CABG, or TLR at 30 days was reduced by 42% in patients assigned to the PercuSurge EPD (Fig. 36.9). This reduction in adverse events was driven primarily by a lower incidence of no-reflow and MI. These findings were independent of GP IIb/IIIa inhibitor use. Use of distal EPDs was associated with a trend toward reduced mortality (1.0% vs. 2.3%). Interestingly, in a subset analysis of the SAFER trial, embolic protection was associated with significantly lower rates of MACE, even in patients that were directly stented (14.1% in the nonprotected group vs. 5.5% in the protected group, \( p < 0.001 \)). The SAFER trial served as an important “proof of concept,” establishing EPD technology as the first adjunctive therapy to dramatically improve the safety of SVG stenting. Embolic protection with the Guardwire was also found to be highly cost effective (49).

A newer generation occlusive device is the Proxis\textsuperscript{TM} (St. Jude Medical, St. Paul, Minnesota, U.S.) device which occludes inflow proximal to the target lesion (Fig. 36.7). Inflation of the balloon interrupts antegrade flow in the SVG during the PCI. The stagnated column of blood can be aspirated throughout the procedure to remove debris particles and must be done before restoring flow. Advantages to the Proxis system include choice of guidewires, the establishment of protection before a wire or bulky device crosses the lesion, and the ability to protect arteries with multiple side branches or distal lesions that prohibit the use other distal EPDs (50). The Proximal Protection During Saphenous Vein Graft Intervention Using the Proxis Embolic Protection System (PROXIMAL) trial was a multicenter, prospective randomized trial comparing proximal protection with distal protection with either a balloon occlusion or a filter wire. The primary composite endpoint of death, MI, or TVR at 30 days by intention-to-treat analysis occurred in 10% of the distal protection group and 9.2% of the proximal protection group (\( p \) for noninferiority = 0.0061). Secondary analyses suggested that among patients whose lesions were amenable to either method of protection, proximal protection was associated with a numerically lower, although not statistically significant, 30-day MACE rate. This study established noninferiority of the Proxis device in preventing 30-day MACE and suggested a possible benefit of protecting the SVG prior to crossing the lesion with a wire or device (51).

A second class of distal EPDs are embolic protection filters that trap debris in semi-porous membranes while allowing antegrade perfusion (Fig. 36.7). Filter wires offer several theoretic benefits over balloon occlusion devices. Since flow is maintained during stent deployment, angiographic landmarks can guide accurate stent placement. In addition, maintenance of flow reduces the occurrence of prolonged no-flow ischemia, which may result in hemodynamic compromise if the treated SVG subtends a large amount of myocardium or if left ventricular function is significantly compromised. Potential limitations include flow compromise from filter sludging, failure to block soluble mediators of no-reflow, embolization of particles during filter recovery, and the embolization of small (<100 \( \mu \)m) particles. The randomized FIRE trial compared the filter-based FilterWire EX\textsuperscript{TM} (Boston Scientific, Natick, Massachusetts, U.S.) to distal protection with the Guardwire (52). The 30-day outcomes of SVG PCI using the FilterWire EX system were noninferior to those with the Guardwire balloon occlusion system. The postprocedural measures of epicardial blood flow and angiographic complications were similar between the two groups, although there was a slightly higher rate of GP IIb/IIIa inhibitor use for bailout therapy in the GuardWire group.

### Figure 36.7
Mechanism of action of the embolic retrieval devices. Distal occlusion (top), distal filtration (middle), and proximal occlusion (bottom). Source: From Ref. 55.
The six-month outcomes from the FIRE trial revealed a 3.5% all cause mortality in the entire study population, MI in 12% of patients at six months, and TVR in 9%. Although the outcomes between the two groups were similar at six months, the rates of MACE in both groups were not insignificant (53).

The favorable results of the SAFER and FIRE trials affirm the causal link between distal embolization and clinical events following SVG stenting, and establish the practice standard for prevention of these complications. However, the six-month outcomes from the FIRE trial reinforce the fact that long-term outcomes after SVG PCI still remain poor. The FIRE trial showed parity between balloon occlusion and filter wires but did not analyze the particulate matter retrieved after intervention. Rogers et al. characterized the size and volume of debris retrieved from either a balloon occlusion device or a filter wire during SVG stenting and demonstrated that with both methods of protection, most particles were <100 μm in the longest dimension. Additionally, both types of EPDs had a similar total embolic load per lesion supporting the findings of equivalency from FIRE trial, assuming that soluble mediators are not major contributors to MACE poststenting (54). Second generation EPDs have incorporated flush and extraction technology to balloon occlusion systems, and newer filter protection systems such as the Spider™ (EV3, Inc., Plymouth, Minnesota, U.S.) allow the operator to cross the stenosis with any 0.014-in guidewire and deliver the filter system over that wire. Despite

Figure 36.8 The PercuSurge embolic protection system. The GuardWire™ (Medtronic, Inc., Santa Rosa, California, U.S.) is positioned in the distal SVG (left). With the distal protection balloon inflated, a stent is deployed across the stenosis (middle). Embolic debris liberated during balloon expansion is aspirated with the Export™ (Medtronic, Inc., Santa Rosa, California, U.S.) catheter (right). Abbreviation: SVG, saphenous vein graft.

Figure 36.9 Survival free from MACE (at 30 days): eventfree survival ±1.5 SEM in all patients. Source: From Ref. 48.
these technologic improvements, major adverse events still occur in 5% to 10% of patients, and half of SVG interventions are performed without EPDs (55).

Covered Stents

Another approach to the prevention of distal embolization following SVG stenting is the use of covered stents. Stents covered with a variety of organic and synthetic compounds have been deployed to exclude aneurysms and seal perforations. The GraftMaster™ (Abbott Vascular, Abbott Park, Illinois, U.S.) polytetrafluoroethylene (PTFE)-covered stent was approved by the U.S. Food and Drug Administration under a Humanitarian Device Exemption for treatment of coronary perforation (Fig. 36.10). It was anticipated that covered stents might also exclude friable atheroma thereby reducing atheroembolic complications and no-reflow states during SVG stenting. In a multicenter series of 109 consecutive patients, Baldus reported successful deployment of the JoMed PTFE-covered stent in all but one of 109 patients with an incidence of periprocedural MI of only 1% (56). In a small series of patients treated with either a PTFE-covered stent or a BMS, those treated with a PTFE-covered stent had a lower incidence of non-Q wave MI (57). However, tempering this initial enthusiasm for the use of PTFE-covered stents in SVG was a report from the Randomized Evaluation of Covered Stent in Saphenous Vein Graft (RECOVERS) trial in which 201 patients with SVG disease were randomized to treatment with either the Jostent Flex BMS or the PTFE-covered JoMed stent. The incidence of no-reflow (5.8% vs. 2.1%) and 30-day major adverse events (15.3% vs. 12.4%) were higher in patients randomized to the PTFE-covered stent (58). A more recent trial, SYMBIOT, which randomized patients to either the Symbiot™ (Boston Scientific, Natick, Massachusetts, U.S.) covered stent or BMS showed no benefit of the covered stents in the treatment of degenerated SVG. The rates of binary restenosis in the stented segment were similar (29.1% Symbiot vs. 21.9% BMS, p = 0.17), however more patients in the Symbiot group had binary restenosis at the proximal edge (9.0% Symbiot vs. 1.8% BMS, p = 0.0211). There was no difference in MACE between groups (30.6% Symbiot vs. 26.6% BMS, p = 0.43) (59). The hypothesis that covered stents may reduce periprocedural complications by potentially preventing distal embolization and serve as a possible barrier to cell migration, thereby reducing restenosis, appears to have been invalidated.

Figure 36.10 The GraftMaster™ polytetrafluoroethylene-covered stent.

CLINICAL OUTCOMES AND SPECIAL CONSIDERATIONS

Restenosis, Recurrent Events, and Long-Term Outcome Following SVG Stenting

Although the SAVED trial demonstrated improved the long-term outcome of stenting compared with balloon angioplasty, and newer technologies such as EPDs have improved procedural safety, the long-term outcomes after SVG PCI are still suboptimal. Recurrent ischemic events are quite common (>50% by 18 months) in patients who have undergone successful SVG stenting (16,60-63). There is controversy as to whether the incidence, time course, and biology of restenosis differs in SVG compared with native coronary arteries following stenting. More clinical events occur beyond 6 to 12 months in stented SVG compared with native coronary arteries, suggesting that the restenotic hazard in SVG has a prolonged time course. Whereas the incidence of TVR and non-TVR is higher in patients with SVG, the rate of revascularization driven by failure of the target lesion is similar to that of native coronary arteries (61). Thus, the incidence of clinical events approaches 50% by five years because of the progression of disease at nontarget sites within the treated SVG, the attrition of other SVG, and the progression of native coronary artery disease (60). Deppe and colleagues examined the histology of previously stented SVG and reported “long-term restenosis” occurs in at least 30% of cases and results from a combination of cellular hyperplasia, thrombosis, and progressive atherosclerosis (64). Another histologic study found abnormal adherence of inflammatory cells and platelets as late as 10 months after implantation suggesting a propensity toward late thrombosis (65). While this may partly explain the observation that late reocclusion often accompanies in-stent restenosis, it is important to remember that other factors such as the absence of side branches and the rapid progression of atherosclerosis at other loci within the SVG may also predispose to thrombotic occlusion. The presence of diabetes mellitus, nonobstructive stenoses in other SVG segments, restenosis, placement of multiple stents, SVG degeneration, peripheral vascular disease, and congestive heart failure were all predictors of MAE following SVG stenting (62,66-68). Although female gender was associated with periprocedural and 30-day MACE, clinical outcome at 12 months was independent of gender (69).

Predictors of angiographic restenosis following SVG stenting include previously dilated lesions, smaller reference diameter, diabetes mellitus, and smaller posttreatment diameter stenosis (17). SVG in-stent restenosis has been treated by a variety of approaches including repeat balloon dilation, excimer laser angioplasty; and directional, rotational, and extraction athrectomy (62,70,71). Repeat PCI does not appear to entail
the high risk of distal embolization associated with treatment of de novo lesions. In a series of 54 patients who underwent treatment of in-stent restenosis, distal embolization resulting in MACE was not observed (72). Despite excellent acute angiographic and clinical outcome, the incidence of recurrent restenosis approaches 50%.

**Contemporary Approaches to the Technique of SVG Stenting**

First generation coronary devices such as the Gianturco-Roubin and Palmaz-Schatz stents were designed to treat focal lesions in native coronary arteries. SVG are larger and contain more diffuse, friable atheroma than native coronary arteries (8). Consequently, multiple stents were commonly required and plaque prolapse was frequently observed when stents designed to treat vessels 3 to 4 mm in diameter were overexpanded to treat larger SVG. In an effort to provide better scaffolding by increasing the metal to surface area ratio, hand-crimped larger biliary stents were used to treat diseased SVG (73). However, these stents were difficult to deliver because of high profile, rigidity, and suboptimal anchoring of the stent to the delivery balloon. This necessitated the use of 8-Fr or 9-Fr guiding catheters, lesion predilatation, and relatively stiff guidewires for delivery. This prompted several vendors to develop modified balloon-expandable stents to treat larger vessels. These balloon-expandable delivery systems are the platforms for both BMS and DES. These large vessel stents are compatible with 6-Fr guiding catheters, have relatively low crimped profiles and greater flexibility, and increased surface area coverage to minimize plaque prolapse. Additionally, with the development of DES and the decreased rates of restenosis seen in native coronary arteries, the use of DES in SVG PCI has rapidly increased.

Guiding catheter selection is an important component of successful SVG stenting. Ideally, the operator should choose a guiding catheter whose shape allows selective, coaxial intubation of the SVG. For SVG anastomosed to branches of the left coronary artery, a Right Judkins catheter will generally engage the SVG and is usually adequate for diagnostic angiography. However, the Right Judkins guiding catheter often provides minimal backup support and frequently disengages from the ostium during balloon or stent delivery. A Hockey Stick or Amplatz Left guiding catheter will allow deeper intubation of the SVG especially if the SVG has a vertical take-off or if maximum support is needed to facilitate delivery of longer stents or through tortuous segments. Care must be taken when manipulating this aggressive catheter as the post-CABG patient often has friable atheroma in the ascending aorta that can dislodge when traumatized. Occasionally, when grafting the left circumflex artery, the surgeon will place the aortic anastomosis on the posterior surface of the aorta. These SVG can be successfully cannulated with either a multipurpose or Right Judkins guiding catheter. SVG to the right coronary artery typically are sutured to the posterior surface of the aorta and usually have a downward orientation. The multipurpose or AR-1 guiding catheters generally provide adequate visualization and support.

Given the dramatic reduction in no-reflow and its clinical sequelae observed in both the SAFER and FIRE trials, the use of an EPD is recommended. Exceptions to this recommendation include SVG less than a year old or treatment of in-stent restenosis. Stenting of SVG with large amounts of angiographic thrombus can be especially challenging. Subgroup analysis from the SAFER trial identified angiographic thrombus as an important predictor of MACE. While the use of GP IIb/IIIa receptor antagonists has not been associated with the same benefit during SVG stenting compared with treatment of native coronary arteries, their use should be considered if a large thrombus burden is angiographically apparent, or suspected clinically, for example, when intervention is performed for an acute coronary syndrome, or the graft is freshly occluded. Intragraft administration of the abciximab may reduce thrombus burden. Alternatively, the use of a mechanical thrombectomy device such as the Excisor or a thrombus aspiration catheter such as the Export catheter with an EPD may be helpful.

Generally, with the propensity of SVG atheroma to embolize, a “less is better” approach to stenting may be warranted even when the EPD is employed. Primary stenting (i.e., without predilatation) should be strongly considered. Webb has shown that primary stenting is associated with a reduced volume of embolized debris (30). Contemporary stents are mounted on balloons that can be inflated to high pressure. Thus, if the operator chooses the correct stent size, postdilatation can be avoided in most cases. However, occasionally one encounters a noncompliant lesion resulting from significant adventitial fibrosis that requires high-pressure postdilatation with a noncompliant balloon. It is important that all subsequent inflations be performed with an EPD as embolism and slow flow can occur even with postdilatation. Occasionally, balloon rupture or severe barotrauma may lead to perforation of the vein graft. Usually, small perforations do not lead to hemodynamic compromise as they rarely cause pericardial tamponade and extensive fibrosis often seals the perforation. When the perforation is large, or associated with hemodynamic instability, the perforation can be reliably sealed with a PTFE-covered stent (74). Before the advent of EPDs, moderate stenoses were often left untreated to avoid additional plaque manipulation. However, since these non-flow-limiting plaques may be associated with rapid disease progression and future ischemic events (66,68), the availability of reliable, easy to use EPDs allows the operator to take a more proactive, aggressive approach to these lesions. When patients with SVG stents develop recurrent symptoms, angiography should be performed since progressive flow impairment may result in thrombotic occlusion of the SVG. Unless clinically contraindicated because of hypotension, we routinely pretreat with vasodilators to decrease rates of no-reflow. One series has reported a low rate of adverse events with vasodilator pretreatment (39).

**Treatment of Early (<1 Month) SVG Failure**

Early ischemic events may manifest as recurrent chest pain, MI, hemodynamic instability, or heart failure and are usually precipitated by SVG thrombosis resulting from a combination of a prothrombotic milieu and technical misadventure. Treatment of thrombosed SVG usually involves a combination of platelet inhibition with GP IIb/IIIa receptor antagonists and a thienopyridine, and thrombectomy, followed by balloon dilation and or stent placement, usually at the aorto-ostial or distal anastomosis (75). Since the flow-limiting lesion is usually located at a freshly sutured site, excessive pressure needed to expand the stent may disrupt the sutures resulting in severe hemorrhage or tamponade. This risk may be highest for stents placed at the distal anastomosis when sutures are placed through the back wall of the native coronary artery.
CONCLUSIONS

SVG disease after CABG is common. One year after surgery, up to 15% of SVG are occluded and only 61% of SVG are patent at 10 years. Among the patent SVG, many are diffusely diseased and repeat CABG is associated with increased morbidity and mortality. Therefore, PCI is the preferred revascularization strategy for SVG disease. However, it is limited by a substantial risk of MACE caused mainly by periprocedural MI as a result of no-reflow and distal embolization. Treatment of SVG disease is associated with a high rate of restenosis ranging from 20% to 37% and high rates of TVR. Recent advances in SVG PCI have included the development of EPDs that have reduced the rates 37% and high rates of TVR. Recent advances in SVG PCI have associated with worse long-term outcomes than native coronary PCI and research is needed to develop pharmacologic as well as mechanical devices to improve the outcomes of SVG PCI.

REFERENCES


Emboli protection devices, atherectomy, thrombus aspiration devices

Fernando Cura

INTRODUCTION
A large armamentarium of medical devices is available for the percutaneous treatment of a variety of coronary atherosclerosis lesions. This chapter describes several aspects related to the biological components of the atherosclerotic plaque and the rationale, clinical evidence, and indications for different interventional devices. The scope of this chapter will range from devices that prepare very hard atherosclerotic plaques prior to stenting, for example, rotational atherectomy, to devices that are either used to remove very soft, friable, or thrombotic lesions, such as thrombectomy, or those preventing distal embolization during the intervention by temporary vessel occlusion or filter placement.

PLAQUE COMPOSITION AND SELECTION OF INTERVENTIONAL STRATEGY
Normal human coronary arteries have three thin layers, namely, the intima, media, and adventitia. The intima interfaces with the arterial lumen and is composed of endothelial cells. The media is composed of smooth muscle cells, collagen, fibroblast, and intercellular matrix molecules, and regulates vascular contraction. The media is separated from the intima and adventitia by the internal and external elastic membranes, respectively. Coronary atherosclerosis is a complex inflammatory-infiltrative disorder affecting the three vessel layers (1). During life, the presence of acquired and inherent coronary artery disease risk factors triggers a series of events that leads to atherosclerosis. Prior results from animal studies have suggested that the first step in atherosclerosis is endothelial cell dysfunction and lipoprotein particle accumulation at the intima level (2). At this stage, lipid oxidation, local release of interleukins, cytokines, reactive oxygen species, and pro-oxidative enzymes generate white blood cell chemotaxis and adhesion to the endothelial surface (3–5). Leukocytes and monocytes penetrate endothelial cells into the arterial wall engulfing lipid particles constituting foam cells (6,7). Then foam cells progress to fatty streaks and ultimately to raised atheromatous plaques (1). Several other factors are also involved in the development of atherosclerosis. Laminar flow elicits atheroprotective properties (8), while turbulent flow, especially at branch points, leads to atheromatous plaque formation. In fact, during plaque growth, lumen reduction increases blood flow velocity, thus, elevating shear stress. A large amount of evidence indicates that high levels of shear stress stimulate outward vascular remodeling of the arterial wall, probably in an attempt to preserve endoluminal dimensions (9,10). At a still unpredictable point in the atherosclerosis process, outward remodeling may fail or just simply stop due to an excess of plaque burden or inherent poor vascular ability to produce outward remodeling and significant arterial luminal stenosis ensues. Despite the previous belief that the presence of high shear stress and continuous outward remodeling were only protective factors, their presence in conjunction with high plaque burden and a thin fibrous cap represent the classic scenario leading to a ruptured and/or eroded plaque (11). This metabolically active, unstable plaque expresses several prothrombotic cytokines leading to thrombus formation and vasoconstriction. This is the most common underlying coronary lesion among patients with acute coronary syndromes. In particular, patients with ST-segment elevation acute myocardial infarction (STEMI) have highly thrombotic lesions. In addition, these patients have different levels of myocardial damage with microvascular embolization, interstitial edema, and vasoconstriction (12).

On the other hand, coronary stenosis due primarily to negative remodeling is associated with low plaque burden and thick fibrous cap, usually showing as stable coronary syndromes (13). Some of these patients have dense fibrocalcified coronary plaques, sometimes difficult to adequately address with balloon angioplasty or stenting alone. This type of lesion has been the target of numerous devices chiefly designed to remove or alter plaque as an adjunctive measure prior to stenting. Devices such as directional coronary atherectomy, rotational atherectomy, excimer laser, and cutting balloon, among others, have been tested (14,15). The two most commonly used devices in current practice for severely fibrocalcified stable coronary lesions are rotational atherectomy and cutting balloon angioplasty.

Atherectomy Devices
Rotational atherectomy (16) is commercially available as the Rotablator System (Boston Scientific, Scimed, Maple Grove, Minnesota, U.S., Fig. 37.1) and consists of a nickel-plated, diamond chip-coated brass burr rotating at 140,000 to 190,000 rpm. Eight burr sizes are available ranging from 1.25 to 2.5 mm. Rotational atherectomy works by the physical principle of differential cutting (17). This principle enables destruction of inelastic material such as atherosclerotic, calcified, and fibrotic plaques while preventing normal elastic tissue from becoming damaged. Debris dislodged after rotational atherectomy are less than 12 μm, and should not create a significant impact in the epicardial and myocardial blood flow with careful technique. However, CK-MB release (myocardial infarction) rates post rotational atherectomy are significantly higher than after conventional angioplasty (18–20). Selection of burr size should not exceed a burr/artery diameter ratio of 0.7. In fact, for undilatable lesions, the use of very small burrs is less aggressive and...
usually sufficient to physically alter the plaque surface, allowing balloon dilatation and stenting. During the bare-metal stent era, substantial evidence indicated that despite achieving greater acute gain with the use of rotational atherectomy, restenosis remained unchanged and increased the risk of the procedure due to distal embolization or slow flow (20). Increased operator experience using shorter runs (<20 seconds) with <5000 RPM decrements, the use of smaller burr size and device improvements have reduced periprocedural complications. Prophylactic use of intracoronary “Rota Flush Cocktails” with different concentrations of nitroglycerine, verapamil, and heparin has improved the epicardial flow after rotational atherectomy (21). However, ventricular arrhythmias, coronary dissection, and vessel perforation are still a concern, especially among patients with severe vessel tortuosity or angulated lesions (22). Thus, the popularity of rotational atherectomy has decreased in the past decade, and it is being predominantly utilized for undilatatable lesions or delivery failures. Unfortunately, the complexity of this device requires proper training and experience for the operator to be comfortable using this unique tool.

Although intravascular ultrasound studies have demonstrated that suboptimal deployment, incomplete apposition, and failure to achieve adequate stent dimensions may lead to stent thrombosis (23–25) and repeat target vessel revascularization, the available anecdotal data comparing rotational atherectomy use prior to drug-eluting stent (DES) deployment versus DES alone does not support its systematic use (26). However, vigorous manipulation of DES through calcified lesions could potentially damage polymer coating integrity and lower DES efficiency. Although there are still some concerns regarding local delivery of drugs through a calcified lesion, clinical trials with paclitaxel-eluting stent did not reveal differences in in-stent restenosis or thrombosis rates between calcified and noncalcified lesions (27).

Cutting balloon angioplasty represents another alternative to overcome fibrocalcified plaques (28,29). It consists of a balloon catheter with three or four atherotomes or microsurgical blades, which are three to five times sharper than conventional surgical blades (29). Atherotomes are placed longitudinally on the outer surface of a noncompliant balloon. Radial expansion of the cutting balloon produces longitudinal incisions in the plaque and vessel, reducing tensile vessel stress (30) and elastic recoil (31). Balloon sizes are 2.00 to 3.25 mm and its unique design protects the vessel from the edges of the atherotomes when the balloon is deflated. The latter is vital to diminish the risk of vessel trauma during device delivery to the lesion or balloon retrieval from the vessel. Usually, lower balloon inflation pressures (4–8 atm) are required. Currently, cutting balloon use is limited to undilatatable coronary artery stenosis, preferably with a reference vessel diameter ranging of 2.0 to 4.0 mm in diameter, without extreme vessel tortuosity (32). Highly tortuous and angulated lesions are technically difficult to access due to the presence of the longitudinal atherotomes in the cutting balloon. Shorter cutting balloons (10 mm) are usually more deliverable than the longer (15 mm) ones in passing a moderately tortuous vessel. Cutting balloons can also be used in aorto-ostial lesions (33). Its anecdotal popularity for patients with in-stent restenosis has been replaced with overwhelming data supporting the use of DES (34,35).

**Thrombus Removal and Prevention of Distal Embolization**

Unstable coronary syndromes are associated with soft, friable, thrombotic and metabolically active atherosclerotic lesions (36). At sites of plaque formation there is substantial inflammation (37,38) with macrophages releasing proteolytic enzymes such as matrix metalloproteinases responsible for thinning fibrous cap leading to plaque erosion or rupture and thrombus formation (39). Besides atherothrombotic debris, unstable plaques contain a milieu of humoral factors that, if released downstream during percutaneous coronary interventions (PCI), have the potential for damaging the distal microcirculation. During STEMI, primary PCI of the thrombotic lesion requires particular care to reduce distal atherothrombotic embolization and its complications. The angiographic observance of distal embolization is rather common (~15%) during primary PCI and translates into poor left ventricular recovery and clinical outcome (40). Even in the absence of this complication and despite successful epicardial recanalization, inadequate myocardial reperfusion at the tissue level, reflected by incomplete ST-segment resolution, is frequently observed immediately following the procedure (~40%) (41,42). Suboptimal myocardial reperfusion at the end of the intervention is associated with reduced myocardial salvage and worse long-term outcome than patients achieving adequate reperfusion (43,44). Lack of myocardial reperfusion or no-reflow is due to mechanical obstruction of the microcirculation, partly explained by the complex interplay of distal atherothrombotic embolization, postischemic arteriolar damage, myocardial edema, reperfusion injury and the downstream release of vasoconstrictors and...
prothrombotic mediators (45). Although distal embolization is a common phenomenon, the amount and composition of distal debris varies largely. Consequently, a variety of techniques have been designed to either reduce or prevent the amount of debris that migrates distally during the procedure. These devices are divided into nonocclusive (distal embolic filter protection) and occlusive (proximal or distal vessel occlusion) devices.

**Distal Embolic Protection with Filter Devices**

These devices provide the ability to maintain distal perfusion while protecting against macroembolization. Thus, they enable antegrade flow and allow the operator to inject contrast during the procedure. Nevertheless, several potential disadvantages should be mentioned. Depending on the filter design, small debris (<80–100 μm) and humoral mediators can go through the filter pores. Moreover, there is a potential risk of embolization while crossing the lesion with the device, especially if predilatation is required to advance the filter distally. Unlike proximal protection, distal filters do not protect side branches proximal to the device. In the setting of STEMI, it can be challenging to perform blinded distal filter placement in patients with baseline epicardial TIMI flow 0–1.

Several studies have shown the benefit of distal protection in carotid stenting (46,47) and saphenous vein graft intervention (48,49). These positive results encouraged their use in the native coronary circulation among patients with acute coronary syndromes. Initial anecdotal data reported an improvement in myocardial reperfusion parameters using different surrogates such as myocardial blush grade or ST-segment resolution (50).

However, the PROMISE (Protection Devices in PCI-Treatment of Myocardial Infarction for Salvage of Endangered Myocardium) trial (51) utilized FilterWire EZ™ Embolic Protection System (Boston Scientific, California, U.S.) and randomized 200 patients undergoing PCI for STEMI and non-STEMI. Surrogate markers such as maximal adenosine-induced flow velocity, infarct size, and incidence of distal embolization as well as 30-day mortality did not differ between the two groups. The inclusion of non-STEMI patients in this trial may have blunted any differences between the two treatment groups.

The PREMIAR (Protection of Distal Embolization in High-Risk Patients with Acute ST-Segment Elevation Myocardial Infarction) trial (41) was a prospective, randomized, controlled study that tested a low-profile distal protection filter device (SpiderFX, ev3, Inc., Minnesota, U.S.; Fig. 37.2), during PCI in STEMI patients at high risk for embolic events. Thus, by protocol, only patients with TIMI grade flow 0–2 were included. The study randomized 150 patients, and visible macroscopic atherothrombotic debris was noted by visual assessment in the filters in 48% of cases. Histopathologic analysis was performed in a subgroup of patients and particles were recovered in all analyzed filters. The number of particles ranged from 8 to 48 per filter. Particle size ranged from 101 to 1299 μm in maximum diameter and from 212 to 1487 μm² in area. Most particles were composed of platelet clumps, red cells, and fibrin, which led to the diagnosis of fresh thrombus (Fig. 37.3). All patients underwent 24-hour ST-segment monitoring to measure the extent of ST-segment recovery. In this trial, the adjunctive use of a distal filter device did not improve myocardial reperfusion either by ST-segment resolution (Fig. 37.4) or by quantitative angiographic markers (TIMI blush grade, TIMI flow, and TIMI frame count). Furthermore, left ventricular function and six-month clinical outcome did not differ between groups. There was no specific subgroup discerned that derived benefit from adjunctive distal protection.

In a published meta-analysis (N = 1467) including 8 randomized clinical trials, the role of distal protection with either filter or balloon occlusion during primary PCI did not show improvement in extent of reperfusion or 30-day mortality when compared to PCI alone (Fig. 37.5) (52).

In summary, due to the lack of positive results and potential disadvantages, the routine use of distal filter protection during primary PCI in native coronary arteries cannot be recommended. Nonetheless, these studies have demonstrated that the use of distal filters appears to be feasible and safe.

Although it is not technically a filter device, the novel stent system MGuard™ (InspireMD, Tel Aviv, Israel, Fig. 37.6) appears promising during intervention of very thrombotic or friable plaques and is worth mentioning. In addition to its low profile, MGuard has an ultrathin polymer mesh sleeve that wraps around the stent, trapping plaque material behind the stent and reducing vessel trauma during stent deployment. In a pilot primary PCI registry (n = 60), angiographic distal embolization was not detected, TIMI 3 flow and blush grade 3 were present in 100% and 77.8% of the patients, respectively (53). Although positive results regarding myocardial reperfusion are encouraging, significant and meaningful data from a larger randomized clinical trial are needed.

**Distal Embolic Protection with Occlusive Devices**

This system is based on transient distal balloon occlusion coupled with an aspiration catheter to prevent plaque debris embolization. Similar to distal filters, this system requires passage through the lesion and does not provide protection to proximal side branches. In addition, it may not have an adequately visible landing zone in the presence of baseline TIMI 0. Unlike distal filters, balloon occlusion provokes myocardial ischemia due to blood flow stagnation, and hence its duration should remain as short as possible. Examples of distal occluding devices include PercuSurge GuardWire Distal Protection Device (54) (Medtronic, Pennsylvania, U.S.) and TriActive System (Kensey, Pennsylvania, U.S.).

The PercuSurge GuardWire Protection Device (Fig. 37.7) occludes distally with a balloon while the Export catheter (Medtronic) is used to aspirate the stagnant debris-containing blood. Thromboaspiration is performed after balloon dilation and stent deployment. This device was used with success in the large, multicenter, randomized SAFER trial (Saphenous Vein

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**Figure 37.2** The SpiderFX Distal Filter (SpiderFX, ev3, Inc., Minnesota, U.S.).
Graft Angioplasty Free of Emboli Randomized. A total of 801 patients were randomized to saphenous vein graft intervention with and without the PercuSurge GuardWire Protection Device System (55). The primary endpoint of the study, major adverse cardiac event (MACE) rate at 30 days, was defined as the composite of death, MI, emergent bypass surgery, or target vessel revascularization within 30 days of the index procedure. There was a 6.9% absolute reduction (42% relative reduction) in 30-day MACE (9.6% for GuardWire vs. 16.5% for controls, \( p = 0.001 \)). This reduction was driven primarily by MI (8.6% vs. 14.7%, \( p = 0.008 \)) and no-reflow (3% vs. 9%, \( p = 0.02 \)). The same protection system was evaluated in the EMERALD (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberalized Debris) trial in the setting of STEMI. EMERALD randomized 501 patients who presented within six hours from symptom onset for primary (81%) or rescue PCI (19%) to receive PCI with the GuardWire Plus (Medtronic) distal balloon occlusion system compared to angioplasty without distal protection (42). Although visible debris were retrieved from 73% of patients randomized to the device, this did not result in improved microvascular flow, reperfusion success, reduced infarct size, or enhanced event-free survival (Fig. 37.4).

Figure 37.3 (See color insert) Different views of particulates obtained from filters and panoramic views of a recent thrombus. An extensive thrombus (A) is compared with very small particles (D). Some areas stained light pink (B, C) are suspicious of being plaque remnants. Hematoxylin and eosin stain, 40x. Source: Courtesy of Dr Jose Milei and From Ref. 41.

Figure 37.4 Complete ST-segment resolution (≥70%) after primary angioplasty in the PREMIAR and EMERALD trials. Source: From Refs. 41, 42.
Embolic Protection with Proximal Occlusion

Proximal occlusion devices cause blood flow stagnation by occluding the target coronary artery “upstream” from the lesion. With flow temporarily interrupted, thromboaspiration is performed and the stent or balloon is delivered to the lesion. Thromboaspiration is performed again and the proximal balloon is deflated, which restores blood flow. Advantages of proximal occlusion devices over distal occlusion or filters are several. First, proximal occlusions do not need to cross the lesion, thereby avoiding device-induced embolization. Second, device delivery is not affected as much by tortuous vessels. Third, the landing zone is always seen at the beginning of the procedure. Fourth, side branches are protected and humoral mediators theoretically do not reach the microcirculation. However, proximal occlusion devices may not have an adequate landing zone in ostial or proximal lesions.

The most studied proximal protection device is the Proxis Proximal Protection System Device (St. Jude Medical, Inc., Minnesota, U.S.; Fig. 37.8). A single-center STEMI registry (55)
(N = 177) has shown encouraging results, with 96% final TIMI 3 and 80% complete ST-segment resolution at 60 minutes, with a 30-day MACE rate of 4%. The PREPARE (Prospective Randomized Trial of Proximal Microcirculatory Protection in Patients with Acute Myocardial Infarction Undergoing Primary PCI) trial enrolled 234 primary PCI patients with the adjunctive use of the Proxis device versus PCI alone. In this study, immediate percentage ST-segment resolution was higher in the device group; however, similar ST-segment resolution was seen at 30, 60, and 90 minutes after the procedure. There was also no difference in 30-day clinical outcome. According to the investigators (personal communication), there was a correlation between early ST-segment resolution and myocardial salvage and long-term outcomes. On the basis of these findings, a larger randomized trial is planned with this device.

**Thrombectomy Devices**

Thromboaspiration devices are used to remove thrombus from the coronary lesions during primary PCI to reduce distal embolization. There is, however, another potential advantage of thrombus removal prior to stent implantation, possibly more so in the DES era. Following primary PCI, an intravascular ultrasound study has detected high rates of late stent malposition (56). This finding might partially explain the increased risk of stent thrombosis in this population when compared to more elective procedures. Stent implantation may compress thrombotic material behind the stent struts, which eventually dissolves in the long term, rendering the stent malapplied. In a primary PCI study (57), thrombus burden was graded from 0 to 4 according to thrombus length. The highest grade (grade 4) was defined as the presence of thrombus length ≥2 times vessel diameter. Patients with the highest thrombus grade had significantly higher late stent thrombosis than patients with lower thrombus grades (Fig. 37.9). In this retrospective study, the adjunctive use of mechanical thrombectomy was independently associated with a reduction in the development of late stent thrombosis. Further retrospective analysis performed by these investigators only in patients with large thrombus burden (n = 266) showed that adjunctive thromboaspiration (72/266, 28.2%) was associated with an improvement in myocardial perfusion and a two-year survival benefit (92% vs. 83%, p = 0.051) (58) when compared to primary PCI alone. Thus, thrombus removal appears to confer short and long-term benefits, possibly avoiding the development of stent malapposition and hence, reducing stent thrombosis rates. Again, however, prospective randomized clinical trials are needed to confirm this hypothesis.

Numerous thrombectomy devices have been tested during primary PCI. Although there is ample heterogeneity in design, aspiration capacity, and operational principles, thrombectomy devices can be further divided into manual and mechanical.

**Manual Thrombectomy Devices**

Manual thrombectomy devices are user friendly; they have minimal learning curve and do not impact overall procedural time. The most studied and most widely used devices include the Export Catheter (Medtronic, Minnesota, U.S.; Fig. 37.7B), Diver CE (Invatec, Roncadelle, Italy; Fig. 37.10), Rescue catheter (Boston Scientific), Pronto catheter (Vascular Solutions, Inc., Minneapolis, Minnesota, U.S.), and the QuickCat (Kensey). Several small randomized studies with different manual devices have shown promising results. Recently, TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in
Acute Myocardial Infarction Study) (59), a single-center randomized trial ($n = 1071$), evaluated the adjunctive use of the Export catheter in an unselected STEMI population undergoing primary PCI. Manual thromboaspiration resulted in better early myocardial perfusion, as assessed by the percentage of complete ST-segment resolution (Fig. 37.11), TIMI blush grade, and TIMI 3 flow. This was associated with a significant reduction in 12-month cardiac death (3.6% vs. 6.7%; OR 1.93; 95% CI 1.11–3.37; $p = 0.020$) and reinfarction (2.2% vs. 4.3%; $p = 0.05$) (60). This trial is the first to report a significant benefit in clinical hard endpoints with the use of an adjunctive distal protection tool during primary PCI.

A meta-analysis including 9 trials and 2417 STEMI patients undergoing primary PCI with or without adjunctive manual thrombectomy was recently published (61). The use of manual thromboaspiration significantly improved myocardial reperfusion (Fig. 37.12B) and 30-day mortality (Fig. 37.12B). These results indicate that manual thromboaspiration offers a significant clinical benefit prior to stenting during primary PCI, and its use should be encouraged.

![Resolution of ST-Segment Elevation](image)

Figure 37.11 ST-Segment Elevation Resolution in the TAPAS trial. Source: From Ref. 59.

![TIMI 3 post](image)

(A) Test for heterogeneity: $x^2 = 3.06$, df = 7, $p = 0.90$, (I$^2$ = 0%); Test for overall effect: $z = 3.00$, $p = 0.001$

![30-Day Mortality](image)

(B) N/E: not estimable; Test for heterogeneity: $x^2 = 1.73$, df = 7, $p = 0.97$, (I$^2$ = 0%); Test for overall effect: $z = 2.03$, $p = 0.04$

Figure 37.12 Final TIMI III flow (A) and 30-day mortality (B) rates according to the use of manual thrombectomy. Source: From Ref. 52.
Mechanical Thrombectomy Devices

The Angiojet Rheolytic Thrombectomy System (Possis Medical, Inc., Minnesota, U.S.) creates an extremely high negative pressure zone (~600 mmHg) at its distal tip by high-velocity saline jets that are directed back within the catheter, resulting in removal of thrombus by suction through the outflow lumen, using the Venturi and Bernoulli effects (Fig. 37.13). For comparison, manual thromboaspiration achieves a negative suction pressure of only ~10 mmHg. The more powerful suction due to the outflow pressure fragments clots as they enter the catheter, hindering catheter occlusion during clot aspiration. In experimental models, clot mass removal is significantly higher using mechanical compared to manual thromboaspiration (Fig. 37.14).

The multicenter AiMI (Angiojet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute MI) trial (63) included 480 STEMI patients evaluating adjunctive use of the Angiojet device during primary PCI versus primary PCI alone. In this study, myocardial reperfusion and myocardial salvage were worse in the thrombectomy group when compared to PCI alone. These results further translated into more 30-day adverse events in the thrombectomy group (6.7% vs. 1.7%; \(p = 0.01\)). To be fair, the control group experienced a surprisingly low mortality rate (0.8% vs. 4.6%; \(p = 0.02\)), much lower than normally observed in STEMI trials. The data safety monitoring committee of the AiMI trial felt that the deaths in the thrombectomy arm were not specifically caused by the device. However, ventricular arrhythmias, hemolysis, and coronary perforation are potential complications associated with this device. This trial included a high percentage of patients without angiographically visible thrombus. The use of this device may derive greater benefit in patients with large thrombus burden (58).

The JETSTENT multicenter trial is enrolling STEMI patients with high thrombus grade to PCI with the adjunctive Angiojet thromboaspiration or PCI alone. Technical aspects related to the use of Angiojet have also been modified to take the greatest advantage of this device and to diminish procedural risk. Until these study results are available, no clearly foreseeable recommendation for its use can be given.
CONCLUSION
The majority of emboli protection devices require that each case be carefully considered, balancing risk and benefit of the chosen device. Such evaluation depends on patient’s demographics, clinical presentation, and coronary anatomy. Profound knowledge of the underlying coronary pathophysiology is crucial in determining the feasibility, safety, and benefit of using any adjunctive interventional device. At this juncture, emboli protection devices are warranted in particular cases of carotid and vein graft interventions. Manual aspiration thrombectomy catheters are effective in primary PCI cases.

REFERENCES


Complications of PCI: stent loss, coronary perforation and aortic dissection

Amir-Ali Fassa and Marco Roffi

Various complications may occur during percutaneous coronary interventions (PCI) (Table 38.1). These may be related to the devices used during the procedure (e.g., coronary perforation, stent loss, or thrombosis) or to the intervention itself (e.g., abrupt vessel closure, distal embolization, side branch occlusion). The circulatory system may also be affected in case of aortic dissection or vascular or atheroembolic events. In addition, access site complications may occur. Finally, PCI may be complicated by systemic events in relation to adjunctive therapies and other aspects of the procedure (e.g., contrast nephropathy, hemorrhage, allergic reactions). These complications may result in adverse events such as myocardial infarction, renal failure, stroke, or death.

Despite the increasing procedural complexity and higher risk profile of patients treated with PCI over the years, there has been a marked reduction of related in-hospital myocardial infarction and mortality rates as well as of the need for emergency coronary artery bypass graft (CABG) surgery (1,2). This trend is likely the result of technological and pharmacological advancements as well as of the increasing experience of operators in management of high-risk situations and prevention and treatment of procedural complications.

The present chapter focuses on three major complications of PCI, which include stent loss, coronary perforations, and aortic dissection. Access site complications are described in chapter 8.

STENT LOSS

Introduction

Stents are currently used during 91% to 96% of PCIs (3,4). Failure to deliver a stent to the target site occurs in 3.9% to 8.3% of the procedures, mostly due to excessive tortuosity and/or calcification of the target lesion or of the proximal vessel segments (5–7). As a consequence, the undeployed stent needs to be retrieved into the guiding catheter. This may lead to stent dislodgement from the delivery balloon catheter and subsequent stent embolization. According to earlier series, stent loss occurred in 0.9% to 3.4% of the procedures, while the incidence decreased to 0.3% to 0.5% in the most recent ones (6–16). This progress is likely due to the abandon of manually crimped stents; the improvement of stent profile, flexibility, and stent adhesion to the balloon catheter; as well as the gained experience of operators with stent utilization (11). Importantly, the trend has been observed despite the increasing complexity of coronary lesions treated by endovascular means (1,2).

Factors favoring stent loss include vessel anatomy, operator technique, and equipment characteristics. The most common situations associated with stent loss are the retraction of an undeployed stent into the guiding catheter without having a proper alignment between the guiding catheter and the stent and the attempt to cross a calcified and tortuous lesion that has not been sufficiently prepared with balloon predilatation or rotational atherectomy. Other mechanisms and favoring factors are listed in Table 38.2. Key points in preventing stent loss include adequate lesion preparation, sufficient guiding catheter and guidewire support, verification of proper alignment with the guiding catheter while retrieving an undelivered stent, use of short and low-profile stents, and stenting of distal segments first if multiple stents are required.

Outcome

Stent loss is associated with a high rate of adverse events. In a series of 387 procedures complicated by stent loss (from a total of 25,558 PCIs), Bolte et al. showed that stent embolization was associated with an in-hospital mortality of 6% and a major in-hospital adverse events rate of 25% (which included death, nonfatal myocardial infarction, CABG, and neurological deficit) (8). The complication rate was as high as 89% among patients with an undeployed stent loss in the coronary tree (N = 47). Conversely, more favorable outcomes were observed with successful stent retrieval (N = 111, complication rate of 9%), peripheral stent embolization (N = 157, complication rate of 15%), and successful intracoronary exclusion (crushing) or deployment of the lost stent (N = 72, complication rate of 31%). In a series of 20 patients by Eggbrecht et al., three patients died following urgent CABG after stent embolization (mortality of 15%) (10). Similarly, Brilakis et al. reported increased rates of hospital mortality (3%) and emergency CABG (5%) following stent embolization (11).

These outcomes may or may not be directly related to stent embolization. For instance, maneuvers to retrieve a lost stent may result in coronary or peripheral artery injury. Likewise, an undeployed stent left in the coronary tree may also result in vessel thrombosis and myocardial infarction. Moreover, if stenting is applied to treat a dissection, failure to deliver the stent at the target lesion may lead to abrupt vessel closure. Finally, stent loss likely identifies a population of patients with complex coronary anatomy and advanced disease at increased risk of adverse clinical events, which may not be the direct consequence of stent loss. As a general rule, peripheral stent embolization is associated with a more favorable clinical course than coronary stent embolization, the latter rarely resulting in limb ischemia or stroke (9–11). On the basis of the potentially catastrophic complications of stent embolization, appropriate management is of paramount importance.
Management
Percutaneous treatments of lost coronary stents include retrieval, exclusion from circulation (crushing), or deployment at the embolization site. To that purpose, several tools and techniques have been described, such as the use of small-diameter balloon catheters, guidewires, vascular snares, vascular baskets, vascular forceps/biopomites, and dedicated fragment retrieval devices (Table 38.3). Retrieval success rates vary widely, ranging from 29% to 100% (7–11,17).

Table 38.2 Conditions Associated with Coronary Stent Loss
- Moderate to severe vessel calcification
- Proximal tortuosity/angulation
- Incomplete lesion preparation
- Insufficient guiding catheter and/or guidewire support
- Advancing or retrieving a stent through a previously placed one
- Retraction of undeployed stent into the guiding catheter
- Use of longer stents
- Use of manually crimped stents

Table 38.3 Tools and Techniques for Percutaneous Retrieval of Lost Coronary Stents
- Low-profile/small balloon catheter technique
- Two-wire technique
- Loop snare\(^a\)
- Biliary or myocardial biopsy forceps
- Retained fragment retriever\(^b\)
- Basket retrieval device

\(^a\)For example, Microvena Amplatz Goose Neck Snare (Microvena Corp., Plymouth, Minnesota, U.S.).
\(^b\)Cook Retrieval Set (Cook Medical, Bloomington, Indiana, U.S.).

Small-Diameter Balloon Catheter Technique
The use of small-diameter balloon catheter is probably the simplest way to attempt stent retrieval. This technique may be used if the stent gets stripped off the balloon but remains on the guidewire. A small caliber balloon catheter (typically with a diameter of 1.0–1.5 mm) is passed through the undeployed stent and is inflated distally. Subsequently, the balloon catheter, the guidewire, the guiding catheter, and the stent are all removed as a unit (Figs. 38.1 and 38.2) (11). To prevent possible embolization to the cerebral circulation, the whole system should always be pulled down to the descending aorta toward the sheath before attempting to pull the stent-loaded balloon catheter into the guiding catheter (9). Alternatively, some authors have also described use of small-diameter balloon catheters to attempt the advancement of the stent and the deployment at the target lesion site (10).

Double-Wire Technique
The double-wire method is also a relatively straightforward technique that can be used if the stent remains on the guidewire. A second guidewire is advanced distal to the stent, following which the two guidewires are twisted to intermingle their distal ends, therefore allowing entrapment of the stent, which can then be retrieved by pulling both wires (Fig. 38.3).

Loop Snare
If the stent is not on the guidewire anymore, a loop snare can be used to retrieve the stent. Loop snares are either commercially available (e.g., Microvena Amplatz Goose Neck Snare, Microvena Corp., Plymouth, Minnesota, U.S.) or can be prepared de novo in the catheterization laboratory using an exchange-length 0.014-in. guidewire and a diagnostic multipurpose catheter.

Specific Vascular Retrieval Devices
The biliary or vascular forceps consists of a curved finger-like projection that can be expanded/extended or contracted/retracted, allowing entrapment of lost stent. The Cook retained fragment retriever (Cook Medical, Bloomington, Indiana, U.S.) has an articulating arm operable from the proximal hub, which

Table 38.1 Complications of Percutaneous Coronary Intervention
- Coronary perforation
- Stent loss
- Coronary dissection
- Abrupt vessel closure
- Distal embolization
- Side branch occlusion
- Stent thrombosis

Vascular complications
- Access site
  - Bleeding
  - Pseudoaneurysm
  - Arteriovenous fistula
  - Arterial thrombosis
  - Venous thrombosis
  - Infection
- Retroperitoneal hematoma
- Dissection or perforation of peripheral vessels
- Late vascular dissection
- Atheroembolism

Other
- Contrast nephropathy
- Gastrointestinal bleeding
- Radiation exposure
- Allergic reactions
- Ventricular arrhythmia, conduction disturbances

Figure 38.1 Small-diameter balloon catheter technique for lost stent retrieval. A small-diameter balloon catheter is advanced on the guidewire toward the lost stent (upper diagram). The catheter is advanced beyond the stent and inflated. Then, the balloon catheter is pulled back, allowing retrieval of the lost stent (lower diagram).
allows grasping and retrieving of retained equipment fragments. The basket retrieval device (Cook Medical) consists of several helically arranged loops that can be expanded or collapsed, allowing entrapment of the embolized stent, in particular if it has been deformed. These devices may not be available in all cardiac catheterization laboratories, and their use should be reserved to experienced operators familiar with their use. Importantly, these devices cannot be used in the coronary vasculature but are typically used to treat stent embolization in large vessels such as the aorta, the iliac, and the femoral arteries (11).

The appropriate strategy for managing stent loss depends on whether the stent has embolized in a coronary artery or in the peripheral circulation and whether the stent is still on the guidewire or not (Fig. 38.4). If the stent has stripped off the delivery balloon catheter in the coronary artery but still remains on the guidewire, recovery with a small profile balloon catheter or the double wire technique should be attempted. Use of a loop snare should also be considered, especially if the guidewire is not on the stent anymore. Alternative options include deployment of the stent at the embolization site or exclusion from the coronary circulation by crushing the undeployed stent with an additional one. However, the two latter strategies should be avoided if the stent is located in the left main trunk or at other strategic locations (11). In fact, both an undersized stent and an undeployed stent crushed against the vessel wall put the patient at risk of subacute or late vessel thrombosis. If none of these options are possible, efforts should be made to at least move the stent into the aortic root, as peripheral embolization usually has a more benign prognosis than coronary embolization (8). Management options of peripheral stent embolization include retrieval with the small-diameter balloon catheter or double-wire techniques or dedicated tools mentioned above (snare, basket, forceps, Cook retrieval set). While deployment of a coronary stent at a peripheral site is rarely indicated due to the mismatch between the stent and the vessel size, crushing the embolized device with a peripheral stent is a possible option. Because of the larger vessel size, this maneuver is far less likely to be associated with vessel thrombosis in the coronary tree. Overall, leaving an undeployed stent in the peripheral circulation should be considered, as the technical difficulties and risk related to retrieval maneuvers may outweigh the risk of local complications related to the embolized device (Fig. 38.5) (11). In addition, the location of the stent embolized in the peripheral circulation often remains unknown.

If percutaneous efforts to treat the lost stent in the coronary tree fail, surgical retrieval should usually be considered—along with coronary bypass grafting if the target lesion is left untreated—because of the intrinsic risk of vessel thrombosis. Conversely, surgical retrieval of a stent that has embolized in the peripheral circulation should be performed only in the presence of symptoms resulting from device embolization.

**Conclusions**

Stent loss is a rare complication of PCI, which is associated with a high rate of adverse outcomes if the stent is lost in the coronary tree. Stent embolization may be prevented by proper patient selection, equipment, and technique. Percutaneous treatment of stent embolization, including retrieval, deployment at embolization site, and exclusion are effective. Operators should
be familiar with these techniques to properly manage this potentially serious complication. In case of failure to retrieve undeployed stents in the coronary vasculature, cardiac surgery should be considered. Stent embolization in the peripheral vasculature has a more benign prognosis and usually does not require treatment.

**CORONARY PERFORATIONS**

**Introduction**

Coronary perforation is a rare but potentially life-threatening complication that occurs in 0.2% to 0.9% of PCIs (18-32). With atheroablative techniques such as directional or rotational atherectomy and excimer laser angioplasty, the risk is somewhat higher (0.3–3.3%) (19–21,33–35). The overall incidence of coronary perforation during PCI has been unchanged over the last 20 years. This is likely explained by a balance between the expected decrease due to changes in technique—such as the more selective use of atheroablative techniques and the abandonment of high-pressure angioplasty with oversized compliant balloon catheters—and the likely increase due to the greater number of high-risk interventions and the use of stiff and hydrophilic guidewires (20,21,36).

The diagnosis of coronary perforation is usually made immediately by visualization of contrast extravasation on coronary angiogram (36,37). However, in case of wire perforation, the diagnosis may be made only later in the presence of hemodynamic compromise and pericardial effusion on echocardiography (18,23). Patients with frank perforation may complain of severe chest pain, dizziness, nausea, and vomiting, out of proportion to what typically observed during balloon inflation. Heart rate usually increases and blood pressure falls, with a rise in central venous pressure when tamponade develops. At times, vagal-mediated bradycardia may occur. ST segment elevation or depression may ensue due to vessel occlusion at the level of the perforation or distally (36).

Ellis et al. proposed a classification of coronary perforation based on angiographic appearance (Table 38.4) (18). Type I perforations are characterized by a focal extraluminal crater limited to the media or adventitia in the absence of contrast extravasation, and cannot be differentiated angiographically from the previously described NHLBI type C dissection,
suggesting a continuum between dissection and perforation (38,39). Type II perforations include pericardial or myocardial blush without contrast jet extravasation (Fig. 38.6), while type III perforations involve persistent extravasation with streaming or jet of contrast through a frank (≥1 mm) perforation (Fig. 38.7). If the jet is directed toward an anatomic cavity (e.g., ventricle, coronary sinus), the perforation is classified as cavity spilling (CS) type, type IV or alternatively type IIIb, as opposed to type IIIA where the jet is directed toward the pericardium. The most frequent type of perforation is type II (37–61%), while type I and III occur less often (18–44% and 19–36%, respectively) and type CS is rarely encountered (2–5%) (20,25,29). Most type I and II perforations are caused by guidewires, while type III are more frequently associated with use of stents or atheroablative techniques (20,24,27). Muller et al. recently proposed a modification of the Ellis classification, adding a type V perforation describing distal coronary perforations by guidewires (40).

Several retrospective series have sought to determine predictive factors of coronary perforation among clinical, anatomical, and procedural characteristics (Table 38.5). The most consistent multivariate predictor of coronary perforation is the use of atheroablative techniques, which has been associated with an odds ratio for coronary perforation ranging from 2.7 to 6.8 in comparison to standard techniques (20,21,24). Additional independent predictors include female gender (likely due to the smaller size of the coronary arteries in women), history of CABG (likely due to the higher prevalence of complex lesions and in particular of chronic total occlusion), lesion complexity (type B2/C according to the ACC/AHA classification), and the use of intravascular ultrasound (IVUS)-guided lumen optimization (20,21,24,41). The latter is probably explained by an incorrect interpretation of IVUS images to maximize the stent lumen area (37). Moreover, advanced age, congestive heart failure, heavy calcification, extreme vessel tortuosity, small vessel diameter, and balloon catheter or stent oversizing have also been associated with an increased incidence of coronary perforations. The use of stiff or hydrophilic guidewires has also been reported in recent series as a cause of coronary perforation, mostly in the distal bed (18–32). Cutting balloon angioplasty has also shown to be associated with a higher risk of coronary perforation that plain balloon angioplasty or stenting (42). Following the widespread use of glycoprotein (GP) IIb/IIIa inhibitors, concern of a potential increase in the occurrence of coronary perforation during administration of these potent drugs has been raised. However, several series have shown that GP IIb/IIIa inhibitors are not associated with a higher incidence of coronary perforations. Nevertheless, coronary perforations occurring in patients under GP IIb/IIIa inhibitors are associated with a higher rate of adverse events, suggesting that these antiplatelet drugs may increase the harmful consequences but not necessarily the occurrence of coronary perforation. In this respect, the association of GP IIb/IIIa inhibitors and hydrophilic wires appears particularly risky (20,23–25).

The mainstay of perforation prevention is the cautious use of atheroablative techniques and of hydrophilic guidewires in complex anatomy, especially if there is concomitant administration of GP IIb/IIIa inhibitors. Of paramount importance is a stable position of the guidewire, especially if it is hydrophilic, during advancement and retrieval of balloon catheters or stents, as distal perforation is frequently the result of an unnoticed wire movement. Finally, provided that the anatomy is suitable, debulking with rotational atherectomy should be favored for preparation of severely calcified lesions resistant to conventional angioplasty over the use of oversized balloons inflated at high pressures.

Table 38.4 Classification of Coronary Perforations

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Extraluminal crater without contrast extravasation</td>
</tr>
<tr>
<td>II</td>
<td>Pericardial or myocardial blush without contrast jet extravasation</td>
</tr>
<tr>
<td>III</td>
<td>Extravasation through frank (≥1 mm) perforation</td>
</tr>
<tr>
<td>Cavity spilling</td>
<td>Perforation into an anatomic cavity (i.e., ventricle, coronary sinus)</td>
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Source: From Ref. 18.

Figure 38.6 Left panel: left anterior oblique view of a distal type II perforation of the left anterior descending coronary artery induced by a hydrophilic guidewire, with pericardial extravasation (arrow). Right panel: right anterior oblique—cranial view of type II perforation, the left circumflex coronary artery with myocardial staining following implantation of an oversized stent (arrowheads).
Outcomes

Coronary perforation is clearly associated with an increased rate of in-hospital and long-term adverse events, which include myocardial infarction, emergency surgery, and death (21,31). These outcomes are mostly the consequence of hemodynamic compromise, resulting from pericardial effusion and tamponade, or of ischemia due to failure to treat the target lesion or vessel occlusion. According to the literature, tamponade may complicate 12% to 55% of coronary perforations (20,22). However, the true incidence is likely lower because of underreporting of “benign” perforations. Tamponade usually appears immediately after coronary perforation, although a late occurrence has been reported in 21% to 52% of patients, with a delay ranging from 2 to 10 hours following PCI (22,23,43–45). Tamponade rarely develops in patients with prior CABG due to obliteration of the pericardial space by adhesions between the epicardium and pericardium as well as the persistence of partial pericardiotomy following surgery (46).

Emergency surgery, usually consisting of pericardial drainage with or without CABG or repair or ligation of the perforated artery, was reported in 24% to 41% of perforations in earlier series (18,34). More recent reports show a lower incidence of emergency surgery (2–20%) (26,30). This reduction is likely related to an improved early detection of coronary perforations, a decreased use of atheroablative devices, a higher proportion of guidewire-induced distal coronary perforations that can often be managed conservatively or percutaneously, the availability of covered stents, and the increasing experience of operators (36).

Myocardial infarction, which can be due to vessel occlusion, either as a direct consequence or as an intended treatment of coronary perforation, may occur in 5% to 37% of cases (25,28).

The mortality rate associated with coronary perforations ranges from 0% to 17% (22,27). Predictors of mortality or major adverse events include older age, female gender, chronic renal failure, use of compliant balloons and treatment of angulated or calcified lesions (19,21,27). Furthermore, type III perforations are clearly associated with far worse outcomes than types I, II, and CS (mortality of 19–22% for type III and <6% for types I, II, and CS) (20,26).

Fasseas et al. reported that patients receiving GP IIb/IIIa inhibitors at the time of coronary perforation more frequently required the placement of a covered stent or emergency surgery in comparison to patients not treated with these agents (20). A recent retrospective analysis has shown that guidewire-induced coronary perforation was associated with a significantly lower incidence of major adverse cardiac events when bivalirudin was used as an adjunctive therapy compared with unfractionated heparin (30). Likewise, a pooled analysis from three randomized controlled trials showed that outcomes following coronary perforation with bivalirudin as an adjunctive therapy were not inferior in comparison to unfractionated heparin (31). These results suggest that bivalirudin may be as safe as unfractionated heparin in the presence of a coronary perforation. This is possibly explained by the short half-life of the drug. However, in the presence of frank perforation, the antithrombotic effect of bivalirudin cannot be immediately reversed while in patients treated with unfractionated heparin protamine can be administered.

Subendocardial or intramyocardial hematoma has been reported as an extremely rare consequence of coronary perforation. This dreadful complication is characterized by a bleed that can progress in a relentless fashion, dissecting the epicardium and the epicardial vessels from the underlying myocardium that can prevent blood from accumulating in the pericardial space. However, cases of subendocardial hematoma more frequent in patients with prior CABG because of adhesions between the epicardium and the pericardium that can prevent blood from accumulating in the pericardial space. However, cases of subendocardial hematoma in patients without prior CABG have also been reported. Finally, it is worth mentioning that bypass graft perforation may result in tamponade, mediastinal hemorrhage, hemoptysis, and subendocardial hematoma (25,46,48–50).

Table 38.5 Predictive Factors of Coronary Perforations

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Anatomical</th>
<th>Procedural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>Complex lesions&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Atheroablative techniques</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Chronic total occlusion</td>
<td>Use of intravascular ultrasound</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>Heavy calcification</td>
<td>Balloon catheter or stent oversizing</td>
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<tr>
<td>Elderly</td>
<td>Extreme tortuosity</td>
<td>Stiff or hydrophilic guidewires</td>
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<tr>
<td>Congestive heart failure</td>
<td>Small vessel diameter</td>
<td>Cutting balloon</td>
</tr>
<tr>
<td>Unstable angina/NSTEMI</td>
<td>Graft anastomosis</td>
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</table>

<sup>a</sup>ACC/AHA type B2/C (41).

Abbreviations: CABG, coronary artery bypass surgery; NSTEMI, non-ST segment elevation myocardial infarction.
Management

The first step in the treatment of coronary perforation is prompt detection and classification of the type of perforation, as this will subsequently dictate the management strategy (Fig. 38.8) (18). Type I perforations can generally be managed either conservatively or by the implantation of a conventional stent, based on the size and prognostic importance of the vessel (36,38). Similarly, type CS perforations may also be treated conservatively, with the vascular communication often closing spontaneously later on. Type II perforation management depends on the extent of the extravasation, as limited pericardial and myocardial staining can usually be observed and treated conservatively, with discontinuation of anticoagulants and/or GP IIb/IIIa inhibitors. Larger type II perforations should be treated more aggressively, with prolonged balloon inflation, reversal of anticoagulation and platelet transfusion if indicated, and echocardiographic assessment of pericardial effusion. Finally, type III perforations require immediate actions with prolonged balloon inflation, discontinuation and reversal of antiplatelet and antithrombotic therapy (if possible), hemodynamic supportive therapy, echocardiographic assessment of pericardial effusion and, if needed, pericardiocentesis, and percutaneous or surgical treatment of perforation. In this respect, the balance between the ongoing ischemia (caused by the management of the perforation) and the hemodynamic instability (caused by the perforation or by the ongoing ischemia) is key (51). Following successful treatment of coronary perforation, surveillance in a coronary care unit for at least 24 hours is indicated, as delayed tamponade may occur.

Prolonged Balloon Inflation

In large type II and all type III perforations, the first maneuver, even before starting cardiopulmonary resuscitation, pericardiocentesis, or reversal of anticoagulation, should be the placement of a balloon catheter (with balloon to artery diameter ratio of 0.9–1.0) at the site of perforation or upstream in case of distal perforation, inflated at a low pressure (2–6 atm). Serial angiographic assessments of the perforation should be performed at 10 to 15 minutes inflation periods. In case of incomplete perforation sealing, the use of a perfusion balloon has been recommended to reduce myocardial ischemia, but the availability of these devices in catheterization laboratories has markedly decreased (24,37,40).

Cessation and Reversal of Adjunctive Therapy

If the patient is receiving GP IIb/IIIa inhibitors or bivalirudin, the drugs should be immediately discontinued in type II and III perforations. Furthermore, in large type II and type III perforations, anticoagulation by unfractionated heparin should be reversed with administration of protamine sulfate to achieve an activated clotting time of less than 150 seconds or a partial thromboplastin time of less than 60 seconds. Treatment with protamine is safe following stent implantation, without any increase in the incidence of stent thrombosis (52). If the patient

![Figure 38.8](image-url)
was receiving abciximab, the platelet inhibitory function of this potent drug can be reversed by platelet transfusions, as abciximab binds platelets with high affinity and has low free plasma levels. Conversely, small molecules like tirofiban and eptifibatide maintain high plasma concentration, and their antiplatelet properties therefore remain unaffected by platelet transfusions. However, in the presence of normal renal function, small molecules are cleared from plasma within a few hours. In case of renal failure, hemodialysis can be useful to diminish the effects of these drugs (24,37). Reversal of anticoagulation cannot be achieved in patients under low molecular weight heparin, fondaparinux, or bivalirudin.

Hemodynamic Support Therapy
Intravenous fluids should be administered immediately. Vasoconstrictor and inotropic therapy as well as cardiopulmonary resuscitation may become rapidly necessary following coronary perforation (24). Placement of an intra-aortic balloon pump may also be required in the presence of depressed left ventricular function or large ongoing ischemia.

Pericardiocentesis
The details of pericardiocentesis are described in chapter 14. If a sizable coronary perforation is observed, an echocardiogram should be performed emergently to assess the presence of pericardial effusion. In case of tamponade, pericardiocentesis is a life-saving maneuver. Once a multiple side-hole catheter is placed in the pericardium and the hemorrhage has stopped, the catheter should be maintained until the following day. In the absence of recurrent effusion on the echocardiogram, the catheter can then be removed. Observation for an additional day in a regular unit with a subsequent control ultrasound is warranted before discharge (24).

Perforation Sealing
Coronary perforations with persistent extravasation despite prolonged balloon inflation can successfully be treated with implantation of polytetrafluoroethylene-covered stents (53–55). The JOSTENT coronary stent graft (Abbott Vascular Devices, Abbott Park, Illinois, U.S.) consists of an ultrathin, biocompatible, and expandable polytetrafluoroethylene layer sandwiched in between two coaxial balloon-expandable stents (for details see chap. 32). Procedural success rates vary from 71% to 100%. The use of covered stents appears to have reduced the need for emergency surgery (55). However, due to their unfavorable profile and stiffness, covered stents may not be delivered in tortuous vessels or distal lesions. Importantly, the minimum vessel diameter that can accommodate a covered stent is 3.0 mm. Covered stents should be placed either at the level of the perforation or at a bifurcation upstream from perforation site to seal the vessel. Dual antiplatelet therapy with aspirin and clopidogrel should also be continued during at least three months following covered stent implantation because of the delayed reendothelialization with the risk of subacute stent thrombosis. Occasional use of autologous venous-covered stents has also been described. The preparation is cumbersome and unsuitable for emergency situations, although time intervals from vein harvest to stent deployment of 20 to 45 minutes have been reported. Other reported percutaneous strategies for treatment of distal coronary perforation include embolization of coils, gelfoam, polyvinyl alcohol, thrombin, glue, or autologous blood clot (56–63).

Emergency Surgery
In the presence of persistent coronary perforation with hemodynamic compromise or large ischemic territory despite optimal nonoperative measures, surgical management should be considered. Emergency surgery can involve pericardial drainage, if percutaneous drainage failed or was insufficient, perforation repair or vessel ligation, and bypass grafting to vessels with significant stenoses. Before transferring the patient to the operating room, a balloon catheter should be kept inflated at low pressure at the perforation site, as previously described, and then removed during surgery.

Conclusion
Coronary perforation is a life-threatening complication of PCI, which usually occurs in high-risk anatomical settings or with the use of atheroablative devices or hydrophilic wires. Prompt recognition of this complication may be life saving, allowing for effective percutaneous or surgical treatment of the perforation as well as its hemodynamic consequences.

AORTIC DISSECTION
Introduction
Iatrogenic aortic dissection (IAD) is an extremely rare complication of cardiac catheterization. Reported incidence ranges from 2 to 4 cases per 10,000 cardiac catheterizations. The incidence is higher during PCI (3–15 cases per 10,000 procedures) than during diagnostic coronary angiography (4–10 cases per 100,000 catheterizations). This complication is more frequently observed in the setting of acute myocardial infarction (19 cases per 10,000 procedures) (64–66). IAD is a retrograde extension into the aortic root of a dissection usually located at the level of the coronary ostia, mainly caused by guiding catheter manipulations (64). Following a coronary artery dissection, contrast injections can cause retrograde progression of the flap up to the level of the coronary sinus of Valsalva, where the shearing forces of blood flow during systole and diastole can further propagate the dissection in the aortic root (66,67). IAD without involvement of the coronary arteries has been reported in very rare instances due to catheter manipulation in the aorta (68).

The diagnosis of IAD is usually straightforward on angiography, characterized by contrast medium stagnating at the level of the aortic root or even extending to the ascending aorta. The spectrum of associated symptoms ranges from none to excruciating chest or back pain. Hypotension, hemodynamic compromise, and shock may ensue (69). On the basis of the extent of the aortic dissection, a classification of IAD was proposed by Dunning et al. (64). Class I is defined as a focal dissection limited to the ipsilateral cusp of the dissected coronary artery. Class II and III include dissections that extend up the aorta <40 mm and >40 mm, respectively (Table 38.6, Figs. 38.9 and 38.10).

| Table 38.6 Classification of Iatrogenic Coronary Dissections with Retrograde Extension into the Aortic Root |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Class I Aortic dissection involving only the ipsilateral cusp |
| Class II Aortic dissection involving cusp and extending up the aorta <40 mm |
| Class III Aortic dissection involving cusp and extending up the aorta >40 mm |

Source: From Ref. 64.
IAD originates most frequently from the ostium of the right coronary artery. In a review of 67 cases published in the medical literature, Carstensen et al. reported that the dissection spread from the right coronary ostium, left coronary ostium, and ostium of a saphenous vein graft in 87%, 12%, and 1% of the cases, respectively (70). IAD occurs more often when deep intubation of the guiding catheter in the coronary artery is required (e.g., in the treatment of chronic total occlusions). The use of left Amplatz guiding catheters also seems to be associated with a higher risk of IAD (64,65). As previously mentioned, IAD appears to occur more frequently during PCI for acute myocardial infarction. This is most likely due to the urgency of the situation and operator haste in attempting to rapidly achieve myocardial reperfusion, while an increased vulnerability of vessel walls in relation with the ongoing inflammatory process cannot be excluded (64,66). Finally, although underlying conditions that can cause spontaneous aortic dissection such as Marfan syndrome or bicuspid aortic valve would probably favor IAD, no apparent increase in incidence of IAD has been reported in such settings. The most likely explanation is that the need to perform PCI on Marfan patients is exceedingly rare. Likewise, although cases of IAD in patients with cystic medial necrosis have been described, it is believed that it does not represent a risk factor for IAD, as low grades of degeneration are nonspecific and associated with advanced age (64).

Outcomes
IAD can lead to extensive dissection involving the ascending aorta up, the aortic arch, the supra-aortic vessels, and even the descending aorta. Furthermore, extension of the intimal flap toward the aortic valve may cause significant acute aortic regurgitation as well as hemopericardium and tamponade. Emergency surgery is necessary in 6% to 33% of cases following IAD. Surgery will usually associate repair or replacement of the ascending aorta with the treatment of the aortic valve, and CABG or pericardial drainage if required. In-hospital mortality rates after IAD may range between 0% and 25% (64–67,70).

Management
The management of IAD has not been yet standardized. A commonly accepted management strategy is the immediate stent implantation at the ostium of the coronary artery from where the intimal flap has spread followed by a conservative approach of watchful waiting for class I and II IAD, while class III dissections should undergo immediate surgical treatment (Fig. 38.11) (64). Some authors also recommend attempting ostial stenting in patients with class III dissections (70). This strategy appears reasonable if the patient is in a relatively stable hemodynamic condition and if stent implantation does not delay the surgical management. In all patients, unfractionated heparin should be reversed with protamine, and in patients treated with abciximab, platelets should be administered. Pericardiocentesis may be needed in patients with tamponade but only if it is estimated that they may not survive the transfer to the operating room.

![Figure 38.9](image1.png)

Figure 38.9 Class II iatrogenic aortic dissection following retrograde extension of a right coronary artery ostial dissection.

![Figure 38.10](image2.png)

Figure 38.10 Left lateral view of an aortic dissection following retrograde extension of a right coronary artery ostial dissection (arrow, left panel), rapidly progressing to a class III dissection involving the entire aorta (arrowheads indicating dissection flap on aortography, right panel). Note also the filling of the left ventricle as a sign of associated aortic regurgitation (arrows, right panel).
the operating room. For less unstable patients, surgical pericardiocentesis in the operating theatre is preferred. Assessment of the extension of the IAD can be achieved with an aortography. Additional diagnostic techniques for the acute phase include transthoracic and transoesophageal echocardiography and computed tomography.

Conclusions

IAD is a rare complication of cardiac catheterization, which occurs more frequently in the setting of PCI for acute myocardial infarction. Patients with a dissection confined to the aortic sinus of Valsalva or extending less than 40 mm up the ascending aorta should be treated with stenting of the coronary ostium and then monitored in the intensive care unit, while dissections extending more than 40 mm up the aorta should be treated with immediate surgery.

REFERENCES


Figure 38.11 Suggested algorithm for the management of iatrogenic aortic dissection. Abbreviations: CCU, coronary care unit; CABG, coronary artery bypass grafting.


Intra-aortic balloon pump counterpulsation, percutaneous left ventricular support

Troy Weirick, Wendell Ellis, and Richard W. Smalling

INTRODUCTION

Currently, no formal guidelines detail the indications for temporary left ventricular (LV) support. This lack of consensus notwithstanding, short-term mechanical cardiac assistance may be appropriate in a few well-defined circumstances. In the setting of acute myocardial infarction (AMI) with severely compromised ventricular function, temporary mechanical support unloads the left ventricle and augments cardiac output. Unloading the ventricle, particularly when initiated prior to reperfusion, may improve myocardial blood flow and reduces reperfusion injury. Improving cardiac output mitigates end-organ damage potentially limiting the systemic inflammatory response. In the case of chronic heart failure, temporary LV support reverses the acute metabolic derangements associated with decompensation. If the ventricle is able to recover sufficiently, medical management may be resumed. If ventricular function remains inadequate, temporary support may serve as a bridge to more definitive therapy. Finally, during high-risk percutaneous coronary intervention (PCI), temporary support provides circulatory protection in the event of acute vessel closure or catastrophic LV compromise.

Cardiogenic shock occurs in approximately 7% of patients hospitalized for acute STEMI and is the leading cause of early death in post-MI patients (1). Despite maximal medical management, including early thrombolysis and intra-aortic balloon counterpulsation (IABC), 30-day mortality from cardiogenic shock following AMI remains unacceptably high at roughly 50% (2). A strategy of early, aggressive PCI appears to have a positive, sustained influence at one-year and on late survival (3,4). However, even with successful mechanical reperfusion, viable myocardium may be stunned and noncontractile for up to a week (5). Without adequate LV support during this period of myocardial recovery, the cycle of shock and further ischemic damage goes unchecked, leading to more profound pump failure, propagation of the systemic inflammatory response syndrome, and eventually death (6).

The safety and durability of PCI has improved dramatically in the past 10 years due to better antiplatelet agents and improved stent technology. Attendant reductions in periprocedural complications, a decreased need for target lesion revascularization and mortality comparable to conventional bypass grafting has lead to greater acceptance of more aggressive PCI strategies (7,8). Despite noteworthy procedural success, early attempts at percutaneous transluminal coronary angioplasty (PTCA) in high-risk individuals demonstrated unacceptable inhospital mortality and required frequent target lesion revascularization. According to work performed by Hartzler and colleagues during the pre-stent era, individuals presenting with left main disease, a low ejection fraction (EF) or with AMI were 10 times more likely to die following PTCA when compared to patients presenting with uncomplicated disease. In a worst-case scenario, the combination of low EF and AMI, periprocedural mortality was 50 times greater in high-risk patients (9). Around the same time, Ellis et al. showed that mortality related to acute vessel closure during PCTA was largely a function of the area of myocardium at risk (10). These studies and other early work with supported PCI demonstrated a role for temporary LV assistance during high-risk procedures.

ANATOMIC CONSIDERATIONS

The primary anatomic considerations limiting percutaneous LV support are access site disease, aortic valve dysfunction, and integrity of the thoracic and abdominal aorta. All of the devices detailed in this chapter require relatively large arterial access conduits. With the exception of sheathless intra-aortic balloon pump (IABP) insertion, all forms of percutaneous LV support described require a minimum of 7.5-Fr arterial access. Furthermore, there is a significant trade-off between the degree of LV support provided and the size of arterial cannula required. The IABP offers minimal augmentation of cardiac output (0.5 L/min), but sheathed insertion is nominal at 7.5 Fr. The TandemHeart offers the greatest cardiac assistance, 4.0 L/min, but requires 21-Fr venous access and unilateral 15- to 17-Fr or bilateral 12- to 15-Fr arterial access. The Impella LP2.5 is intermediate, requiring a single 13- to 14-Fr arterial cannula and offering up to 2.5 L/min of flow. Because of the prevalence of significant peripheral vascular disease in our patients, if vessel anatomy is unknown at the time of intervention, angiography of the aorta with runoff is generally performed prior to device insertion.

Device selection is also limited by aortic valve disorders and diseases of the aorta. Moderate to severe aortic regurgitation is a contraindication to Impella, TandemHeart, and IABP support. All of these devices can potentially worsen the severity of aortic regurgitation negating the benefits of LV assistance. In addition, due to its transvalvular design, the Impella cannot be used in patients with moderate to severe aortic stenosis or in individuals with mechanical aortic valves. When significant valvular disease is suspected, echocardiography prior to arrival in the catheterization laboratory is highly recommended. Lastly, severe atherosclerotic disease or significant aneurysm of the thoracoabdominal aorta is a contraindication to both IABC and Impella support. Repeated balloon inflations and the associated mechanical stress may lead to dislodgement and embolization of atherosclerotic debris. The same repetitive forces combined with systemic anticoagulation may lead to
devastating rupture of aortic aneurysms. Patients with severe disease of the aorta have generally been excluded from previous Impella trials; therefore, the safety of the Impella in this population is uncertain.

FUNDAMENTALS

Two basic concepts provide the rationale for LV assistance during AMI, cardiogenic shock, and high-risk PCI. First, augmentation of cardiac output enhances systemic hemodynamics and improves end-organ perfusion. Second, LV unloading modestly improves coronary artery blood flow while reducing myocardial oxygen demand, thus limiting adverse remodeling. Animal experiments and human trials have demonstrated superior hemodynamics and improved LV unloading with mechanical LV support. An early trial with the Hemopump (Medtronic Inc., Minneapolis, Minnesota, U.S.) elegantly demonstrated enhanced systemic hemodynamics in patients suffering from cardiogenic shock (11). In this trial, 53 patients meeting criteria for cardiogenic shock (cardiac index < 2.0 L/min/m², pulmonary capillary wedge pressure > 18 mmHg, systolic blood pressure < 90 mmHg) were assigned to Hemopump insertion. In the 41 patients with successful placement, cardiac index increased from 1.6 to 2.2 L/min/m², pulmonary capillary wedge pressure decreased from 27 to 17 mmHg, and mean arterial pressure increased from 56 to 67 mmHg. Later, in a sheep model of anterior MI, Meyns et al. demonstrated that the Impella 5.0 improved cardiac output and increased mean arterial pressure while decreasing myocardial oxygen consumption (12). In this trial, fully supported animals demonstrated lower LV end diastolic pressure during ischemia and reperfusion compared to the unsupported group. Furthermore, despite increased mean arterial pressure, device-supported animals demonstrated a lower dP/dt max and reduced myocardial oxygen consumption. Improved systemic hemodynamics including increased cardiac index/cardiac output, decreased pulmonary capillary wedge pressure, and increased mean arterial pressure, as well as reduced cardiac work have also been demonstrated with the Impella LP2.5 (13) and in trials with the TandemHeart (14,15).

In addition to improving systemic hemodynamics, mechanical LV support has a positive effect on coronary blood flow while reducing myocardial oxygen demand, therefore reducing infarct size. In 1992, our lab demonstrated a modest improvement in regional myocardial blood flow and concomitant reduced myocardial oxygen demand in a canine model of anterior MI with LV assistance. When infarction was expressed as a percentage of the myocardium at risk, Hemopump- and IABP-supported animals suffered infarcts of 22% and 27%, respectively, compared to unsupported controls with infarcts of 63%. This difference in infarct size was not significant comparing Hemopump- and IABP-supported animals; however, there was a striking contrast between infarct sizes in supported versus unsupported animals (16). In the Meyns’ sheep model of anterior MI, investigators also demonstrated a significant decrease in the size of infarct in Impella-supported animals. Furthermore, they showed that infarct size was related to both timing and the degree of mechanical support. Animals supported throughout the infarct and recovery period developed infarctions roughly one-quarter the size of unsupported animals, and approximately half the size of animals receiving support only during the reperfusion period (12). Adding further evidence to the theory of ventricular unloading, Remme-

link and colleagues directly measured coronary artery blood flow in 11 Impella-assisted patients undergoing high-risk PCI. In this study, investigators found that as Impella support increased, hyperemic coronary flow velocity increased as well. These investigators also noted an inverse relationship between Impella support and coronary microvascular resistance (17). This combination of improved systemic hemodynamics along with superior myocardial oxygen supply and decreased metabolic demand compose a compelling argument for mechanical LV support during AMI.

INDICATIONS

Clinical applications of the IABP and TandemHeart are fairly well established and generally similar. As a much newer device, indications for the Impella LP2.5 are evolving. On the basis of data from the Benchmark Registry, the most common applications of IABC are hemodynamic support during cardiac catheterization procedures (21%), cardiogenic shock (19%), weaning from bypass (16%), perioperative support in high-risk patients (13%), and refractory unstable angina (12%) (18). Common indications for TandemHeart support include AMI, postcardiotomy pump failure, decompensated heart failure, transplant allograft dysfunction, cardiac arrest, and right ventricular infarction. The Impella has demonstrated effectiveness in support during high-risk PCI, cardiogenic shock, and MI. Table 39.1 provides a more complete list of indications for temporary cardiac support.

EQUIPMENT

Currently there is no ideal device for the acutely decompensated ventricle; however, a great deal has been learned from previous generations of cardiac assist devices. The ideal temporary LV support system could be quickly and easily inserted in the catheterization laboratory, would offer near complete temporary LV support, and could remain in place for days to weeks.

Table 39.1 Indications for Temporary Cardiac Support

- 3-Vessel disease
- Acute myocarditis
- Acutely decompensated chronic heart failure
- Bridge to bridge
- Bridge to destination
- Bridge to transplant
- Cardiac arrest
- Cardiogenic shock
- Catheterization laboratory procedures
- Heart failure
- High-risk percutaneous coronary intervention
- High-risk valvular procedures
- Incessant ventricular arrhythmias
- Last remaining patent conduit
- Low ejection fraction with left main disease
- Mechanical complications of acute myocardial infarction
- Myocardial infarction
- Papillary muscle rupture
- Reinitiation of medical therapy
- Ventricular septal defect
- Postoperative allograft dysfunction
- Surgical
- Perioperative support of high-risk patients
- Failure to wean from bypass
- Postcardiotomy syndrome
Traditional ventricular assist devices (VAD) such as the MicroMed DeBakey, Jarvic 2000, and the HeartMate II are safe, durable, and capable of complete cardiac assistance, but these devices are not well suited for short-term or emergent use (19). A technology that initially showed promise was percutaneous cardiopulmonary bypass (pCPB).

Cardiopulmonary bypass (CPB) was introduced to the surgical theater in the early 1950s and the first report of pCPB was published in 1983 (20). In its simplest form CPB consists of a venous intake cannula, oxygenator, blood pump, and an arterial return cannula. In 1990 two independent groups, Shawl and colleagues and Vogel et al., reported separate experiences of pCPB-supported coronary angioplasty. Shawl reported on 121 patients with low EF (<25%) and either an acute coronary syndrome or cardiogenic shock. Vogel’s group reported on 105 patients undergoing elective high-risk procedures—patient EF <25% and/or a target vessel supplying more than half of the myocardium. Each registry reported a high degree of procedural success; however, they also encountered significant vascular and hematologic complications. Access site complications ranged from 26% to 46% and the need for transfusion was between 30% and 43% (21,22). The frequency of access site complications and bleeding were likely related to the size of cannulae used, 18 Fr arterial and 20 Fr venous, as well as the high level of anticoagulation needed during pump initiation, activated clotting time (ACT) ≥400 seconds. Another limitation of pCPB is the inability to adequately vent the left ventricle. Although pCPB supports systemic circulation, percutaneous bypass actually increase LV wall stress. In the presence of ongoing myocardial ischemia, this increased wall stress leads to further myocardial damage. In contrast, devices such as the TandemHeart and Impella actively decompress the LV leading to a beneficial reduction in wall stress.

Percutaneous CPB-supported PTCA had largely been abandoned, but the recent publication of first-in-human trials with a new pCPB device, the Lifebridge B2T (Lifebridge Medizintechnik GmbH, Ampfing, Germany), offers tempered optimism. The Lifebridge B2T is described as modular “plug-and-play” device. Weighing about 20 kg and easily transported, the device employs 15 Fr arterial and 17 Fr venous access to circulate up to 4 L of oxygenated blood. Initially demonstrated in a swine model, in-humansupported for three-veessle disease and left main PCI has been promising (23-25). The new device does not overcome many of the pitfalls of previous bypass machines, including suboptimal LV decompression, the large blood-foreign body interface, and limited run time, but the intake and outflow cannula are considerably smaller than predecessors and the modular construction is well suited for emergent use. Further testing is necessary to define a role for the Lifebridge B2T in the modern catheterization laboratory.

Surgical VADs are impractical in the acute setting and pCPB is currently unproven. The TandemHeart offers excellent LV support, but even in skilled hands it may take up to 30 minutes to insert and activate. The balloon pump can be rapidly inserted, however, an IABP may not adequately support a failing ventricle, particularly in the setting of arrhythmia or extreme tachycardia— a middle ground is needed. A device that can be quickly placed and that provides adequate support until definitive therapy can be achieved. The device poised to fill this gap is the catheter-based axial flow pump.

The first percutaneous axial flow blood pump was developed and tested by Wampler and colleagues. The Hemopump (Medtronic Inc.) in its initial forms, a 21-Fr femoral and a 24-Fr sternal pump, required surgical access. These devices were capable of flows from 3.5 to 5 L/min depending on loading conditions (26). Later, a 14-Fr device intended for percutaneous femoral insertion and capable of 2.5 L/min was introduced. Initial testing with Hemopump was promising. In an animal model, the Hemopump demonstrated modestly improved regional myocardial blood flow, better LV unloading, and reduced infarct size when compared to the IABP (16). Initial in-human trials also demonstrated improved systemic hemodynamics and suggested a survival benefit in selected patients (11,27). Despite these early successes, further testing demonstrated an unacceptable incidence of access site complications, hemolysis, and bleeding (28). The Hemopump did not receive Food and Drug Administration (FDA) approval, but these early experiences laid the groundwork for the next generation of transvalvular axial blood pumps.

**INTRA-AORTIC BALLOON PUMP**

With a lack of other easy and quickly implanted devices for cardiac support, the IABP has been essential in the management of high-risk patients. The IABP was conceived by two separate groups, Dr Dwight Harken and Drs Adrian and Arthur Kantrovitz. Dr Harken believed the failing left ventricle could be unloaded if arterial blood was returned during diastole while the aortic valve was closed. The Kantrovitz brothers believed that by achieving peak arterial pressure in diastole, coronary blood flow could be significantly increased. Early models demonstrated decreased LV end-diastolic pressure, a reduction in LV work index, and increased peak diastolic pressure (29). Subsequent developments have resulted in devices that no longer require surgical insertion or large arteriotomies, and the current generation of IABP can be placed quickly and easily by experienced cardiologists.

The IABP is an essential tool for managing unstable AMI patients. Cardiogenic shock generally occurs after at least 40% of the heart muscle is damaged in the setting of an AMI. A subgroup analysis of the GUSTO-I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial examined the use of IABC in patients with cardiogenic shock. Of the more than 4000 patients enrolled in GUSTO-I, 310 underwent IABP placement. Patients receiving early IABP support had a 30-day mortality rate of 47% compared to 60% in patients without device placement. One-year mortality was 57% in the early IABP group and 67% in those patients who did not receive IABP support (30). The SHOCK trial also explored the question of IABC and AMI. SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) investigators examined 1190 patients with cardiogenic shock and AMI. Similar to the GUSTO-I cohort, a subgroup of patients undergoing IABP placement also showed a significant reduction in mortality with or without revascularization (2).

When is hemodynamic support needed for PCI and what defines "high-risk” PCI? Califf et al. devised the jeopardy scoring system based on coronary anatomy and the presence of coronary disease as a prognostic indicator for major cardiovascular outcomes. In 462 non-surgically treated patients, investigators demonstrated that patients with a score of 2 had a 5-year survival of 97%, and those with a score of 12 had a 5-year survival of 56% (31). Further analysis indicated that LVEF had a similar correlation with prognosis. Adding the degree of stenosis to each vessel, in particular the left anterior descending artery, further increased the prognostic value of the
jeopardy score. Jeopardy score has been validated and is a good prognostic indicator in patients undergoing coronary artery bypass graft surgery and PCI.

Briguori et al. examined the use of prophylactic IABP placement in 133 high-risk patients undergoing elective PCI with LV dysfunction (EF <30%) and a jeopardy score >6. Of these patients, 61 had elective pre-procedural IABP placement and 72 had conventional PCI. Patients with an IABP suffered fewer intraprocedural complications (15% vs. 0%; p = 0.001) (32). Using stepwise regression analysis, high-risk predictors of intraprocedural complications were provision of prophylactic insertion of an IABP, female sex, and jeopardy score. On the basis of data from the National Registry of Supported Angioplasty, older patients (>70 years) and those with left main stenosis are also at increased risk of intraprocedural complications and may merit consideration of prophylactic IABP support (22).

The question of when to place an IABP during an AMI has been studied in several trials. PAMI II investigators looked at the use of prophylactic IABP placement in high-risk hemodynamically stable patients with AMI undergoing PTCA. The primary combined endpoint (reduction in death, reinfarction, infarct artery reocclusion, stroke, new-onset heart failure, or sustained hypotension) showed no significant difference between treatment groups (28.9% vs. 29.2%, p = 0.95). Routine post-PCI IABP placement was beneficial in terms of reducing recurrent ischemia and limiting repeat unscheduled catheterizations; however, use of an IABP was also associated with a higher incidence of stroke (2.4% vs. 0%, p = 0.03) (33). In another study, Brodie et al. examined prophylactic intra-aortic counterpulsation in high-risk AMI. In this series, Brodie compared placement of an IABP prior to PTCA, after PTCA, and PTCA without IABP support. This study of 1490 AMI patients found a reduction in catheterization laboratory events—defined as ventricular fibrillation, cardiopulmonary arrest, or prolonged hypotension—in the group receiving IAPB support prior to PTCA (15% vs. 35%, p = 0.009). IABP support also demonstrated benefit in patients with an EF <30% (34). Finally, the SHOCK trial provides critical data regarding the management of AMI and shock. The results of the SHOCK trial showed a marked reduction in six-month mortality (50% vs. 63%, p = 0.027) in patients with cardiogenic shock that underwent emergency revascularization. In a subgroup analysis, patients who received IABP support had lower in-hospital mortality than those who did not receive an IABP (50% vs. 72%, p = 0.0001) (4). Additionally, patients who received revascularization and placement of an IABP had the lowest in-hospital mortality of all groups analyzed. Results from these trials strongly support the use of IABC in the setting of AMI complicated by cardiogenic shock.

Unfortunately, in most of the early trials of the IABC in the setting of acute STEMI, investigators waited until after infarct artery revascularization to initiate support. However, as early as 1986 Allen and Buckberg demonstrated the beneficial effects of LV decompression on myocardial salvage prior to reperfusion (35). Similarly, in animal models, we have demonstrated a significant improvement in infarct salvage when left VAD or IABP support was initiated prior to reperfusion compared to support initiated after reperfusion (36,37). The randomized CRISP-AMI (Counterpulsation Reduces Infarct Size Pre-PCI for Acute Myocardial Infarction) trial will soon be conducted to confirm these findings in humans (38).

In patients with severely depressed LV function and hemodynamic compromise who are currently awaiting cardiac transplantation, an IABP is often placed as a temporizing measure until a donor heart becomes available. There is no clinical or statistically significant difference in transplant outcomes between patients who receive IABP support before surgery compared to those who do not receive an IABP (39). If placed before cardiac transplantation, the IABP should remain for at least 24 hours postoperatively in the event of allograft dysfunction. Potential complications with this method of treatment are increased rates of local and systemic infection and prolonged immobilization of the patient while the IABP is in place. Left axillary IABP placement may improve patient mobility prior to surgery. This method has been studied retrospectively in a small number of patients. In one small series, all patients with axillary IABP insertion were successfully transplanted and discharged home (40). The longest time the ambulatory IABP was in place was for 70 days.

IABP insertion technique is well known to most cardiologists and is only reviewed briefly. Access is obtained via the femoral artery by a modified Seldinger’s technique, and then a long J-tipped wire is advanced to the distal ascending aorta. A small incision is made in the skin and bluntly dilated with small curved forceps. Once dilatation has been performed, the sheath and dilator combination are inserted and the dilator is removed. The sheath remains in place. The balloon is then advanced to the proximal descending thoracic aorta, distal to the takeoff of the left subclavian artery (Fig. 39.1). Placement at this level insures there is no obstruction of the renal arteries. Negative suction is applied to the central lumen of the balloon to remove any trapped air and debris. After flushing the central lumen, the balloon is connected to the pressure tubing and gas line. Once proper placement has been confirmed counterpulsation can begin.

TANDEMHEART

Conceptually, the TandemHeart (Cardiac Assist, Inc., Pittsburgh, Pennsylvania, U.S.) device is similar to pCPB as described earlier; however, key modifications offer substantial benefits in the setting of AMI and high-risk PCI. Similar to pCPB, placement of the TandemHeart requires femoral artery and
vein access. Additionally, both devices employ an external pump to augment systemic circulation. However, the TandemHeart uses a unique trans-septal inflow cannula that more effectively unloads the LV during pump operation. The TandemHeart also takes advantage of the individual’s own pulmonary circuit for oxygenation, eliminating the external oxygenator and limiting contact between blood elements and foreign material. Theoretically, this modification minimizes the inflammatory reaction and allows longer run times.

Dennis et al. were the first to demonstrate the feasibility of percutaneous left atrial-to-femoral artery bypass. Their initial design employed a right internal jugular approach and used a stiff metallic trans-septal cannula (41). After refinements in materials and methods, the femoral approach was shown in a small study of animals and critically ill humans (42). Further modifications lead to the first modern demonstration atrial-femoral bypass in a cohort of high-risk PCI patients (43). But it was not until 2001 that Thiele et al. described the initial in-human trial with the TandemHeart (44). A year after Thiele’s pioneering work with the TandemHeart for support during cardiogenic shock, feasibility of TandemHeart-assisted high-risk elective PCI was described (45,46). Since these initial accounts, multiple papers have documented successful support of patients with cardiogenic shock and in patients undergoing high-risk procedures. Most of these accounts are small, descriptive case series indicating excellent procedural success and relatively limited complication rates (47–50). Although the aforementioned trials are noteworthy, two small randomized trials of the IABP versus the TandemHeart merit further consideration (44,48).

In the first of these trials, Thiele et al. randomized 41 patients suffering from cardiogenic shock following an AMI to either IABC or TandemHeart support. All patients underwent revascularization within 24 hours of the onset of cardiogenic shock. During therapy (mean duration of support 3.5 days for the IABP and 4.0 days for the TandemHeart) investigators closely monitored key hemodynamic parameters and adverse events. The primary outcome measure, cardiac power index, was improved more effectively in the TandemHeart group. Similarly, other common hemodynamic parameters and metabolic indicators of perfusion demonstrated greater improvement in TandemHeart patients. Despite the impressive hemodynamic differences, investigators were unable to show a survival benefit. It is likely that the hemodynamic benefits were offset by an increase in device-related complications including bleeding, need for transfusion, and limb ischemia. Investigators also noted higher rates of systemic inflammatory response syndrome and disseminated intravascular coagulation in the TandemHeart group (44). In a similar study, Burkhoff and colleagues randomized 19 patients with cardiogenic shock to TandemHeart support and 14 to IABC. They also observed improved hemodynamics (decreased pulmonary capillary wedge pressure, increased mean arterial pressure, and improved cardiac index) with the TandemHeart as compared to the IABP, but failed to find a survival advantage. The incidence of many prespecified adverse events was similar between groups—hemolysis, thrombocytopenia, renal dysfunction, and infection. But, higher rates of arrhythmia, bleeding, and access site complications were noted in the TandemHeart group (48). Because of slow enrolment the trial was ended early, with a 30-day survival of 53% (10/19) in the TandemHeart group compared to 64% (9/14) in the IABP group.

In its current design, the TandemHeart device consists of four major components: (i) a 21-Fr trans-septal inflow cannula, (ii) an extracorporeal, continuous-flow centrifugal pump, (iii) a 17- to 15-Fr venous return cannula, and (iv) an electronic pump control module. The inflow cannula has a unique design with a large end hole and multiple side holes permitting high flow rates with limited resistance (Figs. 39.2 and 39.3). The inflow cannula can be placed via a standard trans-septal approach. We have modified this slightly by employing a soft-
high-risk PCI will require the near complete support of the IMPELLA. Not all patients presenting with LV compromise or undergoing PCI will likely necessitate a greater role for TandemHeart in coming years. Escalating demand for innovative percutaneous therapies will not have been demonstrated, increasing patient comorbidities and the need for innovative therapies. Mitral valve surgery has proven safe and effective. The external pump unit has a dual chamber design. The upper chamber houses a low-speed centrifugal impeller that is in direct contact with blood elements. The lower chamber is the drive unit consisting of an electromagnetic pump and liquid bearing. The liquid bearing is a heparinized solution that functions as local anticoagulation, pump lubrication, and heat sink. Systemic anticoagulation is typically withheld until successful trans-septal puncture; however, during pump assembly and priming we use a target ACT of 400 seconds. During pump operation an ACT of 200 to 250 seconds is generally sufficient to limit most thrombotic complications. The control module has a simple operational design with a fully redundant battery back-up system. Similar to the Impella device, actual flow rates are not measured. Instead, pump flow is estimated based on pump speed and hemodynamic loading conditions. Total cardiac output can be measured using a thermodilution or continuous monitoring pulmonary artery catheter. Hemodynamic parameters such as systemic vascular resistance and pulmonary vascular resistance should be calculated using the total cardiac output measured from the pulmonary artery catheter. Figure 39.4 shows the TandemHeart fully connected and secured to the thigh-mounting bracket. Figure 39.5 shows an anterior-posterior projection of the TandemHeart in situ.

Since introduction of the TandemHeart pVAD in 2001, the device has been successfully utilized in a multitude of settings. According to company resources, nearly 1500 procedures have been performed worldwide as of November 2008. In the past seven years, the TandemHeart has been used for support of cardiogenic shock following AMI and for mechanical complications of AMI. In the setting of chronic heart failure, the TandemHeart has been used as temporary support, i.e., as a bridge to transplant and as a bridge to bridge. In the surgical arena, the TandemHeart is effective support for postcardiotomy syndrome. More recently, case reports have demonstrated benefit in the setting of critical aortic stenosis, for support during high-risk mitral valvuloplasty and as effective right VAD (51). Versatility of the TandemHeart has also been demonstrated with alternative anticoagulants, including argatroban and bivalirudin. In short, the TandemHeart shows promise as a truly percutaneous, fully supportive VAD. Although a mortality benefit has not been demonstrated, increasing patient comorbidities and the escalating demand for innovative percutaneous therapies will likely necessitate a greater role for TandemHeart in coming years.

**IMPELLA**

Not all patients presenting with LV compromise or undergoing high-risk PCI will require the near complete support of the TandemHeart; however, IABC may not be sufficient without some essential level of cardiac output. Bridging this gap is a relatively new device, the Impella LP2.5 (Fig. 39.6). The Impella family of devices has their basis in the early clinical experiences of the Hemopump (52). Like the Hemopump, the Impella LP2.5 is a catheter-based transvalvular axial flow pump. The LP2.5 is the smallest of four devices developed by Abiomed Inc. for temporary cardiac support. The larger devices in the series are the LD, RD, and the LP5.0. These devices are capable of higher flow rates, up to 4 L/min, but require either surgical access or arterial cutdown for placement. In a randomized trial of 199 CABG patients, the combination of RD and LD support compared favorably with normothermic CPB in terms of mortality, perioperative MI, and length of stay (53). These devices have also demonstrated utility in the setting of shock following AMI, acute myocarditis, postcardiotomy syndrome, and as a bridge to transplant (54–57). The Impella LP2.5 has a 12-Fr maximum outer diameter and is recommended for placement via a 13- to 14-Fr sheath. The drive line is 9 Fr and the assembly is mounted on a 6-Fr pigtail catheter (Fig. 39.7). The device is advanced across the aortic valve over a stiff soft-tipped 0.018 in. coronary wire and directed into the left upper pulmonary vein (LUPV). Holding the needle and wire fixed, the dilator and trans-septal sheath are advanced across the septum and into the LUPV. The wire, needle, and dilator are then removed, and the sheath is aspirated multiple times to eliminate air and debris. After placement is confirmed fluoroscopically, a larger, stiff 0.035 in. wire (Amplatz Super Stiff, Boston Scientific, Natick, MA) is advanced to the LUPV and serves as the working wire. The interatrial septum is then serially dilated and the aspiration cannula secured in place. During trans-septal puncture, the Spartacore wire protects internal structures from inadvertent laceration with the trans-septal needle. So far, this technique has proven safe and effective. The external pump unit has a dual chamber design. The upper chamber houses a low-speed centrifugal impeller that is in direct contact with blood elements. The lower chamber is the drive unit consisting of an electromagnetic pump and liquid bearing. The liquid bearing is a heparinized solution that functions as local anticoagulation, pump lubrication, and heat sink. Systemic anticoagulation is typically withheld until successful trans-septal puncture; however, during pump assembly and priming we use a target ACT of 400 seconds. During pump operation an ACT of 200 to 250 seconds is generally sufficient to limit most thrombotic complications. The control module has a simple operational design with a fully redundant battery back-up system. Similar to the Impella device, actual flow rates are not measured. Instead, pump flow is estimated based on pump speed and hemodynamic loading conditions. Total cardiac output can be measured using a thermodilution or continuous monitoring pulmonary artery catheter. Hemodynamic parameters such as systemic vascular resistance and pulmonary vascular resistance should be calculated using the total cardiac output measured from the pulmonary artery catheter. Figure 39.4 shows the TandemHeart fully connected and secured to the thigh-mounting bracket. Figure 39.5 shows an anterior-posterior projection of the TandemHeart in situ.
The guidewire (Platinum Plus, Boston Scientific, Natick, Massachusetts, U.S.). The Impella LP2.5 is angled to approximate the contour of the aortic outflow tract. The motor unit and impeller are located at the proximal end of the device. The intake cannula sits across the aortic valve with the inflow port near the cardiac apex (Fig. 39.8). The drive line and infusate port connect to a control module and purge pump, respectively. The control module has a simple operational design. Infusate is maintained under constant pressure, minimum recommended 300 psi, creating a liquid seal for the motor unit. Flow and aortic pressure are continuously displayed on the control module. Flow reflects an estimated flow rate based on impeller speed and transvalvular loading conditions.

Although the Impella LP2.5 lacks the power of its larger siblings, the LD and LP5.0, speed and ease of placement make it an attractive option during elective high-risk procedures and in
the setting of AMI. Valgimigli and colleagues published the first in-human use of the Impella LP2.5. The patient, a 56-year-old man with a history of multiple MI’s and reduced EF (27%), underwent PCI of a dominant left circumflex artery. Swan-Ganz monitoring during the case demonstrated a marked reduction in pulmonary capillary wedge pressure, 18 to 11 mmHg, during pump operation and a similar increase in cardiac output, 6.0 L/min compared to 7.4 L/min, as measured by thermodilution (13). Shortly after this initial account, safety and feasibility of Impella LP2.5 support were further demonstrated in 19 elective, high-risk PCI patients. All patients had EF <40%, and many were older (>60 years), diabetic (53%), and had a history of MI (74%). The Impella LP2.5 was successfully placed in all 19 patients and no device-related deaths were recorded. Two in-hospital mortalities were noted; one following prolonged cardiac surgery and another secondary to multi-organ failure. One patient developed a large access site hematoma, and two patients required postprocedural blood transfusion (58). At ACC 2007, Jose Henrique, MD presented a large series of Impella LP2.5-assisted PCI cases, 109 patients. In this series, he found a relatively low rate of in-hospital major adverse cardiac events of 13% (14/109) and excellent tolerability with 100% device placement (109/109) (59). Abiomed Inc. is currently enrolling patients in a randomized multicenter trial of high-risk PCI, Impella LP2.5 support versus IABP. This study, PROTECT-II (A Prospective, Multicenter, Randomized Controlled Trial of the IMPELLA RECOVER LP 2.5 System Versus Intra Aortic Balloon Pump in Patients Undergoing Non Emergent High Risk PCI), will randomize >600 nonemergent patients with low EF and unprotected left main disease, last patent conduit, or three-vessel disease to PCI supported with either prophylactic IABC or Impella LP2.5 placement. Primary safety endpoints will be death, MI, target vessel revascularization, and stroke/TIA’s. The primary efficacy endpoint will be cardiac power output measured during active support.

The Impella may also prove to be a valuable tool in the fight against devastating heart attacks; however, experience with the LP2.5 in the acute setting is currently limited. As previously discussed, the LP2.5 improves coronary artery blood flow (17), and mechanical support prior to reperfusion limits infarct size (12,16,35,37,47). In addition, work from Tayara et al. suggests that an aggressive approach to AMI patients presenting with cardiogenic shock, including mechanical support and provisional transplant, has a significant survival benefit (60). A similar aggressive, multilayered approach is being evaluated by the Henriques group at the Academic Medical Center in Amsterdam (61). In a small pilot trial of 20 AMI patients, 10 receiving Impella support for 3 days following anterior MI and 10 receiving routine care including IABC; if needed, researchers demonstrated improved LV recovery with the Impella LP2.5. At 3-day and 4-month follow-up change in LVEF was greater in the Impella group than in IABP supported patients (62). Notably, groups received similar reperfusion therapy, and the Impella cohort appeared somewhat sicker at the time of enrollment—lower baseline EF (28% vs. 40%), higher peak troponin-T (326 vs. 203), higher peak CK (4494 vs. 3897), and higher NT-proBNP (1619 or 387). Also weighing in on the topic of mechanical assistance in AMI, results of the ISAR-SHOCK (Impella LP2.5 vs. IABP in AMI Cardiogenic Shock) trial are now available. In this small randomized, prospective study of 26 patients presenting with cardiogenic shock within 48 hours of AMI, researchers found improved cardiac power index and enhanced serum lactate clearance in Impella-supported patients. One case of limb ischemia occurred in an Impella patient and transfusion requirements were greater in the Impella group; however, mortality was similar in the two groups (46%) (63).

As of early 2008, Impella devices have been used in nearly 1200 cases worldwide, including 600 Impella LP2.5 procedures. The most common application for the LP2.5 has been support during elective high-risk PCI, followed by assistance for cardiogenic shock, and recovery following AMI. Results reviewed here have been promising, demonstrating improved hemodynamic parameters and excellent patient tolerability. Results of the large ongoing RECOVER II (A Prospective Randomized Trial Investigating the Use of the IMPELLA RECOVER LP 2.5 System in Patients With Acute Myocardial Infarction Induced Hemodynamic Instability) and PROTECT II trials will likely play a significant role in the future of the Impella LP2.5.

CONTRAINDICATIONS
As detailed earlier, many of the contraindications to temporary LV support are common to the IABP, the TandemHeart, and the Impella LP2.5. For review, shared contraindications include severe peripheral vascular disease, moderate to severe aortic valve regurgitation, and uncontrolled bleeding diathesis. In the case of peripheral arterial disease, vessel diameter is the limiting factor. If the operator is skilled in peripheral interventions, these limitations may be partially overcome. We have had excellent success with balloon dilation and occasional stenting of the target artery prior to device insertion. Next, all of these devices can exacerbate aortic insufficiency; therefore moderate to severe aortic valve regurgitation is another shared limitation. Finally, because of the inherent thrombogenicity of foreign material and the need for adequate anticoagulation during device insertion and operation, uncontrolled bleeding diathesis is a shared limitation of these temporary LV support devices. A couple of noteworthy limitations are specific to the Impella LP2.5 and the IABP. Because the Impella is a transvalvular blood pump, passage of the device across an already stenotic aortic valve may increase the transvalvular gradient leading to further clinical decompensation. Therefore, insertion in patients with moderate to severe aortic stenosis is not recommended. Similarly, passing the Impella through a mechanical prosthetic valve is likely to disrupt valve function. Therefore, the Impella should not be used in patients with prior valve replacement. In addition to these limitations, the inflow cannula of the Impella sits at the LV apex; therefore, due to the risk of embolic phenomena, LV mural thrombus is another strict contraindication to Impella support. As detailed earlier in this chapter, significant disease of the thoracic or abdominal aorta—atherosclerosis or aneurysm—is a shared contraindication of the Impella and the IABP. Finally, although not a contraindication, the IABP works best when there is ventricle-pump synchrony. Although programming modifications and control features have largely addresses this issue, rapid or chaotic rhythms decrease the efficacy of IABP support. Table 39.2 summarizes the major contraindications to temporary mechanical LV support.

CLINICAL ASPECTS
Once a decision has been made that temporary mechanical support is required, the interventionalist must select the most appropriate device. In some hospitals, the choice may be
Uncontrolled bleeding diathesis
Significant thoracic or abdominal aortic aneurysm
Severe peripheral vascular disease
Mural thrombus
Moderate to severe aortic valve stenosis
Moderate to severe aortic regurgitation
Mechanical aortic valves

Comments Fast
Left ventricular loading + ++ +++ Unknown
Closure required Manual Perclose or manual Double preclose or surgical Preclose
Estimated time to support (min) < 7–8.5 Fr arterial
Access required 7–8.5 Fr arterial 13–14 Fr arterial 15–17 Fr arterial,
Max duration of support < 7 days, has been reported. IABP support in our institution is limited by device availability. Alternatively, the intervention-alist must carefully assess the urgency and degree of support required along with access limitations. Finally, issues of closure technique, cost considerations, and physician preference play a role. All of the devices described in this chapter will not be available at every hospital. According to Abiomed Inc., as of mid-2008 the Impella LP2.5 was available at 100 U.S. hospitals. The TandemHeart is available at 100 sites worldwide. The IABP has a much longer history than either the TandemHeart or the Impella, and thus the IABP is available in most U.S. medical centers.

Next, the urgency of the patient’s hemodynamic requirements, the relative degree of cardiac support needed, and the duration of therapy play a role in device selection. As stated earlier, the TandemHeart offers up to 4 L/min of cardiac support; however, in a critically unstable patient, rapid device insertion and early initiation of support may be a greater concern. Alternatively, in a patient with unstable angina and severe LV dysfunction scheduled to undergo PCI of an unprotected left main, the time necessary to place the TandemHeart is likely well spent. Finally, the duration of support must be considered. The TandemHeart is FDA approved for 6 hours of extracorporeal support; however, cases reports of support up to 30 days are available. Similarly, the Impella LP2.5 is intended for short-term use, but if weaning becomes difficult prolonged support, up to 7 days, has been reported. IABP support in our institution is generally limited to the 24 to 48 hours following an AMI. However, the duration of balloon pump support at transplant institutions is frequently on the order of weeks, and prolonged support in excess of three months is not without precedent.

There is a significant trade-off between the size of arterial cannula required for a given device and the maximum achievable flow rate. The TandemHeart generally requires large bore (17 Fr) arterial access; however, bilateral 12-Fr access is possible at the cost of decreasing maximum pump flow rate from 4 to 3 L/min. In a large, adult male with isolated coronary artery disease, device options are unlimited; however, in the context of a petite, elderly female with peripheral vascular disease, arterial cannulation may be impossible without prior peripheral intervention.

Finally, closure of vascular access sites, relative cost, and physician preferences play a role in device selection. Simple manual pressure is often sufficient to ensure safe and durable hemostasis following IABP removal; however, for larger arteriotomies, we prefer a preclose technique. Our technique requires deployment of two preloaded vascular sutures prior to final dilation of the arteriotomy site. During device support, the suture ends are left untied, tagged with small hemostats, and then set aside. Following the procedure, while the large vascular conduits are being removed, gentle pressure is applied superior to the access site as the previously deployed sutures are tied and advanced. Similar preclose procedures have been described elsewhere with excellent (94%) success (64). Next, cost and reimbursement must be considered. The 2008 unit cost of each device is shown in Table 39.3; however, reimbursement often varies by diagnosis-related group (DRG). On the basis of DRG, payment for the same device, or more accurately the same procedure, may vary by over $20,000. In general, DRGs for the Impella and TandemHeart will have higher payouts to cover the cost of equipment and the additional technical support required. Lastly, it is a very real element of physician preference and appropriate training. Our general cardiology fellowship provides excellent exposure to the IABP, and most of our senior fellows feel very comfortable managing patients on balloon pump support. However, there is a significant learning curve with the TandemHeart and the Impella. Even when these more advanced devices are available, only experienced operators should consider them as an option. Table 39.3 summarizes the significant clinical aspects discussed in the preceding text.

Table 39.3 Clinical Aspects of Temporary Left Ventricular Support

<table>
<thead>
<tr>
<th></th>
<th>IABP</th>
<th>Impella LP2.5</th>
<th>TandemHeart</th>
<th>Lifebridge B2T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max support (L/min)</td>
<td>0.5</td>
<td>2.5</td>
<td>4.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Max duration of support</td>
<td>&lt;90 days</td>
<td>6 hr–7 days</td>
<td>6 hr–30 days</td>
<td>6 hr</td>
</tr>
<tr>
<td>Access required</td>
<td>7–8.5 Fr arterial</td>
<td>13–14 Fr arterial</td>
<td>15–17 Fr arterial, 21 Fr venous</td>
<td>15 Fr arterial, 17 Fr venous</td>
</tr>
<tr>
<td>Estimated time to support (min)</td>
<td>&lt;10</td>
<td>&lt;20</td>
<td>Double preclose or surgical</td>
<td>Preclose</td>
</tr>
<tr>
<td>Closure required</td>
<td>Manual</td>
<td>Perclose or manual</td>
<td>$20,000</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cost</td>
<td>$820</td>
<td>$20,000</td>
<td>$19,500</td>
<td>Unknown</td>
</tr>
<tr>
<td>Left ventricular loading</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>Experimental</td>
</tr>
<tr>
<td>Comments</td>
<td>Fast Available Limited support Incomplete unloading</td>
<td>Intermediate cardiac support Relatively expensive</td>
<td>Large bore access Superior unloading</td>
<td></td>
</tr>
</tbody>
</table>
requires advanced interventional skills, including trans-septal puncture and manipulation of a very large cannula into the left atrium via the right femoral vein. Additionally, the arterial return cannula, while possible to insert percutaneously, requires either the preclose technique for temporary use or formal femoral artery repair for removal after a more chronic implant. The Impella 2.5 device is potentially capable of pumping at a level of 2.5 L/min, but it is dependent on optimal loading conditions to achieve this level of support. Obviously the Impella, by itself, is not capable of supporting the entire circulation except for very brief periods of time. It does, however, provide active LV decompression and is not dependent on synchronization with the cardiac cycle.

The IABP is simple to insert but provides indirect support of diastolic blood flow and a modest level of LV unloading. Nonetheless, animal models and observational studies in humans suggest that the level of support provided by the balloon pump is sufficient to provide meaningful LV assistance and is associated with reduction in infarct size when implanted prior to reperfusion in the setting of STEMI.

Right-sided support is also feasible with the TandemHeart device, utilizing two atrial cannulas, one inserted into the superior vena cava and one inserted via antegrade access from the right atrium through the right ventricle to the pulmonary artery. LV assist in the setting of right-sided cardiogenic shock has not been beneficial; however, now that percutaneous right-sided cardiac support is available, further evaluation of this technique is warranted. It is not infrequent after implantation of a percutaneous VAD, such as the TandemHeart or Impella, for it to be necessary to wean from the LVAD to IABP support prior to complete cessation of LV support.

It is indeed an exciting time in this area. We anticipate that new percutaneous devices will become available in the relatively near future that will significantly improve our armamentarium for treating circulatory failure without the necessity of requiring major cardiac surgery. As new devices become available it will be imperative to compare them to the existing devices and to delineate the relative merits of each device in given clinical situations.

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INTRODUCTION
In the past years intracardiac echocardiography (ICE) has emerged as a valuable imaging tool for interventional and electrophysiological procedures. ICE allows real-time visualization of important anatomical structures that cannot be visualized on fluoroscopy, and is not associated with radiation exposure to the patient and operator. This imaging modality is used to guide and monitor interventional procedures and for early detection of complications. Importantly, as an alternative to transesophageal echocardiography (TEE), ICE can be performed without general anesthesia. In this chapter, the basic principles and clinical applications of ICE are discussed.

ANATOMIC CONSIDERATIONS
ICE is generally performed from within the right atrium or the right ventricle. The images acquired with ICE should therefore be interpreted from that perspective. Depending on the position and direction of the ultrasound catheter, all large cardiac structures, including the atria, ventricles, atrioventricular and semilunar valves, coronary sinus, and pericardium can be visualized with ICE. Awareness of the orientation of the scanning plane and a good understanding of the three-dimensional (3-D) cardiac anatomy are essential for a correct interpretation.

EQUIPMENT
Currently, two different ICE technologies are available. The first approach utilizes a mechanical ultrasound tipped catheter which can also be used for endovascular echocardiography. The second uses an electronic ultrasound catheter that is equipped with a phased-array transducer at its tip. Both are manipulated and visualized with ICE. The flexibility of the catheter enable the operator to position it inside the right ventricle or coronary sinus. In this view, additional views can be obtained, that cannot be acquired from the right atrium. The phased-array catheter is connected to a dedicated ultrasound machine (Sequoia™, Cypress™, CV70™, Siemens Medical Solutions; and ViewMate®, St. Jude Medical).

Several important differences between the two ICE technologies exist. The phased-array catheter allows adjustment of the ultrasound frequency, thereby enabling depth control. Furthermore, the phased-array catheter has Doppler capabilities, allowing measurement of hemodynamic and physiological variables, and has superior flexibility compared with the rotational catheter. The advantages of rotational ICE include a 360° scanning plane instead of 90° and the considerably lower costs. In daily clinical practice, phased-array ICE is the most commonly used technology in the cardiac catheterization laboratory. The focus of the present chapter is on phased-array ICE; mechanical intravascular ultrasound is reviewed in chapter 28.

FUNDAMENTALS
ICE can be used to visualize nearly all cardiac structures (1). However, unlike for transthoracic echocardiography (TEE) and TEE, there are no widely accepted standard views for ICE. In the following paragraphs, a clinically oriented guide for catheter manipulation and visualization of the various cardiac structures is provided.

ICE is generally performed under conscious sedation. Using local anesthesia and a femoral vein approach, the ultrasound catheter is inserted through the inferior vena cava into the right atrium. While standing at the right side of the patient, the operator can change the orientation of the ultrasound beam by advancing or withdrawing the catheter and by rotating it around its axis. In this chapter, rotation of the ultrasound catheter away from the operator is called clockwise rotation, whereas rotation toward the operator is referred to as counterclockwise rotation. The orientation of the ultrasound beam can also be altered by deflecting the tip of the ultrasound catheter in two orthogonal planes (anterior-posterior, left-right) through manipulation of the two steering knobs at the handle of the catheter.
Even though images acquired with ICE are quite similar to TEE, the large freedom of ultrasound beam orientation can easily cause a sense of disorientation to the inexperienced operator. To gain or regain orientation, a “home view” position is defined and can be used as the starting point for all catheter manipulations. In this chapter, home view position is used as the starting point from which all catheter manipulations are described. To reach this position, the ultrasound catheter is positioned in the midright atrium with the control knobs in a neutral position. The resulting image shows the right atrium, tricuspid valve, and right ventricle (Fig. 40.1A). The operator can use these and other anatomical landmarks to maintain orientation during catheter manipulation. To further improve the operator’s orientation, a marker is present on the ultrasound screen corresponding to the inferior portion of the ultrasound beam.

**Right-Sided Structures**

Starting from home view position and slightly withdrawing the catheter into the inferior right atrium, the Eustachian ridge can be visualized (Fig. 40.1B). The tissue between the Eustachian ridge and the tricuspid valve is known as the cavotricuspid isthmus and is targeted during catheter ablation for atrial flutter. By advancing the catheter back into home view position and rotating it counter-clockwise the crista terminalis and right atrial appendage are visualized. Clockwise rotation will first bring back home view and will then reveal the right ventricular outflow tract, the pulmonary artery, and the ascending aorta (Fig. 40.1B).

**Left-Sided Structures**

Clockwise rotation of the ultrasound catheter from home view position, past the right ventricle and right ventricular outflow tract, provides a view on the left atrium, mitral valve, the interatrial septum, and the coronary sinus (Fig. 40.1C). By gently deflecting the catheter tip in the left direction, the left atrial appendage can be seen (Fig. 40.2A). From this view, clockwise rotation will reveal the left-sided pulmonary veins (Fig. 40.2B). The left inferior pulmonary vein is visualized at the inferior portion of the ultrasound beam and the left superior pulmonary vein at the superior portion. In case of difficulty distinguishing between the left superior pulmonary vein and the left atrial appendage, Doppler flow measurements can be used to differentiate between the two structures. When further rotating clockwise, the posterior left atrial wall and the esophagus can be visualized (Fig. 40.2C). Eventually, continued clockwise rotation will provide a cross-sectional view of the right-sided pulmonary veins and the right pulmonary artery (Fig. 40.2D). Similar to the left pulmonary veins, the right inferior pulmonary vein is visualized at the inferior portion of the ultrasound beam and the right superior pulmonary vein at the superior portion.

To acquire a long axis view of the left ventricle and mitral valve from home view, the catheter is withdrawn slightly into the inferior right atrium and the tip of the catheter is deflected in the anterior direction. By advancing the catheter through the tricuspid valve into the right ventricle and rotating the catheter clockwise, the interventricular septum and left ventricle appear (Fig. 40.3A). This long axis view can be very useful to detect pericardial effusion during interventional procedures. From the long axis view, a short axis view of the left ventricle can be acquired by deflecting the tip of the catheter in the left or right direction (Fig. 40.3B). Advancing or withdrawing the catheter will result in more apical or basal short axis views (Fig. 40.3C).
INDICATIONS AND CLINICAL APPLICATIONS
ICE can be used in a wide variety of diagnostic and interventional procedures. These procedures are summarized in Table 40.1 and are reviewed in the following paragraphs.

Detection of Intracardiac Thrombus
Patients undergoing a left-sided interventional procedure are at high risk for systemic embolism (2,3). ICE can facilitate a safe left-sided procedure by excluding intracardiac thrombus inside the left atrial appendage, left atrium, and left ventricle (4). Furthermore, ICE can be used to assess the presence of spontaneous contrast, thereby identifying patients at high risk for thrombus formation (5). ICE can help to detect the formation of thrombi at an early phase and allow for treatment prior to the occurrence of embolic events (6,7).

The efficacy of TEE to detect intracardiac thrombus has been established by the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial (8). Even though ICE provides high quality images comparable to TEE, only a few studies have compared the sensitivity of the two imaging modalities for the detection of intracardiac thrombus. The Intracardiac Echocardiography-Guided Cardioversion to Help Intervventional Procedures (ICE-CHIP) study was designed to address this issue (9). Preliminary results of the ICE-CHIP study show that ICE has a similar sensitivity for the detection of spontaneous contrast, as compared with TEE (10). In 100 patients with atrial fibrillation, spontaneous contrast of the left atrium was seen in 50% on ICE and in 55% on TEE (p = NS) whereas spontaneous contrast of the left atrial appendage was seen in 22% on ICE and in 24% on TEE (p = NS). However, the results on thrombus detection from the ICE-CHIP study are not yet available. Therefore, more studies are needed to determine the exact value of ICE for the detection of intracardiac thrombi.

Closure of Atrial Septal Defect
Percutaneous transcatheter device closure of atrial septal defect or patent foramen ovale (PFO) has proven to be a safe and effective alternative to open heart surgery (11,12). While percutaneous closure of PFO may be performed under fluoroscopy guidance only, closing procedures of atrial septal defect are typically guided by TEE and fluoroscopy. However, ICE does not require general anesthesia, and may provide similar images as TEE (13,14). It has been shown that the use of ICE during
transcatheter device closure may result in a reduction of fluoroscopy time (9.5 ± 1.6 vs. 6.0 ± 1.7 minutes, \( p < 0.0001 \)) (13), procedure length (47 ± 8 vs. 35 ± 6 minutes, \( p < 0.001 \)), and catheterization laboratory occupation (92 ± 18 vs. 50 ± 12 minutes, \( p < 0.001 \)) compared with TEE guided interventions (15). Importantly, the high costs of an ICE catheter may be balanced by the need for general anesthesia during TEE guided procedures (16).

To guide the placement of a transcatheter closure device, the ultrasound catheter is positioned in the home view position and is rotated clockwise to visualize the interatrial septum and fossa ovalis (Fig. 40.4A, B, C). By using Doppler capacities, the flow between the left and right atrium can be visualized and quantified (Fig. 40.4D). A guiding wire is then placed through the atrial septal defect and inside the left atrium. Subsequently, the catheter that contains the closure device is advanced through the atrial septal defect and the left-sided portion of the occluder is deployed. After this step, the position of the device against the interatrial septum is carefully evaluated before deploying the right-sided portion of the occluder to avoid malposition and the associated risk of migration of the device (Fig. 40.5A). Once the operator is convinced that the position is correct, the right-sided portion of the occluder is deployed (Fig. 40.5B). Once again the position and the stability of the device are checked and then the occluder is released.

**Transseptal Puncture**

A transseptal puncture provides antegrade access to the left atrium and left ventricle during left-sided interventional procedures as an alternative to a retrograde approach through the aortic valve and mitral valve. However, a transseptal puncture can result in serious complications, such as aortic perforation, pericardial tamponade, and perforation of the inferior vena cava (17). The fossa ovalis is considered to be the safest site to perform a transseptal puncture to avoid these complications. ICE allows excellent visualization of the fossa ovalis and can be used to detect a PFO or monitor the transseptal puncture (18). At present, no prospective studies have addressed the question of whether ICE may improve the safety of transseptal punctures.

To visualize the interatrial septum, the catheter is gently rotated clockwise from home view position. The interatrial septum consists of a thicker part (limbus) and thin part (fossa ovalis) (Fig. 40.6A). To detect a PFO, saline/contrast is injected through the femoral vein inside the right atrium and the patient is instructed to perform the Valsalva maneuver (Fig. 40.7A). In the presence of a patent foramen the contrast will cross the interatrial septum, into the left atrium (Fig. 40.7B). In the absence of a PFO, a transseptal sheath with a concealed Brock-enbrough transseptal needle is inserted through the femoral...
Figure 40.4  *(See color insert, only D)*  (A) IAS, LA, and RA. (B) During a Valsalva maneuver, the PFO is revealed. (C) A large type II atrial septal defect *(two markers)*. (D) Doppler flow delineates the flow across PFO during a Valsalva maneuver. *Abbreviations*: IAS, interatrial septum; LA, left atrium; RA, right atrium; PFO, patent foramen ovale.

Figure 40.5  (A) A biodegradable closure device is inserted across the IAS inside LA. Subsequently, the left-sided occluder is deployed. (B) After confirmation of the position of the device, the right-sided occluder is also deployed. *Abbreviations*: IAS, interatrial septum; LA, left atrium; RA, right atrium.
vein inside the right atrium. Using fluoroscopy and ICE, the transseptal sheath is positioned against the fossa ovalis. In case of a stable position of the sheath against the fossa ovalis, a “tenting” phenomenon can be seen on ICE (Fig. 40.6B). The transseptal puncture can now be performed by pushing the needle out from the sheath, through the fossa ovalis. Successful transseptal puncture can be confirmed on ICE by injecting saline/contrast through the needle inside the left atrium.

Electrophysiological Procedures
ICE has become an important imaging tool during electrophysiological procedures. In addition to thrombus detection and guidance of a transseptal puncture, ICE can be used to identify key anatomical structures to facilitate complex procedures like atrial fibrillation ablation and atrial flutter ablation (19–21). ICE can visualize the exact location of the mapping catheter and confirm stable contact of the catheter against the myocardium. Moreover, ICE can be used to visualize morphological changes in the myocardium, such as increased echo density, wall thickening and crater formation as a sign of effective lesion formation (22), and the development of micro bubbles as a sign of tissue heating and potential char formation (23,24). In the following paragraphs, the specific role of ICE in various electrophysiological procedures is reviewed.

Atrial Fibrillation Ablation
Radiofrequency catheter ablation targeting the pulmonary veins is a potential curative treatment option for patients with drug-refractory atrial fibrillation (25,26). However, it is associated with long procedure times and a small risk for severe complications, including pulmonary vein stenosis, systemic embolism, cardiac tamponade, and esophagus injury (2). ICE can facilitate these complex procedures by visualization of the pulmonary veins and monitoring of the location of the ablation.
The esophagus and left atrial posterior wall are very closely related. With the use of ICE, Ren and colleagues demonstrated that the mean distance between the left atrial posterior wall and the esophagus was 5.8 ± 1.2 mm (range 3.2–10.1 mm) and that the left atrial posterior wall and the esophagus were contiguous over a mean length of 36.0 ± 7.7 mm (range 18–59 mm) (27). As a consequence, the temperature inside the esophagus may increase significantly during left atrial ablation (32). Heating of the esophagus can result in esophageal injury varying from transient erythematous changes to tissue necrosis and the development of an atrioesophageal fistula (27,33,34). While monitoring the relation between the esophagus and the ablation catheter with ICE, the ablation power and duration can be adjusted to reduce esophageal damage (27). Monitoring lesion development and the occurrence of micro bubbles as an indication of an increased esophageal temperature, allows the operator to perform additional energy titration, thereby further minimizing the risk of esophageal damage (27,32).

As an alternative to anatomical guidance with ICE, image integration with MSCT or magnetic resonance imaging (MRI) integration is commonly used to guide radiofrequency catheter ablation for atrial fibrillation (35). A 3-D image of the left atrium can be integrated with an electroanatomical map by performing a semi-automatic registration process. However, the validity of this technique is largely dependent on the quality of the registration (36–38). An inaccurate registration process can result in a large shift of landmark points of up to 5 to 10 mm, thereby compromising the safety and efficiency of lesion placement (36,37). Adjunctive real-time imaging with ICE can be used to confirm the accuracy of the registration process to ensure an accurate delivery of radiofrequency energy (36).

An electroanatomical mapping system (CARTOSOUNDTM, Biosense Webster, Diamond Bar, California, U.S.) allows integration of ICE and electroanatomical mapping (39). By integrating ICE and electroanatomical mapping, an accurate 3-D anatomical shell of the left atrium and pulmonary veins can be acquired without performing a registration process (40). A modified phased-array ultrasound catheter with an imbedded navigation sensor at its tip (SoundstarTM, Biosense Webster) is positioned inside the right atrium. The mapping system can detect the position and direction of the ICE catheter, thereby enabling the projection of the scanning plane inside its 3-D environment. By gently rotating the ultrasound catheter, ECG-gated images of the left atrium and pulmonary veins are acquired. On each image, the endocardial borders (contours) are traced manually and are thereafter assigned to a designated map (Fig. 40.8A). Separate maps are created for the left atrial body and each of the pulmonary veins. All contours within a map are used to create a 3-D shell of the structure (Fig. 40.8B).
By combining all maps, the 3-D geometry of the whole left atrium and pulmonary veins is visualized and can be merged with a MSCT image to facilitate the ablation procedure (Fig. 40.8C).

**Complex Atrial Flutter Ablation**

A common atrial flutter is an organized tachycardia with a reentry circuit inside the right atrium and a protected isthmus between the tricuspid valve and the inferior vena cava (cavotricuspid isthmus) (20). Ablation of a common flutter is performed by creating a linear line of block across the cavotricuspid isthmus (41). Even though it is considered unnecessary to use special imaging or mapping during a standard procedure, during complex cases ICE may be used to facilitate the procedure (19). ICE can identify the cavotricuspid isthmus and other anatomical structures that can act as electrical barriers during atrial flutter, like the crista terminalis and Eustachian ridge (20). Ablation of an atrial flutter can be complicated by complex anatomy, for example, in patients with previous surgery for congenital heart disease. Particularly in these patients, ICE can facilitate the ablation procedure by visualizing important anatomical structures and guiding catheter placement (42).

**Ventricular Tachycardia Ablation**

Ablation of ventricular tachycardia is usually limited to inducible and tolerated arrhythmias (43,44). Techniques to identify the arrhythmogenic substrate without inducing the tachycardia are being developed to treat patients who do not meet these criteria. ICE allows identification of akinetic and dyskinetic (aneurysmatic) myocardial segments in patients with ischemic ventricular tachycardia, thereby visualizing the exact location and extent of the substrate (45,46). Furthermore, ICE can be used to visualize small aneurysms of the right ventricle in patients with (suspected) arrhythmogenic right ventricular dysplasia, thereby detecting the arrhythmogenic substrate in these patients (46).

Recently, the feasibility of the integration of ICE and electroanatomical mapping to guide ischemic ventricular tachycardia ablation was demonstrated (47). By creating a 3-D geometry of the left ventricle and marking the akinetic and dyskinetic segments as seen on ICE, the ischemic substrate could be mapped and the ablation procedure could be performed successfully.

**Left Ventricular Lead Placement in Cardiac Resynchronization Therapy**

Cardiac resynchronization therapy (CRT) has a beneficial effect on clinical symptoms, exercise capacity, and left ventricular systolic function in selected patients with drug-refractory heart failure (48–50). Moreover, CRT is associated with an increased survival and a reduction in the number of rehospitalizations for heart failure, as compared with optimal medical treatment (50). However, implantation of a CRT device—usually performed under fluoroscopic and angiographic guidance—can be challenging because of venous anatomy, resulting in a failure to place the left ventricular pacing lead in up to 8% of patients (48–50). A number of case studies report on the use of ICE to visualize the coronary sinus to guide left ventricular lead placement (51,52). However, at present no prospective studies have reported a beneficial effect of ICE guidance on the success rate for left ventricular lead placement.

**Other Interventional Procedures**

**Biopsy of Intracardiac Mass**

ICE can be used to visualize the origin and extent of an intracardiac mass (Fig. 40.9A). Therefore, ICE may be used to guide biopsies (Fig. 40.9B) and to monitor associated complications such as perforation or bleeding as suggested by few preliminary reports (53,54).

**Left Atrial Appendage Closure**

Implantation of a left atrial appendage occlusion device has been advocated as strategy to reduce the risk for systemic embolism in patients with atrial fibrillation and contraindications for anticoagulation, and the procedure is typically guided by TEE. Recently, in a small group of patients the feasibility of ICE guidance as an alternative to TEE was reported (55). ICE provided similar visualization of the left atrial appendage and similar assessment of the left atrial appendage orifice diameter.

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**Figure 40.9**  (A) An intracardiac mass originating from the superior vena cava is extending into the RA and tricuspid valve. (B) Intracardiac echocardiography is used to monitor and guide the biopsy by visualizing both tumor and biopome. Abbreviations: RA, right atrium; RV, right ventricle.
compared with TEE (ICE 22.6 ± 3.4 vs. TEE 19.5 ± 1.5 mm, p = NS). Importantly, the degree of accuracy with respect to exclusion of a thrombus inside the left atrial appendage, the exact positioning of the delivery sheath, and verification of the location and stability of the occlusion device using ICE was comparable to TEE.

**Ventricular Septal Defect Closure**
ICE can be used to guide transcatheter closure of a perimembranous ventricular septal defect (56). This imaging modality allows identification and visualization of the defect and monitoring the placement of a guiding wire through the defect and the deployment of the left-sided occluder. Subsequently, ICE is used to confirm the correct position of the left-sided occluder against the interventricular septum before the deployment of the right-sided occluder. After deployment of the second occluder, ICE can be used to assess any residual shunt and valvular regurgitation that may have resulted from the procedure. In 12 patients, Cao et al. documented that ICE may be used as a safe and effective alternative for TEE to guide closure of a ventricular septal defect (56).

**Alcohol Ablation in Hypertrophic Obstructive Cardiomyopathy**
Alcohol septal ablation is an effective treatment to reduce the intraventricular gradient in patients with hypertrophic obstructive cardiomyopathy (57). However, the efficacy and safety of the procedure is dependent on the identification of the correct septal artery. To identify this branch, echocontrast is commonly injected into a septal artery at the time of coronary angiography and TTE is used to detect the extent and localization of the corresponding myocardial territory. ICE allows high quality visualization of the entire interventricular septum and may be a useful tool to guide alcohol septal ablation (58). In nine patients, Pedone et al. demonstrated that use of ICE to guide the procedure was feasible (59). However, more studies are needed to define the role of ICE in alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy.

**Mitrail Valve Balloon Valvuloplasty**
Percutaneous balloon valvuloplasty is an accepted alternative to surgical commissurotomy in selected patients with symptomatic mitral stenosis. In this setting, ICE can be used to exclude thrombus formation at the level of the left atrium, assess the morphology and function of the mitral valve, guide the transseptal puncture, monitor the positioning of the balloon, and assess any residual valvular gradient or postprocedural mitral regurgitation (60). In addition, it may allow an early detection of complications such as cardiac tamponade.

**Percutaneous Valve Procedures**
ICE may provide online anatomical information useful to guide percutaneous valve repair or replacement (61,62). Accordingly, this imaging modality may be used to determine the appropriate size and site of deployment of the percutaneous valve as well as to monitor the anatomical and functional result of the procedure (61). Studies are needed to define the role of ICE during percutaneous valve procedures.

**Intracardiac Use of ICE**
Positioning the ICE catheter inside the pericardium has the potential to provide valuable information during complex ablation procedures. Recently, the safety and feasibility of this approach was demonstrated in both experimental and clinical setting (63,64). In 10 patients, endocardial structures could be visualized in great detail from various angles (63). The ability to visualize cardiac anatomy from different angles could benefit catheter navigation. However, this invasive approach is limited to patients undergoing epicardial access for catheter ablation (63,64).

**LIMITATIONS**
Although phased-array ICE enables adjustment of the ultrasound frequency, tissue penetration remains a limiting factor in visualizing cardiac anatomy. Use of a lower ultrasound frequency would result in a higher degree of tissue penetration allowing visualization of structures further away from the transducer, but at the cost of lower image resolution. In addition, the costs of phased-array ICE are relatively high as compared with TEE and these expensive catheters are for single use only. However, the costs of ICE are somewhat balanced by the need for general anesthesia and an echocardiographer during TEE. Moreover, ICE provides 2-D monoplane images. This limitation can be partially overcome by the flexibility of the catheter enabling to visualize the same structure from another angle. Nevertheless, operators who are used to multiplane ICE may still have difficulty obtaining the same views. Finally, there are no widely accepted standard views for ICE, in contrast to TEE and TTE. This may be difficult, in particular for the inexperienced operator. Standard manipulation of the ultrasound catheter starting from home view position as well as recognition of landmark structures may be helpful.

**SPECIAL ISSUES**
ICE is an invasive imaging modality and its use is usually confined to patients undergoing a percutaneous interventional procedure. In general, the contraindications for ICE are similar to other right-sided cardiac catheterization procedures using a transfemoral access. In pediatric patients, the use of ICE is limited by the respective diameters of the femoral vein and the ultrasound catheter.

**CONCLUSIONS**
ICE is a valuable imaging tool for a wide variety of interventional and electrophysiological procedures. This imaging modality allows real-time visualization of anatomical structures, catheters, and devices thereby enabling the monitoring and guidance of complex procedures like catheter ablation for atrial fibrillation and placement of a transcatheter closure device for atrial or ventricular septal defects. Since it provides images of quality comparable to TEE, ICE may be used—in the hands of an experienced operator—as an alternative to TEE during closure of an atrial septal defect or ventricular septal defect and during percutaneous occlusion of the left atrial appendage. In addition, ICE is a potentially safe alternative for TEE to detect an intracardiac thrombus.

**REFERENCES**


TEE to guide interventional cardiac procedures in the catheterization laboratory

Matthias Greutmann, Melitta Mezody, and Eric Horlick

INTRODUCTION
Since its development for clinical use almost 30 years ago (1,2), transesophageal echocardiography (TEE) has seen widespread use for diagnostic purposes and has been used to guide many new interventional cardiac procedures. More recently, intracardiac echocardiography (ICE) has begun to replace TEE for some indications. However, the wide availability of TEE, the long-standing clinical experience with this technique, and its well-documented safety profile (3,4) have preserved its important role as guidance for a variety of interventional procedures.

This chapter discusses the role of TEE for guiding cardiac interventions with a special focus on the most commonly performed procedures and on newer developments, such as three-dimensional (3D) and real-time 3D echocardiography.

General Aspects
Periprocedural echocardiographic guidance is most useful for device closure of interatrial or interventricular communications and for interventions on the left-sided (systemic) cardiac valves (5). In the peri-interventional setting, echocardiographic guidance fulfills three fundamental roles in each single procedure:

1. Confirms the indication and excludes contraindications.
2. Guides the procedure to improve its safety and increase its success rate.
3. Confirms early procedural efficacy and identifies immediate or imminent complications.

The role of TEE before, during, and after various non-coronary cardiac interventions is outlined in Table 41.1. There is a large degree of variability in its use among institutions and individual interventionalists.

TEE Vs. ICE
A detailed discussion of ICE for cardiac interventions is given in chapter 40. Compared to ICE, with equipment costs of many thousands of dollars per procedure, the performance of TEE is far less expensive. However, TEE requires general anesthesia and those indirect costs also have to be taken into account. For interventionalists starting to perform structural interventions, it is reassuring to have another expert imager in the catheterization laboratory to help guide the procedure. That being said, many experienced operators continue to rely on TEE. In many laboratories, mainly depending on reimbursement, ICE has begun to replace TEE for guiding septal procedures. ICE has been shown to lower procedure times and to be equivalent to TEE in terms of procedural success and safety for closure of atrial septal defects (ASDs) (6,7). Its main advantage is improved patient comfort and freedom from general anesthesia.

In practical terms, a major advantage of ICE is freedom from additional personnel required to arrange a procedure (sonographer and anesthetist). In many centers, the scarcity of anesthetists remains a challenge in arranging complex procedures. In the pediatric structural laboratory where general anesthesia is the rule, there is little role for ICE, and TEE remains the preferred imaging modality.

The current generation of ICE probes allows two-dimensional (2D) imaging including color and spectral Doppler techniques, while all modern TEE systems allow multiplane imaging with rapidly evolving technology for 3D imaging. Although ICE allows high-quality visualization of most cardiac structures, it remains mostly a tool for interventions on the atrial septum and the aortic root. To date, there is little experience with interventions in other locations within the heart, and standardized protocols for its use are lacking. For example, no literature is available about how to quantify valvular regurgitation or stenosis of left-sided valve lesions with ICE.

3D Echocardiography
Initial experience with 3D and real-time 3D TEE for various procedures has been collected, and results are promising (8,9). 3D imaging improves the interventionist’s perception of the location of the lesion to be treated, which is often lost with omniplane 2D images. The interventionist can gain an improved appreciation of where wires and catheters are in the 3D space related to the target. By virtue of its improved spatial resolution, 3D TEE has the potential to facilitate procedures in patients with complex cardiac anatomy or complex lesion geometry. 3D imaging usually adds little for the post-procedural assessment. Full-volume 3D acquisitions require extensive postprocessing (slice and dice technique) and are therefore not useful to guide a procedure. Procedural guidance by 3D TEE remains a domain of real-time image acquisition. One drawback of real-time 3D is that 3D rendering is coarse and slow. Future generations of technology and faster computer speeds are likely to improve the experience significantly. New generations of ICE probes capable of 3D imaging are on the horizon as well. At present there is generally limited knowledge among echocardiographers with regard to optimal utilization of these new techniques, which in itself serves as a limitation.

Teamwork and Communication
When handling the ICE probe, the interventionist can immediately adjust views to his or her needs. In contrast, when TEE is used to guide a procedure, clear communication between echocardiographer and interventionalist is crucial.
The echocardiographer should be familiar with the procedure, know the critical steps, and understand what information is relevant to the interventionalist. The echocardiographer should also be familiar with potential complications and should know what to expect and when to look for it. Using TEE for guiding interventions therefore requires optimal teamwork. As interventionalists and echocardiographers often speak in different terms of reference, clear communication is important. In our experience, it is of great advantage to have dedicated interventionalists and echocardiographers who work together frequently. Teams who work well together use both verbal and nonverbal communication to improve procedural efficacy.

**Outlook**

In the following sections, the role of TEE for various interventions is outlined, including detailed descriptions of selected critical steps and a summary of key points in a checklist format for some of the most important and most common interventions.

### TEE FOR DEVICE CLOSURE OF INTERATRIAL COMMUNICATIONS

#### General Aspects

Device closure of interatrial communications is among the most frequently performed noncoronary intervention in the cardiac catheterization laboratory. TEE has evolved as a reliable method for guiding percutaneous closure of ASDs with contemporary devices. Its usefulness for planning and guiding the procedure has been demonstrated in numerous studies (10–17). Most procedures are guided by both fluoroscopy and TEE, but even guidance with TEE alone has shown to be feasible (18).

#### The Role of 3D Echocardiography

Although real-time transthoracic 3D echocardiography has shown to be of increasing value for characterization of secundum-type ASDs (19), TEE has remained the gold standard. The accuracy of transthoracic studies remains crucially dependent on image quality, being more often than not suboptimal in the adult population. 3D TEE technology has evolved rapidly since the late 1990s. It allows visualization of the changing geometry of ASDs throughout the cardiac cycle (Fig. 41.1) and allows better definition of their borders as well as their relationship to atrioventricular valves and venous inflows (20–24). Until recently, 3D reconstruction had to be made off-line and therefore was not well suited to real-time procedure guidance. Only the recent evolution of real-time 3D TEE has allowed it to guide procedures in the catheterization laboratory (8). As it potentially allows a better understanding of the 3D geometry in cases of distorted atrial septal geometry, it may have the potential to facilitate successful device deployment. More experience and comparative studies are required to further define its role.

### TEE FOR GUIDANCE OF SECUNDUM-TYPE ASD CLOSURE—PRACTICAL ASPECTS

The technical details of closure of secundum-type ASDs are outlined in detail elsewhere (see chap. 46). This section covers the role of TEE during these procedures. Because of their ease of use, high procedural success, and low complication rates, double-disc septal devices such as Amplatzer® (AGA Medical Corp., Plymouth, Minnesota, U.S.) and Occlutech® (Helsingborg, Sweden) are currently the most frequently used septal closure devices on the market. Other innovative device designs are available as well and the general principles of device implantation for ASDs are similar for all designs. In this section, we will focus on the use of double-disc devices.

An overview of the role of TEE for these interventions is given in Table 41.2, followed by a detailed description of critical steps.

#### Preprocedural

Only defects confined to the oval fossa, so called secundum or “true” ASDs without anomalous drainage of pulmonary veins, are amenable to device closure. The exclusion of a sinus venous defect, primum ASD, coronary sinus defect, and the

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**Table 41.1 Value of Transesophageal Echocardiography for Commonly Performed Noncoronary Cardiac Interventions**

<table>
<thead>
<tr>
<th>Procedure</th>
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<th>During the procedure</th>
<th>Immediate postprocedure</th>
<th>Comments</th>
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<td>++</td>
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<td>3D promising</td>
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<td>Baffle leak closure</td>
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<td>+</td>
<td>+</td>
<td>TEE rarely used</td>
</tr>
<tr>
<td>PFO closure</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>Not mandatory for the procedure</td>
</tr>
<tr>
<td>VSD closure</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>3D potentially helpful</td>
</tr>
<tr>
<td>Balloon aortic valve dilatation</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>Limited use, not mandatory</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>Critical for stent placement</td>
</tr>
<tr>
<td>&quot;Aortic root&quot; interventions (i.e., ruptured sinus Valsalva aneurysms)</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>3D promising</td>
</tr>
<tr>
<td>Pulmonary valve interventions</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Enhances safety</td>
</tr>
<tr>
<td>Transseptal puncture</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>Not mandatory</td>
</tr>
<tr>
<td>Balloon mitral valvuloplasty</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>3D promising</td>
</tr>
<tr>
<td>Paravalvular leak closure</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>3D promising</td>
</tr>
<tr>
<td>Interventional mitral valve repair</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>3D promising</td>
</tr>
<tr>
<td>PDA closure</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not mandatory</td>
</tr>
<tr>
<td>Coarctation stenting</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not mandatory</td>
</tr>
</tbody>
</table>

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The echocardiographer should be familiar with the procedure, know the critical steps, and understand what information is relevant to the interventionalist. The echocardiographer should also be familiar with potential complications and should know what to expect and when to look for it. Using TEE for guiding interventions therefore requires optimal teamwork. As interventionalists and echocardiographers often speak in different terms of reference, clear communication is important. In our experience, it is of great advantage to have dedicated interventionalists and echocardiographers who work together frequently. Teams who work well together use both verbal and nonverbal communication to improve procedural efficacy.

### TEE TO GUIDE INTERVENTIONAL CARDIAC PROCEDURES IN THE CATHETERIZATION LABORATORY

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**Abbreviations:** ASD, atrial septal defect; PDA, patent ductus arteriosus; PFO, patent foramen ovale; VSD, ventricular septal defect.
Table 41.2  Transesophageal Echocardiography Checklist for Atrial Septal Defect Closure

Preprocedural
- Rule out intracardiac thrombus in patients with atrial fibrillation
- Assess left ventricular diastolic function and estimate left atrial pressure
- Define size, anatomy, and location of the defect
- Rule out sinus venosus, coronary sinus, and primum atrial septal defects
- Rule out anomalous pulmonary venous drainage
- Assess severity of tricuspid regurgitation and estimate right ventricular systolic pressure
- Rule out other congenital or acquired cardiac lesions
- Ensure adequate tissue rims toward AV valves, caval veins, and pulmonary veins (at least 5 mm with most Amplatzer® devices)
- Assess whether rims appear floppy or firm
- Rule out or define multiple defects
- Define presence of an atrial septal aneurysm

During the procedure
- Confirm position of guidewire and delivery sheath
- Confirm position of the sizing balloon and cessation of shunting on color Doppler when the sizing balloon is inflated
- Measurement of sizing balloon waist ("stop flow" size)
- Confirm proper alignment of left atrial disc to interatrial septum
- Ensure permanent pacemaker wires are not entrapped
- Confirm absence of entangling in Chiari network
- Confirm absence of prolapse of left atrial disc at aortic margin

Postprocedural
- Confirm proper position and alignment of the device, rule out device prolapse
- Confirm absence of “rubbing” of the device against the aortic root
- Confirm normal function of atroventricular valves and absence of aortic regurgitation
- Confirm unobstructed inflow of caval veins, right pulmonary veins, and coronary sinus
- Confirm absence of pericardial effusion and signs of tamponade

Figure 41.1  (See color insert) Reconstruction of the “true” size and geometry of a secundum atrial septal defect derived from postprocessing of a 3D transesophageal echocardiography acquisition (bottom right). Abbreviations: LA, left atrium; RA, right atrium.
demonstration of normal drainage of four pulmonary veins is usually performed during an outpatient preinterventional study. In case of incomplete assessment on those studies, a thorough examination at the time of the planned closure procedure is mandatory (Fig. 41.2).

The Amplatzer septal occluder is currently available in sizes up to 40 mm and hence defects larger than 38 to 39 mm by balloon sizing are not amenable to device closure. Secundum defects can extend in any direction, toward the orifices of the superior or inferior vena cava and the coronary sinus, anterosuperior toward the aortic root and toward the atrioventricular valves. Given the design of the double-disc devices, a tissue rim of at least 5 mm toward most of these structures is mandatory for stable device positioning. A partially deficient rim is the rule rather than the exception, and its characterization is important for planning the procedure (25). The vast majority of defects larger than 20 mm in size have an absent aortic rim. Table 41.3 gives an overview of the most valuable TEE views to define tissue rims surrounding a defect.

The best angle to identify drainage of pulmonary veins is highly variable and differs from patient to patient. We usually start by identifying the left upper pulmonary vein at an angle of 60° to 110°. It drains just above the left atrial appendage. By gently turning the probe counterclockwise and slightly increasing the angle, the left lower pulmonary vein is identified. The right upper pulmonary vein drains into the left atrium just posterior to the superior vena cava and is easy to identify by turning the probe slightly clockwise from a bicaval view. Keeping the right upper pulmonary vein in view and slowly decreasing the plane angle toward 30° to 60° with slight clockwise rotation of the probe, the right lower pulmonary vein can be identified. As an alternative approach, pulmonary veins can be identified from a 0° angle by gently advancing and withdrawing the probe from a mid-esophageal view while turning the probe either clockwise or counterclockwise. Fortunately, in the presence of a significant left-to-right shunt across the interatrial septum, pulmonary vein flow is markedly increased and helps identifying these vessels. Finding only one
pulmonary vein entering the left atrium on one side is not abnormal as pulmonary veins are often confluent before entering the left atrium. However, a high suspicion for detection of abnormal pulmonary venous drainage needs to be maintained, especially if the dilatation of the right-sided heart chambers is out of proportion to the size of the ASD.

**During the Procedure (Procedural Aspects)**

For device stability not only the size of tissue rims is important but also whether they are characterized as firm or pliable. In the case of an isolated absence of the anterosuperior or aortic rim (Fig. 41.3), device closure is almost universally possible. A stable device position can be achieved by ”straddling” the device around the aortic root. In these cases, the balloon should be sized to the “stop flow” point—the balloon size at which flow across the septum ceases—and not just to the point where a waist appears on the balloon. Using a balloon to stretch the septum should be avoided as it predisposes to selecting a larger device that may increase the risk of erosion through the roof of the atria and the aorta (26,27). In contrast to absent aortic rims, a sufficient inferoposterior rim (Fig. 41.4) is crucial for a stable position of the device. There is a trend to avoid balloon sizing of ASDs before device implantation. Defect size is measured on TEE, and device size is then arbitrarily selected at 4 to 5 mm larger. Little evidence suggests that this practice is safer than balloon sizing.

To rule out multiple defects it is crucial to interrogate the interatrial septum with color Doppler while the sizing balloon is inflated. If residual color flow is noted across the septum while the sizing balloon is inflated, we would advocate entry of the contralateral femoral vein to balloon size any substantial secondary defect. The most important task of the echocardiographer during device closure of ASDs is assessment of the deployed device and the detection of imminent complications after implantation, but ideally before release of the device. We

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**Figure 41.3** Panel A–C: Mid-esophageal transesophageal echocardiography views of an anterosuperior located secundum-type atrial septal defect with absent aortic rim at different degree of angulation. Large Eustachian valve (arrow), which must not be mistaken for an inferoposterior tissue rim (arrowhead). Panel C depicts a bicalvar view and shows the true, in this case large, inferior rim. **Abbreviations:** LA, left atrium; RA, right atrium; RAA, right atrial appendage; AO, aorta.

**Figure 41.4** *(See color insert)* Large atrial septal defect II (secundum) with small posterior tissue rim (arrowhead) and good rim toward the AV valve level (arrow).
spend adequate time verifying tissue margins in multiple views, assessing residual shunting with color Doppler, and confirming the absence of impingement on surrounding structures. It is prudent to be certain of device stability before its release and to reposition or even change to another device size if uncertain. Apart from device embolization, the most feared complication is erosion of the roof of the atrium, which, one-third of the time, involves the aortic root. A high level of awareness of a developing pericardial effusion should be maintained. It is also important to exclude entrapment of a pacemaker wire during device manipulation and final deployment. Some pacemaker leads may be placed in a way that makes it impossible to avoid wire entrapment, especially with large devices. This is not an absolute contraindication for device placement, and the procedure may be performed under special circumstances after careful consideration of alternatives.

Deployment of the left atrial disc in the left atrial appendage or against the left atrial wall may result in damage to these structures and should be avoided. Deploying the left atrial disc after rotation has occurred in the delivery system may lead to “cobra head” malformation, which is easily detectable on TEE. To avoid this complication, it is crucial to guide retrieval of the delivery sheath by TEE to the middle of the left atrium before deploying the left atrial disc of the device, especially if larger devices are required. Although it is thought that only complete withdrawal of the device and manual reshaping outside the body could resolve cobra head malformation (28), in our experience, simply advancing the left atrial disc further into the left atrium usually restores normal device configuration.

With large defects the left atrial disc can become perpendicular to the defect itself leading to prolapse at the aortic valve margin and preventing proper delivery of the device. This problem is less evident on fluoroscopy, but can be easily recognized on TEE. A second maneuver to resolve aortic disc prolapse includes rotating the delivery system clockwise to the right side of the left atrium followed by usual deployment, which is often successful. In these cases, the use of a Hausdorff sheath is advocated; however, we have never required one so far in over 1200 cases. Opening the left atrial disc in the left upper pulmonary vein and rapidly exposing the right atrial disc works well for devices >34 mm in size. After such a maneuver, confirming good alignment of the device toward the interatrial septum and exclusion of prolapse of the device are important to minimize the risk of subsequent device embolization.

The StarFlex® and BioStar® devices have been used infrequently for the closure of small ASDs. It is most important to ensure that the anterior device arm of the distal umbrella does not prolapse into the right atrium before releasing the proximal umbrella, as this may lead to a significant residual shunt and increases the likelihood of device embolization. The best view to ensure good position of the distal arms is a short-axis view through the base of the heart (usually mid-esophageal 20°–50°). Further tips and tricks for troubleshooting with this device are given in chapter 46.

There are reports of entanglement of an ASD closure device in a Chiari network, a complication that should be easily detected on TEE (29). This is a very rare complication and avoiding entanglement of pacemaker or ICD leads during insertion of the sheaths and when deploying the device is of far greater clinical importance.

Post Deployment
After deployment of the device, its position, any degree of residual shunting, functional integrity of atrioventricular and aortic valves, as well as unhindered systemic and pulmonary venous inflow must be documented. Thrombus formation on the left or right atrial disc has become rare with modern devices, proper use of full-dose heparinization, and restricting the use of protamine. The frequency of thrombus occurrence with older-generation devices was up to 7% in early follow-up with TEE (30,31). After implantation it is very important to carefully interrogate each margin for stability. Immediately after the procedure, it is not uncommon to note leaking through the device with color Doppler, which will cease with the expected thrombus formation between the disks. If color Doppler flow is noted at the superior vena cava or the aortic rim, the device should often be up-sized by 2 mm for devices >20 mm and by 1 to 2 mm for devices <20 mm. In large defects, it is common to find minimal residual leaks with color Doppler at the inferior caval vein margin. When the septum is thin, this residual color Doppler flow may be caused by small fenestrations or Thebesian veins. If the inferior septum, however, is seen within the “jaws” of the device, stability is further reassured.

Multiple Atrial Septal Defects or Fenestrated Atrial Septum
Although multiple defects are no longer considered to be a contraindication for device closure, their recognition and detailed delineation is of paramount importance for planning and executing a successful intervention. Particularly in the presence of multiple defects, 3D imaging has proven to be helpful in understanding the spatial relationship of those defects (Fig. 41.5) and hence planning of the intervention (21). Depending on the strategy chosen, it is important to ensure on TEE that the guidewire passes through one of the central defects or through the largest defect. However, it is often difficult to be certain of wire position in the presence of a billowing aneurysmal septum. In those circumstances, we advocate crossing a defect arbitrarily with a wire and inflating a sizing balloon within this defect, before trying to cross secondary defects with another catheter and guidewire. This technique requires a second venous puncture but avoids the possibility of crossing a small defect and assuming it is dominant, leaving a larger defect to be dealt with by the disks of a device placed in a smaller hole.

Device Closure of Patent Foramen Ovale
Echocardiographic guidance for device closure of patent foramen ovale is not mandatory (32,33). However, this issue is still contentious and there is an ongoing debate about the safest way of closing a patent foramen ovale (PFO) (33,34). From a practical point of view, we, as others, use echocardiographic guidance in addition to fluoroscopy only for those patients in whom complex geometry is anticipated. This includes PFOS with long tunnels, large atrial septal aneurysms, or if new devices are used, especially those that cannot be easily retrieved once deployed (35). If TEE or ICE is not used for PFO closure, the use of angiography post implantation is mandatory.
Device Closure of Baffle Leaks After Atrial Switch and Fontan-Type Operations

Baffle leaks after atrial switch operations are common. They behave as ASDs. There is either predominant left-to-right shunt and associated volume load of the subpulmonic left ventricle or right-to-left shunt, typically in the presence of a concomitant distal baffle obstruction. The latter leaves the patient cyanotic and at risk for paradoxical embolism. This is especially true in the company of a transvenous pacemaker lead. As the anatomy in these patients is often complex and distorted, a detailed understanding of the anatomy is crucial to succeed (36). Full visualization of atrial baffles after atrial switch procedures can be difficult on TEE. To visualize the systemic venous baffles, one practical approach is to find the mitral valve (at \(0^\circ\)–40\(^\circ\)) and then to follow the inferior and superior cava baffles by slowly withdrawing [superior vena cava (SVC)] and advancing [inferior vena cava (IVC)] the probe, while simultaneously rotating gently clockwise. Sometimes adequate assessment of the systemic venous baffles can also be achieved from a modified bicaval view. The pulmonary venous baffle is posterior to the systemic baffle. Pulmonary venous baffle obstructions are much less frequent. Visualization of pulmonary venous drainage is comparable to visualization of pulmonary veins in the normal heart. Bubble contrast echocardiography is the most sensitive way for detection of even small right-to-left shunts. The role of TEE to guide the closure of baffle leaks is limited but in some instances may be helpful for defining the optimal treatment strategy (37–39). The ability to delineate spatial relationships with real-time 3D echocardiographic imaging may become more important in guiding these procedures, so far however, experience is limited.

In contrast to baffle leaks after atrial switch operations, residual fenestrations in the systemic venous limb of the Fontan circulation are often deliberately created at the time of surgery to reduce immediate postoperative complications. This occurs at the price of persistent right-to-left shunting. Many fenestrations do not close spontaneously. Elective device closure of these residual right-to-left shunts is therefore often performed when significant cyanosis persists. We rarely use TEE guidance for these procedures but some cases have been reported where it has been useful (40,41).

TEE FOR DEVICE CLOSURE OF VENTRICULAR SEPTAL DEFECTS

General Aspects

Device closure of congenital muscular ventricular septal defects (VSD) or residual VSDs after open heart surgery is a well-established procedure with a low complication rate and a high rate of procedural success. In contrast, device closure of perimembranous VSDs is associated with a risk of complete heart block of up to 5% in a mostly pediatric population. Device closure is therefore more contentious in patients at low risk for elective surgical repair and especially in children. Finally, postmyocardial infarction VSDs are associated with a high mortality rate both when left untreated and when treated successfully with device closure in the acute setting. Device
Assess residual shunting before device release

Confirm position and device stability before release (multiple views)

During the procedure
✓ Confirm position of guidewire and delivery sheath
✓ Confirm position and device stability before release (multiple views)
✓ Assess residual shunting before device release

Postprocedural
✓ Confirm proper position and alignment of the device
✓ Document any degree of residual shuntinga
✓ Exclude significant aortic regurgitation/distortion of aortic rootb

aColor Doppler tends to underestimate the degree of a residual shunt and one needs to be cautious not to overestimate the success of a given procedure. Even small residual shunts may predispose to hemolysis.
bMost important for device closure of perimembranous VSDs.

Abbreviation: VSD, ventricular septal defect.

closure of postoperative or subacute postmyocardial infarction VSDs is usually associated with acceptable outcomes.

In many series, VSD device closure was performed under fluoroscopic and TEE guidance. Fluoroscopic guidance alone or guidance by fluoroscopy and transesophageal echocardiography was used in others, especially for single muscular VSDs (42,43). In patients with complex anatomy, for example, residual postoperative shunts after complex repair of congenital heart disease, TEE usually shares the same obstacles and difficulties as angiography, namely atypical imaging planes. Shadowing artifacts created by calcified VSD patches from previous surgical repair or prosthetic valves can hamper image quality significantly. The utility of TEE can only be assessed on a case-by-case basis. It may be helpful in patients with multiple defects or in those with defects in proximity to other cardiac structures such as atrioventricular and aortic valves. A peri-interventional diagnostic study often clarifies this. Sizing of VSDs is performed by angiography and TEE at end-diastole or with a compliant sizing balloon (Table 41.4).

Practical Aspects

Detailed preprocedural echocardiography is important not only for defining defect size, location, and relationship to the surrounding structures but also for planning the technical details of a procedure. If the defect is located anterior or toward the outlet septum, a transesophageal approach is preferred, while in the past, for most other defect localizations, a transjugular access was chosen. In the adult heart it is, however, easy to form a loop in the right atrium, especially with the availability of braided sheaths, which mimic a jugular orientation of guidewire and delivery sheath. This allows the performance of most VSD closures from a femoral approach. If a muscular Amplatz septal occluder is used, the distance to atrioventricular and aortic valves must be at least 4 mm. The asymmetric Amplatz perimembranous VSD occluder allows implantation if the distance to the aortic valve is as little as 1 to 2 mm.

The best views on TEE to define a muscular VSD are the mid-esophageal four-chamber (usually 0°–20°), two-chamber (usually 70°–100°), and long-axis views (100°–135°) as well as transgastric short-axis views and deep transgastric four-chamber views (both at 0°). It is important to visualize a defect in several planes to appreciate its size and geometry. In addition, for perimembranous VSDs, a short-axis view through the base of the heart (20°–60°) is helpful. As apically located VSDs may be hard to visualize on TEE, complementary transesophageal imaging might be helpful in these cases; we generally do not use TEE guidance in patients with apical defects.

3D Echocardiography

As for other indications, 3D echocardiography is particularly useful for delineation of spatial relationship between multiple defects and hence might help planning of optimal interventional or surgical strategies (44).

Postinfarction VSDs

VSDs after myocardial infarction differ in many ways from congenital VSDs. Interventionalists can be involved in the care of these patients when they present either as acute postinfarction VSDs or when patients have residual defects after surgical closure of a postinfarction VSD. The outlook for the former is bleak when left untreated, and every intervention, either surgical or interventional, remains at very high risk. Those treated after “a trial of life” in the subacute phase often have a much improved outlook; however, if patients deteriorate during their trial, late intervention is usually at even greater risk. Rather than being well-defined defects, postinfarction VSDs are often jagged edged, irregular, and serpiginous ruptures of the interventricular septum with poorly defined borders. They often have multiple exit points toward the right ventricle. To allow proper planning of interventional closure, it is therefore crucial to define defect size, location, borders, and inflow and outflows.

As the largest dedicated double-disc device size at present is 24 mm, proper sizing of the defect is critical. Apart from defining defect location and morphology, echocardiography defines left ventricular function, integrity of the valvular apparatus, and defect location (Fig. 41.6). It is important to detect pericardial effusion, as this may herald free wall or contained rupture. The location of the defect with respect to the rims is quite critical, as one tries to avoid putting stress on a structurally weakened septum to free wall junction, which might result in free wall rupture. As there is often more than one defect, it is also crucial to assure that at time of the intervention, the guidewire is crossing the largest defect (45–47).

**Table 41.4** Transesophageal Echocardiography Checklist for Ventricular Septal Defect Device Closure

<table>
<thead>
<tr>
<th>Preprocedural</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Define size, anatomy, exact location, and number of defects (multiple views)</td>
</tr>
<tr>
<td>✓ Rule out aortic valve cusp prolapse and malalignment VSD</td>
</tr>
<tr>
<td>✓ Rule out additional congenital cardiac defects</td>
</tr>
<tr>
<td>✓ Define relation and distance to AV valves and aortic valve</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>During the procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Confirm position of guidewire and delivery sheath</td>
</tr>
<tr>
<td>✓ Confirm position and device stability before release (multiple views)</td>
</tr>
<tr>
<td>✓ Assess residual shunting before device release</td>
</tr>
</tbody>
</table>

Postprocedural

| ✓ Confirm proper position and alignment of the device |
| ✓ Document any degree of residual shuntinga |
| ✓ Exclude significant aortic regurgitation/distortion of aortic rootb |

Practical Aspects

Access to the left atrium from a systemic venous path is a prerequisite for many cardiac interventions. This includes percutaneous mitral valve repair, mitral balloon valvuloplasty, device closure of left atrial appendage, device closure of para-valvular leaks, and many electrophysiological procedures (48). Although echocardiographic guidance is not mandatory, it provides additional safety and helps to localize the optimal site of puncture for a specific intervention. Different procedures require puncture at different sites in the interatrial septum, for example, a high posterior puncture when a mitral valve clip repair is planned (49,50). Younger interventionists are increasingly dependent on TEE guidance as the need for
Transseptal puncture has become less frequent in the last two decades due to a decrease in rheumatic mitral valve disease and the relative rarity of transseptal puncture for diagnostic purposes (e.g., assessment of mitral or aortic valve disease). Proper position of the transseptal needle is confirmed by “tenting” of the interatrial septum with the needle withdrawn into the tip of the Mullins (Medtronic, Minneapolis, Minnesota, U.S.) sheath. The puncture of the septum can be confirmed on TEE by injection of agitated saline contrast through the transseptal needle, though more often radiographic contrast is used for this purpose (51,52). Transseptal puncture across patches, baffles, or conduits in patients with repaired congenital heart disease is particularly challenging, and optimal delineation of an individual’s cardiac anatomy is important to enhance the safety of this step of the procedure (53) (Table 41.5).

### Table 41.5 Transesophageal Echocardiography Checklist for Interatrial Transseptal Puncture

**Preprocedural**
- Define optimal site of puncture (usually in the region of the oval fossa)
- Define anatomical distortion due to congenital heart disease, mitral valve disease, or pulmonary hypertension
- Define localization of the aortic root
- Rule out clot in left atrium or left atrial appendage
- Define presence and extent of lipomatous interatrial septum

**During the procedure**
- Confirm position of transseptal needle on the interatrial septum (tenting)
- Confirm intra-atrial location of needle tip after puncture (saline contrast)

**Postprocedural**
- Rule out pericardial effusion or tamponade
- Define size of residual atrial septal defect

### 3D Echocardiography
Real-time 3D imaging has recently been shown to be helpful for some interventions. Because of its unique ability to delineate spatial relationship, it might prove useful for guiding transseptal puncture in certain patients with high-risk anatomy. This includes patients with congenital heart disease, pulmonary artery hypertension, left to right bowing of the septum in the presence of mitral stenosis, or in cases of a thickened lipomatous septum (54).

### TEE for Left-Sided Heart Valve Procedures

#### Balloon Aortic Valvuloplasty
The role of TEE in guiding aortic valve balloon dilatation is limited. When used, its purpose is accurate sizing of the aortic annulus to choose the appropriate balloon size and to detect immediate complications after each dilatation. Increasing aortic regurgitation is prohibitive for further dilatations. Should the patient become hypotensive following dilatation, TEE provides an excellent tool to immediately detect or rule out complications such as massive aortic regurgitation, aortic dissection, tamponade, or new wall motion abnormalities suggestive of coronary emboli.

#### Catheter-Based Aortic Valve Replacement
If catheter-based aortic valve replacement—either by the transfemoral or the transapical approach—is performed under general anesthesia, TEE is usually used together with angiography to guide the interventions. Alternatively, the transfemoral procedure—particularly with the Corevalve Revalving System (Medtronic CV, Luxembourg, E.U.)—can be performed in local anesthesia under pure angiographic guidance. Independently of that, accurate sizing of the aortic annulus is critical, as the available prosthetic valve sizes are limited and some patients are disqualified for the procedure on the basis of their annulus size. TEE has been shown to be more accurate than transthoracic echocardiography in sizing the annulus, especially in patients with heavily calcified valves (55,56).

In addition to the sizing of the annulus, the main role for TEE is the optimal centering of the valved stent relative to the native aortic annulus (Fig. 41.7). With the transfemoral approach using the balloon-expandable Edwards SAPIEN valve, the aim is for a ventricular-to-aortic ratio of the stent of 60:40—that is, the larger part of the stent before implantation sits in the left ventricular outflow tract (LVOT)—as a slight “travel” of the stent during deployment is expected. With the transapical approach less aortic travel is observed and therefore the aim for centering is 50:50. Communication between the interventionalist and the echocardiographer during the procedure is the key to success. We have used the term “ventricular” and “aortic” to describe the position of the valve instead of “in and out” to avoid any ambiguity during this critical step (57). When using the transapical approach, TEE is even more important, as fluoroscopy in many operating rooms is provided by a portable C-arm with less optimal image quality. In patients in whom a transapical approach is chosen, entanglement of the delivery system in the mitral valve apparatus can be life-threatening and must be immediately detected by TEE. After deployment of the stent, TEE should confirm stable stent position and define the amount of paravalvular leakage. In cases of severe paravalvular regurgitation, postdilatation with a slightly

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**Figure 41.6** (See color insert) An 84-year-old patient in cardiogenic shock due to subacute postmyocardial infarction ventricular septal defect. The arrow points to the left ventricular disc of an Amplatzer® ventricular septal defect occluder (white arrow), entangling the subvalvular mitral valve apparatus, leading to severe mitral regurgitation (arrowhead). Abbreviations: LA, left atrium; LV, left ventricle.
larger balloon volume might be efficacious. If the prosthesis is placed too low, a second valve may need to be deployed to correct for the resulting severe aortic regurgitation (Table 41.6).

**Sinus Valsalva Aneurysm and Other Aortic-to-Atrial Communications**

Congenital or acquired communications between the aorta and various cardiac structures (i.e., ruptured sinus Valsalva aneurysms) are often amenable to device closure. In an individual patient it always has to be decided whether device closure is expected to be equivalent to surgery, taking into account the patient’s estimated perioperative risk. Figure 41.8 depicts the successful closure of a postoperative aortic to left atrial fistula after bioprosthetic aortic valve replacement, and Figure 41.9 describes an attempted device closure of a ruptured sinus Valsalva aneurysm. TEE is very helpful in exact delineation of a patient’s lesion anatomy, and the most useful views are generally mid-esophageal short-axis view through the aortic root and long-axis views at 110° to 140°. Sometimes, however, off-axis views may be required, especially for facilitating guidewire and sheath placement across a defect. Special note should be made of multiple perforations of these aneurysms, which may compromise the result.

### Table 41.6 Transesophageal Echocardiography Checklist for Catheter-Based Aortic Valve Replacement

<table>
<thead>
<tr>
<th>Preprocedural</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Rule out mobile clot or active endocarditis</td>
</tr>
<tr>
<td>✓ Rule out plaques grade IV or mobile clots in the thoracic aorta</td>
</tr>
<tr>
<td>✓ Accurate measurement of aortic annulus (between hinge points of the valve)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>During the procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Avoid entanglement of delivery system in mitral valve apparatus in case of transapical approach</td>
</tr>
<tr>
<td>✓ Confirm optimal position of valved stent before deployment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postprocedural</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Confirm stable position of the valved stent</td>
</tr>
<tr>
<td>✓ Confirm normal prosthetic valve function</td>
</tr>
<tr>
<td>✓ Assess severity and localization of paravalvular leaks</td>
</tr>
<tr>
<td>✓ Assess immediate complications (new wall motion abnormalities may help localizing the site of coronary obstruction)</td>
</tr>
</tbody>
</table>

**Balloon Valvuloplasty of the Mitral Valve**

The most important role of TEE in balloon valvuloplasty of the mitral valve is the assessment of valve characteristics predicting the success of the procedure (thickening, calcification, mobility of valve, and subvalvular apparatus) and is discussed elsewhere in detail (see chap. 43). The absence of left atrial thrombus is a prerequisite for a safe procedure and must be confirmed by TEE even in patients with therapeutic anticoagulation or in those in sinus rhythm (58).

During the procedure itself, TEE guidance is not mandatory but may ease transseptal puncture. It allows assessment of...
the severity of mitral regurgitation and other complications immediately after the procedure (59). In addition, compared with fluoroscopy alone, TEE guidance might improve placement of the dilatation balloon and decrease procedure and fluoroscopy time (60).

**Device Closure of Paravalvular Leaks After Prosthetic Heart Valve Surgery**

Paravalvular leaks after surgical prosthetic heart valve replacement can cause significant morbidity due to residual regurgitation or hemolysis. To avoid the complications of a reoperation, device closure has become an attractive alternative to conventional surgery in poor surgical candidates. For these technically demanding procedures, TEE plays an important role for planning and executing these interventions. A detailed description of the defect localization, size, and relationship to adjacent structures is of paramount importance (61–63). Again of great importance is a clear communication between the echocardiographer and the interventionalist as localization on echocardiography may not be easily translated into a biplane radiographic view. Because of its unique ability to delineate spatial relationships within the heart and its ability to visualize the true geometry of a defect, real-time 3D TEE will likely become the modality of choice for guidance of these procedures in the future (Fig. 41.10). The application of real-time 3D TEE to this intervention has provided tremendous improvement in periprocedural success and sustainability. During the procedure, TEE provides invaluable assistance to help target the defect with a guidewire and delivery sheaths in 3D space (Table 41.7).

**RIGHT-SIDED VALVE LESIONS**

The role of TEE for guiding right-sided heart valve procedures is limited. Balloon dilatation of native pulmonary valve stenoses and implantation of percutaneous pulmonary valves is usually performed under fluoroscopy alone, and the additional yield of echocardiography is small. For optimal positioning of the stent valve in the case of percutaneous treatment of a stenosed or regurgitant conduit, calcifications within the wall of the conduit are the most important landmarks for placement of the device. The almost inevitably present heavy calcification of these conduits hampers image quality on TEE significantly because of shadowing artifacts. Interventional procedures on the tricuspid valve are rarely performed and the role of TEE is yet to be defined.

**MISCELLANEOUS AND “FREESTYLE” INTERVENTIONS**

As many evolving procedures in the cardiac catheterization laboratory, such as percutaneous mitral valve repair (see chap. 43), are critically dependent on optimal imaging, which is provided by TEE (64), its role will be increasing. The emerging technology of 3D TEE will even enhance its importance in the future. To cover all these interventions in detail is beyond the scope of this chapter and we therefore refer to the corresponding chapters dealing with individual interventions. Whether TEE or echocardiography is at all helpful for a particular intervention is determined by several factors. First, if diagnostic TEE
Figure 41.9 (See color insert) Attempted device closure of ruptured sinus Valsalva aneurysm. Panel A and B: Mid-esophageal short-axis view through aortic root without and with color Doppler. The arrow points to the perforation of the sinus Valsalva aneurysm toward the right atrium. Panel C: Angiographic view of the sinus Valsalva aneurysm. Panel D: Balloon sizing of the defect (white star). Panel E: Amplatzer duct occluder sealing the perforation of the sinus Valsalva aneurysm (not released). The device seals only one of three communications between the aorta and the right ventricle, leaving a large residual shunt. The device was therefore retrieved and the patient was referred for surgical repair. Abbreviations: LA, left atrium; RA, right atrium; RV, right ventricle; AO, aorta.

Figure 41.10 (See color insert) Device closure of paravalvular mitral leak (bioprosthesis). Panels A and B: 74° Mid-esophageal transesophageal echocardiography views demonstrating paravalvular mitral regurgitation (arrow). Panel C: Live 3D image of the mitral valve prosthesis, seen from the left atrium demonstrating a large inferomedial paravalvular leak (arrow). The arrowhead points to the delivery sheath crossing the leak. Panel D: Live 3D image after device closure of paravalvular leak with two Amplatzer duct occluder (white stars). Abbreviations: LA, left atrium; LVOT, left ventricular outflow tract; AO, aorta.
Table 41.7 Transesophageal Echocardiography Checklist for Device Closure of Paravalvular Leaks

Preprocedural
✓ Define localization, size, and geometry of the defect
✓ Define relationship to adjacent structures (heart valves, coronary arteries)
✓ Rule out intracardiac clot and malfunction of the prosthetic valve
✓ Rule out “rocking” of the valve and confirm stability of the prosthesis

During the procedure
✓ Guide transseptal puncture
✓ Ease proper guidewire position (to AVOID entangling in mechanical valves)
✓ Rule out prosthetic malfunction caused by the closure device—BEFORE release

Postprocedural
✓ Confirm normal prosthetic heart valve function
✓ Detect immediate complications
✓ Define the amount of residual paravalvular leakage and assess whether a second device is necessary
✓ Define the size of the residual atrial septal defect

was unable to visualize the structure of interest in high quality, any yield in adding this modality is to be expected. This is the case for any structure remote from the esophagus, as, for example, a patent ductus arteriosus, aortopulmonary collaterals, or peripheral pulmonary artery stenoses. Some clinical scenarios preclude the use of TEE, including patients with esophageal disease (e.g., strictures, varices) and those in whom it is safer to perform a procedure without general anesthesia. The latter may be the case in hemodynamically unstable patients or patients with severe respiratory compromise. In those cases we avoid the use of TEE as we feel discouraged about the safety of TEE with topical anesthesia and sedation only. However, TEE without general anesthesia is a widely practiced technique in many European centers. Intracardiac echo might be more helpful in cases of this nature.

Some lesions, such as pulmonary artery stenoses and coarctation of the aorta, are easily and fully visualized by angiography and therefore echocardiography is not routinely used for guiding these procedures. Its role remains limited to immediate assessment of acute catastrophic complications, such as aortic dissection and tamponade.

SUMMARY AND CONCLUSIONS

The introduction of TEE into clinical practice has not only supported the development of many innovative cardiac interventions but has become an essential tool for guiding many of them. For some interventions ICE will likely replace TEE in the future but the advent of real-time 3D TEE may lead to an extension of its role in others.

REFERENCES


Percutaneous therapy for aortic valve disease

Peter Wenaweser, Lutz Buellesfeld, and Eberhard Grube

INTRODUCTION AND HISTORICAL PERSPECTIVE

Valvular aortic stenosis represents an important cardiac disease affecting up to 5% of the elderly population (1). A severe, symptomatic stenosis signifies a class I indication for valve replacement (2), as patients with medical treatment face a high morbidity and mortality (3). Similar to the pathogenesis of arteriosclerosis, shear stress, inflammation, and lipid accumulation play an important role in the development of aortic stenosis (4). Attempts to reduce the progression of aortic valve disease with different drugs have failed since the use of lipid-lowering drugs (5), or angiotensin-converting enzyme (6) inhibitors have demonstrated no beneficial effect so far. Until 2002, the only therapeutic treatment for severe aortic valve stenosis consisted of surgical open-heart valve replacement. Perioperative and clinical short-term data show a low operation-related morbidity and mortality (7,8), but the incidence of perioperative, major adverse cardiovascular events increase with age (9) and with the number of comorbidities or cardiac factors such as depressed systolic left ventricular function or concomitant coronary artery disease.

The first interventional treatment of valvular heart disease goes back to 1953 when Rubio-Alvarez et al. reported on the first intracardiac valvulotomy by means of a catheter (10). In 1979, “balloon valvulotomy” of a congenital pulmonary stenosis was successfully performed (11), and in the following decades percutaneous balloon valvuloplasty for pulmonary valve stenosis become the therapeutic gold standard (12,13). The technique of balloon valvuloplasty was adopted for the treatment of recoarctation (14), rheumatic mitral valve stenosis (15), and valvular degenerative aortic stenosis (16). After the first promising procedural results of balloon valvuloplasty for valvular aortic stenosis (16), the analysis of larger patient populations demonstrated mediocre short-term and poor long-term clinical outcome (17). Balloon valvuloplasty of heavily calcified degenerative aortic stenosis provided an acute gain of the aortic orifice area by fracturing calcified nodules, separating fused commissures, and stretching of the aortic valve ring. However, as only microfractures are achieved, the rate of restenosis remains high (~50%) within the first months after intervention, and the procedure is limited by a considerable periprocedural morbidity and mortality. As a consequence, balloon valvuloplasty for the treatment of severe aortic stenosis is currently only considered in emergency cases as a bridge to valve replacement (2).

In 1992, almost 40 years after the first surgical implantation of a prosthetic ball valve device in the descending aorta for the treatment of aortic regurgitation, Anderson et al. succeeded in transluminally implanting a prosthetic heart valve in the ascending aorta of closed chest animals (18). In parallel to the improvement of cardiac surgery techniques, the percutaneous approach has been improved constantly over the past years. The first successful animal studies of porcine valves sutured into a self-expanding stent were published at the beginning of the new century (19). In 2002, the first-in-man percutaneous valve implantation within a stenotic aortic valve using the antegrade approach (trans-septal puncture) was achieved by Cribier et al. (20) using the Cribier-Edwards valve and in the following year the Edwards-SAPIEN valve (Edwards Life sciences Inc., California, U.S.). The antegrade approach was challenging and prone to complications, and in a second phase, the retrograde approach was used. The retrograde approach turned out to be less demanding and is now the sole approach used in transfemoral access cases. In 2004 another device, the CoreValve Revalving System (CRS TM, CoreValve Inc., Irvine, California, U.S.) was successfully applied and became the second technically feasible system (21). As a further step forward, the first transapical implantation with the Edwards system was introduced into clinical practice in 2005 (22).

ANATOMIC CONSIDERATION

Aortic stenosis represents the most common cause of left ventricular outflow tract obstruction and has three principal etiologies: congenital, rheumatic, and degenerative. The aortic valve can be unicuspid, bicuspid, or tricuspid. A congenitally unicuspid valve is rare and provokes severe symptoms in infancy. A congenitally bicuspid aortic valve may degenerate very early in childhood due to turbulent flow inducing trauma to the leaflets and finally resulting in fibrosis and calcification of the valve. Age-related degenerative, former senile, aortic stenosis is the most common cause of acquired aortic stenosis, whereas rheumatic disease is rarely pathogenetically involved in Western communities. The major types of aortic stenosis are depicted in Figure 42.1 (23). The development of degenerative, calcific aortic stenosis shares the risk factors of vascular atherosclerosis. Mechanical stress damages the endothelium of the leaflets, facilitating the subendothelial accumulation of oxidized low-density lipoprotein, production of angiotensin II, and inflammation with T lymphocytes and macrophages (4). Progressive calcification leads to severe obstruction and stenosis.

A detailed assessment of the aortic valve, aortic root, and descending aorta including the iliofemoral axis is warranted before attempting transcatheter aortic valve implantation (TAVI). First, and of main interest, are the valvular anatomic details, for estimating the amount and distribution of calcification, as well as the cusps. For balloon dilatation and TAVI, a large block of calcification in one cusp and a functionally bicuspid valve represent a formal contraindication for the intervention as the risks of emboli, insufficient dilatation, and a misplacement of the inserted bioprosthesis are markedly
increased. Second, the location of the orifices of the coronary arteries, usually within the two anterior sinuses of Valsalva, may vary. Of special interest with regard to transcatheter bioprostheses is the distance between the basal attachment of the leaflets and the corresponding orifice. In a morphometric and topographic study of the coronary ostia the distance amounted to 12 to 13 mm (24). The currently used transcatheter bioprostheses are constructed with a sealed skirt at the distal, left ventricular end of the prosthesis measuring 8 to 11 mm in height for the Edwards-SAPIEN valve and 12 mm for the CoreValve Prosthesis. In optimal positioning 4 to 6 mm of the prosthesis will be placed below the annulus providing enough distance of the sealed skirt to the coronary ostia. Dilatation of the aortic root is associated with aortic stenosis, especially with a bicuspid valve (25). The etiology however remains to be determined as hemodynamic but also intrinsic pathological factors of the aortic wall are involved in the process of dilatation. The current guidelines recommend to consider a replacement of the ascending aorta for a diameter >45 mm (2). Accordingly, TAVI is contraindicated in patients with dilated ascending aorta. The descending aorta and the iliofemoral arteries need to be assessed with regard to technical feasibility of introducing the transcatheter valve systems. Severe atherosclerosis of the peripheral vascular bed is often associated with aortic stenosis (26) and represents a concern for retrograde, transfemoral TAVI with respect to risk of dissection, perforation, and embolization of debris.

**SCREENING FOR TAVI**

The screening exams are an essential condition for a successful TAVI. Table 42.1 provides the most important exams during the screening phase categorized into mandatory exams like echocardiography (TTE or TEE), right and left heart catheterization,

<table>
<thead>
<tr>
<th>Table 42.1 Screening Process for Transcatheter Aortic Valve Implantation</th>
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<tbody>
<tr>
<td><strong>Mandatory exams</strong></td>
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<tr>
<td>Physical exam</td>
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<tr>
<td>Blood tests</td>
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<tr>
<td>Electrocardiogram</td>
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<tr>
<td>Transthoracic and transesophageal echocardiography</td>
</tr>
<tr>
<td>Left and right heart catheterization</td>
</tr>
<tr>
<td>Aortography (thoracic, abdominal, iliofemoral)</td>
</tr>
<tr>
<td>Angiography or Doppler ultrasound of carotids</td>
</tr>
<tr>
<td>CT angiography (thoracoabdominal)</td>
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<tr>
<td><strong>Ancillary tests</strong></td>
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<tr>
<td>Duplex of iliofemoral arteries</td>
</tr>
<tr>
<td>Chest X ray</td>
</tr>
<tr>
<td>Pulmonary function test</td>
</tr>
<tr>
<td>Neurologic exam, CT scan of brain</td>
</tr>
<tr>
<td>Evaluation of renal impairment</td>
</tr>
<tr>
<td>Assessment of quality of life</td>
</tr>
<tr>
<td><strong>Estimation of operative risk</strong></td>
</tr>
<tr>
<td>EuroScore</td>
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<tr>
<td>STS Score</td>
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and aortography and ancillary tests indicated in certain circumstances and according to the patient history like, for example, a neurological exam including a CT scan of the brain in patients with prior stroke (Table 42.1). Echocardiography allows the exclusion of different contraindications for TAVI-like left ventricular thrombus, severe mitral regurgitation, severe left ventricular hypertrophy, and subvalvular stenosis. A severely depressed left ventricular systolic function represents a high-risk condition and indicates the need for a hemodynamic assist (e.g., TandemHeart or ECMO) during the procedure or a contraindication for an intervention. The invasive evaluation embodies the most important part of the screening assessing valve area, cardiac output, pulmonary artery pressure, and pulmonary and systemic vascular resistance by hemodynamic measurements. Furthermore, the retrograde passage of the calcified valve is attempted, and concomitant coronary artery disease may be treated with percutaneous coronary intervention during the screening procedure. Aortography provides a good image of the annulus-to-aorta angle and the angle of the aortic arch as well as the calcification of the large arteries. CT scan may further help to estimate the angulation of the annulus-to-aorta part and the degree of calcification of the valve, the aorta, and the peripheral vessels. Additional use of contrast identifies the lumen and tortuosity of the aorta and the great arteries and is nowadays mostly performed. It may preclude problems during the introduction of the devices. Detailed imaging of the route of implantation during catheterization may allow to omit the CT scan in certain condition but latter is currently mostly performed as a two-dimensional reconstruction of the aortic valve and root allows an exact measuring of the aortic annulus and the distance between insertion of valve leaflets and the coronary ostia as well as the dimensions of the sinus Valsalva and the ascending aorta (Fig. 42.3). Measuring the native aortic annulus can be performed by transthoracic (TTE), transesophageal echocardiography (TEE), CT scan, or supra-annular aortography. Personal experience shows that exact measurement is best achieved using either TEE or CT scan. Of note, the current two devices with CE mark, the CoreValve Revalving System (CRS) and the Edwards-SAPIEN valve (ESV), cover only about 90% of the observed diameters of the aortic annulus. The ESV may be used for a native annulus measuring between 18 and 25 mm and the CRS for an annulus diameter of 19 to 27 mm. A patient selection matrix provided by the companies was introduced in clinical practice and facilitate the screening of candidates (Fig. 42.4).

Apart from the screening of technical feasibility, the clinical part often turns out to be more challenging for the treating physician as the intended patient population is old of age and at high-risk for operative complications. Last but not least the general clinical condition and the accompanying frailty of the patient may turn the scale to turn down the candidate. Geriatric assessment tools need to be tested to better identify patients at high risk for postprocedural perturbation and prolonged rehabilitation.

**PATIENT SELECTION AND RISK ASSESSMENT**

The patient selection represents the most challenging part of the whole process from screening until TAVI. Risk assessment plays a crucial role and should consist of multidisciplinary consultation between cardiologists, cardiac surgeons, anesthesiologists, and other specialists previously involved in the treatment of the patient. The evaluation of the risk for TAVI is based on the estimation of the risk for conventional surgery. Different risk scores have been created and validated.
EuroScore (27), the STS-predicted risk mortality score (28), and the Ambler score (29) are among others of main interest. However, several limitations of these scores need to be kept in mind. The predictive value in high-risk patients is limited, as especially the EuroScore tends to overestimate the risk of mortality in patients with high-risk features (30). As high-risk patients represent a small part of the patient population included into the models for generating a score, the predictive ability of the scores is limited, last but not least because of a large heterogeneity of the patient characteristics.

The primary indication for TAVI were patients with severe (aortic valve area <1 cm² or <0.6 cm²/m²), symptomatic aortic stenosis who were refused for conventional surgery. Correspondingly, the initial studies with the ESV and the CRS included patients with contraindications for conventional open-heart surgery, like porcelain aorta, but also high-risk patients for surgery with a logistic EuroScore >20% or an STS Score >10%. For the 18 Fr CRS study patients with age ≥80 years irrespective of the risk calculation (31). After publication of the first clinical results showing procedural success rates of approximately 90% and after CE approval of the two devices, the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC) in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI) published in a position statement that TAVI should currently be restricted to patients at high-risk or with contraindications for surgery. They underscored the point that it is too premature to establish TAVI in patients who are good surgical candidates (32). The estimation of risk for surgery is based, therefore, not only on quantitative assessment of risk scores but also on clinical judgment. The formal indication criteria are depicted in Table 42.2.

### Table 42.2 Indications for TAVI.

- Severe symptomatic aortic stenosis (aortic valve area <1 cm² or <0.6 cm²/m² or a mean gradient >40 mmHg) and
- Contraindication for conventional surgery (e.g., previous chest radiation, porcelain aorta)

or
- Logistic EuroScore >20% or STS Score >10%

**Source:** From Ref. 32.

### DEVICES AND TECHNIQUE

#### Edwards-SAPIEN Valve

The Edwards-SAPIEN prosthesis (Edwards Lifesciences) (Fig. 42.5) is based on the prototype PVT prosthesis (Percutaneous Valve Technologies, Inc.) first described and clinically tested by Alain Cribier et al. in 2002 (20). The ESV consists of a tubular slotted stainless steel stent with an attached bovine pericardial trileaflet valve and fabric-sealing cuff. Two sizes are
available: the 23- and the 26-mm device. Immediately before implantation, the prosthetic stent valve is mechanically crimped onto a balloon catheter. The smaller prosthesis is intended to be expanded with a 22-mm diameter balloon to achieve a 23-mm external diameter; the larger prosthesis is intended to be expanded with a 25-mm balloon to achieve a 26-mm external diameter. The 23-mm valve is considered suitable for an annulus diameter of 18 to 22 mm and the 26 mm valve for an annulus diameter of 21 to 25 mm. In case of transfemoral access, a 22-Fr (23 mm device) or a 24-Fr (26 mm device) introducer sheath is needed. The prosthesis is then delivered using a steerable catheter, the FlexCath device (Fig. 42.6). In case of transapical approach, a 33-Fr introducer sheath is being used.

CoreValve Revalving Prosthesis
The CoreValve Revalving prosthesis (CoreValve), first described by Eberhard Grube et al. 2006 (21), consists of a trileaflet bioprosthetic porcine pericardial tissue valve, which is mounted and sutured in a self-expanding nitinol stent frame (Fig. 42.7). The prosthetic frame is manufactured by laser cutting of a nitinol metal tube with a length of 50 mm. The lower portion of the prosthesis has high radial force to expand and exclude the calcified leaflets and to avoid recoil. The middle portion is constrained to avoid the coronary arteries, while the upper portion is flared to center and fix the stent frame in the ascending aorta and to provide longitudinal stability and coaxial positioning. The pericardial valve is located in the transmission zone between the lower and the middle part, resulting in a supra-annular position compared to the native valve. The sizes of three subsequently developed delivery systems have been gradually reduced from 25 to 18 Fr over time to facilitate vascular access and deployment of the device (Figs. 42.8 and 42.9). The currently commercially available third-generation device (18F) is offered in two different sizes for different annulus dimensions: the small 26 mm prosthesis for aortic valve annulus sizes from 20 to 24 mm and the large 29 mm prosthesis for aortic valve annulus sizes from 24 to 27 mm. A comparison of device characteristics is depicted in Table 42.3.
Table 42.3 Comparison of Edwards-SAPIEN and CoreValve Device Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Edwards-SAPIEN</th>
<th>CoreValve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent material</td>
<td>Stainless steel</td>
<td>Nitinol</td>
</tr>
<tr>
<td>Valve material</td>
<td>Bovine pericardium</td>
<td>Porcine pericardium</td>
</tr>
<tr>
<td>Release mechanism</td>
<td>Balloon expansion</td>
<td>Self-expandable</td>
</tr>
<tr>
<td>Diameter of valve annulus</td>
<td>18–25 mm</td>
<td>19–27 mm</td>
</tr>
<tr>
<td>Sheath size</td>
<td>22, 24 Fr</td>
<td>18 Fr</td>
</tr>
<tr>
<td>Femoral artery diameter</td>
<td>≥8 mm</td>
<td>≥6 mm</td>
</tr>
<tr>
<td>Valve size</td>
<td>23, 26 mm</td>
<td>23, 27 mm</td>
</tr>
<tr>
<td>Worldwide number of implantations</td>
<td>≥3500</td>
<td>≥3500</td>
</tr>
<tr>
<td>Transapical application</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Transaxillary application</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CE certification</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FDA approval</td>
<td>No</td>
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Rapid pacing by a provisional pacemaker in the right ventricle helps avoiding a dislocation of the balloon into the ventricle and minimizes the risk of wire-induced perforation of the ventricle. After dilatation of the native valve, the bioprosthesis is inserted, directed around the aortic arch (using the Retroflex catheter with the Edwards system) and deployed under fluoroscopic guidance and repeated dye injections. An effective rapid pacing with drop of systolic blood pressure down to 40 mmHg is only mandatory for the deployment of the ESV (33) but not for the CRS. Functional assessment of the bioprosthesis is assessed by simultaneous measurement of pressures in the ascending aorta and the left ventricle. Aortic regurgitation is evaluated primarily by aortography and eventually further assessed by TEE to discriminate between transvalvular and paravalvular regurgitation.

Routes of Implantation

**Antegrade Approaches**

The *transfemoral* antegrade approach using a femoral vein with trans-septal puncture has been primarily used in the early beginning of transcatheter aortic valve replacement (20). After standard trans-septal catheterization, a straight 0.035-in. guidewire was advanced across the stenotic aortic valve through a balloon flotation catheter. After advancement of the balloon catheter into the descending aorta, the guidewire was exchanged for a stiff long guidewire, which was snared from the left femoral arterial access site to create a loop for optimal device deployment support when advancing the device antegrade. Additional septal dilation was usually necessary to bring the prosthesis through the intra-atrial septum. Because of the complexity as well as the higher complication rate compared to the retrograde access, the transfemoral antegrade approach has been almost completely abandoned. Potential interferences with the mitral valve apparatus during the procedure were some of the specific severe complications leading to hemodynamic instability in some cases reported by Cribier et al. (34).

The *transapical* antegrade approach is a popular surgical approach for transcatheter aortic valve implantations. This technique has been described first for the balloon-expandable valve prosthesis (Cribier-Edwards) in 2006 by Lichtenstein et al. (22). The technique requires an anterolateral minithoracotomy, pericardiotomy, and then puncture of the apex of the left ventricle using a needle through purse-string sutures. Today, this technique is evolving to a new standard surgical procedure particularly for patients considered for catheter-based valve implantation but unfavorable peripheral arteries. However, the usage of transapical versus truly percutaneous transfemoral approaches is significantly varying among heart centers, depending on operator experiences and local politics. Being more invasive than a transfemoral approach, the transapical access is a valuable route for patients with inappropriate peripheral access. Cardiopulmonary bypass should be on standby in patients in whom surgical conversion is an option in case of complications.

Given the particular deployment characteristics, only the Edwards balloon-expandable valve prosthesis has currently the option for antegrade insertion.

**Retrograde Approaches**

The retrograde approach is presently the most popular way for TAVI. Various arterial access sites are iliac, femoral, or subclavian access.

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**Procedural Points**

TAVI is performed either under local anesthesia and mild sedation in case of a pure transcatheter, retrograde approach using suture devices or under general anesthesia in case of a transapical approach or surgical cut-down. Prophylactic use of antibiotics and the use of unfractionated heparin (targeted ACT: 200–250 seconds) are standard of care. The access for the large sheath is mostly gained from the right groin as the right iliofemoral axis is often less tortuous. From the left common femoral artery a pigtail is advanced to the descending aorta followed by angiographic visualization of the right iliofemoral axis before puncture. In the following, the pigtail is used to mark the level of the native annulus. Repeated injections of dye help to evaluate the degree of aortic regurgitation during and after the deployment of the prosthesis. After introducing a closure device and a 9-Fr sheath over a regular wire, the native, stenotic valve is usually passed retrogradely with a straight wire directed by an Amplatz left 1 catheter. An extra-stiff wire (e.g., Amplatz extra or superstiff short tip), preshaped manually like a pigtail, is then carefully placed into the left ventricle. The large 18 Fr (CoreValve) or 22 Fr/24 Fr sheath (Edwards) is then inserted over the stiff wire followed by the balloon valvuloplasty (e.g., with a Nucleus or a Tyshak II balloon).
Table 42.4 Advantages and Disadvantages of Antegrade and Retrograde Approaches

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Transfemoral antegrade</th>
<th>Transapical antegrade</th>
<th>Transfemoral retrograde</th>
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<tbody>
<tr>
<td>• No large arterial access needed, less arterial complications</td>
<td>• Direct access with antegrade crossing</td>
<td>• Ease of technique</td>
<td></td>
</tr>
<tr>
<td>• No need for surgical preparations</td>
<td>• Independent of peripheral vessel status</td>
<td>• No interference with other cardiac structures as opposed to the transfemoral antegrade technique</td>
<td></td>
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<tr>
<td>• Antegrade crossing of the aortic valve is potentially less prone to cause embolizations</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Technically more challenging (longer route, trans-septal puncture)</td>
<td>Invasive surgical technique</td>
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<td></td>
<td></td>
<td>Requires general anesthesia</td>
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<td></td>
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<td>Large arterial access needed</td>
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<td></td>
<td></td>
<td>Retrograde aortic valve crossing</td>
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</tbody>
</table>

Disadvantages

| • Technical more challenging (longer route, trans-septal puncture) | • Invasive surgical technique | • Large arterial access needed |
| • Interference with mitral valve | • Requires general anesthesia | • Retrograde aortic valve crossing |

First transcatheter retrograde device implantations described by Webb et al. (Cribier-Edwards prosthesis) (35) and our group (CRS) (36) have been performed via the iliac access given the profile size of the early device prototypes. After surgical cut-down and subsequent wire placement into the left ventricle, the devices are advanced retrogradely through the native aortic valve and then implanted. Retrograde crossing of heavily calcified aortic valves may occasionally be problematic, but technical developments with lower device profiles as well as steerable catheters facilitated this procedural part remarkably. The progressive device size reduction over the past five years led to the truly percutaneous access in the common femoral artery. Reliable access site closure is usually achievable using a Prostar XL suture device (Abbott Vascular, Abbott Park, Illinois, U.S.) or multiple “closure” suture devices that are preloaded at the beginning of the procedure. Fluoroscopic guidance should be mandatory for correct puncture; echo guidance might be helpful as well.

The subclavian access has been first described by our group as an alternative route for patients with diseased iliaca/femoral arteries (31,36,37). Access can be obtained after surgical cut-down either directly or after placement of a graft trunk onto the subclavian artery to both avoid access dissections and facilitate final closure. Because of the higher technical complexity as well as the need for surgical preparations, this approach should be considered a backup technique in case that standard alternative insertion sites are inaccessible.

The direct surgical aortic access with thoracotomy and retrograde catheter-based implantation of a valve prosthesis is a new technique just recently tested by cardiac surgeons. As compared to standard surgical aortic valve replacements, there is no need of suture fixation of the prosthesis when using one of the catheter-based balloon-expandable or self-expanding devices. However, this technique is still in its infancy. The advantages and disadvantages of antegrade and retrograde approaches are depicted in Table 42.4.

**CLINICAL ASPECTS AND OUTCOME**

The technology of transcatheter aortic valve implantation has significantly improved with the development of delivery catheters with smaller profiles and better prostheses with various size options. Together with increasing operator experience, these progresses are reflected in the improved clinical outcome observed over the past few years. Today, more than 4000 patients have been treated with one of these two CE-approved devices with almost exponentially increasing numbers particularly in the last 18 months. However, scientific outcome reports are still limited, mainly originating from few leading high volume centers. Given the initial study enrollment criteria as well as the present conventional treatment practice recommending surgery as the gold standard, patients are mostly above 80 years old and considered high risk or with contraindications for surgical valve replacement.

**Procedural Success and Clinical Outcome**

The procedural success rate increased remarkably over the past two to four years with rates between 90% and 99% in experienced hands (Tables 42.5 and 42.6) (38) Mortality at 30-day follow-up is between 6% and 15%, procedural myocardial infarction rate 0.7% and 16%, procedural stroke rate 1.4% and 9% with current devices (Tables 42.5 and 42.6). Direct coronary obstruction is rare (<1%) and is only reported for the Edwards valve. Permanent pacemakers due to significant postprocedural atrioventricular conduction disturbances are needed in up to 20% of patients (39,40). It is currently unknown if results are affected by the device itself, but according to the first reports, periprocedural myocardial infarction—although relatively rare—is observed more frequently with the ESV than with the CoreValve.

**Table 42.5 Edwards Short-Term Clinical Outcome**

<table>
<thead>
<tr>
<th></th>
<th>REVIVE II</th>
<th>REVIVAL II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural success rate (%)</td>
<td>88.0</td>
<td>87.3</td>
</tr>
<tr>
<td>30-Day all mortality (%)</td>
<td>13.2</td>
<td>7.3</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>8.5</td>
<td>16.3</td>
</tr>
<tr>
<td>Neurologic events (%)</td>
<td>2.8</td>
<td>9.0</td>
</tr>
</tbody>
</table>

**Table 42.6 CoreValve Short-Term Clinical Outcome**

<table>
<thead>
<tr>
<th></th>
<th>21 Fr S&amp;E study</th>
<th>18 Fr S&amp;E study</th>
<th>18 Fr EE registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural success rate (%)</td>
<td>90.4</td>
<td>94.4</td>
<td>98.2</td>
</tr>
<tr>
<td>30-Day all mortality (%)</td>
<td>15.4</td>
<td>14.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Cardiac deaths (%)</td>
<td>7.7</td>
<td>11.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>3.8</td>
<td>3.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Pacemaker (%)</td>
<td>17.3</td>
<td>25.8</td>
<td>12.2</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>17.3</td>
<td>6.5</td>
<td>1.4</td>
</tr>
<tr>
<td>TIA (%)</td>
<td>0.0</td>
<td>5.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**Abbreviations:** S&E, Safety and efficacy evaluation; EE, extended evaluation.

**Source:** From Ref. 51.
CRS. On the other hand, the CRS is associated with a larger need for permanent pacemaker implantation. To address these adverse effects in detail, more data and eventually randomized trials are warranted.

Patients with successful implantation procedures and uneventful 30-day follow-up improve clinically and benefit durably from the procedure as expressed in the NYHA grade comparisons (Figs. 42.10 and 42.11) as well as the survival curves (Figs. 42.12 and 42.13). Immediate or late embolization of a valve prosthesis is also rare, reported only for the Edwards device (41).

**Echocardiographic Outcome**

As seen in all published series, the hemodynamic status improves immediately after successful device implantations with a reduction of the mean transvalvular gradient to around 10 mmHg with a mean neo-orifice area of 1.5 to 1.8 cm² (Figs. 42.14 and 42.15). Paravalvular aortic regurgitation, mostly mild or mild to moderate, is observed in around 70% of patients and partially related to focal excessive load of calcifications (Figs. 42.16 and 42.17) that prohibits optimal device expansion with complete paravalvular sealing. However, severe regurgitations are rare given the improved screening process (matching dimensions of annulus and prosthesis) as well as various procedural techniques and strategies to deal with high-degree regurgitations occurring immediately after device deployment. In long-term follow-up, serial echocardiographic studies have consistently shown good prosthetic valve function with no structural deterioration of valve tissue (38, 42, 43).
Outcome for Transapical Technique
More than 400 patients with significant aortic valve stenosis have presently been treated by transapical aortic valve implantation. Reports are available only for the ESV from two experienced centers (22,44,45). Further data of the TRAVERCE study (Fig. 42.18), the SOURCE registry, and the PARTNER EU registry were presented at TCT 2008. Implantation success rate was about 90%. The majority of patients is being done off pump, and the rate of perioperative conversion is 9% to 12%. Mortality rates range from 9% to 18%. Strokes occur in about 0% to 6%. Nonrandomized comparison of transapical and transfemoral approaches from the SOURCE and the PARTNER EU trial indicate a higher mortality rate for the transapical approach in selective patients with higher estimated risk than patients undergoing retrograde TAVI. Randomized studies are needed to finally assess superiority of one technique over the other.
LIMITATIONS
Several limitations with regard to percutaneous treatment of aortic stenosis need to be addressed.

- First, the simple approach of balloon valvuloplasty has failed showing significant improvement of clinical symptoms and increasing the valve area in the midterm follow-up. In addition, a considerable rate of complications were associated with the procedure leading to abandoning this method (17,46).
- Second, degenerative, former senile, aortic stenosis represents currently the only considerable indication of TAVI in a selective, high-risk patient population. Aortic insufficiency embodies another potential target for the use of transcatheter bioprosthesis. However, an only mildly calcified native valve may hinder a sufficient anchoring of the prosthesis and moreover the often-associated dilatation of the ascending aorta might contraindicate the sole treatment of the valve problem. Nevertheless, in patients with prior surgical valve replacement (biological valve), TAVI appears to emerge as valuable treatment option.
- Third, vascular access limits the use of transcatheter-based devices in a substantial number of patients. Further technical improvements are required to provide smaller sheaths and to reduce the associated risk of peripheral
vascular complications. Latter have been reported with an incidence ranging from 2% to 15% remaining a substantial cause of morbidity and mortality (31,34–36,38,40,47). Recent data reveal however that an operator learning curve and the use of smaller sheaths as well as a more detailed screening help reducing this type of complication (38).

- Forth, myocardial infarction is rarely associated with TAVI and occurs only in cases of misplacement of the valve.
- Fifth, major cerebrovascular events occur in 2% to 4% (40,43) and maybe related with balloon dilatation, passing of the aortic arch with the device or a hemodynamic compromise during valve placement. Indirect comparison with surgical data shown comparable event rates (9), but further technical developments need to address this procedure-related limitation of TAVI.
- Sixth, mild-moderate aortic regurgitation is observed in up to 50% of the treated patient populations, but severe, clinically relevant insufficiency remains rare in case of correct matching of the prosthesis with the size of the aortic annulus as well as in case of correct positioning.
- Seventh, the need of a permanent pacemaker implantation after TAVI is reported in up to 20% of the cases. CRS seems to induce more frequently atioventricular disturbances, probably due to the sustained radial force of the Nitinol frame and an interference with the subvalvular, closely situated conduction system.
- Eighth, embolization of the device is very rare (<1%). It is related either with a mismatch of the diameters (device—annulus) or with a misplacement of the bioprosthesis during deployment. The CRS provides the possibility retrieving the not completely deployed valve into the sheath. After reloading into the delivery catheter, the same bioprosthesis can be positioned again.
- Ninth, severe bleeding is caused either by vascular access complication or by vessel dissection/perforation induced by the sheaths. Careful screening of implantation routes

and operator experience markedly reduces this type of complication. Cardiac tamponade provoked by wire perforation is rare (~1%) and associated with the presently inevitable use of a stiff wire for the placement of the currently used devices. Patients with prior large myocardial infarction or chronic steroid treatment maybe at higher risk for this complication.

SPECIAL ISSUES AND FUTURE DEVELOPMENTS

There are multiple new concepts under scientific as well as clinical evaluation designed to provide new features overcoming some of the shortcomings of the first-generation techniques. Only two already clinically tested devices are mentioned in the following:

The SADRA Lotus valve, for example, is a self-expanding device providing the ability of correcting and repositioning the valve prosthesis before releasing and permanently seating the device. The user is able to verify functionality and anchoring properties as well as the position of the device in relationship to the coronary arteries, the native aortic valve, and the mitral apparatus before final implantation (48) (Fig. 42.19). As opposed to the “one-shot” release of the balloon-expandable techniques, this technology of repositioning aims to offer a more controlled way of device deployment. Once the device is in correct position, a locking mechanism stabilizes the system. In addition, to avoid a paravalvular leak, a sealing membrane is attached to the outside of the prosthesis filling out paravalvular gaps. The fist-in-man study using the SADRA Lotus valve is currently ongoing.

The DirectFlow valve is another new concept that is repositionable and retrievable at all time points during the procedure (49). The device consists of a stentless tissue valve with bovine pericardial leaflets, which are located within an expandable nonmetallic framework. Results of the presently ongoing first-in-man study are shortly available.

The indication for TAVI is currently limited to a selective, high-risk patient population with severe, symptomatic aortic stenosis but further possible indications have already been tested clinically or by compassionate use. The use of TAVI for the indication of a stenotic or insufficient degenerated bioprosthesis appears very attractive. Two major arguments favor TAVI over conventional cardiac reoperation. Latter is complicated by resternotomy and the positioning of the new valve is facilitated by clear visualization of the annulus. The CRS (50) as well as the
ESV have already been successfully used for the treatment of degenerated bioprosthesis with severe regurgitation (Fig. 42.20). The use of TAVI for this indication is limited by the inner diameter of the previously implanted valve and a potential infectious etiology of the degeneration of the valve that needs to be ruled out before intervention. Aortic regurgitation represents another possible indication for TAVI but is limited by the usually mild calcification of the valve and the often associated dilated ascending aorta.

CONCLUSIONS

Transcatheter aortic valve replacement represents an innovative, rapidly evolving technique with already proven feasibility in a selective patient population. The high technical success rate up to 99% is related to an improved screening process, advanced device properties like a reduced profile size in comparison with the initial generation as well as improved operator skills and the interdisciplinary team. In experienced hands, the procedure may be performed under local anesthesia, in less than an hour without hemodynamic or surgical support. Furthermore, the present experience demonstrates the large potential of this technique currently revolutionizing the treatment practice for patients with significant aortic valve disease. Today, surgical valve replacement is still standard of care, but less invasive transcatheter methods are prone to challenge this standard in the future. A prerequisite is, however, that the encouraging clinical results are confirmed in larger patient populations, and further progress of the technology is achieved. Moreover, valve durability needs to be clinically proven and further achievements with respect to in positioning and repositioning as well as with regard to embolic protection are warranted to improve the procedural safety. Last but not least, head-to-head comparisons between surgery and TAVI in different patient subsets will help us to discriminate the best therapeutic option in the future.


Percutaneous therapies for mitral valve disease

Ryan D. Christofferson, Patrick L. Whitlow, E. Murat Tuzcu, and Samir R. Kapadia

INTRODUCTION
The prevalence of mitral valve disease, especially mitral regurgitation (MR), is increasing. Despite significant gains in the eradication of rheumatic fever, rheumatic mitral stenosis (MS) remains a significant problem in underdeveloped countries. In addition to the increased incidence of degenerative mitral valve disease due to the aging population, the growing congestive heart failure epidemic has led to further increase in the proportion of patients with severe MR. The emergence of new percutaneous technologies for mitral valve disease has generated great interest in the interventional community. Although percutaneous balloon mitral valvuloplasty (BMV) is a well-established technique, the skill set necessary for this procedure remains critical to the well-rounded structural heart disease interventionalist. This chapter reviews the indications and techniques for percutaneous therapies for mitral valve disease.

PERCUTANEOUS TREATMENT OF MITRAL STENOSIS
Fundamentals and Anatomic Considerations

Etiology
The most common cause of MS is rheumatic heart disease. Less commonly, congenital MS may be detected in children. Rarely, MS is a result of collagen vascular disease, mucopolysaccharidoses, amyloid deposits, or is drug-induced. In rheumatic mitral valve disease, fusion of the mitral valve apparatus may occur in the commissures, the cusps, or the chordae tendineae. While the majority of patients have a combination of the above, 30% of patients have isolated commissural thickening, 15% have thickening of the cusps only, and 10% have only chordal thickening. Generally, the mitral cusps thicken at the edges and fuse at the commissures, while the chordae thicken, shorten, and fuse. This leads to a funnel-shaped valve with reduced leaflet mobility and a fish-mouth shaped orifice (Fig. 43.1). If the commissures are predominantly involved, this leads mainly to MS. Isolated thickening and shortening of the chordae results mainly in MR; however, if the cusps are thickened and adherent, they cannot adequately open or close, a combination of MS and regurgitation occurs.

Pathophysiology and Diagnosis
Clinical manifestations of MS are caused by increased left atrial pressure (shortness of breath), atrial fibrillation (thromboembolism), or increased pulmonary pressures (fatigue). The presence of symptoms is the most important indication for intervention. Gradients or size of mitral valve should not be used to time intervention in asymptomatic patients with normal pulmonary artery (PA) pressures. Exercise echocardiography at times is very useful to document functional status and hemodynamic changes with exercise.

Echocardiography is the cornerstone for diagnosis. Transthoracic echocardiography (TTE) is most useful to image the subvalvular apparatus. Transesophageal echocardiography (TEE), especially with 3-D reconstruction, is very helpful to identify commissural fusion. However, in good proportion of patients TTE provides adequate information in this respect. If the severity of MR is unclear, TEE is very helpful. The mitral valve splitability score (1) is the most common method of assessment for suitability for BMV, although there are other validated methods (2,3).

Indications
Symptomatic Mitral Stenosis: ACC/AHA Guidelines
According to the American College of Cardiology and American Heart Association (ACC/AHA) guidelines, class I indication for mitral valvuloplasty is the symptomatic patient with MS with favorable anatomy for BMV. Asymptomatic patients with pulmonary hypertension have class IIa and atrial fibrillation with favorable anatomy has Class IIb indication. It is not appropriate to perform BMV in patients with nonrheumatic mitral valve disease and patients with prosthetic mitral valve stenosis.

Surgical Mitral Valve Replacement Vs. Percutaneous Balloon Mitral Valvuloplasty
Surgical options for MS include close commissurotomy, open commissurotomy and mitral valve replacement. Close commissurotomy skills are not available in the United States because this procedure is rarely indicated or performed (4). In developing countries where BMV may be more expensive than surgery, close commissurotomy can be considered for economic reasons if surgical expertise is available. Open commissurotomy is rarely indicated because if the valve is suitable for this procedure, it is suitable for BMV. The outcomes of BMV are very comparable to surgical procedures even in randomized trials and with long follow-ups (Fig. 43.2) (5). Valve replacement is reserved for patients who need mitral valve intervention but are not candidates for BMV or BMV has failed.

Procedure
In the current era, BMV is exclusively performed using Inoue Balloon (Toray International America, Inc., Houston, Texas, U.S.) in the United States and most of the world (Fig. 43.3). Although BMV can be performed with double balloons, this method is rarely used (6,7). A special metal dilator, the Cribier’s dilator, has been used to reduce costs but because of technical challenges and a potential safety issue, it did not gain widespread acceptance (8).

Patient selection is the most critical step in the success of the procedure. Patients with asymmetric commissural calcification, severe subvalvular scarring, significant MR, and
significant tricuspid regurgitation are not ideal candidates for BMV. TEE is very helpful at the time of the procedure to make sure there is no left atrial clot and to assess the mechanism as well as severity of MR after each balloon inflation. Online assessment of MR and commissures with 3-D TEE helps to optimize BMV, and hence helps to improve procedural outcomes. Further, TEE can also help in making transseptal puncture safer.

It is standard procedure to perform BMV under the guidance of invasive hemodynamic monitoring, requiring two pressure transducers for simultaneous measurement of left atrial and left ventricular pressure. In addition, it is useful to monitor PA pressure and cardiac output during the procedure. Therefore, it is necessary to have venous access in two locations and arterial access. The most straightforward configuration to begin the procedure includes an 8-Fr short venous sheath in the left groin, a 4-Fr arterial sheath in the left groin, and an 8-Fr short venous sheath in the right groin.

The left groin arterial sheath is used to perform diagnostic cardiac catheterization, if necessary, and to allow placement of a pigtail catheter into the noncoronary sinus. The pigtail catheter is useful in this position as a landmark to guide the transseptal puncture. If necessary for anatomic assessment prior to transseptal puncture, the left groin venous sheath can be used to introduce an NIH or pigtail catheter into the right atrium at the junction with the superior vena cava (SV). A power injection at this location will opacify the right atrium and pulmonary vasculature during the dextro phase, followed by the pulmonary veins and left atrium (LA) during the levo phase. A PA catheter is always placed for PA pressure monitoring and assessment of cardiac output. The wedge position can be used to evaluate left atrial pressure and monitor for ventricular wave (V wave).

An 8-Fr Mullins (Medtronic, Inc., Minneapolis, Minnesota, U.S.) sheath is advanced to the SVC over the wire and then the wire is exchanged for the Brockenbrough needle (Medtronic, Inc., Minneapolis, Minnesota, U.S.). The sheath, dilator, and needle are slowly brought down with some clockwise rotation. Three drops are typically felt when the system crosses from SVC to right atrium, limbus, and aorta. The location is confirmed by
anteposterior (AP) and lateral views to see the needle on the right border of spine in AP view and facing posteriorly away from the aorta in the lateral view just below the level of non-coronary cusp. If there is good tactile pulsation of the LA, the needle is advanced across the septum, with the hemodynamic tracing showing a change from a right atrial waveform to a left atrial waveform without any loss of pressure. If there is a sudden drop in pressure during transit, this may indicate the needle has passed through the pericardial space, and should be withdrawn and pericardium should be carefully investigated. If the passage is clean, the Mullins sheath can be advanced into the LA, and the dilator removed. Once the appropriate position of the sheath is confirmed, heparin (70 U/kg) may be administered. Following introduction of a coiled floppy Torray wire, the Mullins sheath is removed and the septum is dilated for one minute with a long 11-Fr dilator.

Inoue balloon is sized according to height of the patient. A 26-mm balloon is used for patients up to 170 cm, 28-mm balloon for patients 170 to 180 cm, and 30-mm balloon for patients taller than 180 cm. Gradual dilatation with 1- to 2-mm increment should be used. Careful assessment of hemodynamics (LA pressure, gradient, V wave, PA pressure), and TEE assessment of valve (MS and MS) help one to decide how far to push. Commisural MR indicates that commissural splitting has been achieved. Sometimes ventriculogram can help if the severity of MR remains questionable after TEE interrogation.

Clinical Aspects
The most important predictor of long-term success of BMV is the procedural result. If MVA after the procedure is >1.6 cm², the long-term outcome is excellent (9–11). Some predictors of poor outcome include age, atrial fibrillation, and valvular anatomy (10–15). If the BMV is successful, PA and LA pressure will decrease immediately and cardiac output will improve. Patients also feel an immediate difference in their exercise tolerance.

Adequate control of heart rate and diuretic therapy are the cornerstones of medical management. It is also worthwhile to try and maintain sinus rhythm. Antiarrhythmic medications like flecaïnide or sotalol can be very useful in these patients. Anticoagulation is imperative in patients with a history of thromboembolism or atrial fibrillation. In patients taller than 180 cm. Gradual dilatation with 1- to 2-mm increment should be used. Careful assessment of hemodynamics (LA pressure, gradient, V wave, PA pressure), and TEE assessment of valve (MS and MS) help one to decide how far to push. Commisural MR indicates that commissural splitting has been achieved. Sometimes ventriculogram can help if the severity of MR remains questionable after TEE interrogation.

Limitations
Patients with mixed MS and MR need mitral valve replacement and cannot be treated with BMV. Severe MR following BMV is typically from flail mitral leaflet and usually requires surgery. Emergent surgery is rare but should be available because BMV is usually performed in very young patients with otherwise excellent prognosis even with emergent surgery. Restenosis after BMV is 10% to 30% at five years depending on the initial results (16). A repeat procedure can be attempted depending on the cause of restenosis or failure of the first procedure.

Conclusions
BMV is the treatment of choice for patients with severe symptomatic MS with favorable anatomy for the procedure. Procedural success determines long-term outcomes. Careful monitoring with TEE, fluoroscopy, and hemodynamics during the procedure makes this technique safe and effective.

PERCUTANEOUS TREATMENT OF MITRAL REGURGITATION

Introduction
Significant morbidity and mortality can be attributed to MR. This is true for patients with degenerative valve disease, as well as the growing population of patients with functional MR. Although surgical repair of MR has been shown to be superior to valve replacement, a significant number of patients currently still undergo valve replacement. Percutaneous repair of the mitral valve is under investigation with the potential to provide decreased morbidity, improved recovery time, and shorter hospital stays compared with open-heart surgery. These percutaneous techniques are predominantly based on existing surgical strategies, and each technique provides a different advantage based on the anatomical and functional characteristics of the MR. Proper patient selection will ultimately determine the success of these emerging technologies. In addition, imaging technologies in and outside of the catheterization laboratory and integration of multiple imaging modalities will be important for safety and efficacy of these percutaneous technologies. Finally, evaluation of MR devices will be challenging as they will be compared with traditional surgical techniques, which may have different goals in patient management (e.g., need for repeat procedures, residual MR). These devices may possibly have a complimentary role to surgery in the future.

Fundamentals and Anatomic Considerations for Percutaneous Repair

Mitril Regurgitation; Etiology, Diagnosis
Normal mitral valve closure depends on the appropriate anatomy and function of each component of the mitral valve, including the annulus, the anterior and posterior leaflets, the chordate tendineae and papillary muscles (17). Primary mitral valve disease refers to myxomatous degeneration of the leaflets and chordae, resulting in chordal elongation or rupture, flail leaflet, or mitral valve prolapse. This is known as degenerative MR. Secondary valve disease (functional MR) is caused by disruption of the structural arrangement of the mitral apparatus, most commonly resulting from dilated cardiomyopathy, leading to ventricular dilatation, mitral annular dilation, and altered papillary muscle-leaflet interaction. Moreover, ischemic cardiac disease may be associated with papillary muscle dysfunction or rupture, sometimes referred to as ischemic MR. In this condition, changes in left ventricular geometry lead to leaflet “tenting” and anterior leaflet override, which prevents proper coaptation (Fig. 43.4) (18,19).

In addition to the above categorization based on etiology and mechanism, a morphologic classification proposed by Carpenter (43.5) (20) groups the mechanism of regurgitation according to leaflet pathophysiology. This simplification has utility in terms of surgical and percutaneous approach, as the goal of therapy may be to restore normal leaflet function, but not necessarily normal valve anatomy.

Various methods exist for quantification of MR but echocardiography is considered the gold standard. Direct measures including regurgitant orifice area, regurgitant flow, or diameter of vena contracta constitute the major quantitative parameters used in clinical trials. However, MR severity is judged after taking into account many other secondary effects like size and...
function of LA and left ventricle (LV), blunting of the pulmonary venous flow, serial changes in all these parameters over time, and loading conditions. Further, postprocedural MR is even harder to quantify at times because of anatomical distortion of the valve from various procedures which may lead to very eccentric jets (e.g., after edge-to-edge repair).

**General Indications for Invasive Treatment of Mitral Regurgitation**

In accord with guidelines released by the ACC/AHA, any patient with symptomatic chronic severe MR should undergo valve surgery (21). When the patient is asymptomatic, the development of LV dysfunction (ejection fraction <60%) or dilation (end-systolic dimension ≥40 mm) indicates the need for surgical intervention. In surgical centers that are experienced in mitral repair, surgery can be considered in asymptomatic patients with less dilated LV and preserved systolic function, if repair is feasible. The development of atrial fibrillation or pulmonary hypertension in an asymptomatic patient can also be an indication for surgery. Among patients with primary valve disease and severe LV dilation or dysfunction, the role of surgery is controversial. In case of valve dysfunction secondary to LV dysfunction (functional MR), repair may be considered after medical optimization and cardiac resynchronization, if indicated. There are several caveats to these general guidelines and individualization of therapy is critical after considering functional status, anatomy of the mitral apparatus, LV function, and risk of surgery.

Although no guidelines exist for determining the optimal utilization of percutaneous techniques, the surgical guidelines can serve as a template for the patient populations thought to be most likely to benefit from percutaneous repair. The indications for percutaneous techniques, however, will likely differ from surgical indications given the nature of each approach and the possibility for early, less invasive intervention before development of sequelae such as LV dysfunction.
Surgical Considerations

Reviewing the surgical approaches to mitral valve repair is useful because the majority of percutaneous repair techniques attempt to mimic established surgical techniques. Therefore, an understanding of the surgical approaches with their respective results and limitations is necessary to understand and evaluate emerging percutaneous techniques.

The most common methods of surgical repair are based on restricting the mobility of the posterior leaflet (and at times prolapsing anterior leaflet) and reducing the size of annulus to achieve proper coaptation of leaflets. Therefore, these techniques address the leaflets and annulus at the same time. Annuloplasty is typically performed using a ring, although the choice of rings depending on the shape, stiffness, and extent of annular coverage remains controversial (22–24). The classic leaflet repair techniques include triangular resection, quadrangular resection, sliding annuloplasty, or edge-to-edge repair. Although techniques of annuloplasty and leaflet repair are usually combined when treating degenerative valve disease, isolated ring annuloplasty without leaflet repair is the dominant strategy for functional and ischemic MR (25,26).

Annuloplasty for functional MR results in improvement in NYHA class, favorable LV remodeling, and decreased admissions for heart failure, but has failed to demonstrate a mortality benefit (27). This may be in part due to the high recurrence rate of MR after isolated annuloplasty (28). The combination of annuloplasty and leaflet repair (Carpentier’s technique) for degenerative MR has shown the most favorable results in terms of mortality and recurrent MR. In experienced centers, Carpentier’s technique has provided results that are better than with mitral valve replacement (29) and has resulted in a mortality rate similar to that of the general population (86–93% survival at five years) (29–32). The recurrence rate of severe MR (grade 3+ or 4+) after repair is 3.7% per year (32).

Classes of Percutaneous Mitral Valve Repair Devices

As a result of the variable anatomy and etiology of MR, a number of different approaches have been developed for percutaneous repair of magnetic resonance (Table 43.1). The goal of each approach is to bring the leaflets together to improve coaptation. The most advanced approach to date is edge-to-edge leaflet repair, based loosely on the surgical repair championed by Dr. Alfieri. Another approach takes advantage of the proximity of the coronary sinus (CS) to the mitral annulus to create favorable geometric changes in the annulus, moving the posterior leaflet closer to the anterior leaflet, improving coaptation. This approach is termed indirect annuloplasty or CS reshaping. Additionally, there are devices under investigation that perform a direct annular repair by plication from the left ventricular chamber. Other devices take a more direct approach to the annulus by applying suture-based plication systems. Cardiac chamber reshaping has been explored as a means to bring the leaflets into coaptation by decreasing the septal-to-lateral (SL) dimension of the ventricle or atrium. Finally, an early effort is underway to develop percutaneous valve replacement. The devices selected for review are those with some clinical or early clinical data, although many other devices and approaches in development are not mentioned in this chapter.

Clinical and Anatomic (Imaging) Screening for Each Class of Device

The dominant imaging modality for assessment of MR is echocardiography. Two-dimensional echocardiography is useful to evaluate valvular structure, the presence of calcification, leaflet tethering, flail leaflet, or wall motion abnormalities. The severity of the regurgitation can be accurately quantified, as well as the specific hemodynamic consequences of the regurgitation. In most cases, a combination of clinical information and echocardiographic data will establish the etiology of MR and the particular anatomy of the mitral valve, which is important in assessing candidacy for surgical or percutaneous intervention. TEE can be used to supplement the evaluation, often allowing greater definition of mitral valve structures and regurgitation severity. This can be particularly useful to determine if edge-to-edge valve repair is feasible, as valve anatomy such as coaptation depth and annulus size can be critical to chip feasibility.

Other imaging modalities including cardiac computed tomography (CT) (33), cardiac magnetic resonance (34), and 3-D echocardiography (35) may be useful to determine which patient and which device is appropriate. In particular, indirect annuloplasty via the CS relies on proximity of the CS to the valve annulus. Cardiac CT is particularly well suited to assess for this anatomical relationship, as well as proximity to the left circumflex artery, where such devices have the potential to cause ischemia. With cardiac MR it is possible to obtain significant structural information regarding the geometry of the LV, mitral annulus and leaflets, and quantitative regurgitant volumes (34). Finally, 3-D echocardiography may become important in assessing valve characteristics and geometry, in addition to the possibility of providing “real-time” guidance of percutaneous valve interventions, an application limited by current technological capabilities.

Clinical Aspects

Percutaneous valve repair technology shows promise for reducing the morbidity and mortality associated with traditional invasive surgical repair. The success of these techniques is dependent on proper selection of patients according to the clinical presentation and the anatomy along with appropriate imaging of the valve before and at the time of procedure. The major advantage of a percutaneous approach, beyond its less invasive nature, is the ability to perform procedures in a beating heart, which allows immediate evaluation of the results. If percutaneous technologies can be made simple, relatively fail-safe, and preserve surgical options, they represent the future of
valve intervention. Proper training of the interventionalists not only in device manipulation but also in patient selection, imaging techniques, and catheter skills will be necessary for wide adaptation of these techniques with favorable results.

**Edge-to-Edge (Double-Orifice) Leaflet Repair**

An isolated edge-to-edge repair, championed by the Italian surgeon, Alfieri, has been shown in a small series to have reasonable long-term results (36). This repair technique was the basis for one of the earliest applications of surgical repair techniques to percutaneous valve intervention. Like its surgical counterpart, the percutaneous edge-to-edge procedure produces a double-orifice and a fibrosing bridge segment without the development of significant MS (37). Early in the inception and development of this technique there were two major devices with significant preclinical and clinical data. However, the device developed by Edwards Lifesciences was a suture-based device, and development has been halted because of technical difficulties. The device with continued clinical activity is the MitraClip™ Endovascular Cardiovascular Valve Repair System (CVRS) developed by Evalve, Inc. (Menlo Park, California, U.S.). This v-shaped clip device is delivered through a 24-Fr steerable guide catheter by transseptal approach (Fig. 43.6) (38). The clip is used to grasp the leaflets from beneath the valve, creating the double-orifice repair. Positioning is confirmed by echo and fluoroscopy and the clip is locked into position. If needed, the clip can be reopened and repositioned prior to release.

Initial data from a porcine model was published in 2003 showed that in adult pigs with no MR (n = 14), a functional double-orifice could be successfully created by endovascular placement of a mitral valve clip (38). In the vast majority of the pigs, clip attachment was durable with no clip embolization. Progressive healing was observed so that a mature, continuous bridge of tissue developed between the anterior and posterior leaflets at the site of the clip with complete endothelialization and encapsulation of the clip.

Endovascular Valve Edge-to-Edge Repair Study (EVEREST) I, a phase I prospective, multicenter safety and feasibility trial has been completed, with short-term and six-month results in the first 27 patients published in 2005 (39). This study enrolled patients with moderate to severe MR (3+ or 4+ by core laboratory evaluation) who were candidates for traditional open surgery in the event of complications. Exclusions included patients with rheumatic or infectious MR, recent surgical or interventional procedure, dilated ventricle, severe ventricular dysfunction, severe anular calcification, or mitral orifice area <4 cm². On echocardiogram, the MR needed to occur between A2 and P2 and meet certain parameters for flail dimensions or leaflet tethering so that the device could be expected to capture the leaflets adequately. Degenerative valve disease was the leading etiology (93%), although there were some ischemic patients (7%).

Successful clip placement was achieved in 24 (89%) patients. Three patients had clip placement but not enough reduction in MR, and went on to successful surgical repair. The complication rate was low, and all patients were discharged home after an average of 2.5 days. In follow-up there was partial clip detachment in three patients, necessitating elective surgical repair. An additional six patients had moderate or severe MR, with two patients undergoing elective repair or replacement. Of the 27 original patients, 13 (48%) received a clip successfully and remained with MR severity ≤ 2+ at six months of follow-up. The protocol was modified midway through the study allowing two clips to be placed, which may have improved the subsequent success rate for MR reduction. With respect to safety, only 15% of patients experienced a major adverse event, including the three clip detachments and one permanent stroke. This was significantly lower than the 34% predicted for a similar surgical cohort.

The EVEREST I feasibility registry completed enrollment with a total of 55 patients. A pivotal phase II trial (EVEREST II) has also completed enrollment, and compares the endovascular CVRS approach with standard cardiac surgery. The study design is a prospective, multicenter, randomized controlled trial with a 2:1 randomization to study and control arms, respectively. The study has two primary endpoints, safety and efficacy. The primary efficacy endpoint is noninferiority to cardiac surgery with respect to a composite endpoint of freedom from surgery for valve dysfunction, death, and MR ≥ 2+. The safety endpoint is superiority of an endovascular strategy over surgical valve repair or replacement, defined as freedom from 30-day major adverse events. This is a unique study because it is the first randomized trial comparing surgical therapy with percutaneous device implantation for valvular heart disease with an independent core laboratory evaluating MR. A total of 279 patients have been enrolled in this study from 35 centers in the United States and Canada.

Follow-up data has been made available at major national meetings from the EVEREST I feasibility study and non-randomized, roll-in EVEREST II patients. The most recent reporting on 107 patients deemed the “EVEREST preliminary cohort” (55 patients from EVEREST I and 52 patients from EVEREST II) shows a success rate of 76% for clip implantation. If acute procedural success was obtained, results were durable with 63% of patients remaining free from death, surgery, or MR ≥ 2+ at 36 months of follow-up. Death in follow-up was very uncommon (4%), and most patients (82%) remained free from surgery at 36 months. Significant LV reverse remodeling has been demonstrated when the clip successfully reduces the MR grade to ≤ 2+. The 30-day major adverse event rate was low at 9%, with only one patient requiring prolonged ventilation (>48 hours), one stroke, and one death unrelated to the
clip procedure. In the subgroup of patients with functional MR (n = 23), similar results have been noted with 87% freedom from major adverse events at 30 days, 80% freedom from severe heart failure (=NYHA class 3), and 79% freedom from severe MR (>2+) at one year.

Preliminary results from the high-risk registry have also been reported at a major national meeting but are as yet unpublished. The registry was designed to demonstrate the superiority in terms of safety of the clip to traditional surgery in high-risk patients by comparing the cohort with the predicted morbidity and mortality from the Society of Thoracic Surgeons (STS) database risk predictor model. The patients enrolled (n = 78), unlike the EVEREST I and II cohorts, were mostly functional (64%) and fewer degenerative MR patients. The success rate for clip implantation was high (96%) and two clips were placed in over one-third of patients. The primary safety endpoint was met, with 7.7% 30-day mortality in the clip cohort, with a predicted mortality of 18.2% (p < 0.008). Of those surviving, the NYHA class improved in 76%, with three-fourths of patients having NYHA Class I-II symptoms at 30-day follow-up.

In addition to the determination of safety and efficacy as defined in the pivotal trial, additional questions need to be answered with the Evolve CVRS prior to widespread adoption of this procedure. One important issue is the prolonged procedure time (204 ± 116 minutes) and steep learning curve for device implantation. It appears from unpublished EVEREST I data that compared with first procedures (device time for one clip = 181 minutes), subsequent procedures for an individual operator have a much shorter duration (134 minutes) (40). Similar experience has been noted with approval of this device in Europe where careful training has resulted in reasonable procedural time and good success. A second issue is whether the clip will eliminate subsequent surgical options, thus failing the “nothing to lose” standard. This question was addressed in a publication detailing the initial experience in the first six patients undergoing surgery after clip placement, showing that in all cases the clip was uneventfully removed and the surgical options were not limited (five repairs and one replacement) (41). Similar unpublished data are now available for 36/107 patients from the EVEREST I and roll-in patients from EVEREST II, showing 67% were successfully repaired and 33% replaced. Finally, it remains to be seen if this device is useful only for degenerative disease, or whether it can also be used for functional MR.

**Indirect Annuloplasty via Coronary Sinus**

The proximity of the CS to the mitral annulus has provided the opportunity for a creative approach to reduction of MR. The indirect annuloplasty approach utilizes devices placed in the CS to modulate the shape and size of mitral annulus. This approach is promising given the fact that most patients undergoing surgical repair have an annuloplasty either alone (as in functional MR) or in conjunction with other repairs (degenerative MR). The challenges to this procedure include anatomic variability in the location of the CS with respect to the mitral annulus (42) and the proximity of the left circumflex coronary artery (Fig. 43.7) (42,43). Imaging techniques, such as CT angiography and echocardiography may be useful to identify suitable candidates for these procedures. The long-term success of this approach will also depend on the long-term safety of CS instrumentation (e.g., displacement of device or forces, thrombosis, perforation) and the need for other devices in the CS (e.g., biventricular pacing).

**Viacor Percutaneous Transvenous Mitral Annuloplasty.**

The Percutaneous Transvenous Mitral Annuloplasty (PTMA) system was developed by Viacor, Inc. (Wilmington, Massachusetts, U.S.) (Fig. 43.8). This device utilized implantable rods to reshape the CS and mitral annulus by impinging on the annulus and decreasing the septal-lateral mitral annular diameter. This change in annular geometry increases leaflet coaptation to reduce or eliminate MR. The device is composed of nitinol and stainless steel rods coated with Teflon and plastic, and ranges from 35 to 85 mm in length. It has a rigid distal element, connected to a flexible push rod for delivery. Via subclavian venous access, the device is passed through the lumen of a guiding catheter, causing a conformational change in the annulus that can be assessed in real time by echocardiography. Rods of varying length and stiffness are implanted in sequence up to a maximum of three rods, until the optimal

**Figure 43.7** Computed tomography images of the anatomic relationships near the mitral annulus. The left panel shows the relation of MA, CS, and the circumflex artery. The LCX crossed between the CS and MA in 80% of patients studied, with significant variability in location of crossing (CS/LCX intersection). 2C, 3C, and 4C refer to the typical two-, three-, and four-chamber views used in echocardiography. The right panel shows that the distance between the CS and MA is less anteriorly and posteriorly but maximum in the lateral aspect (arrow). Abbreviations: MA, mitral annulus; CS, coronary sinus; LCX, left circumflex artery. Source: From Ref. 42.
configuration is determined. The guide catheter is removed and a permanent implant is placed and capped. The cap is located in a subcutaneous pouch, like a pacemaker, and can be reaccessed at a later date for revision of implants as needed for MR reduction.

A sheep model of ischemic MR, induced by experimental circumflex artery ischemia, was used for early device experimentation (44). Within one minute of circumflex occlusion, all animals developed 3+ to 4+ ischemic MR. A single annuloplasty rod was placed, its impact on the MR assessed, then circumflex flow was reestablished and the device removed. This cycle was repeated up to five times in each animal, using devices of different strengths in the bottom (top). The proximal end of the device (middle). The rods can be inserted depending on the need and response of the device in displacing posterior leaflet anteriorly (bottom).

Figure 43.8 The Viacor Percutaneous Transvenous Mitral Annuloplasty (PTMA) system (origin). The system features an external sheath depicted below with implantable rods that provide tension to the mitral annulus, improving leaflet coaptation and mitral regurgitation. The delivery sheath on the top and three implantable rods with different strengths in the bottom (top). The proximal end of the device (middle). The rods can be inserted depending on the need and response of the device in displacing posterior leaflet anteriorly (bottom).

decreased from 6.5 ± 2.2 to 0.4 ± 0.5 cm² (p < 0.03), and the vena contracta width was reduced from 8.2 ± 4.7 to 2.6 ± 0.9 cm² (p = 0.03). The mitral annular diameter went from 30 ± 2.1 to 24 ± 1.7 mm (p = 0.03) following device placement. There was no MS induced by the device, and left ventricular ejection fraction was improved.

A subsequent sheep experiment using 3-D echocardiography assessed the effect of percutaneous placement of up to three annuloplasty devices of varying size and stiffness in the custom multilumen CS catheter (45). At eight weeks following experimental induced posterior myocardial infarction, the annuloplasty device significantly reduced the MR jet area, the mitral annular A-P dimension in systole and diastole, and mitral valve tenting area in all three planes.

Human implantation began initially on 10 patients undergoing open heart surgery for functional MR (46). The study included the single lumen prototype device and the multilumen next-generation device. Successful implantation and removal took place in nine patients, confirming the feasibility of alteration of annular geometry and MR. Subsequently the Percutaneous Transvenous Mitral Annuloplasty (PTOLEMY) I study has been completed, the initial human feasibility trial with permanent implantation. The results of this trial are not yet published, but have been presented orally at national meetings. The study included 31 patients, and showed successful implantation in 11 patients. A single device fracture, one CS perforation, two CS dissections, and two device slippages occurred. The MR reduction was on average one grade (MR 3+ to 2+), and 3-D TEE showed significant annular modification in patients with successful implant.

The PTOLEMY I experience was valuable to improve the device, with changes in the rod to improve push (reduction in AP diameter of the mitral annulus) and changes in the suture to decrease slippage. Device design is now frozen, and a second feasibility and efficacy trial will begin (PTOLEMY II). This trial will enroll 60 patients in the United States and abroad and will have primary endpoints of six-month freedom from major adverse events and MR reduction efficacy. In addition, secondary endpoints will include reverse remodeling, quality of life, and six-minute walk test. Patients must have moderate functional MR, symptomatic heart failure, and left ventricular dysfunction. Patients may be excluded on anatomic or clinical concerns, including left dominant coronary circulation, planned bypass surgery, or prior mitral repair.

Advantages of the Viacor PTMA device include the ease of placement, the number of combinations of devices of varying lengths and strengths that can be used to optimize the reduction in MR, and the ability to return later and change the device to further reduce MR if it recurs. The major drawback to the device includes the limitations inherent to a CS device: CS proximity to the mitral annulus and left circumflex artery. There have been no reports to date, however, of left circumflex artery ischemia with this device.

CARILLON™ Mitral Contour System. Under development by Cardiac Dimensions (Kirkland, Washington, U.S.), the CARILLON Mitral Contour System is a fixed length, double-anchor device (Fig. 43.9) that is advanced through a catheter and positioned in the CS. After the device is deployed and locked into position, tension between the proximal and distal anchors of the device results in tissue plication and reduces mitral valve annular diameter, resulting in decreased MR. Via jugular venous access, the nitinol annuloplasty device is positioned in the CS after cannulation and measurement of the CS,
ment. The cardiac output increased and pulmonary capillary left atrial area from $41.9 \pm 0.14$ to $3.24 \pm 0.05\text{ cm}^2$. MRI of moderate severity was confirmed by echocardiography. The device was successfully placed in all animals, with a success rate of $98\%$.

Seven dogs with a successful implant, at four weeks there was a statistically significant reduction in mitral annular area ($0.11 \pm 0.04\text{ cm}^2$, $p < 0.001$), as well as percentage MR jet area to left atrial area ($2.8 \pm 3.73\%$, $p < 0.05$). Six-minute walk tests improved by about $100\text{ m}$ ($307–403\text{ m}$, $p < 0.001$). The device did not cause coronary impingement or was able to be recaptured and repositioned to avoid coronary impingement. MR was reduced by $27\%$, and functional class was reduced at six-month follow-up by about one class, from average $2.86$ to $1.76$ ($p < 0.001$).

The earliest preclinical testing with this device was done in a canine tachycardia-induced cardiomyopathy model (49), showing similar one-month results to the canine model, with respect to mitral annular diameter percent reduction ($23.7 \pm 1.45\%$) and percentage MR jet area to left atrial area ($27.84 \pm 1.96\%$), decreased to $2.40 \pm 0.98\%$ post procedure, $p < 0.05$.

There were no premature deaths in the ovine study. However, in the sheep the left circumflex artery does not run in the atrioventricular groove, precluding an assessment of safety with respect to ischemia.

Early human experience was obtained on the initial device design, but some failures due to distal anchor slippage led to a change in device design with a larger distal anchor and interlocking wire forms to improve device stability (CARILLON XL). On the basis of this experience, a multicenter human safety and feasibility study has been completed in Europe entitled AMADEUS. This trial enrolled 48 patients with $2+ \text{ to } 4+\text{ functional/ischemic MR}$ and NYHA Class II-IV. The primary endpoints was 30-day safety with secondary efficacy endpoints of MR reduction, functional class improvement, quality of life, and six-minute walk test. This trial has been reported in preliminary form at a major national meeting. This report showed successful implantation in 30 patients ($63\%$), with one death, three myocardial infarctions and three CS perforations at 30-day follow-up. There were no device embolizations and no patients needed surgery. The total major adverse event rate was $13\%$. The coronary arteries were crossed by the device in $84\%$ of cases, but only prohibited device placement in $14\%$ of cases. In the remainder of cases the device did not cause coronary impingement or was able to be recaptured and repositioned to avoid coronary impingement. MR was reduced by $27\%$, and functional class was reduced at six-month follow-up by about one class, from average $2.86$ to $1.76$ ($p < 0.001$).

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Figure 43.9 The CARILLON Mitral Contour System, developed by Cardiac Dimensions, Inc. (Kirkland, Washington, U.S.). The device consists of the distal and proximal anchor with a connector that synchs the annulus (top). The device is inserted via the SVC in the CS and positioned depending on the anatomy of the CS, circumflex artery and the effect on mitral regurgitation as tension is applied to synch the mitral annulus (bottom). Abbreviation: CS, coronary sinus.

The earliest preclinical testing with this device was done in a canine tachycardia-induced cardiomyopathy model, with both acute and chronic (four-week) hemodynamic evaluation of the device (47). The early canine experience highlighted some of the anatomical, design, and safety issues, as $3$ of $12$ dogs had coronary anatomy that precluded placement without left circumflex artery and the effect on mitral regurgitation as tension is applied to synch the mitral annulus (bottom). Abbreviation: CS, coronary sinus.

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The Edwards MONARCTM CS annuloplasty device

Figure 43.10 The Edwards MONARCTM CS annuloplasty device (Edwards Lifesciences, Irvine, California, U.S.). The device is implanted in the CS (top). The bridging element has shape memory and provides tension to the posterior mitral annulus, bringing the leaflets into coaptation, reducing mitral regurgitation. **Abbreviation:** CS, coronary sinus.

Initial results in humans were reported for five patients with chronic ischemic MR (50). Implantation of the device was successful in four patients, with one failure due to difficulty in advancing the device, leading to perforation of the anterior interventricular vein and pericardial effusion. A subsequent reattempt was also unsuccessful. The patients were followed for 180 days with serial exam, chest x-ray, and echocardiogram. There was one late death (day 148) due to progressive heart failure unrelated to the device. Coronary angiogram at 90 days showed no evidence of circumflex artery compromise and the CS remained patent in all three surviving patients. Separation of the device bridge element was documented on follow-up chest x-ray in three patients (days 22, 28, and 81). Although migration of the anchors was not observed and no adverse clinical events occurred in these patients, the feasibility study enrollment was discontinued. There was no significant change in the mitral annulus diameter, NYHA failure class, or MR grade at follow-up.

Following this early experience, the device was redesigned, and is now called the MONARC system. The nitinol bridging segment was replaced with a “delayed-release system,” which utilizes a slow conformational change in the bridge element to shorten the distance between the proximal and distal anchors. The shape change occurs due to the slow breakdown of a biodegradable polymer in the bridge segment. This shortening induces a conformational change in the CS, extending to the mitral annulus, further reducing any postprocedural MR.

The EVOLUTION trial is the first multicenter feasibility and safety study for the MONARC system and has completed enrollment in Europe and Canada. Preliminary results have been presented at major national meetings. This study enrolled 72 patients with functional/ischemic MR, grade 2+ to 4+, with appropriate CS dimensions to fit device specifications. Patients with recent ischemia or planned intervention were excluded, as were patients with an implanted cardiac defibrillator (ICD) or pacing leads in the CS. Other exclusions included patients with a low ejection fraction (<25%), mitral valve prolapse, or moderate to severe mitral annular calcification. The primary safety objective of the study was procedural success and 30- and 90-day safety. Acute procedural success was defined as device implantation without occurrence of in-hospital death, tamponade, or myocardial infarction, and was achieved in 82% of patients. The 30-day safety endpoint defined as freedom from death, tamponade, or myocardial infarction occurred in two patients who had tamponade, but no deaths or myocardial infarctions occurred. In long-term follow-up, however, three patients had myocardial infarctions, all thought to be device related, with one leading to death. There were nine unrelated deaths, leading to an overall 70% event-free survival at two years. The 90-day efficacy endpoint of reduction in MR by one grade was met, with mean MR grade going from 2.48 to 1.78 (p = 0.0002). There were some favorable changes in ventricular dimensions and hemodynamic parameters. Overall NYHA functional class was reduced from 2.66 at baseline to 2.0 at follow-up. Responders did better if the initial MR grade was 3+ to 4+.

The EVOLUTION study is the largest human cohort of CS implants, and interim results from this study shed some light on potential device-related issues over time. The procedure is straightforward and reproducible, and early efficacy data suggest that moderate to severe MR patients are the most likely to benefit from this device. The preliminary experience in the mild to moderate MR (grade 2+) patients is intriguing given the interest in the use of percutaneous devices for less severe MR to prevent adverse remodeling of the LV. Although data regarding LV parameters are not yet available, results from the EVOLUTION study indicate that there is no MR reduction in these patients. It remains to be seen if there are long-term clinical benefit to early implantation of the device for prevention of MR progression. The EVOLUTION II trial will soon begin enrollment and should answer some or all of these questions.

**Septal-to-Lateral Annular Cinching (Transatrial or Transventricular)**

Geometric alterations in the LV and mitral annulus are a result of left ventricular enlargement from dilated or ischemic cardiomyopathy. This leads to MR labeled as functional/ischemic MR as detailed above. The observation that the SL or AP mitral annular diameter is increased in a tachycardia-induced model of functional MR (51) has led to the development of a new surgical technique for prevention of MR. This technique, known as septal-to-lateral annular cinching (SLAC), is based on reduction in the SL annular diameter. This method has the potential to address some limitations of typical ring annuloplasty; namely the fact that the trigone, thought to be fixed in size, is not actually constant—it also dilates with rest of the annulus. Therefore, a ring that does not address this part of the annulus is only partially successful, especially in ischemic patients. The SLAC approach may overcome this problem because it remodels the ventricular apparatus. Initially, there were two major percutaneous approaches to this method, one involving placement of a transventricular chord (iCoapsys™) and a second involving placement of a chord from the interatrial septum to the CS (PS3). The iCoapsys device trial was recently discontinued because of a lack of funding with closure of the Myocor company. Edwards Lifescience has acquired the intellectual property from Myocor but has not indicated that they are going to pursue device development at this time.
**PS3 system.** The Percutaneous Septal Sinus Shortening (PS3) system, developed by Ample Medical, Inc. (Foster City, California, U.S.) pulls two sides of the annulus by placing an anchor in the CS and interatrial septum with a rod across the atrium (Fig. 43.11). The anchors are composed of nitinol and supplied by AGA Medical.

Using a 12-Fr sheath in the right internal jugular vein, a catheter with incorporated magnet on its tip called the GCV MagneCath™ (Ample Medical, Inc., Foster City, California, U.S.), is advanced into the CS and positioned behind the posterior mitral leaflet. The left atrial (LA) MagneCath is introduced through the Mullins sheath placed in the LA via right femoral vein after transseptal puncture. The catheter from the LA is advanced until it magnetically mates with CS catheter. A crossing catheter, introduced via the LA MagneCath, is advanced into the GCV MagneCath, making a small hole in the left atrial wall. A glide wire is then advanced from the LA MagneCath into the CS and positioned behind the posterior mitral leaflet. The left atrial (LA) MagneCath is introduced through the Mullins sheath placed in the LA via right femoral vein after transseptal puncture. The catheter from the LA is advanced until it magnetically mates with CS catheter. A crossing catheter, introduced via the LA MagneCath, is advanced into the GCV MagneCath, making a small hole in the left atrial wall. A glide wire is then advanced from the LA MagneCath into the CS and remains as a continuous externalized loop across the LA after both MagneCaths are removed. A T-bar element (CS anchor) is placed over the wire into the CS, and an attached suture is pulled across the LA and externalized at the right common femoral vein. Advanced over the suture element, the septal anchor (an Amplatzer patent foramen ovale occluder, Golden Valley, Minnesota, U.S.) is deployed in standard fashion. Tension is applied on the suture to cause septal-lateral shortening, improving leaflet coaptation and reducing MR. The suture is locked into place with tension element, completing the procedure. The company is in the process of changing the septal anchor to more specific device for this application.

This device has been applied to an ovine model of tachycardia-induced cardiomyopathy caused by rapid right ventricular pacing (53). The degree of reduction in functional MR, and in the septal-lateral systolic distance, was the primary efficacy measure of this study. Sheep underwent short-term (n = 19) and long-term (n = 4) evaluation. The device was successfully placed in all animals with no evidence of circumflex coronary artery impingement and maintaining patency of the CS. The short-term results indicated a significant reduction in septal-lateral diameter from 32.5 ± 3.5 mm before procedure to 24.6 ± 2.4 mm post procedure (p < 0.001). This was maintained at 30 days in the long-term animals where the septal-lateral diameter was 30.4 ± 1.9 mm before procedure and 25.3 ± 0.8 mm after 30 days (p value not given). The results for reduction in MR in the short-term were similar, with an MR grade of 2.1 ± 0.6 before procedure versus 0.4 ± 0.4 post procedure (p < 0.001). This result was maintained at 30 days (MR grade 0.2 ± 0.1). Additional hemodynamic and laboratory data were consistent with improved cardiac function.

The first human implant was recently performed without complication and the case was presented at TCT 2006 (54). Acute human studies have been reported in patients outside the United States with significant (up to 35%) reduction in annular dimensions but no long-term testing has been reported. The advantages of the PS3 system include relative ease of placement, avoidance of circumflex coronary artery impingement, and potentially safer use of transseptal puncture when compared with the similar transventricular cinching device (discussed below). However, the transventricular device may have additional advantages in terms of LV remodeling.

**Coapsys™ and iCoapsys™.** Myocor, Inc. (Maple Grove, Minnesota, U.S.) developed a device termed Coapsys, which was surgically implanted with two pads in the pericardium (anterior and posterior) with a wire passing through off-pump with a cord placed between the pads through the LV. This cord is then cinched up to decrease the SL diameter and eliminate MR. In initial animal studies using a canine tachycardia-model of functional MR (n = 10), this device reduced the mean MR grade from 2.9 ± 0.7 to 0.6 ± 0.7 (p < 0.001), without adverse consequence on ventricular function (55,56). A randomized trial (RESTORE-MV) in humans is enrolling patients with coronary artery disease and ischemic MR, comparing traditional open CABG and mitral repair with CABG and Coapsys device placement. Intraoperative results from this trial have been reported in the first 19 patients receiving the implant, showing a reduction in MR grade from 2.7 ± 0.8 to 0.4 ± 0.7 after implantation (p < 0.0001) (57). All implants were performed successfully without cardiopulmonary bypass and no hemodynamic compromise or structural damage to the mitral apparatus.

Myocor subsequently developed a system to deploy this device totally percutaneously without thoracotomy and called it iCoapsys (Fig. 43.12). A specifically designed needle, guide-wire, and sheath were used to obtain controlled access in to the pericardial space. Steerable suction-based catheters with intracardiac echocardiographic guidance were positioned on the
suture annuloplasty, the Mitralign Direct Annuloplasty System ring implant (22,23). Based loosely on the concept of direct of preservation of annular contraction, usually impaired by the comparable to ring annuloplasty, with the possible advantage annuloplasty has been shown to have good long-term results, with the possible advantage to this approach is the ability to apply a repair directly to the annulus, where the pathologic mechanism of MR is frequently located, eliminating the anatomic uncertainty regarding circumflex artery anatomy and CS proximity to the annulus that plagues CS approaches.

Advantages of this device include direct placement on the mitral valve annulus, avoiding the concern for left circumflex artery compromise. The device is adjustable to deliver the appropriate amount of tension to the annulus, and because of its design, there are no sizing issues, as a single device is intended for use with all patients. The CS remains free of permanent implant, allowing for subsequent placement of CS leads for biventricular pacing. Long-term durability will be an issue to follow with this device. The Mitralign pilot study in humans is currently enrolling patients in Germany and Canada.

QuantumCor. The application of radio frequency to remodel the mitral annulus is under development by QuantumCor (Lake Forest, California, U.S.). The concept is termed transventricular annulus remodeling, and relies on scarring and shrinkage of the mitral annulus after application of radio frequency energy directly to the annulus. The device is intended both for surgical and transcatheter use (transseptal) and has a malleable tip with eight electrodes to deliver energy. The catheter is connected to a pulse generator that is modulated by temperature sensors in the electrodes to regulate the amount and time of energy delivered. The catheter can be manipulated to deliver radio frequency energy to specific locations on the annulus, allowing for adjustment of the procedure to individual anatomy. The device has been tested in the chronic sheep model (n = ?) showing a 21.4% reduction in annular diameter at 30 days and further 26% reduction in diameter over 180 days. A human study should start in 2010.

SUMMARY
The percutaneous treatment of MR is currently under investigation using a variety of devices and the initial data are fairly encouraging for many of them. However, none of them can currently be recommended for clinical use outside of a clinical protocol. It is possible that more than one device may be needed to properly treat MR percutaneously. However, initial trials have to be conducted with one device and therefore patient selection will shape the future for each device. Clinical trials for the percutaneous treatment of MR are particularly

Figure 43.12 Myocor, Inc. (Maple Grove, Minnesota, U.S.) developed a device termed iCoapsys™, which was percutaneously implanted with two pads in the pericardium (anterior and posterior) with a wire passing through offpump with a cord placed between the pads through the left ventricle. This cord is then cinched up to decrease the septal-lateral diameter and eliminate mitral regurgitation. Abbreviations: MV, mitral valve; RV, right ventricle; LV, left ventricle; AoV, aortic valve. Source: From Ref. 58.
difficult to conduct because of several challenges. The MR population is heterogeneous in terms of etiology, limiting the comparison with best medical treatment and surgery. Since there are no standards for treatment and follow up reported in randomized controlled fashion, investigators have to depend on retrospective, single center, self reported experiences for study design and statistical planning. Definition and selection of endpoints is equally problematic. Finally, there is no clear-cut way to judge the severity of MR and the degree of ischemia dependent on hemodynamic loading conditions. Therefore, the efforts of all different investigators have to be applauded for continuing research in this challenging field.

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Matthew C. Becker, Gus Theodos, Samir R. Kapadia, and E. Murat Tuzcu

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a unique cardiovascular condition that may become symptomatic at any phase of life, from infancy to beyond 90 years of age (1–6). The hallmark of the disease is myocardial hypertrophy that can be manifest in a variety of recognized morphologies. Dynamic left ventricular outflow tract (LVOT) obstruction may or may not be present due to asymmetric hypertrophy of the interventricular septum. With recent estimates suggesting that 1 in 500 of the general adult population is affected by this autosomal dominant condition, HCM is one of the most common cardiac genetic disorders known, and over 12 involved genes have been identified (3,5,6). The genotypic foundation of HCM is directly related to abnormalities of the genes encoding sarcomeric proteins that regulate the contractile, regulatory, and structural functions of the myocardium. The consequent myocardial disarray and hypertrophy result in a complex pathophysiologic interplay among LVOT obstruction, diastolic dysfunction, myocardial ischemia, and mitral regurgitation. Depending on their particular phenotype, patients with HCM may have a wide spectrum of clinical and pathologic presentations ranging from exertional dyspnea, angina, palpitations, or syncope. The most fearsome and dramatic complication of HCM, sudden cardiac death, is one of the frequent causes of cardiovascular death among young athletes (7). Fortunately, HCM patients at high risk for sudden cardiac death constitute only a small proportion of the affected population (Table 44.1). Despite the widespread availability of genetic screening tests, the diagnosis of HCM remains primarily clinical, involving the use of echocardiography to evaluate for characteristic features such as asymmetric septal hypertrophy, systolic anterior motion of the mitral valve, and LVOT obstruction.

Given the heterogeneity of the disease process, clinical course and long-term outcomes may differ significantly in patients sharing the same mutation or even within the same family. HCM can be a dynamic disease process that can evolve with age, and the development of left ventricular hypertrophy has been observed at all ages (8–10). Consequently, therapeutic interventions must take into consideration individual patient characteristics and preferences. Accordingly, management strategies range from medical therapy with close outpatient follow-up to surgical or percutaneous remodeling of the myocardium.

Medical therapy should be the initial therapeutic approach for the treatment of symptomatic patients with HCM. However, given the paucity of randomized trials, current recommendations are based on expert opinion, clinical experience, and retrospective analyses. β-Blocking agents, verapamil, and disopyramide (often titrated to high doses) have historically been utilized as first-line agents, although limited data suggest that amiodarone may reduce the risk of sudden cardiac death and improve survival in selected high-risk patients with nonsustained ventricular tachycardia (11–13). Given that ventricular fibrillation or tachycardia is the primary mode of sudden cardiac death in patients with HCM, a growing body of data suggest that there is a significant benefit to implantable cardioverter-defibrillator (ICD) therapy in patients who have survived an episode of sudden cardiac death (secondary prevention) or who are at high risk for such an event (primary prevention) (Table 44.1) (5,14–16).

Historically, the gold standard for the treatment of symptomatic HCM has been surgical septal myotomy. Evolved from the original septal myotomy first performed by Cleland (17) in the 1960s, the widely employed Morrow myectomy (18) consists of the resection of a variable amount of myocardial tissue from the septum extending from the base of the aortic valve to a region just distal to the mitral leaflets such that the LVOT is enlarged and systolic anterior motion of the mitral valve (and the resultant mitral regurgitation) is abolished (19–21). Myectomy results in a durable reduction in outflow tract obstruction; a significant improvement in a patient’s functional capacity, heart failure symptoms, quality of life; and may offer a lifestyle expectancy similar to that of the general population (19,22–25). The operative mortality rate for the modern-day septal myectomy is approximately 1% to 3% overall but is <1% when performed in very experienced centers (25–31).

Introduced by Sigwart in 1995, catheter-based alcohol septal ablation has become a widely utilized alternative treatment strategy to relieve outflow tract obstruction in symptomatic patients who are suboptimal surgical candidates due to comorbidities, personal preference, or who are located in areas without sufficient surgical expertise (32). Given the less invasive nature and the promise of a significant reduction in recovery time, the procedure has seen a rapid increase in popularity over the past 10 years, and is now performed 15 to 20 times more frequently than surgical myectomy, resulting in >5000 ablations performed worldwide in total (33,34). The septal ablation technique attempts to mimic the effect of the more traditional Morrow myectomy by the infusion of 100% ethanol into either the first or second septal perforator artery supplying the septal bulge. This induces a controlled infarct in the basal portion of the hypertrophied interventricular septum resulting in scarring, thinning, and akinisia. Under optimal conditions, the result is a significant and rapid reduction in the LVOT gradient as well as the systolic anterior motion of the mitral valvular apparatus (32,35–41). Limited by a paucity of long-term follow-up data and the absence of randomized trials, short-term observational studies suggest that ablation results in a significant reduction in LVOT gradient, a reduction in
Table 44.1 Risk Factors for Sudden Cardiac Death in Hypertrophic Cardiomyopathy

- Prior history of cardiac arrest
- Unexplained syncope (particularly if occurring with exertion)
- Spontaneous sustained ventricular tachycardia
- Abnormal response (particularly blood pressure) with stress testing
- Early onset of disease
- Family history of cardiac arrest or sudden cardiac death
- Nonsustained ventricular tachycardia on Holter monitoring
- Left ventricular thickness >30 mm
- Ischemia detected on perfusion testing (may be a result of microvascular circulation)
- Atrial fibrillation
- Concomitant severe aortic stenosis
- Concomitant congestive heart failure
- Other comorbidities, including pulmonary embolus and malignancy

Table 44.2 Comparison of Alcohol Septal Ablation and Surgical Myectomy

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<thead>
<tr>
<th></th>
<th>Myectomy</th>
<th>Ablation</th>
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<tbody>
<tr>
<td>Mortality</td>
<td>&lt;1–2%</td>
<td>1–2%</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Decreased</td>
<td>Decreased</td>
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<tr>
<td>Gradient</td>
<td>Decreased to</td>
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<td></td>
<td>&lt;10 mmHg</td>
<td>&lt;25 mmHg</td>
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<tr>
<td>Need for pacemaker</td>
<td>1–2%</td>
<td>5–10%</td>
</tr>
<tr>
<td>Sudden death risk</td>
<td>Low (long term)</td>
<td>Low (midterm)</td>
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<tr>
<td>Intramyocardial scar</td>
<td>Absent</td>
<td>Present</td>
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</table>

Symptoms Decreased Decreased

ANATOMIC CONSIDERATIONS

In recognition of the fact that in current practice most patients with HCM are diagnosed noninvasively via echocardiography and many have not had invasive hemodynamic studies performed prior to presenting for ablation, most experienced operators will confirm the presence of significant LVOT obstruction by positioning an end-hole catheter in the ventricular apex and recording a slow pullback under fluoroscopy. Alternatively, one may place a catheter in the ascending aorta and an end-hole catheter in the ventricle to provide simultaneous measurement of the ascending aortic and intracavity pressures. If the operator has difficulty identifying an LVOT gradient under basal/resting conditions, provocation with either amyl nitrate or the strain phase of the Valsalva maneuver may be attempted (51). Induction of a premature ventricular contraction with the pigtail catheter may also aid in the diagnosis, as it commonly results in the Brockenbrough-Braunwald phenomenon, which refers to the diminished aortic pulse pressure and increased LVOT gradient secondary to a transient increase in obstruction (Fig. 44.1). This maneuver can also be useful during the procedure, as it may isolate the appropriate septal perforator branch to intervene upon (52). The left ventriculogram may have a variety of findings including systolic cavity obliteration, varying degrees of mitral regurgitation, and occasionally the hypertrophied septum prolapsing into the LVOT.

Standard diagnostic coronary angiography is performed as a first step to clearly define the patient’s anatomy, identify the location and size of the septal perforator branches, and evaluate for the presence of concomitant coronary artery disease. Sometimes septal perforator branches originating from the left anterior descending (LAD) artery may be compressed during systole due to contraction of the hypertrophied septum that contains them (53). Similarly, systolic compression of the LAD artery resulting in a “sawfish” appearance has also been described (54). In addition to evaluating for the presence of coronary artery disease, a critical component of the diagnostic angiogram is proper selection of the appropriate septal perforator branch through which the ablation will be performed (Fig. 44.2).

The right anterior oblique (RAO) or posterior-anterior (PA) cranial views usually provide the best view of the septal branches as they travel through the basal interventricular septum and will allow proper evaluation. Often there can be substantial variation in the septal anatomy such that one sub-division runs along the left side of the septum while another runs along the right. The operator may gain a better understanding of this variation (i.e., on the right or left side) utilizing the left anterior oblique (LAO) projection. To reduce the likelihood of inducing complete heart block during ethanol infusion, selection of the left-sided subdivision whenever possible is optimal for the ablation. This can be accomplished in the LAO view by avoiding the subdivision of the septal branch supplying the right side of the septum.

During angiographic assessment of the septal anatomy, a number of important factors must be considered with regard to proper vessel selection. It is critical that the operator pay close attention to vessel size, angulation, and distribution of myocardial territories served by the given vessel. By virtue of the fact that larger vessels generally provide blood supply to a larger segment of myocardium, selection of septal branches with a diameter >2.0 mm may result in a large infarct; this should be taken into consideration in making the decision. Another, often underappreciated, consideration in vessel...
selection relates to the degree of angulation of the septal vessel with regard to its parent vessel. The interventionalist should consider that septal vessels with a high degree of angulation and tortuosity may be a difficult target for the delivery of the angioplasty balloon since the coronary wire may often prolapse back into the LAD coronary artery (51) (Fig. 44.2).

Substantial anatomic variation exists with regard to the vessel of origin as well as the distribution of blood flow supplied by the septal perforators in patients with HCM. Most commonly noted to originate from the proximal LAD, septal perforators have been observed to arise from virtually every major branch of the coronary tree including the left main trunk, left circumflex coronary artery, ramus intermedius, diagonal branches, and, rarely, from branches of the right coronary artery (51).

Previous work has demonstrated that the first septal artery may provide blood flow to a substantially larger region of myocardium than might be expected. In addition, septal branches can exhibit marked variability in their course and provide blood flow to various regions of the myocardium—including the right ventricle. Furthermore, cases in which both the first and second septal arteries provide blood supply to the basal septum have been described (51,55). As a result, it is imperative that the operator have an intimate understanding of the distribution of blood flow supplied by the selected septal branch to accurately target the correct area for ablation and to avoid infarction of an unanticipated region or an oversized infarction of the septum itself. To better delineate the area of myocardium subtended by the selected septal vessel prior to ethanol infusion, most experienced operators will elect to

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**Figure 44.1** Brockenbrough–Braunwald phenomenon.

**Figure 44.2** Diagnostic angiogram depicting the relationship of the first septal perforator to the plane of the aortic valve (beneath) and to the left ventricular cavity (panels A and B). Panel C displays simultaneous injection through both the guide and pigtail catheters demonstrating the location of the interventricular septum (white arrows and shaded segment) in relation to the left ventricular cavity. The anterior leaflet of the mitral valve is outlined the white line and black arrows.
perform a selective injection of contrast under cine with the concomitant use of transthoracic echocardiography utilizing injectable contrast material. Intracardiac echocardiography may be utilized during this procedure to better visualize the hypertrophied septum and the course of the injected contrast material (56) (Fig. 44.3).

It is important to thoroughly evaluate for anatomical abnormalities that would require surgical management prior to proceeding with a catheter-based intervention. Such abnormalities include anomalous papillary muscle insertion into the mitral valve, anatomically abnormal mitral valve with a long anterior/posterior leaflet, coexistent coronary artery disease, primary valvular disease (aortic or mitral), or subaortic membrane or pannus—none of which can be adequately addressed by septal ablation (Fig. 44.4) (5,51). Furthermore, a subset of patients may be found to have an abnormal elongation and myomatous degeneration of the anterior mitral leaflet resulting in an anterior displacement of the line of coaptation with resultant outflow tract obstruction. These gene-positive HCM patients have dynamic LVOT obstruction from papillary muscle orientation independent of septal hypertrophy (57,58). These patients will require surgical consultation for consideration of myectomy with plication and should not be considered for catheter-based therapy (59). In addition, results of alcohol ablation in patients with severe hypertrophy (i.e., >3.0 cm) are inconsistent, and these patients are frequently referred for surgical correction.

**PROCEDURAL TECHNIQUE AND EQUIPMENT**

Placement of a prophylactic temporary transvenous pacemaker prior to beginning the procedure is an essential initial step, given the high incidence of complete heart block during, or in the days following, ablation. To reduce the possibility of dislodgment during the procedure or in patient transport, some operators place a screw-in type pacing lead (rather than the blunt-tip models) into the right ventricular apex under fluoroscopy. Subsequent to placing the transvenous pacemaker, arterial access is obtained using a 6- or 7-Fr short sheath, and intravenous unfractionated heparin is administered with a target activated clotting time of 250 to 300 seconds to prevent development of thrombus in the guide catheters or on the wires.

A guiding catheter capable of providing sufficient support, such as the 6- or 7-Fr XB catheter, is usually selected and used to engage the left main coronary artery (Table 44.3). As with standard coronary interventional procedures, a 0.014-in. extrasupport wire with a soft tip is subsequently advanced into the preselected septal perforator branch (Fig. 44.4). At this point, an over-the-wire style angioplasty balloon, usually a 1.5 to 2 mm \( \times \) 8 to 12 mm, is advanced over the guidewire and into the proximal aspect of the septal vessel. Given that septal vessels often have an acute angle at their origin from the LAD, the operator may occasionally encounter difficulty in delivering equipment to the selected vessel. In these situations, stiffer guidewires are often helpful in providing the necessary support for balloon placement (51). It is critical for the operator

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**Figure 44.3** Intracardiac echocardiogram demonstrating the hypertrophied interventricular septum prior to (panel A) and after ethanol infusion (panels B and C). Note the increased echogenicity of the basal septum following injection.

**Figure 44.4** Angiogram depicting the course of the left anterior descending artery and a septal perforator appropriate for ablation of basal-most portion of the septum (panel A). 0.014-in. extrasupport coronary wire in the selected septal vessel with subsequent inflation of an over-the-wire style angioplasty balloon prior to infusion of ethanol (panel B). Angiogram documenting the integrity of the left anterior descending coronary artery and total occlusion of the recently injected septal branch (Panel C).
to ensure that the balloon is situated deeply enough into the septal vessel to prevent the infused ethanol from accidentally refluxing into the LAD proper. However, balloon placement too distally may result in the ethanol infusion, missing the basal-most portion of the septum, and result in a suboptimal gradient reduction.

Prior to proceeding further, it is critical to assess the amount and location of myocardium supplied by the selected septal vessel. This is typically accomplished through the use of both echocardiographic and angiographic techniques. Following optimal placement, the balloon is inflated to approximately 10 to 12 atm to occlude the vessel, and 1 to 2 cc of contrast are slowly injected through the distal end of the balloon to assess the full extent of myocardium supplied. While slowly infusing the contrast material to simulate the forthcoming ethanol injection, it is imperative for the operator to confirm that the balloon occlusion is sufficient to prevent any of the infused contrast from refluxing backward into the proximal LAD proper—which, during the actual ethanol infusion, would result in diffuse and unintended myocardial necrosis.

Contrast echocardiography utilizing a transthoracic approach is the second commonly employed method of verifying the myocardial distribution subtended by a particular septal vessel. Following a complete examination of the morphology of the interventricular septum, most commonly in the parasternal short axis and apical three and four chamber views, 1 to 2 cc of echocardiographic contrast material is infused through the balloon into the septal branch through a tuberculin-type syringe. We find that many of the currently available contrast agents are too concentrated, and their infusion may result in echocardiographic “shadowing” from the opacified ventricles. To avoid this problem, the protocol in our laboratory is to open the contrast vials 10 to 15 minutes prior to the time of expected use and to further dilute the agent with a sterile saline solution in a 1:5 or 1:10 mixture at the time of injection. It is also our standard practice to utilize pulsed-wave Doppler when employing the newly diluted contrast so as to avoid destruction of the microbubbles with the higher frequency continuous wave ultrasound. Given that the basal portion of septum is responsible for the greatest extent of septal to mitral contact and therefore the LVOT obstruction, the optimal septal vessel will deliver contrast material filling to this region alone (Fig. 44.5).

Given the extensive variability of the septal anatomy in this patient population, the operator should verify that the chosen vessel primarily supplies the proximal interventricular septum and does not provide blood flow to portions of the inferior wall (as in the presence of an occlusion of the right coronary artery), left ventricular papillary musculature, or the right ventricular free wall (49). Should it be noted that the selected septal vessel provides flow to the distal septum or other regions of myocardium, ethanol infusion is contraindicated as proceeding could result in infarction of an undesired territory or of unanticipated size. Given that it has been demonstrated that a rapid reduction in gradient can be observed with balloon occlusion of a septal perforator branch in many, but not all, patients, documenting a reduction in LVOT gradient (generally >30%) during balloon inflation is another method to verify that the correct septal distribution has been targeted for ablation (51) (Fig. 44.5).

At this point, confirmation of balloon placement and appropriate function of the temporary pacemaker must again be verified. The balloon can migrate during the above process, so another 1 to 2 cc contrast injection under fluoroscopy will ensure proper placement. Ethanol injection into the selected septal perforator may now be performed. In most cases, 1 to 3 cc of desiccated ethanol is sufficient—although the necessary volume can vary on the basis of the patient’s septal anatomy.

![Figure 44.5](image-url) Transthoracic echocardiogram (parasternal long axis) demonstrating the grossly hypertrophied basal interventricular septum of a patient affected by hypertrophic cardiomyopathy prior to contrast injection (panel A). Note the increased echogenicity of the basal septum following infusion of contrast (panel B) and the echolucency immediately after ethanol infusion (panel C).
and the behavior of contrast during the test-infusion as performed earlier (Table 44.3) (35,37,45,51,60). If rapid washout of the contrast was observed due to collateral flow, standard practice is to reduce the volume and rate of ethanol injection to ensure that other areas of myocardium are not inadvertently damaged via these branches (51,61). Accordingly, it should be the goal of the operator to use as little ethanol as possible during the procedure to avoid excessive or unintended myocardial necrosis. Importantly, it has been demonstrated that smaller volumes of ethanol are equally effective with regard to midterm gradient reduction while significantly reducing the rate of complications (62). Furthermore, the volume of alcohol used in the procedure has also been shown to be an independent predictor of survival—the lower, the better—in a single center over 10 years of follow-up (63).

With the balloon still inflated, the ethanol is injected into the septal branch over a period of one to five minutes. It is important that the operator adequately flush the catheter with normal saline following infusion to ensure complete delivery of the previously infused ethanol into the distal vessel and, of great importance, to prevent reflux of infused ethanol at the time of balloon deflation. To provide maximal contact between ethanol and myocardium, many operators will continue balloon inflation for up to 5 to 10 additional minutes. This maneuver also helps to ensure that no reflux of ethanol into the LAD following balloon deflation will occur. During ethanol infusion the resting LVOT gradient should be continuously monitored to gauge the relative success of the procedure. A successful procedure is generally regarded as one in which the resting LVOT gradient is reduced from >50 mmHg to <30 mmHg, or in which the provocative gradient is reduced by >50% (37,51).

The coronary guidewire is then repositioned into the septal branch prior to disengaging the balloon to facilitate removal of the balloon catheter and to maintain access to the LAD in case of the need for reinstrumentation at a later point in the procedure. A cineangiogram should then be performed to document the integrity of the left main trunk and LAD. Although total occlusion of the recently injected septal branch is most commonly observed, some phasic flow may persist in the moments following ablation (Fig. 44.4).

Prior studies have demonstrated that patients with HCM have a reduction in coronary flow reserve—either due to a reversible adaptive response to systolic contraction overloading or from a chronic remodeling process of the coronary microcirculation. However, recent work suggests there is an immediate improvement in coronary flow reserve following alcohol septal ablation suggesting that the dynamic response to the pressure overload from the LVOT obstruction is a critical component of this pathophysiology (64).

Given the potential for serious intra- and periprocedural complications, observation of the patient in a coronary intensive care unit experienced with the nuances of the postprocedural care of such patients is advisable for 24 to 48 hours. Measured serum levels of creatinine phosphokinase (CPK) often reach levels between 800 and 1200 U/L following ethanol injection, though variation in the observed value is dependent on caliber of the injected vessel, volume of ethanol applied, and assays used (4,23,25,70,51,66,67). Therefore, patients meeting these objective criteria that continue to experience significant functional limitation due to symptoms of chest pain, exertional dyspnea, or recurrent syncope while compliant with optimal medical therapy and who are ineligible for surgical myectomy may be considered for septal alcohol ablation.

It is generally inadvisable to perform either surgical or percutaneous septal modification in minimally symptomatic patients with obstructive HCM, given the short-term risks inherent to both procedures and the paucity of data suggesting that the long-term outcome of untreated patients is worse than those undergoing the procedure. Furthermore, as outlined earlier, both forms of septal reduction may potentially be associated with serious complications—the risk of which may well outweigh any possible benefit in a minimally symptomatic

**INDICATIONS**

A number of patients will continue to experience lifestyle-modifying symptoms despite optimal medical therapy. A small but definite percentage of these patients may be candidates for either surgical myectomy or septal alcohol ablation. As has been stressed previously, it is of critical importance that a careful screening process be in place to identify which patients are appropriate for a septal modifying procedure and which type of procedure is best suited to the individual patient. Furthermore, it should be underscored that any form of septal modification is not a curative, but rather symptom-reducing intervention. The clinical circumstances in which a surgical septal-modifying procedure may be considered have been outlined in the updated American College of Cardiology/European Society of Cardiology consensus statement and includes patients with severe septal hypertrophy (i.e., >18 mm), resting/basal or inducible LVOT obstruction with gradient >50 mmHg, and severely limiting heart failure symptoms (i.e., NYHA functional class III–IV) despite optimal medical therapy (Table 44.4) (4,23,25,27,31,51,66,67).

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**Table 44.4 Selection Criteria for Alcohol Septal Ablation**

- NYHA heart failure symptoms (class III–IV) despite maximal medical therapy
- Left ventricular outflow tract gradient >30 mmHg at rest or >50 mmHg with provocation
- Absence of mitral valve or papillary muscle abnormalities
- Septal thickness >16–18 mm
- Compatible anatomy of septal branches
- Absence of significant coronary artery disease
patients. In addition, it should be stressed that these procedures should be performed at experienced centers as there is a significant learning curve that impacts the odds of a successful outcome and the amelioration of symptoms (68). Finally, it is important to emphasize that at present there is no clear data suggesting that relief of the outflow tract gradient through septal modification will positively alter a patient’s overall risk of progressing to the end-stage disease state.

CLINICAL ASPECTS
It is of critical importance that the clinicians thoroughly evaluate the patient for anatomical abnormalities that would require surgical management prior to proceeding with a catheter-based intervention. These abnormalities would include anomalous papillary muscle insertion into the mitral valve, anatomically abnormal mitral valve with a long anterior/posterior leaflet, coexistent coronary artery disease, primary valvular disease (aortic or mitral), or subaortic membrane or pannus—none of which can be adequately addressed by septal ablation (4,51). In addition, outflow tract obstruction resulting from abnormal elongation and/or myomatous degeneration of the anterior mitral leaflet is a rare but important discovery that would not be readily amenable to a percutaneous solution. Therefore, these patients will require surgical consultation for consideration of myectomy with plication and should not be considered for catheter-based therapy (Table 44.5) (59).

A thorough patient history including a detailed assessment of functional status is essential for appropriate patient selection. Regardless of the magnitude of the resting or dynamic LVOT gradient it is inadvisable to perform either surgical or percutaneous septal modification in patients without significant symptoms (or symptoms that are easily controlled with medications), given the short-term risks inherent to these procedures and the paucity of data suggesting that the long-term outcome of untreated patients is worse than those undergoing the procedure. Therefore, given that both forms of septal reduction can have potentially serious complications, the risk of either form of procedure may well outweigh any possible benefit in a minimally symptomatic patient.

LIMITATIONS
Complications following ethanol septal ablation are infrequent and comparable to those following myectomy. Although a left bundle branch block is often observed following septal myectomy, a right bundle branch block is observed in up to 80% of patients following septal ablation (43,37,51). The incidence of complete heart block exists and ranges widely across the literature (anywhere from 5–40%), with an average value of 12% to 15% at high-volume centers (43,30,37,51,69). High-degree atrioventricular block requiring permanent pacemaker implantation following the procedure has been correlated with pre-existing left bundle branch block and rapid injection of ethanol during the procedure (69). As discussed previously, special care must be taken to ensure no ethanol spills into the LAD. When this occurs, it is a catastrophic event, often resulting in a large mid- to distal anterior wall myocardial infarction, with an associated increase in mortality. Rare cases of coronary dissection related to use of an extrasupport guidewire or guide catheter trauma have been reported in the literature. Cardiac tamponade is another rare complication most commonly the result of perforation through the right ventricular apex during temporary pacemaker insertion or during interatrial septal puncture for hemodynamic monitoring. Another infrequent complication following the ablation is ventricular septal rupture, which can occur when an excess of ethanol is injected, resulting in an extensive area of infarction (51). Ventricular arrhythmias following the procedure are rare in the first 48 hours and can usually be managed conservatively while on telemetry observation. It remains a source of concern whether, due to the intramyocardial scar that develops following ablation, patients (particularly younger ones) may be at risk for late ventricular arrhythmias. However, this has so far not been convincingly demonstrated in the literature (4,37,60,70).

A recent prospective study has demonstrated a reduced number of ICD discharges in patients with HCM following alcohol septal ablation, arguing against the assumption that the procedure is proarrhythmic (71).

SPECIAL ISSUES/CONSIDERATIONS
As with any specialized procedure, local expertise must be considered when deciding between surgical myectomy and alcohol septal ablation. To treat this condition successfully, the interventionalist should not only be technically skilled but also ensure appropriate clinical follow-up and management post-procedure. Each patient is unique, and his/her individual anatomy, symptoms, and risk of surgery will impact the decision to perform alcohol septal ablation versus surgical myectomy.

Advances in MRI have improved diagnosis of the condition and give valuable information regarding location of papillary muscle insertion. Local expertise in this field is therefore also important. Given the risk of high-degree atrioventricular block and potential need for permanent pacemaker implantation, centers with adequate electrophysiology support are also preferable. Recall that right bundle branch block is more common with alcohol septal ablation, which differs from surgical myectomy, in which left bundle branch block is more common. When surgical myectomy must be performed following failed alcohol septal ablation, the risk of requiring permanent pacemaker increases further.

CONCLUSIONS
HCM is a unique cardiovascular condition associated with many different genetic mutations that result in a variety of phenotypes and variable clinical presentations at any age. Present in a minority of this patient population, outflow tract obstruction may vary significantly depending on physiologic
loading conditions, adrenergic state, and specific medications. Despite rapid advances in genetic screening, imaging modalities such as echocardiography and MRI remain the primary methods of diagnosis. Given the substantial variation in this population of patients, therapeutic interventions must take into consideration individual patient characteristics and preferences. Accordingly, management strategies range from medical therapy with close outpatient follow-up to surgical or percutaneous remodeling of the myocardium. While the initial intervention for symptomatic patients should be medical therapy, patients at high risk for sudden cardiac death should be considered for ICD therapy. In the setting of symptoms refractory to optimal medical management, surgical myectomy continues to be the gold standard therapy for HCM in appropriately risk-stratified patients in areas where an experienced team and facility are available. However, when surgical therapy is not feasible or possible, alcohol septal ablation provides an excellent alternative treatment modality when performed in appropriately selected patients in an experienced center.

REFERENCES


Atrial appendage exclusion

David R. Holmes, Jr. and Rebecca Fountain

INTRODUCTION

Stroke is the most feared complication of cardiovascular disease and occurs with an incidence of approximately 780,000 cases per year in the United States (1). Brain ischemia is the most common cause, occurring in almost 90% of cases. Stroke is the third most common cause of mortality and a leading cause of disability and accounts for approximately $60 billion in annual costs. The impact of stroke on a patient and family cannot be overemphasized because it brings with it the threat of loss of independence and irreparable loss of function. Accordingly, because of these issues, attempts at stroke prevention have received considerable emphasis.

Atrial fibrillation is the most common sustained cardiac arrhythmia and is increasing in frequency as the population ages (2–11). In individuals who are over 40 years of age, the lifetime risk of atrial fibrillation is one in four. The relationship between increasing age, atrial fibrillation, and stroke has been studied intensively. Stroke occurs at an annual rate of 5% in patients with atrial fibrillation; this rate increases with increasing age of the patients. In patients >80 years of age, atrial fibrillation is the cause of approximately 25% of all strokes. As the population ages and atrial fibrillation increases, there will be increased need for strategies to prevent stroke.

Although multiple randomized trials have documented the effectiveness of warfarin therapy for stroke prevention in the setting of atrial fibrillation compared with placebo, aspirin alone, or aspirin in combination with clopidogrel, many patients are not treated with warfarin (12–27). This is a result of the narrow therapeutic index associated with warfarin, patient compliance, the presence of absolute or relative contraindications particularly related to the potential for bleeding, and the wide variability in dosing schedules that make treatment difficult and inconvenient. These issues form the basis for the fact that only approximately 50% of high-risk patients with atrial fibrillation are treated with warfarin (27). Although new agents are being evaluated, the lifetime potential for costs, side effects, and compliance, as well as side effects make these less attractive (28,29).

Multiple sources of data including pathological and echocardiographic studies have documented that the left atrial appendage is the site of thrombus formation in approximately 90% of patients with nonvalvular atrial fibrillation (Fig. 45.1) (30). This finding has led to the development of several approaches for exclusion of the left atrial appendage and one randomized trial. The intent of these approaches has been to prevent stroke without the need for warfarin anticoagulation.

ANATOMIC CONSIDERATIONS

Consideration of the application and potential role of these approaches requires understanding of the anatomy of the left atrial appendage (31–33). The left atrial appendage is a diverticulum that arises from the left atrium and lies within the pericardium superior to the left ventricular free wall and next to the superior and lateral aspect of the main pulmonary artery. It varies significantly in structure, volume, and three-dimensional configuration (Fig. 45.2).

Veinot et al. (33) evaluated 500 normal autopsy hearts. This series included 25 male and 25 female subjects from each decade of life for a total of 10 decades. A striking finding was that 54% of specimens had two lobes of the left atrial appendage while only 20% of specimens had a single lobe. These lobes were found to lie in multiple planes and have a variable distance from ostium to the distal tip. More recent data from the SPARC study also found that approximately 50% of patients have multiple lobes (34,35). In addition to wide variability in number of lobes, the volume and dimensions also vary. In a study of 220 cases (34), the left atrial appendage volume varied widely up to 19.2 mL and the length ranged from 16 to 51 mm.

This variability in dimensions has significant implications for approaches aimed at left atrial appendage exclusion. The approach with the best chance to most completely and reliably abolish stroke will require the ability to fully cover the ostium of all lobes as well as the origin of the left atrial appendage. Exclusion of that portion of the left atrial appendage that contains pectinate muscles may also be important as thrombus could potentially develop between adjacent muscles. Residual flow into a patent lobe may still result in an increased incidence of stroke. The length of the left atrial appendage and its angulation is also important, as any implantable device must be able to fit into the body of the left atrial appendage without protruding out into the body of the left atrium itself.

Assessment of the specific details of left atrial appendage anatomy is essential for patient selection and procedural performance. Transesophageal echocardiogram (TEE) is the most commonly used approach but computed tomography (CT) is used with increasing frequency (Fig. 45.3).

There are several essential pieces of information: Identifying the presence or absence of thrombus. If a thrombus is present as a filling defect or is suspected because of the presence of a dense cloud of echoes (smoke), then percutaneous approaches and perhaps all nonsurgical approaches should be avoided because of the potential for embolization during the procedure. In this setting, warfarin should be administered and repeat imaging performed to document either persistence or disappearance of the thrombus. If the thrombus is found to have disappeared, then device implantation can be planned and performed.

Dimensions of the left atrial appendage and relationship to the pulmonary veins. Budge et al. (31) compared left atrial appendage morphology in patients with atrial fibrillation using TEE,
planar CT, and segmented three-dimensional CT in 53 patients. They measured maximal left atrial appendage orifice diameter, width, and depth with each modality. In addition, they assessed the relationship of the left atrial appendage with the left pulmonary veins. There were quantitative differences in measurements depending on which modality was used (Table 45.1). In general, the orifice diameter values measured by TEE and planar CT were similar while values obtained using segmented reconstruction were larger. This has important implications for device sizing, because with the current device, there are multiple different sizes depending on the orifice diameter. There were also differences in the mean left atrial appendage depth which ranged from 25.1 mm with planar CT to 35.9 mm with TEE. This also has important implications for device selection and size. Early generation devices were relatively long; more recent devices are shorter and can fit in most anatomic situations. Of importance is the fact that in the Budge et al. (31) study, in contrast to the pathology series, the majority of appendages studied were single lobed. The presence of multiple lobes can compound the issue of device placement. In some patients, not all lobes can be covered, while in others, to cover the ostium adequately, one of the lobes must be entered deeply for device placement. If the angulation between lobes is large, this can create problems trying to achieve a stable position.

The relationship between the left atrial appendage and pulmonary veins. Budge et al. (31) found that the superior aspect of the plane of the left atrial appendage was typically located in the mid portion of the left superior pulmonary vein while the inferior aspect was high relative to the plane of the left inferior pulmonary vein. These relationships may have important implications for accessing the left atrial appendage as well as for device placement. Depending on the amount of protrusion into the left atrium by a device, it is possible to impinge on the orifice of one of the left pulmonary veins thereby impeding normal flow.

**APPROACHES AND OUTCOME**

Although several devices have been evaluated for left atrial appendage occlusion (36–44), the single randomized trial involves the Watchman™ device (40) (Fig. 45.4), which is a self-expanding nitinol frame structure with fixation barbs and a permeable polyethylene membrane (39,40,42,43). This device is available in diameters ranging from 21 to 33 mm to accommodate variations in left atrial appendage anatomy.
The device is implanted using a trans-septal approach and a catheter-based delivery system to cover the ostium of the left atrial appendage (Fig. 45.5). Device implantation is guided by fluoroscopy as well as TEE to verify proper position and stability.

**IMPLANTATION**

Typically, three vascular access sheaths are placed: these include two femoral venous sheaths, one for the appendage occlusion device itself, one for the intracardiac ultrasound catheter, and one for arterial access. The arterial access sheath should be small (e.g., 4 Fr); this sheath allows placement of a pigtail catheter to identify the level of the aortic valve for optimizing the trans-septal procedure as well as for monitoring aortic pressure. The venous sheaths placed need to accommodate the intracardiac ultrasound catheter using an 8- to 10-Fr device as well as the occlusion device. The venous access for the occlusion device should be from the right femoral vein because that facilitates trans-septal puncture; the site should be prepared so that eventually a 14-Fr sheath can be placed. The other two sheaths are usually placed on the contralateral left femoral side.

Approaches to the trans-septal catheterization vary considerably. The goal is to cross the atrial septum at the level of the fossa ovalis. In many laboratories, biplane fluoroscopic imaging is used with orthogonal views either AP and lateral or 30° RAO/60° LAO. The most important complication to avoid is entry into the ascending aorta. While entry with the Brockenborough needle into the aorta does not necessarily lead to catastrophic bleeding, if high pressure is identified with needle puncture, it is essential to avoid placement of a larger dilator and sheath, because that results in major hemorrhage.

More recently, intracardiac ultrasound has been used more extensively for trans-septal catheterization. With this approach, the needle can be visualized within the right atrium and the details of septal anatomy can be characterized. In some patients, particularly those who have had prior trans-septal procedures, the atrial septum is fibrotic and the needle may slide cranial leading to a puncture site that is too superior. Similarly, a fatty limbus may impact on the entrance site. With intracardiac ultrasound, the needle can be visualized as it enters the left atrium using injection of saline or contrast. The level of puncture of the intra atrial septum is of importance because it impacts on the ability to optimize a guiding sheath into the left atrial appendage. If the left atrial appendage angulates quickly caudally, then a lower septal puncture helps so that the guiding sheath can be placed more coaxially into the appendage. The development and subsequent wide use of steerable guiding sheaths will help to minimize this issue.

Once safe access to the left atrium is accomplished, heparin is administered. Typically, an activated clotting time is measured with a goal of approximately 250 seconds. It is important to administer heparin promptly because thrombus can form in the long sheaths and can embolize during the procedure.

The goal of the procedure is safe access onto the left atrial appendage once a sheath has been placed into the left atrium. Knowledge of the detailed anatomy is important, particularly the relationship between the left atrial appendage and pulmonary veins. The large 14-Fr sheath for device delivery can easily damage the left atrial wall particularly the dome, or the left atrial appendage itself. Although several approaches can be used, the current recommended approach is to engage the left atrial appendage with a pigtail catheter. This approach minimizes the potential for trauma that can result in perforation of the left atrial appendage. Once the left atrial appendage is entered with the pigtail catheter, the sheath is advanced to the ostium where a stable position is obtained and documented by angiography.

The current sheath has marker bands at its distal tip that facilitate placement of the device. The device is selected on the basis of the dimension of the orifice determined by contrast angiography as well as TEE, although as previously mentioned, CT image analysis prior to the procedure may be helpful in selecting the optimal device size (Fig. 45.3). The device is advanced being careful to minimize the chance for entrapment of air. Avoidance of trapping air is best accomplished by a high-pressure saline line that infuses saline during advancement of the device. Once the device is positioned in the left atrial appendage and confirmation has been obtained that there is no damage to the left atrial appendage, the sheath is withdrawn leaving the occlusion device in place. If the device is positioned too deeply in the left atrial appendage, it can be recaptured and withdrawn to a more ideal position. If the
The primary endpoint of this trial was to determine if the Watchman device was noninferior to treatment with warfarin with respect to a composite efficacy endpoint of freedom from all stroke, both ischemic and hemorrhagic, cardiovascular death, and systemic embolization during follow-up out to 1500 patient-years. Analysis of this trial continues. The results of this randomized trial will be important to assess both safety and efficacy of this device and approach. On the basis of the outcome of that analysis, the number of patients that could be treated if an approved device was available would increase dramatically.

Fountain et al. (40) evaluated the frequency with which the Watchman device might be used if the randomized trial resulted in FDA approval. They used a screening log of 1798 patients to assess this. Of this group of patients who were screened, only 31 patients were enrolled in the randomized trial. Among the patients who were not enrolled in the randomized trial, 21% would have been excluded from device use even after potential approval. The most common reason was the requirement for long-term anticoagulation either because of a prosthetic cardiac valve or for some other reason. The remaining patients (79%) would have been candidates for the device. Given the large number of patients with atrial fibrillation, the number of patients who could be candidates for the device such as this would be substantial.

PLAATO

The PLAATO (38,45) occluder (Fig. 45.7) was the first device designed for percutaneous left atrial appendage occlusion. This device was a self-expandable nitinol cage that was covered with an impermeable e-PTFE membrane. Similar to the Watchman device, it had anchors to prevent embolization and came in different sizes ranging from 20 to 32 mm to ensure optimal sealing. This device was also delivered by a trans-septal approach as described above using a special 12-Fr sheath. Although this device is no longer marketed because of commercial issues, there are important data available regarding the patient population in which it was used and its outcome. Ostermayer et al. (45) reported on the outcome of two international multicenter feasibility trials that included 111 patients. All of these patients had a contraindication for anticoagulant therapy and were at risk for stroke. Implantation of the PLAATO device was successful in 108 patients. Three patients required pericardiocentesis for hemopericardium and one
patient required urgent cardiovascular surgery and subsequently died of neurologic causes. The primary endpoint for these registries was the incidence of major adverse events defined as a composite of stroke, death, myocardial infarction, or need for procedural related cardiovascular surgery during follow-up. All of these patients received aspirin and clopidogrel initially but no warfarin. Long-term treatment varied but at a minimum consisted of aspirin-administered indefinitely. During follow-up that averaged 9.8 months, there were six deaths (5.4%) and the observed annual stroke rate was 2.2%. On the basis of the baseline CHADS-2 score, this 2.2% event rate was improved compared to the predicted 6.3% rate.

In a larger experience of 210 patients treated with the PLAATO device worldwide (36) device implantation success was also high at 97.6%. In this group during a follow-up of 258 patient years, only 5 patients had a stroke that was again less than predicted by the baseline CHADS-2 score.

AMPLATZER OCCLUSION DEVICES
Amplatzer atrial septal occluder devices have also been used (Fig. 45.8) (37,42). These double disk devices are made of a nitinol wire frame mesh with Dacron patches inside. Using a standard trans-septal approach, an introducer sheath compatible with the chosen occluder device is advanced deeply within the left atrial appendage. Typically, the left side of the device is deployed within the left atrial appendage itself, while the right disk is deployed at the left atrial side of the ostium. The position is ascertained by hand injection of contrast medium through the sheath. Intracardiac ultrasound can be used to also confirm device position. If the position is acceptable, the device is released. In an initial experience of 16 patients (42), there was one technical failure with device embolization that required surgery. Subsequent to this, a somewhat larger experience of 27 patients has been reported. In this series of 27 patients, device embolization immediately after implantation was identified in four, and two patients had to undergo surgery for this. Another occluder embolized during follow-up and was snared using percutaneous techniques. At that time of that presentation, no patient had experienced a stroke during a follow-up time of 30 patient years. The Amplatzer device is currently being modified for optimizing placement in the left atrial appendage and will be studied in a subsequent randomized clinical trial.

OPEN SURGICAL LIGATION
Open surgical ligation has also been studied and is the focus of a multicenter randomized trial. The approach that has been documented uses either a suture or a stapling device for closure at the time of elective coronary artery bypass graft surgery. A pilot study (Left Atrial Appendage Occlusion Study, LAAOS) has been reported (46). In this study, 97 patients were consented but 20 had unsuitable left atrial appendage anatomy. This was predominantly because the left atrial appendage was either too broad or too small. In the 77 patients who were randomized, 52 had occlusion of the left atrial appendage and 25 patients served as controls. During surgery, complications occurred with a torn left atrial appendage in nine patients. Left atrial appendage occlusion was achieved in only 45% of patients in which sutures were used and 72% of patients where a stapler approach was used. For a mean follow-up of 13 ± 7 months, 2.6% of patients had thromboembolic events. This pilot study has been used to plan a larger ongoing study.

EXTRACARDIAC OBLITERATION
An additional invasive approach includes thoroscopic extracardiac obliteration. An initial experience with 15 patients was reported by Blackshear et al. (47). With this approach, a double lumen intratracheal tube is used. Selective intubation and ventilation of the right lung results in reduction in the volume of the left lung. Using video-assisted thoroscopic instruments, the pericardium is opened and the tip of the left atrial appendage can be grasped. A loop is then manipulated to position it at the base of the appendage where it is cinched to occlude the appendage. In this small series, success was achieved in 14 of 15 patients; one patient developed bleeding and was converted to open thoracotomy. In all of these patients, there was a contraindication to anticoagulant therapy.

Patients were followed up for a mean of 42 ± 14 months. One fatal stroke occurred 55 months after surgery and one nondisabling stroke 3 months after surgery. There were two other deaths. In a subgroup of 11 patients with a history of prior thromboembolism, there was an annualized rate of stroke of 5.2% per year, which compared with a historical control rate of 13% per year for similar aspirin-treated patients from the Stroke Prevention in Atrial Fibrillation trials.

SUBXIPHOID TRANSPERICARIAL APPROACH
A final approach that is being developed is a subxiphoid transpericardial approach. Using this, the pericardial space is entered percutaneously. A videoscope is inserted. A grasping device is manipulated around the pericardial space to the region of the left atrial appendage and is used to capture the tip of that structure. Following this, similar to the thoroscopic approach described earlier, a loop is positioned at the base of

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**Figure 45.8** Amplatzer septal occlusion devices (AGA Medical Corporation, Plymouth, Minnesota, U.S.) have also been used “off label” to occlude the left atrial appendage. Typically, the distal disk is deployed within the left atrial appendage (LAA) and the proximal disk is deployed just at the ostium.
the left atrial appendage and tightened to occlude that structure. There is limited data available using this approach.

CONCLUSIONS
Stroke is one of the most feared complications of cardiovascular disease because of its attendant morbidity and mortality. Prevention of stroke has received great attention. The relationship between stroke, atrial fibrillation, and increasing age has been clearly identified. Multiple series have documented that in the setting of nonvalvular atrial fibrillation that thrombus develops and originates in the left atrial appendage. Given the constellation of stroke, atrial fibrillation and left atrial appendage, multiple efforts are currently aimed as exclusion of the latter. If successful left atrial appendage exclusion is documented to be effective in preventing subsequent strokes and safe, then this approach will be widely used in patients who do not want to take coumadin indefinitely or in patients who cannot take coumadin.

REFERENCES
Percutaneous closure of atrial septal defect and patent foramen ovale

Yves Laurent Bayard, Andreas Wahl, and Bernhard Meier

INTRODUCTION
Over the past decades, transcatheter techniques for closure of atrial septal defects (ASD) and patent foramen ovale (PFO) have emerged not only as an alternative to surgery, but as therapy of first choice in most patients. While the first interventional devices for this purpose were afflicted with rather high rates of complications and residual shunts, current occlusion systems achieve high occlusion rates and complications are rare.

ATRIAL SEPTAL DEFECT
Anatomical Considerations
ASD within the oval fossa (ASD of secundum type) occur in 1.5 to 2 of 1000 newborns and are two to three times more common in females (1,2). They are the most common ASDs (about 70%), and may be singular or multiple. Implantation of a transcatheter device requires sufficient cranial, caudal, and posterior rims. However, an anterior rim (behind the aortic root) is not necessary. Furthermore, a minimal distance of the ASD margins to neighbor structures is required (right upper pulmonary vein, coronary sinus, atriocventricular valves). To determine whether these morphologic conditions for interventional ASD closure are given, a tranesophageal echocardiogram with measurement of the atrial dimensions is required prior to closure in most adults. Not suitable for catheter treatment are ostium primum defects or sinus venosus defects.

Pathophysiology
Defects of the atrial septum represent the second most common congenital heart disease after ventricular septal defects. Many patients with an isolated secundum ASD do not develop any clinical symptoms during childhood. Therefore, the diagnosis of ASD is frequently missed until adult life. Patients may present with unspecific symptoms such as dyspnea, fatigue, or palpitations. Typical auscultation findings are a soft ejection systolic murmur resulting from the relative pulmonary stenosis and a characteristic wide and fixed splitting of the second heart sound. In secundum type ASD, the electrocardiogram may show right-axis deviation and incomplete right bundle branch block, whereas left-axis deviation might be noted in ostium primum defects. Chest X-ray may reveal prominent pulmonary arteries and right heart enlargement. Endocarditis is not an issue because the shunt between low pressure chambers is free of turbulence.

Left-to-right shunt patients with an ASD are at-risk for right heart overload with consecutive cardiac arrhythmias or heart failure. In addition, irreversible injury of the pulmonary vascular bed with secondary pulmonary hypertension or even Eisenmenger’s syndrome can result from volume overload of the lung vessels. The possibility of a transient right-to-left shunt during Valsalva maneuvers includes the risk of paradoxical embolism via the ASD.

Indications for ASD Closure
Regardless whether the patient is symptomatic, defect closure is indicated if a significant left-to-right shunt (Qp/Qs ratio > 1.5:1) is measured during right heart catheterization or a right heart dilatation (right ventricle end-diastolic diameter >30 mm) can be detected in transthoracic echocardiography (TTE). In addition, ASDs may be closed to prevent paradoxical embolism, even if there is no evidence for hemodynamic relevance. As small ASDs are easy to close percutaneously, the indication for closure can be generalized.

PATENT FORAMEN OVALE
Anatomical Considerations
The interatrial septum is formed by two structures, the left-sided more fibrous septum primum, and the right-sided muscular septum secundum. After having grown from the periphery to the center, they form a slit valve that opens with pressure from the right. When pulmonary circulation is established after birth and left atrial pressure exceeds right atrial pressure, the valve shuts. In most individuals, the overlapping parts of the septa fuse permanently. Nevertheless, the prevalence of PFO is high. Autopsy studies have shown a prevalence of up to 30% in healthy subjects (3). In these individuals, the PFO permits intracardiac shunting during periods when right atrial pressure exceeds left atrial pressure.

In 50% to 85% of subjects with an atrial septal aneurysm (ASA), a PFO is present. This congenital abnormality of the atrial septum is formed by an elongated, muscular membrane in the region of the fossa ovalis. ASA is usually defined as excursion of the atrial septum ≥10 mm in either direction or both directions combined. Additionally, the base of the flimsy portion of the interatrial septum must exceed 15 mm (4).

Pathophysiology
In contrast to an ASD, a PFO alone is not considered a pathologic finding. A possible relationship between PFO and stroke was first suggested by Cohnheim in 1877 (5). Nowadays, PFO and ASA when associated with PFO have been recognized as potential mediators of several disease manifestations, including paradoxical embolism, orthostatic desaturation in the setting of the platypnea-orthodeoxia syndrome, refractory hypoxemia due to right-to-left shunt in patients with right ventricular infarction or severe pulmonary disease,
neurologic decompression illness in divers, high-altitude pulmonary edema (6), and migraine with aura.

In 35% to 40% of all patients with an ischemic stroke the cause of the stroke remains “cryptogenic” (7). Several studies have shown that the prevalence of a PFO in these patients is significantly higher than in control groups. The incidence of a PFO in patients with cryptogenic stroke varies between 44% and 66% compared with only 9% to 27% in the control groups (8–11). Therefore, the PFO should be considered as the source of the embolic event, even if the thrombus crossing the atrial septum can only be shown very rarely (12,13). Serena and Davalos found that large shunts in PFO patients are associated with a higher risk for stroke than small shunts (7).

ASA in the absence of PFO is not a risk factor for strokes (14). However, ASA is an important reason for the foramen not closing and has been suggested to increase the diameter of a present PFO because of the highly mobile atrial septal tissue. This leads to a more frequent and wider opening of the channel (15). ASA or a Eustachian valve might as well promote a right-to-left shunt by directing the blood flow from the inferior vena cava toward the PFO (16). Mas et al. found a significantly higher risk for transient ischemia attack (TIA) or stroke in patients with a PFO in combination with an ASA of about 20% at four years compared with patients with PFO only (17).

**Indications for PFO Closure**

It is not scientifically supported, but common, to exclude all other potential sources for the embolic event such as atrial fibrillation, carotid stenosis, or thrombophilia before closing a PFO. Transcatheter PFO closure is still considered to be indicated only after an otherwise unexplained (cryptogenic) embolic stroke, TIA, or peripheral embolism, if the potential for right-to-left shunt via a PFO can be demonstrated by contrast transesophageal echocardiography (TEE).

**Preparations, Implantation Technique, and Follow-up Regimen**

If an atrial septal communication is suspected, TEE is recommended to anatomically define the defect, measure its dimensions and margins, for quantification of shunting and exclusion of a multiperforated septum. In case of a PFO, TEE in combination with a Valsalva maneuver is the most sensitive and specific instrument to prove right-to-left shunting through the structure, to recognize the presence of ASA, and to estimate the severity of the shunt as additional risk factors for paradoxical embolism.

During the intervention, patients are administered heparin and endocarditis prophylaxis (e.g., cefuroxim IV). Echocardiographic guidance is not recommended for PFO closure. It is not required for a safe procedure, but prolongs the procedure considerably and increases complications (18). For ASD closure the use of either TEE or intracardiac echocardiography (ICE) guidance is debatable. When TEE guidance is used, atropine to prevent hypersalivation is given. Conscious sedation (midazolam, propofol) or general anesthesia with endotracheal intubation is used.

Venous access is gained via the right femoral vein. The shunt is passed directly with the guidewire or with a multipurpose catheter. Balloon sizing (Fig. 46.1) with a soft measuring balloon is recommended for ASDs. The waist of the balloon caused by the margins of the ASD is measured to determine the size of the defect (stretched diameter) and choose the appropriate device size. If the balloon sits stable in the septum, the device is oversized by 20% to 40%, if not by 40% to 60%, assuming a nonrobust rim.

The further implantation technique of the respective occluders is described in the corresponding chapters later. Generally, for larger ASDs only the Amplatzer ASD Occluder should be used, for small ASDs or PFOs other systems are also suitable. Only the Amplatzer Septal Occluder comes in an ASD and a PFO version.

If the procedure is conducted under echocardiographic guidance, a contrast study with Valsalva maneuver is performed after device implantation to evaluate the immediate closure rate. If not, a right atrial dye injection confirms position and informs about the residual shunt (Fig. 46.2). Hemostasis is achieved by manual compression of the femoral vein. The procedure can be performed on an outpatient basis and may take <30 minutes, with a fluoroscopy time of about five minutes. The patient can resume unrestricted physical activity a few hours post procedure.

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**Figure 46.1** Balloon sizing of an ASD. The waist of the balloon caused by the margins of the ASD (30 mm) is used to choose the appropriate device size (36 mm). The inset shows the perfect closure at a bubble test during a follow-up transesophageal echocardiogram at six months. *Abbreviations: ASD, atrial septal defect; LA, left atrium; RA, right atrium; LV, left ventricle.*
Acetylsalicylic acid 100 mg and clopidogrel 75 mg are prescribed for a minimum of five and one months after implantation, respectively. Endocarditis prophylaxis is recommended for two to six months. Follow-up is performed with TTE to confirm device position before hospital discharge and with TEE after six months to confirm complete closure of the intra-atrial communication and exclude thrombosis of the device (19). If the PFO proves completely closed, no further follow-up measures need to be planned. In case of persistence of a relevant residual shunt after six months, later spontaneous closure is possible, the PFO proves closed, no further follow-up measures need to be planned. In case of persistence of a relevant residual shunt after six months, later spontaneous closure is possible.

**Double-Disk Devices**

In 1974, King and Mills (20) used double-umbrella devices to occlude experimentally created ASDs in a canine model. In 1976, they successfully performed this technique in a 17-year-old female (21). After having treated five additional patients they reported excellent long-term results (22) in 1984 as well as in 2003 (23). Transcatheter PFO closure was first described by Bridges et al. in 1992 (24). They used the Clamshell device in 36 patients after presumed paradoxical embolism. Berger et al. reported their experience with the Amplatzer Septal Occluder in 200 patients (26); 68 of them had a PFO. They claimed complete closure of the defect in all patients without adverse events. More recently, Sievert and colleagues reported a larger series with 650 patients who were implanted success rate was 98%. During follow-up of up to eight years, complete defect closure could be documented in 96% of the patients with a single ASD and 71% of the patients with a multifenestrated septum. There were no septic complications or outcomes related to the device.
Figure 46.3  Occluder overview. (A and B) Amplatzer ASD Occluder (AGA Medical Corporation, Golden Valley, Minnesota, U.S.); (C and D) Amplatzer PFO Occluder (AGA Medical Corporation); (E) STARFlex Occluder (NMT Medical, Inc., Boston, Massachusetts, U.S.); (F) BioSTAR Occluder (NMT Medical, Inc.); (G) Helex Septal Occluder (W. L. Gore & Associates, Inc., Flagstaff, Arizona, U.S.); (H) AtriaSept Occluder (Cardia, Inc., Eagan, Minnesota, U.S.); (I) Occlutech Occluder (Occlutech, Jena, Thuringia, Germany); (K) Solysafe Occluder (Swissimplant AG, Solothurn, Switzerland); (L) Premere Occluder (St. Jude Medical, Inc., St. Paul, Minnesota, U.S.); (M) SeptRX Occluder (Secant Medical, Perkasie, Pennsylvania, U.S.).
two device embolizations but the devices could be recovered without need for surgery. The most common complication during follow-up was new onset of atrial fibrillation in 4%.

We reported a series of 620 patients who underwent PFO closure using the Amplatzer PFO Occluder (18). All implantations were successfully conducted without echocardiographic guidance. Procedural complications occurred only in five patients: one patient sustained a TIA and four showed arteriovenous fistulae at the puncture site, requiring elective surgical correction. Mean follow-up time was three years. Freedom from recurrent ischemic stroke, TIA, or peripheral embolism was 99% at one year, 99% at two years, and 97% at five years post procedure.

CardioSEAL/STARFlex/BioSTAR
CardioSEAL (NMT Medical, Inc., Boston, Massachusetts, U.S.) is a revised version of the Clamshell occluder. It can be delivered as a 11-Fr sheath and is available in sizes up to 38 mm. Two rectangular disks, each consisting of four wire spring arms, form the frame of this double-umbrella system. Each disk is covered with a knitted polyester patch. The centers of the umbrellas are connected.

STARFlex (NMT Medical, Inc.), a newer version of the CardioSEAL, has an additional microspring system (Fig. 46.3). It also comes in a version with six arms with a diameter of 38 and 43 mm. The microsprings connect the distal tip of each arm with the opposing arm. This system allows some self-centering of the device inside an ASD. In addition, the microsprings provide a close attachment of each disk to the septum, which allows for a low profile and is helpful in more complex defects (e.g., presence of ASA). The STARFlex device has the possibility to implant relatively large devices into small defects. This is advantageous in patients with a multiple perforated septum, just like the cribriform Amplatzer occluders. The device can be introduced through a 10-Fr sheath, and the implantation technique resembles the procedure with the Amplatzer occluders to a large extent.

Carminati et al. performed PFO closure using the CardioSEAL device in 79 patients and the STARFlex device in 38 patients (28). Either device was successfully implanted in all patients. A second device had to be placed immediately in six patients. During follow-up, there were no complications and no recurrent cerebral ischemia. STARFlex showed a significantly lower wire frame fracture rate than its predecessor, CardioSEAL. Additionally, the occlusion rate was significantly higher using the newer STARFlex device.

A larger series of PFO patients who received a STARFlex device has been reported by Taaffe and colleagues in 2008: 220 patients were implanted with a device; in two of them, the device had to be exchanged for another size. Post procedure, 10 patients developed atrial fibrillation, which resolved spontaneously in seven patients. Within 30 days after implantation, a thrombus formation was found on the occluder of eight patients. They were administered oral anticoagulation for three months, and all thrombi resolved without clinical sequelae.

The relatively high thrombosis rate has prompted the manufacturer to replace the fabric with collagen. This new device is called BioSTAR because the collagen is bioabsorbable more rapidly and more completely than the fabric used previously (Fig. 46.3). In the BioSTAR Evaluation Study (BEST), the device was successfully implanted in 57 of 58 patients (29). There were no procedural complications. The occlusion rate assessed by contrast TTE was 92% after one month and 96% after six months.

Helex Occluder
The Helex Occluder (W. L. Gore & Associates, Inc., Flagstaff, Arizona, U.S.) is a device with a unique spiral shape. It consists of two disks connected in the center by an eyelet mechanism (Fig. 46.3). It is available in diameters of up to 35 mm. Both disks are formed by one continuous wire (nitinol) in the shape of a spiral. An expanded polytetrafluoroethylene patch is attached to this wire. Bringing the wire in a straight configuration allows loading inside a 9-Fr delivery sheath. The spiral design provides a very low profile and an atraumatic healing process after implantation. As another unique feature, the Helex implantation system has a security cord attached to the device which allows retrieval at any point during the procedure, even after initial release from the delivery catheter.

Before implantation the Helex device attached to a control catheter is loaded into a delivery catheter. The delivery catheter is advanced through the ASD until the tip containing the collapsed device is positioned inside the left atrium. The device is advanced through the delivery catheter allowing the left atrial disk to expand in the left atrium. The sheath and the catheter are pulled back simultaneously until the released part is positioned close to the septum as seen in TEE. Thereafter, the right atrial disk is opened. After control of a stable and correct position of the device by TEE, the device is detached. Finally, the security cord is removed.

In 2007, Jones and colleagues reported the results of the U.S. pivotal study on ASD closure with 119 Helex device patients versus 128 surgical closure patients (30). In the interventional group one device had to be retrieved after embolization. In the surgical group one patient died from cardiac tamponade. With an implantation success rate of 92% and significant residual leak in only 2% of the patients treated with the Helex device, noninferiority to surgical closure could be demonstrated.

In 2006, Billinger et al. reported their experience of PFO closure using the Helex device in 128 patients (31). Device implantation was successful in all but one patient. In a mean follow-up time of 21 ± 11 months, one device embolization and one TIA occurred. There were no strokes, deaths, perforations, or thrombus formations on the device. Other reports have signaled relatively poor closure rates with this device (32).

Atriaspct Occluder
The Atriaspct Occluder (Cardia, Eagan, Minnesota, U.S.) is the newest generation of double-disk devices based on the PFO Star device from 1998 (Fig. 46.3). Atriaspct is made of a nitinol frame covered by two equally sized disks of polyvinyl alcohol foam. The implantation technique resembles the Amplatzer device procedure. In 2008, Luermans and colleagues presented the results of a European multicenter study including 430 patients who had their PFO closed using the Atriaspct Occluder (33). Device malpositioning occurred in 4 patients and new onset atrial arrhythmia was observed in 22 patients (5%). In a median follow-up time of one year, two patients (0.5%) sustained a stroke and seven patients (2%) a TIA.

Occlutech Occluder
Occlutech is a meshwire nitinol occluder (Occlutech, Jena, Thuringia, Germany) that copies the Amplatzer occluders both in appearance and implantation technique (Fig. 46.3). The main difference is the knitting technique of the Occlutech device and the absence of a left atrial knob. Thus, the risk for thrombus formation on the device might be even lower than in Amplatzer devices. In a first feasibility study, 37 PFO patients...
were enrolled. One patient could not be implanted because the PFO could not be crossed with the catheter; one patient developed transient atrial fibrillation. Of the 34 patients seen at six month follow-up, complete occlusion could be shown in 30 patients. There was one case of significant left-to-right shunt. There was no recurrent stroke or peripheral embolism.

**SolySafe Occluder**

The SolySafe Occluder (Swissimplant AG, Solothurn, Switzerland) consists of a device with two foldable polyester patches attached to eight metal wires, folding to a very flat-profiled double-disk occluder during intervention (Fig. 46.3). In a pilot study, the occluder was successfully implanted in 29 PFO and 15 ASD patients without procedural complications (34). Follow-up TEE six months after implantation showed complete occlusion of all interatrial communications.

**Premere Occluder**

The Premere PFO Closure System (St. Jude Medical, Inc., St. Paul, Minnesota, U.S.) is a dual-anchor arm device (Fig. 46.3). The anchors are made of nitinol and the right anchor is sandwiched between two layers of knitted polyester fabric. A flexible polyester braided tether running through the center of the anchor holds the two anchors together. The anchors are retrievable and repositionable. After delivery, they are locked together and the tether is cut. The distance between the two anchors is selectable before release, depending on the length of the PFO track. The device comes in 15, 20, and 25 mm diameter. Buscheck and colleagues reported the results of the CLOSEUP trial, a multicenter, nonrandomized study to determine the safety and effectiveness of the Premere device for PFO closure (35). The procedure was technically successful in all 73 patients. One patient developed transient atrial fibrillation. Six months post procedure, follow-up TEE was conducted and showed complete PFO occlusion in 86% of the patients. There were no device dislocations, recurrent strokes, or deaths.

**NOVEL DEVICES AND NONDEVICES**

**SeptRX Device and Coherex Flatspent**

The SeptRX device (Stout Medical Group, Perkasie, Pennsylvania, U.S.; Fig. 46.3) and the Coherex Flatspent (Coherex Medical, Inc., Salt Lake City, Utah, U.S.) have been designed to plug the tunnel of the PFO and expose as little foreign surface to either side of the atrial septum as possible. Thereby, the risk of thrombus formation is minimized and the amount of foreign material in the body is reduced.

The SeptRX device is made of a nitinol wire mesh and a nitinol frame with small left and right atrial anchors. In an initial feasibility study, complete occlusion of the PFO within the first 30 days after implantation could be achieved in only 6 of 11 patients. After six months, complete occlusion could be observed in all subjects.

The Coherex Flatspent device is designed to stent the PFO tunnel. So far, the self-expanding device is only suitable for tunnel lengths >4 mm and a balloon stretched diameter of 4 to 10 mm. Clinical experience is limited to a few preliminary cases in humans.

**Sutura Super Stitch Device**

The Sutura Super Stitch device is a suture-based closure device (Sutura, Inc., Fountain Valley, California, U.S.) based on a puncture site closure technique. The device has a working length of 90 cm and is introduced via a 12-Fr sheath. The PFO is crossed with the tip of the device. When drawing the system back, first the septum primum and then the septum secundum are caught and sewn together. Experience with this device in humans is very limited, however, a clinical trial is planned.

**BioTREK Device**

The BioTREK device (NMT Medical, Inc.) represents the next stage of development of the BioSTAR Occluder. Other than the BioSTAR with its nitinol frame, the BioTREK device is made of poly-4-hydroxybutyrate, a completely bioresorbable material that is isolated from bacteria. The device is flexible, radiopaque, and repositionable. Clinical studies are currently ongoing.

**PFx Closure System**

Despite the favorable safety and efficacy of permanent implant devices, apprehensions and disadvantages exist with a foreign structure that remains in the heart. Potential complications associated with PFO implant devices include thrombus formation, device erosion, device embolization, and atrial fibrillation.

The PFx Closure System (Sierra, Inc., Redwood City, California, U.S.) allows device-free closure of PFOs, leaving no foreign material behind after the procedure is finished. It consists of a catheter with a metal electrode at the distal end and an elastomeric distal housing covering the electrode. Electrical leads exit the proximal end of the device and connect to a radio frequency generator.

The PFx catheter is inserted through a 16-Fr sheath. Under TEE guidance, the distal housing is moved against the atrial wall so the electrode covers the PFO mouth. After confirmation of a correct device position, suction is applied. When adequate seal is achieved, the guidewire is removed and the radio frequency generator is engaged in accordance with a prescribed power algorithm resulting in heating of the cardiac tissue.

In 2009, Sievert and colleagues reported intermediate results of PFO closure using the PFx system within a nonrandomized, multicenter study (36). In 130 of 144 patients enrolled, radio frequency energy could be successfully applied. Besides a procedural bleeding complication with need for transfusion, there were no acute or intermediate complications of this technique such as recurrent strokes, deaths, conduction abnormalities, or perforations following the procedure. In a mean follow-up time of six months, complete occlusion of the PFO was achieved in only 55% of the patients. In patients with a PFO stretched diameter of <8 mm, the occlusion rate was 72%, suggesting that the vacuum created by the first generation of PFx devices to achieve tissue apposition might not be sufficient in larger PFOs. The device has since been pulled off the market.

**PERSPECTIVE**

A PFO may lead to paradoxical embolism and stroke. How to treat patients with (cryptogenic) stroke and PFO is still discussed controversially. Possible treatments are antiaggregation or anticoagulation, surgery, or transcatheter closure of the defect. Medical treatment has a risk of recurrent embolic events of 2% to 14% per year (11,14,17,37–40). The annual recurrence for stroke and death is 1% to 7% (17,36,37,39). In addition, anticoagulation encounters a risk for hemorrhagic complications of 9% to 15% per year and 2% to 5% per year for severe bleeding (cerebral
Overall, complete closure can be expected in about 90% of cases with Amplatzer devices and in 70% to 85% with other devices. The result at four to six months is final. So-called “late closures” are usually a product of less sensitive screening techniques. The degree of residual shunt is conceptually likely to correlate with further paradoxical embolisms, although this was not universally confirmed by respective analyses.

### RANDOMIZED PFO CLOSURE STUDIES

So far, no randomized PFO study has been finished (Table 46.1) (45) to prove superiority of the interventional versus medical approach in patients with cryptogenic stroke. The PC-Trial with the Amplatzer PFO Occluder was the first one commenced and concluded enrollment in early 2009 with roughly 400 patients. It will putatively be published in 2012. In the “CLOSURE I trial,” device PFO occlusion using the STARFlex Occluder is randomized to medical therapy with warfarin, acetylsalicylic acid, or both during 24 months of follow-up. Preliminary results might become available in 2011. Other randomized studies are still recruiting: in the CLOSE trial, patients are randomized either to oral anticoagulation, antiplatelet agents, or PFO closure. In the RESPECT study, PFO patients are randomized either to catheter occlusion using the Amplatzer PFO Occluder or best medical therapy (antiaggregation or anticoagulation).

### PFO Closure in Migraine Patients

Besides the prevention of cerebral ischemia, PFO closure has been shown to improve migraine in several observational studies (46–48). The only randomized study of migraine patients with PFO was the Migraine Intervention with STARFlex Technology (MIST) trial (49). Evaluating a possible benefit of PFO closure for the prevention of migraine, it has failed to show significant benefits over medical therapy. More recently, however, a small study by Vigna and colleagues examined a collective of migraine patients with large PFOs and subclinical brain MRI lesions. The investigators showed that in these patients, a significantly higher reduction in the frequency and severity of migraine recurrence can be obtained by PFO closure compared with control subjects (50).

We occluded the PFO in 17 migraine patients with the Amplatzer PFO Occluder (51). Complete PFO closure could be achieved in 16 patients. There were no procedural complications and no embolic events in a mean follow-up time of 2.7 years. The migraine disappeared in four patients (24%) and improved in eight patients (47%), whereas the headaches remained unchanged in five patients (29%). The prevalence of migraine with aura decreased from 82% to 24%.

### Table 46.1 Current Ongoing Trials on PFO Closure

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Device</th>
<th>Sponsor</th>
<th>Estimated enrollment</th>
<th>Results expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPECT</td>
<td>Amplatzer PFO Occluder</td>
<td>AGA Medical Corporation</td>
<td>500</td>
<td>2013</td>
</tr>
<tr>
<td>CLOSURE I</td>
<td>STARFlex Septal Closure System</td>
<td>NMT Medical, Inc.</td>
<td>900</td>
<td>2011</td>
</tr>
<tr>
<td>PC-Trial</td>
<td>Amplatzer PFO Occluder</td>
<td>AGA Medical Corporation</td>
<td>400</td>
<td>2012</td>
</tr>
<tr>
<td>CLOSE</td>
<td>Any device</td>
<td>Assistance Publique–Hôpitaux de Paris</td>
<td>900</td>
<td>2013</td>
</tr>
<tr>
<td>REDUCE</td>
<td>Helex Septal Occluder</td>
<td>W. L. Gore &amp; Associates, Inc.</td>
<td>664</td>
<td>2013</td>
</tr>
</tbody>
</table>

**Abbreviation:** PFO, patent foramen ovale.  
**Source:** Adapted from Ref. 45.
CONCLUSION

In patients with appropriate anatomical dimensions of ASD, interventional closure should be favored. This technique provides low complication rates, a short hospitalization, and acceptable costs. Surgical ASD closure should be reserved for patients with septic primum defects, sinus venous defects, or very large secundum defects. The significant coincidence of residual leak and recurrent embolic events suggests that PFO closure is the right way to prevent a patient with (cryptogenic) stroke and PFO from recurrences. However, randomized data are still lacking. In the last years, many new PFO devices with different approaches for stroke prevention have entered the market. There is a trend toward PFO specific devices that leave less or no foreign material in the heart to minimize device related complications. Percutaneous PFO closure can be performed safely with a high success rate and low morbidity. In observational studies, it has been shown to be effective in preventing recurrent cerebral ischemia in patients with a history of (cryptogenic) stroke.

REFERENCES

Atrial septal defect (ASD) and patent foramen ovale (PFO) closure are discussed in chapter 46 and are not further discussed here. Atrial septal defect and patent foramen ovale closure are INTERVENTIONS that should be readily available.

Since an interventional procedure for CHD should never fail because it is not a life-saving procedure, the primary goal is to perform the procedure with minimal risk and in a timely manner. This requires the establishment of an interventional program for CHD with well-trained cardiologists and a well-equipped cardiac catheterization laboratory. A description of the training requirements for interventionalists performing the procedures is beyond the scope of this chapter. Biplane fluoroscopy imaging is preferred by the team without subjecting the patient to cardiopulmonary bypass. This involves collaboration between the surgeons and the interventional cardiologists. The percutaneous approach (e.g., transfemoral, transvenous, transapical) has been advocated as an alternative to the surgical approach. In children, however, only 2% of patients died due to the percutaneous approach; however, if the surgeon's access is not present, the surgical approach has been used for this purpose. The most widely used device in the United States and Europe is the Amplatzer Vascular Plug (AGA Medical, Plymouth, Minnesota, U.S.).

In this chapter, we will discuss the congenital cardiovascular conditions for which the interventional therapy has been established as the preferred management strategy, including atrial septal defect, patent foramen ovale, and ventricular septal defect (VSD) device closure, as well as semilunar valvuloplasty and the percutaneous pulmonary valve implantation for patients with severe pulmonary insufficiency and/or stenosis.

The performance of interventional cardiac catheterization procedures for CHD both in adult and pediatric patients requires well-trained interventional cardiologists. The development of interventional laboratories has a better understanding of the anatomy and location of the defect, and minimizes the amount of contrast agent administered. The use of interventional procedures is mandatory in any institution that performs pediatric congenital heart disease (CHD) procedures. The percutaneous closure approach has been increasingly implemented with obvious advantages to the patient. This concept involves direct exposure of the heart via a median sternotomy performed by the surgeon, followed by an interventional procedure performed by the team without subjecting the patient to cardiopulmonary bypass.

In addition, we will summarize the value of interventional therapy in selected adult congenital cardiac lesions, such as coarctation of the aorta, pulmonary artery stenosis, and patent ductus arteriosus. Interventional therapy is not feasible due to limited access or associated conditions that may require surgical repair, a hybrid approach (e.g., transposition of the great arteries, double outlet right ventricle) may present with signs and symptoms of congestive heart failure or failure to thrive. All VSDs can be repaired surgically. Mortality and morbidity rates increase with multiple VSDs. The overall risk for VSD surgical repair is 0.2% of all myocardial infarction patients.

Approximately 7% of muscular VSDs and 30% of membranous VSDs close spontaneously within five years after initial diagnosis. Patients with signs and symptoms of congestive heart failure or failure to thrive may be treated with surgical repair. All VSDs may be repaired surgically. Approximately 75% of muscular VSDs and 30% of membranous VSDs are the most common cardiac abnormalities found in children, accounting for approximately 30% of all defects (1,2).

EQUIPMENT

Percutaneous VSD Closure

VSDs are considered the most common cardiac abnormalities found in children, with an incidence of over 1% in the general population. The VSD device closure (VSD device closure, patent foramen ovale, and ventricular septal defect (VSD) device closure, as well as semilunar valvuloplasty. In addition, we will summarize the value of interventional therapy in selected adult congenital cardiac lesions, such as coarctation of the aorta, pulmonary artery stenosis, and patent ductus arteriosus. Interventional therapy is not feasible due to limited access or associated conditions that may require surgical repair, a hybrid approach (e.g., transposition of the great arteries, double outlet right ventricle) may present with signs and symptoms of congestive heart failure or failure to thrive. All VSDs can be repaired surgically. Mortality and morbidity rates increase with multiple VSDs. The overall risk for VSD surgical repair is 0.2% of all myocardial infarction patients. Approximately 7% of muscular VSDs and 30% of membranous VSDs close spontaneously within five years after initial diagnosis. Patients with signs and symptoms of congestive heart failure or failure to thrive may be treated with surgical repair. All VSDs may be repaired surgically. Approximately 75% of muscular VSDs and 30% of membranous VSDs are the most common cardiac abnormalities found in children, accounting for approximately 30% of all defects (1,2).
For single muscular VSD, the procedure can be safely performed without transesophageal echocardiographic (TEE) guidance; however, for multiple defects/Swiss cheese septum, it is advisable to perform the procedure under TEE guidance. Femoral artery and vein are accessed routinely. If the VSD is located in the mid, posterior, or apical septum, the right internal jugular vein is also accessed. The patient is heparinized to achieve an activated clotting time of >200 seconds at the time of device placement. Routine right and left heart catheterization is performed to assess the degree of shunting and to evaluate the pulmonary vascular resistance. Angiography in single plane (35° LAO/35° cranial) is performed to define the location, size, and number of VSDs. This projection profiles the muscular septum. A complete TEE study is performed. Specific attention is paid to the characterization of the VSDs and nearby structures, including the papillary muscles, moderator band, and the chordae tendineae. The atrioventricular valves are interrogated at baseline for any regurgitation. The appropriate Amplatz VSD device size is chosen to be 1 to 2 mm larger than the VSD size as assessed by TEE or angiography at end diastole (the bigger of the two diameters). The authors depend mainly on echocardiographic and/or angiographic sizing of the defect while others rely on balloon-sizing. A long venous sheath (6-8 Fr) is then placed across the VSD. This is accomplished in a variety of ways. The most common approach used for the mid-muscular VSDs is to advance a curved 4-Fr end-hole catheter (Judkins right or Cobra) from the left ventricle (LV) across the VSD into the RV. An exchange-length 0.035-in. J-tipped guidewire is advanced through the VSD and the RV into either pulmonary artery branch. This wire is then snared and exteriorized through the right internal jugular vein. This provides a stable arteriovenous loop and allows a 6- to 8-Fr long Mullins type sheath (AGA Medical) to be advanced from the jugular vein to the RV and positioned into the LV. The approach from the jugular vein provides a straight course for mid, apical, or posterior defects. Some larger mid-muscular or apical VSDs can be easily crossed from the RV side. However, care should be exercised not to go through the trabeculae in the RV. Once a catheter crosses into the LV, an exchange-length guidewire is positioned into the LV apex and a 6- to 8-Fr long Mullins type sheath is advanced over this wire and positioned into the body of the LV. On occasion, after removal of the dilator and wire from the long sheath, kinking of the distal part of the sheath (at the ventricular septum) is encountered. In such circumstances, a 0.018-in. J-tipped guidewire is advanced through the dilator and left inside the sheath while advancing the device beside it. This helps minimize kinking of the sheath. Once the device approaches the tip of the sheath, this wire is removed and the device is deployed in the usual fashion. TEE and angiography using a pigtail catheter positioned in the LV are very helpful imaging techniques in guiding device position. The LV disk is deployed in the middle of the LV, and the entire assembly (cable/sheath) is pulled into the VSD with further retraction of the sheath to expand the waist inside the septum. Repeat TEE and angiography to confirm optimal device position prior to deployment of the RV disk is of great importance. Once position is confirmed, further retraction of the sheath to expand the RV disk is performed. Again, prior to device release, repeat TEE and angiography are performed. If device position is satisfactory, the device is released by counterclockwise rotation of the cable using the pin vise. For anterior muscular VSDs, we prefer the femoral vein approach as it is an easier course for the delivery sheath. Once the wire crosses the VSD into the pulmonary artery it is snared and exteriorized out into the femoral vein. The delivery sheath is then placed over this wire into the LV apex. The remaining steps are similar to the above. After device release, a brief complete TEE study is performed with additional imaging in multiple planes to confirm device placement and to assess for residual shunting or any obstruction or regurgitation induced by the device. The device orientation commonly changes slightly to align with the septum as it is released from the delivery cable and all tension on the device is eliminated. Additional VSDs are then occluded in the same fashion. Repeat LV angiogram in 35° LAO/35° cranial view is performed 10 minutes after final device release to assess the result. Patients receive a dose of an appropriate antibiotic (commonly Cefazolin at 20 mg/kg) during the catheterization procedure and two further doses at eight-hour intervals. The patients are recovered in an appropriate setting (usually intensive care unit) and are routinely discharged home the following day. Observation of subacute bacterial endocarditis prophylaxis is recommended for six months or until complete closure is obtained. Patients are instructed to avoid contact sports for one month. Follow-up includes TTE, chest radiograph, and electrocardiogram at six months post closure and yearly thereafter. Figure 47.1 demonstrates closure steps in a patient with VSD.

**Congenital Aortic Stenosis/Pulmonary Stenosis**

Valvular aortic stenosis (AS) occurs in approximately 3% to 6% of patients with CHD (2). The stenotic valve is usually secondary to aortic valve maldevelopment with increased thickening and rigidity of the valve tissue and variable degrees of commissural fusion. Compensatory left ventricular hypertrophy is proportional to the degree of obstruction. With severe hypertrophy and valvar obstruction, myocardial ischemia may result from the combination of limited cardiac output, reduced coronary perfusion, and increased myocardial oxygen consumption.

In neonatal critical AS, congestive heart failure and shock occurs around the time of natural patent ductus arteriosus closure. In older children and adolescents, the presentation could be the systolic ejection murmur characteristic for valvar AS.

Balloon aortic valvuloplasty is a safe initial treatment in most patients with congenital aortic valve stenosis. Patients with severely dysplastic valves may have less favorable results with balloon aortic valvuloplasty, but in most patients the results are similar to those obtained with surgical valvotomy (7,8). The overall goal, especially in neonates and infants, is to relieve the aortic valve obstruction sufficiently without development of significant valve insufficiency, thereby resulting in normalization of left ventricular systolic function. Achievement of this goal typically entails performing a conservative balloon valvuloplasty by reducing the peak-to-peak systolic gradient by 50%. Balloon diameters are usually 85% to 90% of the aortic valve annulus dimension measured via aortic angiography. If unsatisfactory result is encountered and no significant increase in aortic regurgitation is noticed, a higher balloon size can be used to repeat the procedure. In critically ill patients, surgical backup and circulatory support in the form of an extracorporeal membrane oxygenator should be available.

Right and left heart catheterization assessment is indicated prior to valvuloplasty to evaluate the right-sided pressure and the left ventricular end-diastolic pressure. It is best to measure the gradient across the valve by placing a catheter above the valve and another one in the LV (simultaneous). In
symptomatic patients, this condition may be treated by valvuloplasty even in the presence of a lower gradient. In asymptomatic patients, a peak-to-peak gradient of over 55 mmHg is an indication to proceed. However, often under general anesthesia, the gradient is lower than under normal conditions. Therefore, prior assessment by echocardiography or the administration of dobutamine during catheterization will unmask significant obstruction. Patients with an aortic gradient <55 mmHg should be followed medically unless they become symptomatic.

Retrograde crossing of the aortic valve via the femoral artery is preferred; however, in neonates, a carotid cut-down is employed by many interventionalists to allow crossing of the valve. Trans-septal approach is another technique to cross the valve in an antegrade fashion that was reported to decrease the risk of silent cerebral embolism frequently seen with the retrograde approach at a rate of 22% (9).

Left ventriculography demonstrates the stenotic valve orifice. It is also helpful in evaluating the subaortic and supra aortic areas for the presence of an additional level of stenosis. Selection of the balloon size depends on the orifice size measured during angiographic assessment. The chosen balloon should be 85% to 90% of the size of the stenotic valve to minimize the risk of regurgitation. Figure 47.2 demonstrates TEE images in an adolescent with valvar AS who underwent successful balloon valvuloplasty.

Isolated valvar pulmonary stenosis (PS) represents 8% to 10% of all patients with CHD. The stenotic valve is usually dome shaped, with diffuse thickening and commissural fusion. Patients with mild PS are usually asymptomatic. The diagnosis is usually made during routine physical examination with audible ejection systolic murmur. Patients with moderate or severe degree of PS may have mild exertional dyspnea. Adults may be asymptomatic irrespective of the severity of their obstruction. Patients with severe PS present with signs of congestive heart failure and cyanosis due to shunting of blood across patent foramen ovale or atrial septal defect. Treatment is indicated in asymptomatic patients with severe PS (peak-to-peak gradient >55 mmHg) or in symptomatic patients with evidence of right ventricular dysfunction irrespective of the gradient.

Balloon pulmonary valvuloplasty was initially described by Kan et al. (10). The success rates are excellent (85%) for children with classical PS; however, for patients with dysplastic valves or supravalvular and/or subvalvular PS, success rate is low (35–65%).

In selected infants with membranous pulmonary atresia and adequate size RV, perforation of the membrane with either a stiff end of a wire or radiofrequency perforation catheter followed by balloon dilation has been successful in creating an open right ventricular outflow tract (11–14).

Femoral venous access and right heart catheterization to assess the hemodynamics are performed. Femoral artery access is rarely needed. In neonatal critical PS, umbilical vein access may be used. Right ventricular angiography is performed in both anteroposterior and lateral projections to identify the pulmonary valve and measure the annular size (between the hinge points). The balloon size is selected to be no more than
1.2 times the diameter of the valve annulus. A balloon end-hole catheter is advanced to the distal right or left pulmonary artery. A stiff exchange-length guidewire is then placed in the branch pulmonary artery. We prefer to insert the balloon via a sheath. This we believe minimizes access vessel injury. The balloon is introduced over the guidewire and is centered at the pulmonary valve. Adjustment of the balloon position may be performed by repeated small pressure inflations and waist verification. The balloon is inflated rapidly until the waist disappears then it is deflated immediately. If suboptimal results are obtained, repositioning of the balloon and repeating the previous steps may be done. Larger balloon size may be used for the second inflation if optimal results are not achieved and no pulmonary regurgitation is observed.

Indications for COA treatment are basically the same as those for surgery and include hypertension proximal to the coarctation with a resting systolic pressure gradient across the narrowed segment >20 mmHg or angiographically severe coarctation with extensive collaterals (15).

Coarctation angioplasty requires femoral venous and arterial access. The patient is heparinized to achieve an activated clotting time of >200 seconds. Retrograde approach is the most commonly used technique; however, on occasions in severe coarctation or if there is acquired atresia, crossing from above (trans-septal or left subclavian artery) is indicated. Right and left heart catheterization with hemodynamic assessment is performed. Biplane aortography is performed. The narrowest area of the coarctation is measured as well as the proximal, distal, and the aorta at the level of the diaphragm. Balloon size selection depends on the nature of the coarctation. In native coarctation, the balloon is chosen to be around 2.5 to 3 times the diameter of the narrowed segment but not more than the area immediately distal to the coarctation (post-stenotic dilatation).

The selected balloon is centered at the coarctation area. The balloon is inflated until the waist disappears and then deflated immediately. Simultaneous pressure measurement between the ascending and descending aorta pressures is obtained. Angiography is performed after balloon inflation to determine the effect of angioplasty on the coarctation area. Tears or dissection of the aorta may be also detected. If optimal results are not achieved, a larger balloon may be used for a second inflation. Temporary chest pain during balloon inflation is acceptable. If chest pain persists after balloon deflation,
Pulmonary Artery Stenosis

PAS accounts for 2% to 3% of all CHD. PAS may be isolated (Williams syndrome, Alagille syndrome) or associated with more complex CHD, such as tetralogy of Fallot or transposition of the great arteries. PAS may also be central, peripheral, intermediate, unilateral, or bilateral.

Gay et al. established four PAS classes according to the anatomic location of the narrowing. Type I includes single constriction of varying length confined to the main pulmonary artery (MPA), the right pulmonary artery (RPA), or the left pulmonary artery (LPA) (types IA, IB, and IC, respectively). Type II includes bifurcation stenosis where the constriction involves the distal end of the MPA, RPA, and LPA. This type is further subdivided into IIA where the narrowing segment is short and localized and IIB where the narrowing segment is long. Type III includes multiple peripheralstenoses, and type IV includes combined central and peripheral stenoses (16).

Patients with mild to moderate arterial obstruction are usually asymptomatic. Cases with severe stenosis may have dyspnea on exertion, easy fatigability, and occasional right-sided heart failure. Treatment of PAS depends on the site of the stenotic segment. Percutaneous pulmonary angioplasty is suitable for distal lesions unreachable by surgery, and surgical pulmonary arterioplasty is feasible for more proximal lesions.

Variable modalities of percutaneous techniques include balloon pulmonary angioplasty using high-pressure balloons, cutting balloon angioplasty, and intravascular stent placement.

Despite advances in balloon types and pressure achieved, around one-third of vessels, more often distal, are resistant to angioplasty. The use of cutting balloons is an effective treatment for small lobar PAS refractory to balloon angioplasty (17).

Stenting of branch pulmonary arteries is frequently used in children with PAS and/or hypoplasia (18–20). Because of the higher immediate success and less incidence of restenosis, stenting of pulmonary arteries may be a reasonable first-line therapy.

The most commonly used access is the femoral vein. Right heart catheterization with hemodynamic assessment is performed first. Pulmonary artery angiography is then performed to localize the affected segment(s). Selective injection to the lung and the lobe affected is highly recommended. Before starting the balloon dilation procedure, a stiff exchange-length wire should be placed in a large vessel distal to the stenotic branch.

The selected balloon diameter should be two to four times the diameter of the narrow segment but not more than two times the diameter of the normal vessel on either side of the lesion (21).

The balloon is inflated until the waist disappears. After dilation, the area is reassessed by pressure recording across the dilated area and angiography. Successful dilation results in improved diameter of the segment, increase in distal pressure, and/or a decrease of >20% in systolic right ventricular to aortic pressure ration.

Cutting balloons may be used for vessels resistant to conventional balloon angioplasty. Initially, the vessel is dilated with the cutting balloon then a high-pressure balloon is employed to open up the vessel to a larger diameter. One limiting factor about cutting balloons is the lack of availability of large sizes, since the largest cutting balloon available is 8 mm. Therefore, cutting balloon angioplasty is good for vessels up to 8 mm in diameter.

Stent placement of the affected area will avoid the recoil nature encountered after balloon angioplasty. However, stent placement is technically more challenging, and potentially could have more complications and could commit the patient to repeat interventions, especially if continued growth of the patient is expected. Figure 47.4 demonstrates a patient who underwent placement of two stents to treat bilateral stenoses at the origin of the branch pulmonary arteries from the MPA.

Intraoperativeintravascular stent placement is a hybrid technique that could be used in difficult situations. It is suitable in the early postoperative period, difficult vascular anatomy, bilateral stenoses requiring simultaneous stent implantation, short proximal segment stenosis (too short for the shortest stent...
available), marginal hemodynamics, severe bilateral branch stenosis, patients on extracorporeal membrane oxygenator, and patients with other cardiac lesions requiring concomitant surgery (22).

**Coronary Artery Fistula**
CAF is a connection between one or more of the coronary arteries and a cardiac chamber or great vessel, bypassing the myocardial capillary bed. The abnormality is rare—the exact incidence is unknown—and usually occurs as an isolated finding.

The fistulas originate from the right coronary artery in more than half of the cases. The left anterior descending coronary artery is the next most frequently involved, in approximately one-third of cases, followed by the circumflex coronary artery (23). Most of the fistulas from either coronary artery drain into the right side of the heart. The RV is the most common site for drainage followed by the right atrium, coronary sinus, and lastly the pulmonary artery trunk.

Most patients with CAF are asymptomatic. Diagnosis is usually suspected when a continuous murmur is detected during a routine visit or examination for other reasons. Symptoms depend on the size of the fistula, which is usually small, and the pressure difference between the two sides of the fistula. Rarely, congestive heart failure occurs. CAFs usually are small in size and close spontaneously by the second decade of life. If not closed, complications may be the first presenting symptom. Reported complications include steal from the adjacent myocardium causing myocardial ischemia, thrombosis and embolism, cardiac failure, atrial fibrillation, rupture, endocarditis/endarteritis, and arrhythmias (23–26). Other reported rare complications include thrombosis within the fistula, leading to acute myocardial infarction; atrial or ventricular arrhythmias; and spontaneous rupture of the aneurysmal fistula, causing hemopericardium (27,28).

Cardiac catheterization is the main diagnostic technique. Cardiac catheterization is needed initially to assess the hemodynamic significance of the fistula and to provide detailed anatomy including size, origin, course, presence of any stenosis, and the drainage site.

The main goal of treatment of CAF is complete occlusion with no residual fistulae. Catheter closure of the fistulas is now considered to be a safe and effective alternative to surgery. Catheter closure should be as distal to the end point of the fistula as possible to avoid possible occlusion of branches to the normal myocardium.

Selective coronary angiography is needed to confirm the diagnosis and the detailed anatomy of the fistula. Detailed angiographic views in multiple projections are essential to the successful treatment of these fistulas.

Access is usually obtained in both femoral arteries and one femoral vein. One artery is used for angiographic assessment and the other for the actual closure of the fistula. We use a coaxial system to manage these fistulas. A coronary guide catheter of proper size and shape is advanced to the ostium of the involved coronary artery. The fistula is crossed with the proper coronary exchange-length wire. Then a Berman end-hole balloon catheter is passed over this wire inside the guide catheter, and the balloon is positioned distal to the last viable myocardial branch and is inflated with contrast to temporarily occlude the vessel for 5 to 10 minutes to assess the risk of ischemia with fistula occlusion. If no detectable ischemic changes are noted, then the choice of technique is based on the size of the fistula and on the available equipment. Coils or devices (Amplatzer PDA device, Amplatzer vascular plug, Amplatzer VSD devices) can be used to close the fistula. If coils are chosen, they are usually deployed retrograde (going from the guide catheter inside the delivery catheter positioned distal) and if devices are chosen, usually, the wire is snared and exteriorized from either femoral or jugular vein and the proper
Aortopulmonary Collaterals

Collateral vessels occur in a wide variety of conditions, including pulmonary atresia with VSD, tetralogy of Fallot, scimitar syndrome, and in hearts undergoing Fontan-type reconstruction. They may be arterial or venous and may shunt left-to-right or right-to-left. APCs typically originate from the descending aorta and connect with true pulmonary arteries at different levels. The potential disadvantage of APCs in patients with univentricular physiology include left-to-right shunts causing volume overload on the ventricle and unwanted blood return on the operative field during cardiopulmonary bypass. The increased pulmonary blood flow also raises the pulmonary artery pressure. Ventricular volume overload and elevated pulmonary artery pressure have been identified as risk factors for the Fontan operation. Hemoptyisis from rupture of thin-walled vessels may also occur as one of the adverse effects of APCs.

Before an aortopulmonary collateral artery is embolized, the presence of dual blood supply from the true pulmonary arteries to the affected segment of the lung should be determined. Embolization should only be performed if true pulmonary arteries supply the same territories as the collateral vessel.

Various agents are used for embolization of APCs, including tissue adhesives, Gelfoam, detachable balloons, and coils. Sharma et al. reported on APC occlusions in one of the largest series in this field (31). Indications for occlusion in this study were hemoptyisis, intractable cardiac failure, and routine preoperative procedure in most of the patients. Complete occlusion was achieved in 76% of cases with an 8% failure rate secondary to migration of the coils to the distal pulmonary arteries.

The technique of closure is similar to the techniques used in CAF embolization and other extracardiac vascular abnormalities. Coil migration is still one of the most common complications and use of detachable coils leads to a marked decrease in the risk of coil migration.

Pulmonary Arteriovenous Fistula

Pulmonary arteriovenous fistula is an abnormal communication between pulmonary arteries and pulmonary veins. It can be either congenital (in most of the cases) or sometimes acquired, especially in patients after bidirectional Glenn anastomosis for single ventricle.

The clinical presentation varies from no symptoms to severe illness. The most common clinical presentation includes epistaxis, dyspnea, and hemoptyisis. Cyanosis may occur from the right-to-left shunt between the pulmonary arteries and pulmonary veins. The resultant shunt may lead to paradoxical embolus resulting in stroke or transient ischemic attack. Acquired fistula is seen in patients after cavopulmonary anastomosis and less in patients after Fontan surgery. Transcatheter embolization of pulmonary arteriovenous fistula is considered the mainstay of treatment of this abnormality (32-35). The technique of embolization is not different from closure of the other extracardiac vascular anomalies (CAFs and APCs). The most commonly used device is the Gianturco coils. Embolization of the entire nidus of the malformation is important to prevent recanalization. All feeding vessels should be identified and embolized. The risk of coil migration through the malformation into systemic circulation has been eliminated with detachable coils. Detachable balloons are reserved for malformations with larger feeding vessels >1 cm in diameter.

Percutaneous Pulmonary Valve Implantation

The presence of severe pulmonary insufficiency may lead to RV enlargement and dysfunction. Surgical placement of a competent valve between the RV and pulmonary arteries to treat this condition requires cardiopulmonary bypass, which may aggravate an already compromised RV. Bonhoeffer was the first to place a valve in this position percutaneously (36) and since then...
hundreds of patients have benefited from his technique (37). Currently, two valves are being evaluated for the percutaneous management of patients with severe conduit failure due to regurgitation and or stenosis. The Medtronic Melody valve developed by Bonhoeffer (Fig. 47.6) consists of a bovine jugular vein with a valve inside sewn into a Platinum Cheatham stent. The Edwards SAPIEN THV (38) is made of bovine pericardial leaflets sewn inside a stainless steel stent. Both valves are balloon expandable and require a large delivery system for deployment (up to 22–24 Fr). Clinical trials in the United States are under way to assess their safety and efficacy.

CONCLUSIONS
This chapter has summarized interventional techniques used for treating CHDs in the catheterization laboratory. Adult CHD is a growing field and requires skilled personnel trained in both adult and CHDs who understand the physiology and anatomy of the cardiac lesion. The practice of interventional cardiology for CHD also requires a fully equipped catheterization laboratory to help minimize the risks of such procedures. Surgical backup is crucial in any institution practicing congenital cardiac intervention. Lastly, cardiac intervention is a rapidly growing and expanding field that now involves at its far end percutaneous valve placement and valve repair. In the near future, further major advances in this field are likely.

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Embolization for fistulas and AVMs

Nicholas Kipshidze, Robert Rosen, and Irakli Gogorishvili

PERIPHERAL ARTERIOVENOUS MALFORMATIONS

Introduction
An arteriovenous fistula is an abnormal connection between an artery and a vein. As a consequence, the blood bypasses the capillary bed. The majority of arteriovenous malformations (AVMs) are congenital, but some can be acquired due to trauma, infection, or malignancy. An arteriovenous fistula may be the result of a vascular catheter insertion or may be created surgically to provide access for hemodialysis in end-stage kidney failure patients. AVMs can occur anywhere in the body, including the central nervous system. Congenital AVMs are present at birth and, although they may be asymptomatic, they always persist and do not involute (1,2), unlike true hemangiomas. AVMs may become symptomatic with age, sometimes at puberty in female patients, during pregnancy, or after local trauma. Of special interest are pulmonary AVMs, mostly related to hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu syndrome), which is discussed later in this chapter.

Anatomic Considerations
Vascular malformations are divided into low- and high-flow lesions. Low-flow malformations are venous, lymphatic, or mixed—therefore, causing congestion of either type. They will be discussed later. High-flow lesions contain an arterial component and determine left-to-right shunt.

These subtypes differ from each other with respect to clinical course and treatment options. High-flow malformations are less common, more difficult to treat, and are prone to recurrence. High-flow AVMs result in a similar pathophysiology to arteriovenous fistulas and may result in:
1. Compressive and erosive effects
2. Venous stasis
3. Ischemia due to peripheral steal phenomenon
4. High-output heart failure

Although AVMs can occur anywhere in the body, the pelvis and the extremities are the most common locations for peripheral AVMs.

Clinical Aspects
Pelvic AVMs (Fig. 48.1) may produce pain, pelvic venous congestion, sexual dysfunction, and, occasionally, high-output cardiac failure and hemorrhage. With respect to hemorrhage, this is generally a lower gastrointestinal bleed or hematuria, while hemorrhage in the abdominal cavity is extremely rare. Although the most frequent blood supply of pelvic AVMs arises from the hypogastric arteries, there may also be multiple feeding branches from the inferior mesenteric artery, middle sacral artery, lumbar artery, and femoral arteries (3). Extremity AVM (Fig. 48.2) symptoms range from mild swelling or soft tissue mass, extremity overgrowth or growth retardation, bleeding, ulceration, gangrene, or rarely congestive heart failure.

Indications for Treatment
Treatment of AVMs, especially high-flow AVMs, is challenging and not always successful regardless of the type of procedure chosen (percutaneous, surgical, or combined). Treatment should therefore be undertaken only when clinically indicated (3). Asymptomatic lesions that are discovered incidentally generally do not require treatment. Absolute and relative indications for treatment are as follows:

Absolute indications for treatment
- Hemorrhage, major or recurrent minor
- Gangrene or ulcer of arterial, venous, or combined origin
- Ischemic complication of acute and/or chronic arterial insufficiency
- Progressive venous complication of chronic venous insufficiency with venous hypertension
- High-output cardiac failure (clinical and/or laboratory)
- Lesion located at life-threatening vital areas that compromise vision, hearing, eating, or breathing

Relative indications for treatment
- Various symptoms and signs affecting the quality of life; disabling pain and/or functional impairment
- Lesions with a potentially high risk of complications (e.g., hemarthrosis) and/or limb-threatening location
- Lesions causing limb length discrepancy
- Cosmetically severe deformity with or without functional disability

Principles of Treatment
The mainstay of treatment of high-flow AVMs is permanently closing or eliminating the vascular nidus where arterial blood is shunted to the veins.

Historically, surgical treatment alone proved to be inadequate or even disastrous, often leading to extensive damage to adjacent structures with high recurrence rates or major amputation (4,5). The reason for failure is that it is rarely possible to completely resect the nidus, which can be large or supplied by multiple collaterals. Proximal ligation of feeding arterial branches is ineffective as aggressive recruitment of new feeding collaterals is common (6,7).

Disappointing results of surgical treatment stimulated development of alternative approaches. The introduction of
Embolotherapy in the early 1970s (8,9) and advancements in catheter technology made it possible to treat AVMs less invasively. Although AVMs are uncommon, data about interventions and follow-up is increasing (10–15). Some centers document very promising results with interventional treatment. However, several reports have documented worsening of symptoms after embolization (16). This is why most authors recommend intervention only for patients with significant symptoms (11,13).

Embolization Technique

The goal of treatment is to occlude the nidus of the malformation through selective catheterization and embolization of feeding branches (Fig. 48.3).

Embolization of the nidus of an AVM often requires super-selective catheterization of numerous arterial feeding branches. This is facilitated by use of coaxial microcatheter systems. A 2- to 3-Fr microcatheter is coaxially introduced through a 4- to 5-Fr selective catheter and can be manipulated into the terminal feeding artery. Embolic agents are then delivered via the microcatheter, an ideal tool for the delivery of liquid agents, particles, and small coils.

Embolic Agents for High-Flow Lesions

Use of the proper embolic agent (Table 48.1) is critical when treating AVMs, as the wrong agent may not only fail to treat the lesion but may also interfere with future attempts at treatment. In most cases, the goal is penetration and eradication of the nidus of the lesion. Fibered coils (Fig. 48.4) have been the material of choice for vessel occlusion since their introduction 30 years ago (17). However, their value in treating AVMs is limited as they result in proximal occlusion, which is functionally equivalent to surgical ligation. Therefore, fibered coils are appropriate only in lesions with a fistula-like architecture.

The basic fibered coil consists of a length of guidewire with multiple polyester threads attached transversely along most of its length. Fibered coil emboli are preshaped into a
variety of different configurations and then stretched out in a cartridge for delivery into a catheter. Coils are made of steel and platinum with spring sizes 0.035 to 0.038 and 0.018 in. Selecting the correct coil size is extremely important for the success of the procedure. The coils should be slightly oversized relative to the diameter of the target vessel to allow them to grip the vessel wall and be closely packed. Significantly oversized coils tend to pass through the vessel like a guidewire and may elongate to a feeding branch rather than coiling up. Undersized coils may fail to lodge and migrate causing unintended embolization into other vessels.

Guglielmi detachable coils without fibers were introduced for controlled and safer embolization. But their high cost and limited thrombogenicity confine their use to treatment of intracerebral aneurysms.

Detachable balloons were used to occlude large arteriovenous communications, but their complexity and cost remain significant drawbacks. In addition, they are not commercially available in the United States at this time.

Polyvinyl alcohol particles ranging from $<100 \mu m$ to $>1000 \mu m$ in size are used for permanent vessel embolization. The particles wedge in vessels of corresponding diameter and produce a permanent occlusion by thrombosis and subsequent fibrosis. The particle-contrast suspension is injected slowly in small aliquots under continuous fluoroscopic control once the delivery catheter is positioned in the desired location. While the particles themselves are permanent, the effect on the malformation is often temporary, with collateral recruitment and recanalization around the particles.

Liquid occlusive agents, including sclerosants and glue, are very attractive for AVM nidus occlusion (Fig. 48.5). Absolute ethanol is a very potent sclerosant and should be used with great care. Although good long-term results have been reported, intraarterial ethanol injection carries a significant risk of damage to normal tissues if nontarget embolization occurs.

Glue or tissue adhesives, such as N-butyl cyanoacrylate and isobutyl cyanoacrylate, are another category of liquid embolic agents that polymerize on contact with an ionic environment such as blood. In experienced hands, these are very effective for AVM occlusion, but require frequent, time-consuming catheter exchanges, and as with ethanol, great care should be taken to avoid nontarget embolization.

### Complications

Embolotherapy, although minimally invasive and relatively safe, is not without complications. Therefore, patients need to be fully informed of the potential risks of the treatment. Probably the most common complication is ischemia due to nontarget embolization or distal migration of the embolic agent. Sometimes superficial tissue necrosis occurs, and extensive lesions may require skin grafting.

Postembolization syndrome caused by tissue necrosis may be encountered after embolotherapy. The symptoms of pain, fever, leukocytosis, and nausea arise shortly after embolotherapy and usually resolve within a few days; however, they may persist up to a week. Compared to tumor embolization and organ embolotherapy, postembolization syndrome occurs less frequently after the treatment of AVMs.

### PULMONARY ARTERIOVENOUS MALFORMATIONS

Pulmonary arteriovenous malformations (PAVMs) are discussed separately because of their unique pathologic mechanisms, associated risk factors, and different treatment approaches. Like other arteriovenous fistula malformations, PAVMs consist of a congenital connection between a pulmonary artery and vein without normal capillary bed. Unlike other AVMs, the shunt is from right to left. This carries significant implications in terms of clinical presentation and treatment. Approximately 70% of PAVMs are congenital and simple (19), and 60% to 90% of them are associated with hereditary hemorrhagic telangiectasia, also called Osler–Weber–Rendu syndrome. The remainder are isolated lesions in otherwise healthy patients with no family history. Rarely, PAVMs are acquired and related to cirrhosis, congenital heart disease (Glenn and Fontan shunts), tumors, trauma, and infection.

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**Table 48.1 Embolic Agents**

- Metallic coils
- Detachable balloons
- Covered stents
- Particulate agents
  - Polyvinyl alcohol particles
  - Trisacryl gelatin microspheres (Embosphere)
  - Yttrium-90 glass radioactive microspheres (TheraSphere)
  - Embogold
  - Gelfoam
  - N-butyl 2-cyanoacrylate
  - Onyx
- Liquid sclerosing agents
  - Ethanol or absolute alcohol
  - Hypertonic dextrose
  - Sotradecol
  - Ethibloc
- Liquid occlusive agents
  - Polyvinyl alcohol particles
  - Trisacryl gelatin microspheres (Embosphere)
  - Yttrium-90 glass radioactive microspheres (TheraSphere)
  - Embogold
  - Gelfoam
  - N-butyl 2-cyanoacrylate
  - Onyx
  - Ethanol or absolute alcohol
  - Hypertonic dextrose
  - Sotradecol
  - Ethibloc

---

**Figure 48.4 Nester coils (Cook Inc., Bloomington, Indiana, U.S.).**
Anatomic Considerations and Clinical Aspects

PAVMs are classified as simple (80–90% of cases), which are supplied by an artery contained within one pulmonary segment, or complex, which are fed by arteries from more than one pulmonary segment (Figs. 48.6 and 48.7). Approximately 65% of the lesions are located in lower lobes (22). PAVMs vary in size from tiny, angiographically invisible structures to giant malformations occupying an entire lobe (Fig. 48.8).

Up to 55% of PAVMs are asymptomatic and are discovered incidentally. Those that are symptomatic can present in a variety of ways (23). The most common presentations are dyspnea, cyanosis, easy fatigability, clubbing, hemoptysis, or hemothorax. Pathologic mechanisms related to PAVM are hypoxemia due to right-to-left shunt, rupture and bleeding of pathologic vessels, and paradoxical embolism due to loss of lung-filtering function. Paradoxical embolism is the main complication associated with PAVMs. It is estimated that in patients with PAVMs the lifetime probability of transient ischemic attack or stroke is 25% and of cerebral abscess is 10% (23,24). For this reason, PAVMs tend to be treated more aggressively than other lesions, even when asymptomatic.

Indications for PAVM Treatment

A PAVM with >3 mm feeding artery is generally considered an indication for intervention. Diagnostic tests for pulmonary vascular malformation include pulse oximetry (platypnea orthodeoxia may be seen), chest X ray, contrast echocardiography (high sensitivity >90%), computed tomographic (CT) angiography, magnetic resonance imaging (MRI), and finally pulmonary angiography—considered the gold standard for diagnosis. In recent years, the availability of multidetector CT scanning has allowed noninvasive diagnosis and reconstruction of pathologic anatomy with high resolution (25).

Treatment Considerations

The initial treatment for PAVMs was surgical including vascular ligation, lobectomy, or pneumonectomy and was associated with up to 10% recurrence and serious morbidity. In 1977, Porstmann performed the first PAVM embolization and over time this has become the standard of treatment.

The embolization procedure is generally performed from a femoral approach using 6- to 7-Fr guiding catheters positioned in the feeding artery. Embolization is performed using one of a variety of macroscopic devices, including coils, microcoils, detachable plugs, and detachable balloons. During the procedure, the patient is anticoagulated, commonly with 5000 units of heparin, and meticulous care must be taken to avoid air bubble injection, which can result in procedure-related stroke.

The most popular embolization devices for PAVMs today are coils. There are several techniques of deploying different types of coils (Figs. 48.9-48.11). Usually the first coil selected has a diameter at least 20% larger than the vessel to be
Figure 48.6 Diagrammatic examples of simple PAVMs (supplied with only one feeding artery). The nidus on the lower two panels consists of a network of small branches and septations. Abbreviations: PAVM, pulmonary arteriovenous malformation; PA, pulmonary artery; PV, pulmonary vein. Source: From Ref. 21.

Figure 48.7 Complex pulmonary arteriovenous malformation. Abbreviations: PA, pulmonary artery; PV, pulmonary vein. Source: From Ref. 21.

Figure 48.8 Angiography in left anterior oblique projection demonstrating a huge PAVM in the right lung of a 24-year-old woman. Abbreviation: PAVM, pulmonary arteriovenous malformation. Source: From Ref. 21.

Figure 48.9 Anchor technique. The guide catheter maintains position in the artery and the first 1 to 2 cm of coil is placed in the side branch. The remaining coil is deposited as a tight coil mass. Source: Courtesy of Cook, Inc.
occluded. Cross-sectional occlusion is the goal to minimize the chance of future recanalization. It is important to perform the embolization with coils placed as distally as possible in the feeding vessel. This technique avoids the occlusion of branches to normal lung and reduces the risk of pleuritic pain or pulmonary infarction. Detachable balloons have the advantage of flow guidance, but have largely been replaced by detachable coils and plugs that are easier to use. Amplatzer vascular plugs, which are made of tightly woven nitinol mesh, can be repositioned prior to detachment and have provided excellent results (Fig. 48.12). Figure 48.13 shows two examples of complex PAVMs treated with coils.

Procedural success in recent studies is 85% to 95% (26, 27). Although overall results during follow-up have been satisfactory, in patients with diffuse PAVMs, improvement of dyspnea, oxygenation, and shunt fraction may not be complete (28). Major neurologic complications such as cerebral abscess, transient ischemic attack, or stroke related to reperfused or newly perfused PAVMs also have been reported (27). On the basis of this experience, helical CT scans at 6 and 12 months and then every 3 to 5 years afterward are recommended. Complications of the procedure are uncommon and include device migration (1%) and air embolism (up to 4%). The most frequent symptom postprocedure is pleuritic pain (13%), which usually resolves within 24 hours.

**LOW-FLOW VASCULAR MALFORMATIONS**

Low-flow malformations include venous and lymphatic lesions. Venous malformations are the most common type of congenital lesion encountered clinically. They may occur anywhere in the body but have a predilection for the lower extremities. Venous malformations may be of the cavernous type (sometimes incorrectly referred to as cavernous hemangiomas) or consist of abnormal venous channels. In some patients, such as those with Klippel-Trenaunay syndrome, there may be a combination of both types of lesion.

Presenting symptoms may include pain, swelling, cutaneous lesions causing bleeding, venous hypertension, and spontaneous thrombosis. Some of the venous syndromes may be associated orthopedic or growth disturbances. Evaluation is by ultrasound, CT, and MRI, where they are particularly well demonstrated.
Conservative treatment may be effective in mild cases, with measures such as elevation and elastic support. For larger or more symptomatic lesions, embolization techniques can be highly effective. Since these are by definition venous lesions, embolizing the arterial supply to the area is generally ineffective. Direct injection of sclerosing agents is the mainstay of treatment, using agents such as ethanol and sodium tetradecyl sulfate (Sotradecol). These agents cause thrombosis of the venous spaces, followed by an inflammatory reaction, and finally shrinkage and fibrosis. While multiple treatments may be required, clinical improvement or resolution of symptoms can be achieved in most patients.

Lymphatic malformations are less common and more difficult to treat. They range from large cystic lesions (cystic hygroma) to cutaneous lesions with vesicle formation. One of the distinguishing characteristics of lymphatic malformations is their tendency to infection. The presence of infection in a vascular malformation nearly always indicates presence of a lymphatic component.

Treatment varies according to the type of lesion. Large cystic lesions can be treated surgically or by percutaneous drainage followed by sclerotherapy. Agents shown to be particularly effective in lymphatic lesions include OK-432, bleomycin, and doxycycline. Superficial lesions are particularly difficult to manage and may require surgical resection and/or laser therapy.

CONCLUSIONS
Over the past two decades, catheter-based embolization has assumed a primary role in the management of AVMs. With improvements in technology, procedures have become increasingly safe and effective. While peripheral AVMs are usually treated only in the presence of symptoms, PAVMs may be treated in asymptomatic patients to prevent ischemic neurologic events or cerebral abscesses.

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Lower and upper extremity intervention

Tahir Mohamed and Mark Robbins

LOWER EXTREMITY
Introduction
Atherosclerotic peripheral arterial disease (PAD) is highly prevalent, present in at least 8 to 12 million adults living in the United States. As the population ages, its incidence will undoubtedly continue to increase (1). PAD can have a major impact on quality of life, and it remains a significant source of morbidity and mortality. Because atherosclerosis is a systemic process, patients with PAD are at high risk of coronary and cerebrovascular ischemic events, and thus the diagnosis of PAD has strong prognostic implications. Over the last 10 years, there has been an exponential growth in the number of endovascular repair procedures for lower extremity claudication and critical limb ischemia. The procedures have grown in almost every subspecialty including cardiology, vascular surgery, and interventional radiology. Advances in technology have allowed the development of more effective endovascular approaches that has prompted a swing away from open surgical repair. This being accepted we must continue to recognize which modality is the best suited to assure the lowest risk procedure that result in the most durable outcome.

Indications and Evidence Based Approach
The decision to perform a revascularization procedure—surgical or endovascular—in a patient with PAD cannot be made exclusively on the basis of the angiographic extent of disease. Patients should be selected on the basis of the severity of the symptoms, disability as assessed by the patient and physician, failure of medical therapy, and a favorable risk/benefit ratio. In patients with intermittent claudication (IC) limiting quality of life and in those who progress to ischemic rest pain, ulceration, or gangrene revascularization attempts are warranted. Guidelines for the performance of endovascular treatment for claudication have been published by a joint ACC/AHA task force (2). In general, endovascular repair is most successful when utilized in the larger inflow arteries with discrete lesions. Less favorable long-term outcomes are associated with endovascular repair of diffuse disease in smaller outflow and runoff vessels. Comorbid conditions also play a role in the decision process with more aggressive endovascular approaches being accepted in patients at higher risk for open surgical repair.

Anatomic Considerations
The lower extremity arterial supply begins with the bifurcation of the common iliacs from the distal aorta. It is then subdivided into inflow, outflow, and runoff vessels as outlined in Figure 49.1. Inflow arteries include the common, external, and internal iliacs as well as a portion of the common femoral artery (CFA). The superficial femoral artery (SFA), profunda femoris, and popliteal arteries constitute the outflow vessels while the anterior tibial (AT), posterior tibial (PT), and peroneal arteries are commonly known as runoff vessels. Different locations within the lower extremity vasculature deserve special attention when performing endovascular procedures as not all areas carry the same procedural risk and some may be more device specific as generalized in Table 49.1. The proximal CFA and the iliac arteries are retroperitoneal and therefore are not constrained by soft tissue as the SFA. Therefore, perforations within the proximal CFA and iliac arteries can lead to rapid blood loss and should be considered an emergency. As will be discussed later, emergency equipment must be available and ready to treat this life-threatening complication. The CFA should not be stented because it is the site for vascular entry and a flexure point. Similarly, stenting the popliteal artery should be avoided if possible. Both the CFA and the popliteal artery are ideal locations for rotational or directional atherectomy as well as novel angioplasty techniques. The distal SFA—as it enters into the adductor hiatus (Fig. 49.2)—is a common location for occlusive vascular disease. This location is also associated with an increased incidence of stent fractures due to torsion during knee flexion and extension. Debunking the distal SFA with or without adjunctive angioplasty remains a valuable option for this location to limit stent fracture and associated restenosis. Below the knee repair has historically been withheld for severe limb ischemia and primarily treated with open surgical repair. However, endovascular repair continues to gain acceptance for infrapopliteal disease as will be discussed later in the chapter.

Fundamentals
The basic fundamentals for performing endovascular repair once indications have been satisfied begin with an in-depth understanding of vascular anatomy, collateral supply, and the ability to perform an imaging work-up, allowing for a detailed planning of the upcoming intervention. There are pathways to gain clinical competence either through a dedicated training program or physician experience tract (2,3). Comprehensive knowledge of the equipment available is another vital component of a successful endovascular program. Unlike coronary equipment, peripheral interventional devices may be 0.014, 0.018, or 0.035 in. guidewire compatible and may require varying sheath and guide diameters. In addition, the working length of devices may range from 70 to 150 cm. The main focus of this chapter will be on the fundamental technical aspects of endovascular repair.

Equipment
Sheaths
The sheath becomes the delivery catheter for most endovascular repair procedures. The main advantage to using sheaths is that its internal diameter is much larger than the one of a same
size guide catheter. Length and diameter of the sheath to be used will depend on distance from access site to lesion and the internal diameter required to deliver the interventional equipment. Most iliac and distal aortic interventions will be performed via unilateral or bilateral retrograde CFA access using sheaths that are at least 23 cm in length enabling adequate visualization of the lesion as seen in Figure 49.3. Most iliac and aortic interventions can be performed via a 6-Fr sheath but occasionally a 7-Fr sheath will be needed for larger stent and post dilatation balloons. CFA and SFA procedures typically call for crossing over the aortic bifurcation from the contralateral CFA, which requires a sheath at least 45 cm in length. A 6-Fr diameter is usually adequate to deliver most of the interventional equipment (see exceptions listed in Tables 49.3–49.6). Although most infrapopliteal interventions can be performed with 45-cm 6-Fr sheaths on occasion a 65-cm length sheath placed deep into the SFA may provide better visualization of the target vessel. When approaching the lower extremity via the brachial artery a 90-cm 6- or 7-Fr sheath is usually adequate for iliac and CFA lesions.

**Wires**

Wires most commonly used for lower and upper extremity interventional procedures are listed in Table 49.2. When crossing a nonocclusive stenosis, virtually any wire can be used for

**Table 49.1** Lesion Characteristic and Optional Equipment for Endovascular Intervention

<table>
<thead>
<tr>
<th>Lesion characteristic</th>
<th>Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iliac and distal aorta</td>
<td>PTA with adjunctive stent</td>
</tr>
<tr>
<td>CFA noncalcified</td>
<td>SilverHawk, POBA, cryoplasty, cutting balloon</td>
</tr>
<tr>
<td>CFA calcified</td>
<td>RockHawk, Diamondback 2.25 ± PTA</td>
</tr>
<tr>
<td>SFA ostial</td>
<td>SilverHawk, POBA, cryoplasty, cutting balloon, RockHawk, Diamondback</td>
</tr>
<tr>
<td>SFA proximal and mid nonocclusive &lt;5 cm in length</td>
<td>RockHawk, Diamondback 2.25 ± PTA for heavy calcification</td>
</tr>
<tr>
<td>SFA proximal and mid nonocclusive &gt;10 cm in length</td>
<td>RockHawk, Diamondback 2.0–2.25 ± PTA for heavy calcification</td>
</tr>
<tr>
<td>SFA occlusion</td>
<td>Subintimal angioplasty ± reentry catheter with adjunctive self-expanding stent ± ViabHan, ELA</td>
</tr>
<tr>
<td>SFA distal and popliteal</td>
<td>SilverHawk, POBA, cryoplasty, cutting balloon, RockHawk, Diamondback</td>
</tr>
<tr>
<td>Runoff vessels</td>
<td>SilverHawk, POBA, cryoplasty, cutting balloon, Diamondback 1.5–1.75 ± PTA for heavy calcification</td>
</tr>
</tbody>
</table>

**Abbreviations:** CFA, common femoral artery; ELA, excimer laser angioplasty; POBA, plain old balloon angioplasty; PTA, percutaneous transluminal angioplasty; SFA, superficial femoral artery.
advancement of balloons and stents as long as it provides adequate support. Therefore, 0.035 in. and 0.018 in. wires are usually chosen to deliver larger devices. Chronic total occlusions (CTOs) more commonly require a hydrophilic-coated wire that will penetrate the initial cap and allow for subintimal dissection and distal reentry to the true lumen. Certain devices require a 0.014 in. platform for their delivery (Tables 49.3–49.6). On occasion, reentering the true lumen with the tapered Confianza Pro 0.014 in. wire (Abbott, Abbott Park, Illinois, U.S.) can be accomplished when unsuccessful with the hydrophilic 0.035 in. wires and prior to using reentry devices.

**Angioplasty Balloons**
A select sample of balloons used for lower extremity angioplasty is listed in Table 49.3. Despite improvements in balloon catheter materials, lower balloon crossing profiles, and the availability of longer balloons for peripheral arterial use, plain old balloon angioplasty (POBA) remains limited by residual dissection, acute elastic recoil, and restenosis (4). Although POBA can be an effective modality for focal lesions in the iliac

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**Table 49.2 Examples of Guidewires Used for Endovascular Intervention**

<table>
<thead>
<tr>
<th>Guidewire</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.035 in. Magic Torque (Terumo Medical)</td>
<td>CTO, tortuous calcified vessels</td>
</tr>
<tr>
<td>0.035 in. Supracore (Abbott Vascular)</td>
<td>Nonocclusive stenosis, good support</td>
</tr>
<tr>
<td>0.035 in. Wholey (Abbott)</td>
<td>Nonocclusive stenosis, good support</td>
</tr>
<tr>
<td>0.035 in. Amplatz Super Stiff (Abbott)</td>
<td>Extra support wire for railing purposes</td>
</tr>
<tr>
<td>0.035 in. Steelcore (Abbott)</td>
<td>Smaller profile balloons</td>
</tr>
<tr>
<td>0.014 in. Confianza Pro (Abbott Vascular, Asahi)</td>
<td>Penetrating distal cap of CTO</td>
</tr>
</tbody>
</table>

Abbreviation: CTO, chronic total occluded vessel.

**Table 49.3 Selected Examples of Angioplasty Balloons for Endovascular Intervention**

<table>
<thead>
<tr>
<th>Device</th>
<th>Device diameter (mm)</th>
<th>Minimal sheath (Fr)</th>
<th>Wire</th>
<th>RX/OTW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aviator (Cordis)</td>
<td>4–6.5</td>
<td>4</td>
<td>0.014</td>
<td>RX</td>
</tr>
<tr>
<td>ViaTrac (Abbott)</td>
<td>7</td>
<td>4</td>
<td>0.014</td>
<td>RX</td>
</tr>
<tr>
<td>Magic Torque (Terumo)</td>
<td>4–4.5</td>
<td>5</td>
<td>0.014</td>
<td>RX</td>
</tr>
<tr>
<td>AgilTrac (Abbott)</td>
<td>9–10</td>
<td>6</td>
<td>0.018</td>
<td>OTW</td>
</tr>
<tr>
<td>Powerflex (Cordis)</td>
<td>4–8</td>
<td>6</td>
<td>0.035</td>
<td>OTW</td>
</tr>
<tr>
<td>Dorado (Bard)</td>
<td>3–7</td>
<td>5</td>
<td>0.035</td>
<td>OTW</td>
</tr>
<tr>
<td>EverCross (ev3)</td>
<td>7–10</td>
<td>6</td>
<td>0.035</td>
<td>OTW</td>
</tr>
</tbody>
</table>

Abbreviations: RX, rapid exchange; OTW, over the wire.

**Table 49.4 Predictors of Poor Outcome After Plain Old Balloon Angioplasty**
- Length of the diseased segment
- Total occlusion
- Diabetes mellitus
- Poor distal runoff
- Critical limb ischemia
arteries (4), the results of balloon angioplasty for complex infrainguinal arterial disease have been disappointing (5–8). Numerous clinical and lesion specific factors have been identified that negatively affect the long-term results of POBA (Table 49.4). Locations where POBA is desirable are distal SFA, popliteal, CFA, and runoff vessels. Stent fracture makes stenting less desirable for distal SFA and popliteal arteries, while reaccess makes CFA stenting a relative contraindication.

Advances in technology for balloon angioplasty have included the production of cutting and scoring balloons, as well as cryoplasty balloons—as described below—to help alleviate the need for adjunctive stenting. Recent data have suggested significant reduction in restenosis with paclitaxel-coated balloons compared to POBA for infrapopliteal arteries (9,10). Peripheral drug-coated balloons have entered the market of some European countries but are not approved by the U.S. Food and Drug Administration (FDA).

Cryoplasty is a technique that combines balloon angioplasty and cold therapy. Cooling of the balloon is achieved by the use of liquid nitrous oxide as the balloon inflation media rather than the usual mixture of contrast and saline. The combination is proposed to reduce the incidence of restenosis by inhibition of neointimal hyperplasia. Nonrandomized clinical studies have suggested improved patency associated with cryoplasty compared to conventional angioplasty, but the benefit remains to be adequately demonstrated (11). The PolarCath (Boston Scientific, Natick, Massachusetts, U.S.) is a commercially available FDA-approved cryoplasty system for peripheral arterial use. The PolarCath system was evaluated in a prospective multicenter registry of cryoplasty for the treatment of lesions in the SFA and popliteal artery. A total of 102 patients with stenoses or occlusions up to 10 cm in length were enrolled at 15 centers in the United States. Procedural success was 94%, with a need for bailout stenting resulting from a suboptimal angiographic result in 9% of cases and flow-limiting dissection in 7% of cases. Primary clinical patency was 83% at nine months. Primary assisted and secondary patency rates were 94% and 98%, respectively (11). These findings compare favorably with POBA historical data.

Cutting and Scoring Balloons

There is extensive experience with cutting and, to less extent, with the scoring balloons in the coronary circulation. Recently, the cutting balloon (Boston Scientific)—initially designed for the coronary circulation—was made available in larger diameters and was approved by the FDA for peripheral vascular use. The device consists of four microsurgical blades bonded to the balloon. The cutting balloon has shown promise, in treatment of anastomotic or intragraft lesions within saphenous vein bypass grafts. A recent study compared POBA with the cutting balloon as the primary treatment for failing infrainguinal bypass grafts in 36 patients; the initial technical success was higher with the cutting balloon (74% vs. 82%). In addition, the primary patency rate at 12 months was 36% for POBA and 50% for cutting balloon angioplasty (12). Ansel et al. reported cutting balloon angioplasty results in 73 patients with critical limb ischemia. The procedure was successfully completed in all patients, although 4% of cases required predilation with POBA. Severe intimal dissection or inadequate hemodynamic result necessitated adjunctive stenting in 20% of the procedures. There were no vessel perforations or surgical target vessel revascularization. After mean follow-up of one year, 89.5% of threatened limbs were salvaged (13). The Scoring balloon (AngioSculpt, Inc., Fremont, California, U.S.) has been developed for both coronary and peripheral use. They differ from cutting balloons in that they have rectangular spiral struts. Scoring balloons come in sizes ranging from 2 to 6 mm in diameter with 20 and 40 mm lengths.
Nitinol Stents

Nitinol is an alloy composed of nearly equal parts of nickel and titanium. Nitinol has two unique characteristics: great elasticity and better conformity and thermal shape memory. These properties make nitinol stents resistant to compression at body temperature and help them to resist external deformation (4). The Intracoil stent was one of the first nitinol stents approved by the FDA. Ansel et al. studied 93 patients with obstructive femoropopliteal artery disease up to 15 cm in length treated with the Intracoil stent. Nine-month follow-up revealed that 78% of patients remained free of major adverse clinical events and that 82% had not required target lesion revascularization (14). The SMART stent (Cordis, Bridgewater, New Jersey, U.S.) was evaluated in a prospective study involving 137 lower limbs in 122 patients with chronic limb ischemia. The mean lesion length was 12 cm and 57% of the lesions were at least 10 cm in length. Technical success was achieved in 98% of cases, and that 82% had not required target lesion revascularization (14). Schillinger and colleagues randomized 104 patients with severe claudication caused by stenosis or occlusion of the SFA to either primary stent implantation or bailout stenting (53 patients). Bailout stenting was performed in 32% of patients in the angioplasty group mostly due to suboptimal endovascular results as well as avoiding stenting of sites with high degrees of vessel torsion such as distal SFA, and popliteal artery to limit stent fracture. Table 49.5 provides information on a variety of self-expanding and balloon-expandable stents for peripheral use. Drug-eluting stents (DES) do intuitively represent the logical answer to restenosis, although data from The Sirolimus Coated Cordis SMART Nitinol Self-Expandable Stent for the Treatment of SFA Disease (SIROCCO) trials that randomized patients with SFA disease to sirolimus-coated SMART stents or noncoated SMART stents found no statistical differences in terms of restenosis at 18 months (20,21). There are two ongoing DES trials using different drugs and drug-release concepts. Currently, one study is investigating the paclitaxel-eluting Zilver PTX stent (Cook Medical, Inc., Bloomington, Indiana, U.S.). A second DES platform for SFA treatment is addressed in the STRIDE registry using longer elusion times with everolimus from the DYNALINK-E stent (Abbott Vascular, Diegem, Belgium). Both studies and platforms were designed to correct flaws in drug dose, and release kinetics believed to be responsible for the disappointing results in the SCIROCCO trials. The application of DES for infrainguinal lesions has recently shown more promise than for infrapopliteal lesions. The combined results of four observational studies evaluating the coronary Cypher stent (Cordis) for below-the-knee procedures resulted in 100% freedom from major amputation, 96% limb salvage rates, and only a 4% need for target vessel revascularization, which compared well with the historical surgical revision rates as high as 49% (22-25).

Although balloon-expandable stents are commonly used for distal aortic stenosis and ostial iliac disease, self-expanding nitinol stents have been shown to result in primary patency rates of greater than 90% at 12 months. The Cordis Randomized Iliac Stent Project-US (CRISP-US) trial evaluated the SMART nitinol self-expanding stent and the stainless steel Wallstent (Boston Scientific) for treating iliac artery disease after suboptimal POBA. Primary patency at 12 months was 95% with the SMART stent and 91% for those lesions treated with the Wallstent. Acute procedural success rate was higher in the SMART stent group (98.2% vs. 87.5%; P = 0.02).

Nitinol Stent Grafts and Covered Stents

The Viabahn endoprosthesis (W.L. Gore & Associates, Inc., Flagstaff, Arizona, U.S.) is a self-expanding helical nitinol stent mounted to the outside surface of a tube of expanded polytetrafluoroethylene. The Viabahn endoprosthesis, delivered through a 7- or 8-Fr sheath, is currently approved by the FDA for use in patients with symptomatic superficial femoral arterial lesions with reference vessel diameters of 4.8 to 7.5 mm (4). The Viabahn stent has been tested in a randomized prospective study and was compared to surgical femoral-to-above knee popliteal artery bypass with synthetic graft material. A total of 100 limbs in 86 patients were treated. Follow-up evaluation with ankle-brachial indices and color flow duplex sonography imaging were performed at 3, 6, 9, and 12 months after treatment. Although underpowered to be conclusive, no statistical difference was found in the primary patency, secondary patency, or reintervention between the two treatment groups (26). Stent grafts and covered stents may be useful for aneurismal disease, given their ability to exclude the vessel wall from the lumen as has been reported for popliteal aneurysms (26,27). Additionally, the Viabahn endoprosthesis is very effective for bailout SFA perforations as seen in Figure 49.4. The iCAST (Atrium Medical Corp., Hudson, New Hampshire, U.S.) is balloon-expandable lower profile covered stent with diameters ranging from 5 to
10 mm, which can be delivered through a 6- and 7-Fr sheath. The iCAST may be preferable for coverage of iliac aneurysms and in emergent cases of iliac perforations secondary to its crossing profile, precise placement that a balloon-expandable stent affords, and having the character of being able to expand to the desired diameter with post dilatation.

**Debulking Devices**

Atherectomy has been used to treat PAD in the past with mixed results. More recently, there has been renewed interest in debulking devices with the development of the SilverHawk (Fox Hollow Technologies, Redwood City, California, U.S.), as a new excisional atherectomy system, and the Diamondback 360 Orbital Atherectomy System (Cardiovascular System Inc., St. Paul, Minnesota, U.S.), as a rotational atherectomy device. Both devices are FDA approved. Although there are no randomized trials comparing excisional atherectomy to balloon angioplasty or stenting, there are several registries and single-center experiences with SilverHawk system. Treating Peripherals with SilverHawk: Outcomes Collection Registry (TALON) enrolled 601 consecutive patients in 19 institutions. A total of 1258 symptomatic lower extremity atherosclerotic lesions were treated with mean lesion lengths of 63 mm above the knee and 69 mm below the knee. The primary endpoints of the study were target lesion revascularization (TLR) at 6 and 12 months. Procedural success was 98% and the 6- and 12-month freedom of TLR rates were 90% and 80%, respectively. Predictors of TLR were a history of MI or coronary revascularization, increasing Rutherford category, and lesion length. Multiple single center series have also reported good initial success with similar mid- and long-term outcomes with this device within the femoropopliteal and infrapopliteal vessels (28–31). The advantage of the SilverHawk system is the ability to remove plaque with or without the performance of adjunctive angioplasty. This treatment may be particularly useful for locations where stenting should be avoided such as the distal SFA, popliteal, and CFA. The system comes in various sizes allowing treatment from the CFA to the tibial vessels (Table 49.6). Limitations to the device have been its inability to cut calcified plaques, needing to use more than one device if treating varying size vessels in the same patient, and the risk of distal embolization requiring distal protection especially for patients with limited patent runoff vessels.

The Diamondback 360° Orbital Atherectomy System is a promising new device for treating symptomatic PAD within the major and branch arteries of the leg. The device differs from other atherectomy technologies by its unique orbital action to remove plaque and the ability to increase treatment diameter by increasing orbital speed. Orbital Atherectomy System for Treating Peripheral vascular Stenosis (OASIS), a prospective multicenter clinical study, was conducted to evaluate the efficacy and safety of this system; from September 1 through December 31, 2007, more than 350 cases with the Diamondback 360° were documented. Results revealed low rates of dissection (2%), perforation (2.3%), and embolism (2%). Advantages for this device over the SilverHawk are its ability to cut through calcified lesions and the ability to increase cutting size by increasing rotational speed, thus potentially limiting the number of catheters needed per case. It is hampered by its inability to cut soft plaque and tendency for distal embolization without the potential for distal protection given its need for a dedicated wire (Table 49.6).

**Excimer Laser Atherectomy**

Excimer laser-assisted angioplasty (ELA) for the treatment of PAD has been commercially available in Europe since 1994. The technique is based on intense bursts of ultraviolet light in short pulse durations. The advantage of ELA lies in the ability to break molecular bonds directly by photochemical rather than by pure heat, which limits continuous-wave hot-tip lasers. ELA is most applicable in the treatment of long complex lesions—calcified or noncalcified—and to facilitate crossing of CTO. The most advanced system used is the TURBO elite laser system (Spectranetics, Colorado Springs, Colorado, U.S.). When combined with the TURBO-Booster guiding catheter, the elite laser...
can be used to create larger lumens for infrarenal arteries. Scheinert and colleagues analyzed data from 318 consecutive patients, who underwent ELA of 411 SFA with chronic occlusions averaging 19.4 ± 6.0 cm in length. Initial and secondary crossing success were 82% and 90.5%, respectively. The primary patency at one year was 33.6% with the one-year assisted primary and secondary patency rates being 65.1% and 75.9%, respectively (32). In the Laser Angioplasty for Critical Limb ischemia (LACI) trial, a prospective registry at 14 sites in the United States and Germany, 145 patients with 155 critically ischemic limbs were enrolled. At six-month follow-up, limb salvage was achieved in 92% of surviving patients (33).

**Devices for Chronic Total Occlusions**

The Frontrunner XP CTO Catheter (Cordis) enables controlled crossing of CTO. It uses blunt microdissection to create a channel through the occlusion to facilitate wire placement. It features a crossing profile of 0.039 in. with actuating jaws that open to 2.3 mm. The shapeable distal tip and effective torque control enhance maneuverability while supported by a 4.5-Fr Micro Guide catheter. Once the lesion is crossed, the guide catheter is advanced into the true lumen and the Frontrunner is removed and replaced with a guidewire up to 0.035 in. Mossop et al. prospectively evaluated the technical success and safety of controlled blunt microdissection for the treatment of resistant peripheral CTO. They enrolled 36 patients with 44 symptomatic CTO (2 terminal aortic, 24 iliac, 16 femoral, and 2 popliteal), which had previously failed conventional percutaneous revascularization. Procedural success was achieved in 91% of the 44 CTO (34). This device is most helpful when the proximal cap of a CTO is refractory to initial guide wire penetration.

The CROSSER (FlowCardia, Inc., Sunnyvale, California, U.S.), a novel device for recanalization of CTO, is on a monorail catheter that delivers vibrational energy to facilitate the crossing of occluded arteries. Although the CROSSER system has been proven safe and feasible in the totally occluded coronary circulation with procedure success rate reaching 73% (35), there is no clinical trial to assess the safety of this system in PAD. The peripheral system is advanced over a 0.018 in. guidewire until it reaches the lumen cap when the wire is retracted within the Crosser catheter. Once the catheter crosses the lesion of the length of the lesion and reenters the true lumen, the wire is then reintroduced into the true lumen and the catheter removed making way for advancement of adjunctive equipment. This device relies on remaining within the true lumen and therefore may not be effective in long total occlusions. Its niche may be in initial crossing of heavily calcified initial caps. Both devices are FDA approved.

**True-Lumen Reentry Devices**

The OutBack LTD reentry catheter (Cordis) was first evaluated in a series of 36 patients with peripheral—mainly iliac and femoral—CTO initially approached with percutaneous controlled blunt microdissection. Of all successful cases, 35% (14 of 40) required true-lumen reentry, which was successfully achieved in all cases with this first generation device (34). Additional evidence has been reported for the use of both the Outback and Pioneer catheter (Medtronic, Inc., Minneapolis, Minnesota, U.S.), by Jacobs et al. in which 87 CTO in 58 iliac and 29 superficial femoral arteries were treated. In 24 (26%), the true lumen could not be reentered by using standard catheter and wire techniques. Intravascular ultrasound-guided true lumen reentry using the Pioneer catheter (21 CTO) or fluoroscopically-guided true lumen reentry using the Outback catheter (30 CTO) was successful in achieving true lumen reentry in all cases. During this study, the time to reentry was routinely less than 10 minutes (36). The Outback LTD device can be delivered through a 6-Fr sheath and has a smaller crossing profile than the Pioneer catheter that requires a 7-Fr sheath. The Outback’s lower profile is achieved by using a system of angiographic views to align the catheter prior to needle reentry, while the Pioneer has a bulkier ultrasound tip to help locate the true lumen prior to needle reentry (37). Both devices are FDA approved for peripheral intervention.

**Rheolytic Thrombectomy**

Although the FDA has approved many mechanical thrombectomy devices for use in thrombosed hemodialysis grafts, only the AngioJet LF140 (Possis Medical, Inc., Minneapolis, Minnesota, U.S.) is currently approved for use in peripheral arterial occlusive disease (38). The AngioJet rheolytic thrombectomy system has been shown to be effective in the treatment of acutely occluded infra-aortic native arteries and bypass grafts, with the majority of acute thrombotic material being removed. Rheolytic catheter has been used successfully in conjunction with catheter-directed thrombolysis in one series of 86 patients with acute and subacute limb-threatening ischemia. After primary rheolytic thrombectomy was performed, secondary catheter-directed thrombolysis was performed in 50 patients, yielding a high acute success rate with a reported six-month patency rate of 79% (4,39). Additional evidence has been reported in a retrospective analysis by Ansel et al. in which 99 consecutive patients underwent rheolytic therapy for thrombotic occlusions in 80 native arteries or 19 bypass grafts. Complete thrombus removal was accomplished in 71% of patients and partial in 22%. Mortality and amputation rates at 30 days were 7.1% and 4.0%, respectively (40). Although the AngioJet system likely provides a more forceful and complete thrombus aspiration, other more simple devices are available; Pronto V3 extraction catheter (Vascular Solutions, Minneapolis, Minnesota, U.S.), Export XT catheter (Medtronic Vascular, Santa Rosa, California, U.S.), Fetch (Possis Medical, Inc.), and the Diver CE (ev3, Plymouth, Minnesota, U.S.). Similarly, simple straight end-hole catheters can be used for thrombus aspiration.

**Embolic Protection in Lower Extremity Revascularization**

Since initial introduction for distal protection during carotid stenting, embolic protection devices (EPD) are now routinely used in coronary vein graft intervention as well as carotid artery stenting. These devices are either balloon based, GuardWire Plus (Medtronic Vascular), or filter-based, AngioGuard (Cordis), FilterWireEX (Boston Scientific), NeuroShield (MedNova, Galway, Ireland), and the Spider (ev3, Plymouth, Minnesota, U.S.). Although there are no randomized trials currently accessing EPD for lower extremity revascularization, there have been studies that suggest these devices may be efficacious (41–43). The use of these devices is limited in the lower extremity by their micropores—which are designed to retain cholesterol particles—and their susceptibility to becoming overwhelmed with fibrous debris (41,44). Although routine use of EPD for lower extremity interventions cannot be routinely recommended, there are specific cases in which protection may be efficacious. Consideration should be given for EPD for any lesion proximal to a single-vessel runoff, SilverHawk atherectomy in heavily calcified lesions, and prior to rheolytic thrombectomy.
access in an antegrade manner. Infrapopliteal repair is most commonly performed either in a retrograde approach from the contralateral CFA or in an antegrade approach via the ipsilateral CFA. Rarely the PT or the AT artery will be accessed if the lesion cannot be crossed via either of the previously mentioned access locations. Once the lesion is crossed via the access in the PT or AT, the wire can be snared and externalized through the larger sheaths in the ipsilateral or contralateral CFA. Because of the workable length of interventional equipment, a brachial approach can only be utilized for the most proximal segments of the SFA. On rare occasions, the operator may choose an axillary access to utilize the most workable length possible if there are no other alternatives.

Endovascular Repair
Iliac and CFA intervention  Endovascular repair of the common iliac can be one of the most straightforward lower extremity interventions, especially when the lesion does not involve the bifurcation of the distal aorta. In this case, a retrograde approach from the ipsilateral CFA with a 23-cm 6- to 7-Fr sheath will provide adequate length and size for most interventional equipment, as seen in Figure 49.3. In the absence of a total occlusion, any straight floppy tip 0.035 in. wire can be used. In many occasions, a 0.018 in. wire will also provide sufficient support. The size of the common iliac artery ranges from 7 to 10 mm in diameter. If the deployment of a stent has been deemed necessary and the ostium of the distal aorta is not involved, a self-expanding stent may be the preferred device. Accordingly, its flexibility allows for better vessel conformity and apposition in tortuous and ectatic vessels while allowing for over sizing without the risk of perforation or vessel rupture. Once the stent is in place, it can be post-dilated up to the size of the stent chosen. Balloon-expandable stents are commonly used when radial strength and precise location is needed such as the aortic bifurcation and when reforming the distal aorta bifurcation with a kissing stent technique. In distinction from self-expanding stents, balloon-expandable stents may be post-dilated to larger sizes.

When performing iliac interventions, the operator must be prepared for the rare but potentially lethal complication of perforation. Once recognized a balloon must be rapidly placed across the lesion to occluded flow. Access of the contralateral CFA is obtained, and an occlusion balloon is placed within the aorta and inflated. Once occlusion of the distal aorta is established, the balloon in the ruptured iliac can be deflated and an appropriately sized covered stent is then deployed to seal the rupture. A list of emergency equipment is found in Table 49.7.

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Minimal sheath (Fr)</th>
<th>Wire RX/OTW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusion balloon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equilizer (Boston Scientific)</td>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>Atrium (iCAST)</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td>Covered stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viabahn (Gore)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>7–8</td>
<td>8</td>
<td>0.035</td>
</tr>
</tbody>
</table>

**Abbreviations: RX, rapid exchange; OTW, over the wire.**

Clinical Aspects and Technique

Access

**Aortoiliac and common femoral repair** Access for endovascular interventions will depend on the territory to be intervened upon and the access availability of the patient, as outlined in Figure 49.5. Most aortoiliac interventions are best approached from the ipsilateral CFA in a retrograde approach, as seen in Figure 49.3. This allows for good visualization while ensuring the most straightforward intervention. If the ipsilateral CFA is occluded, consideration can be given to access of the contralateral CFA as long as the lesion to be treated is not in the ostium or proximal segment of the common iliac, allowing enough distance from the tip of the sheath and the lesion to adequately deliver the interventional equipment. Brachial access in this situation is a good alternative. Lesions at the bifurcation of the common iliacs will require accessing both CFAs for the deployment of simultaneous balloons and or stents at the distal aorta reforming the bifurcation. In the case of occlusion of one or both CFA, access from a brachial artery and contralateral CFA or both brachial arteries will allow the same ability for simultaneous placement of stents at the aortoiliac bifurcation. One limitation to using the brachial artery for common iliac interventions is the need for larger sheath size (7 Fr) when stent size exceeds 8 to 10 mm in diameter. Access for endovascular repair of the CFA most commonly will be from the contralateral CFA in a retrograde approach or brachial if the contralateral CFA cannot be utilized.

**Femoral-popliteal and infrapopliteal repair** A retrograde crossover approach from the contralateral CFA access is commonly used to treat SFA lesions in any location along its course. This access is not recommended or not possible in the presence of severe disease of the contralateral CFA, severe calcification or narrow angle of the aortoiliac bifurcation, and in the presence of aortobifemoral or bi-iliac graft. In these cases, an antegrade access from the ipsilateral CFA is an alternative as long as the proximal segment of the CFA is patent allowing good seating of your sheath. When the proximal SFA is diseased or occluded, the possible access options are either through a retrograde ipsilateral popliteal approach or repairing the CFA from a brachial access with subsequent ipsilateral CFA

Figure 49.5 Access sites and different approaches to lower extremities intervention.
CFA intervention must be accomplished with preservation of future access and without affecting the profunda femoris. Bearing these factors in mind stents should be avoided and either stand-alone angioplasty, as seen in Figure 49.6, or atherectomy, as seen in Figure 49.7, should be the modalities of choice. Either a retrograde approach from the contralateral CFA or a brachial artery access is most commonly used.

**SFA intervention**

SFA repair is most commonly performed from the contralateral CFA with the use of a 45-cm 6- to 7-Fr sheath. The sheath is advanced into the CFA or into the proximal SFA of the affected side, if the vessel will allow such placement. The operator may desire placement of the tip of the sheath prior to the takeoff of the profunda femoris in the setting of a CTO of the SFA. This will allow for better visualization of the distal SFA via collateral flow from the profunda femoris. In the absence of a CTO, the lesion in the SFA can usually be wired with any 0.035 in. wire. Predilation will allow trouble-free crossing with the appropriately sized self-expanding stent. Self-expanding stents are usually sized one vessel size up from the estimated vessel size. Post-dilation of the stent is then performed with a one-to-one balloon to vessel size ratio. Care must be given in heavily calcified vessels not to overdilate, which may result in vessel rupture. Patient discomfort during balloon inflation is commonly used to detect when the maximal size has been reached. In locations within the SFA where stent placement is not recommended (distal to the Adductor Hiatus), SilverHawk atherectomy is a good option. In heavily calcified lesions, Diamondback atherectomy or ELA should be...
considered. Both atherectomy and ELA outcomes may be enhanced with post-atherectomy low atmosphere balloon angioplasty. Cryoplasty, cutting, and scoring balloons also remain options in this location. In the presence of a CTO, there are various techniques and devices at the operator’s disposal. For long occlusions subintimal angioplasty has become the standard approach to revascularization. A stiff hydrophilic wire is advanced the proximal cap with the aid of a backup catheter. The wire is then used to probe the cap until a small loop is formed in the subintimal space. The backup catheter is then advanced forward, keeping the wire loop as small as possible limiting the size of the dissection plane. Maintaining the smallest dissection plane possible will increase the likelihood of reentering the true lumen with your guidewire. Once the distal cap is reached, the wire is then retracted into the catheter and redirected without the loop in attempts to cross back into the true lumen, as seen in Figure 49.8. Typically, reentry into the true lumen is the most time consuming and tedious aspect of treating a CTO. Reentry catheters such as the Outback or Pioneer have shown remarkable success if reentry into the true lumen is not possible with standard catheter and guidewire technique. When used to cross CTO, the Turbo elite laser catheter can be advanced in proximity to the initial occlusive cap and activated for 5 to

Figure 49.7 (A) Noncalcified high-grade CFA stenosis (arrow); (B) post atherectomy using SilverHawk MS system. Abbreviation: CFA, common femoral artery.

Figure 49.8 Subintimal dissection of CTO. Abbreviation: CTO, chronic total occluded vessel.
Table 49.8  Devices for Use in CTO Endovascular Intervention

<table>
<thead>
<tr>
<th>Device Description</th>
<th>Minimal sheath (Fr)</th>
<th>Wire</th>
<th>RX/OTW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontrunner (Cordis)</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Crosser 14S (Flow Cardia)</td>
<td>5</td>
<td>0.014</td>
<td>RX</td>
</tr>
<tr>
<td>Crosser 18 (Flow Cardia)</td>
<td>6</td>
<td>0.018</td>
<td>RX</td>
</tr>
<tr>
<td>Outback LTD (Cordis)</td>
<td>6</td>
<td>0.014*</td>
<td>RX</td>
</tr>
<tr>
<td>Pioneer (Medtronic)</td>
<td>7</td>
<td>0.014*</td>
<td>RX</td>
</tr>
</tbody>
</table>

*Ironman or Grandslam wire.

Pioneer (Medtronic) 7 0.014 a RX aIronman or Grandslam wire.

Reentry devices

Outback LTD (Cordis)6 0.014 a RX

Reentry devices

Crosser 14S (Flow Cardia) 5 0.014 RX

Reentry devices

Crosser 18 (Flow Cardia) 6 0.018 RX

Reentry devices

Outback LTD (Cordis) 6 0.014* RX

Reentry devices

Pioneer (Medtronic) 7 0.014* RX

Reentry devices

10 seconds in a trial to penetrate the fibrous cap. The guidewire is then used to probe antegrade to find a channel through the occlusion. This process is repeated until the entire length of the CTO is crossed (4). The Frontrunner and the Crosser 18 be used in situations when the proximal cap cannot be penetrated as described earlier. Either device can then be continued if it passes easily through the occlusion. Once across the distal cap, full-length angioplasty is performed followed typically by self-expanding stent implantation. CTO equipment and compatibility is listed in Table 49.8.

**Popliteal intervention** Similar to CFA interventions operators should avoid stenting the popliteal artery due to the increase likelihood of stent fracture. The Supera stent (IDev Technologies, Houston, Texas, U.S.) may expand the role of bailout stenting in this location due to its superior flexibility and resistance to fracture. The Viahban stent graft has been used for coverage of popliteal aneurysms exceeding 2.0 cm in diameter. A critical limitation of the Viahban in this location has been the occurrence of stent thrombosis following prolonged knee flexure. Patients receiving a Viahban stent in the popliteal artery should be warned to avoid prolonged excessive knee flexion. Favored modalities for treatment of atherosclerotic disease of the popliteal artery remain SilverHawk atherectomy, balloon angioplasty, cryoplasty, cutting balloon angioplasty, ELA, and Diamondback orbital atherectomy for calcified lesions. Figure 49.9 illustrates Diamondback atherectomy followed by low atmosphere balloon angioplasty of the popliteal artery.

**Infrapopliteal intervention** Historically, revascularization of the infrapopliteal vasculature has been open surgical and reserved for critical limb ischemia and limb salvage. One reason for this conservative strategy has been the poor long-term patency of surgical grafts and also of the initial endovascular experience, the latter characterized by a high restenosis rate (45). Another major factor limiting an aggressive endovascular approach has been the fear to compromise a situation already critical with the risk of a subsequent amputation. However with advances in technology endovascular repair appears to have many advantages over open surgical repair (2). The results of the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial revealed that endovascular repair compared to open repair for critical limb ischemia was associated with lower morbidity, length of hospital stay, and necessity for high intensity units—all resulting in lower costs. Overall clinical outcomes in the Basil trial were similar between the two groups with respect to amputation-free survival (46). Most below-the-knee vessels are 2 to 5 mm in diameter and therefore best suited for 0.014 in. platform devices that are commonly employed for coronary intervention. The sheath should be placed as close to the lesion as possible to ensure adequate visualization either from a retrograde or antegrade CFA approach. The simplest approach is POBA with prolonged inflation times. Cryoplasty and cutting balloon devices may have theoretical advantages over POBA, but data has not been convincing (47,48). Long diffuse or bifurcating lesions may be better suited for atherectomy devices (SilverHawk and Diamondback) with or without adjunctive balloon angioplasty, as seen in Figure 49.10. An area currently being investigated is the use of coronary DES that have been shown to markedly reduce restenosis compared to bare metal stents for bailout purposes in infrapopliteal vessels (49). Should these results be reproduced and should longer and more deliverable drug-eluting devices come to the market, stenting may become the therapeutic modality of choice for below-the-knee interventions, particularly for focal stenosis or occlusions. It is important to underscore that even a temporary patency—for example, following angioplasty—may be sufficient to allow for wound healing in patients with foot ulcers. On a broader perspective, it seems likely that endovascular repair for infrapopliteal lesions will soon become standard of care (50,51).

**UPPER EXTREMITY REVASCULARIZATION**

In contrast to lower extremity disease, upper extremity vascular disease is uncommon and usually manifests with arm claudication, rest pain, and ischemic ulcerations. Rare manifestations of a subclavian stenosis are vertebralbasilar insufficiency if the contralateral vertebral artery is diseased/occluded and angina in a patient with previous mammary artery used as a conduit for CABG. The most common cause of large artery disease of the upper extremity is atherosclerosis. The involvement is typically limited to the proximal segments of the innominate and subclavian arteries, while more distal lesions are rare. The majority of the remaining cases of occlusive disease are associated with vasculitis, post-radiation, and external compression. Goals of revascularization of the upper extremity include relief from claudication, prevention of digit or limb loss, protection of antegrade flow to the internal mammary artery after CABG and of arterial-venous shunts for hemodialysis. Historically, upper extremity ischemic disease involving the large vessels was managed surgically using bypass or endarterectomy techniques. Currently, endovascular repair is the most accepted modality of treatment with data to support the lack of difference in long-term patency rates compared to surgery (52). More recently, Bates et al. reported a success rate of 97% and one-year patency of 96% in 89 patients who underwent subclavian artery stenting (53).

**Anatomic Considerations**

The proximal segments of the large arteries are seen in Figure 49.11. The primary anatomical consideration when stenting the proximal left subclavian artery is the location of the left vertebral artery. Appropriate angulations should be performed to see the true ostium of the vertebral artery prior to stent implantation. The majority of cases will allow a landing zone prior to the vertebral origin. When there is no landing zone prior to the vertebral artery, the operator must be aware of the consequences of jailing or shifting plaque into the vertebral artery. In this case, to avoid compromise of a dominant or sole vertebral artery, a (subselective) angiography of both vertebral arteries—including intracranial views—is recommended.
When approaching the right system, the operator must adequately visualize the bifurcation of the right common carotid and right vertebral arteries when repairing the innominate and right subclavian artery, respectively. Typically, the bifurcation of the right common carotid and innominate artery is best seen in the RAO projection. In the setting of significant atherosclerotic burden, distal protection within the vertebral system has been advocated by some, although the risk of stroke is small potentially due to delayed reversal of vertebral artery blood flow from retrograde to antegrade following angioplasty of the subclavian artery (54,55). Similarly, distal protection within the right internal carotid artery during repair of the right innominate may be considered for bulky atherosclerotic lesions.

**Access and Technique**
Access for endovascular repair of the innominate or subclavian artery can be via the common femoral, brachial, or radial arteries. The CFA approach will permit the use of either a sheath or guide catheter. When using a sheath the operator can either wire the lesion through a diagnostic catheter and replace the entire system with a sheath (usually 6–7 Fr and 90 cm in

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**(A)** High-grade stenosis of the popliteal artery; **(B)** post atherectomy with 2.25 Diamondback catheters in the popliteal artery (arrow); **(C)** low-pressure balloon inflation after Diamondback atherectomy the popliteal artery (arrow); **(D)** final result after Diamondback atherectomy.
length) or more simply telescope the diagnostic catheter through the sheath and once wired advance the sheath into the appropriate location over the diagnostic catheter. Guiding catheters are limited by their smaller internal diameter when compared to that of similar sized sheath. Sheaths are routinely used during brachial (6–7 Fr, 45 cm) and radial (6 Fr, 65–90 cm) access. Once the lesion has successfully been crossed with a standard 0.035 in. wire, balloon predilatation can be used to gage size and length prior to stent implantation. Subclavian arteries usually accommodate 7 to 10 mm diameter stents, while innominate arteries may require larger devices. Balloon-expandable stents are primarily used for their radial strength and precise placement. If the lesion is located aorto-ostially, the stent should protrude 1 to 2 mm into the aorta to have a complete coverage of the lesion. Although most investigators believe that no distal protection of the vertebral artery is required at the time of proximal upper extremity intervention, thoughtful consideration must be given to protecting the right internal carotid for bulky innominate lesions. Protection of the right internal carotid can be accomplished via access and deployment of the protection device through an additional sheath in the right brachial or radial artery while primarily working through a sheath from the CFA to repair the innominate.

Figure 49.10  (A) Bifurcation of the popliteal artery into the anterior tibial artery and tibioperoneal (TP) trunk revealing a totally occluded TP trunk (arrowhead) and severe disease in the AT (arrow); (B) 1.25 Diamondback catheter advanced for multiple runs in the AT; (C) final result in the PT trunk and AT after atherectomy and low-atmosphere balloon inflation. Abbreviations: AT, anterior tibial; PT, posterior tibial.
CONCLUSIONS AND FUTURE DEVELOPMENTS

Endovascular repair can be accomplished today with success in the majority of cases throughout the upper and lower extremity arterial bed with a low complication rate. Advances in technology and skills will further expand the proportion of patients undergoing endovascular interventions compared to open surgical procedures. Current major limitations of this technique, such as fracture and restenosis of self-expanding stents in the femoropopliteal circulation and the high reocclusion rate in below-the-knee procedures need to be resolved. In this respect, the role of DES and balloons is currently being investigated, but the pathway appears to be more complex than in the coronary tree. Programs addressing best medical treatment and early disease detection should be implemented to prevent the development of vasculopathy that results in limb loss.

REFERENCES


Renal and mesenteric artery interventions

John H. Rundback and Robert Lookstein

RENA L ARTER Y INTERVENTIONS

Introduction
Renal artery stenosis (RAS) is a common clinical condition. Atherosclerotic RAS (ARAS) is found in up to 75% of individuals at autopsy (1) and is frequently coexistent with atherosclerosis occurring in other vascular beds (2,3). Fibromuscular dysplasia (FMD) is a unique arteriopathy, often affecting the renal arteries, and typically occurring in Caucasian females in their third to fifth decade of life, with a high predilection for bilateral disease (4). Regardless of etiology, RAS may be an incidental finding, may be associated with or causative of hypertension, or, in the case of ARAS, may contribute to declining renal function or cardiac syndromes including congestive heart failure (CHF) and angina pectoris (5). In addition, there is some evidence that ARAS confers an increased risk of stroke independent of blood pressure control, myocardial infarction (MI), and cardiovascular death (6), although no interventional strategy has yet been proven beneficial in mitigating this risk. The currently enrolling U.S. National Institute of Health (NIH)-sponsored CORAL trial (Cardiovascular Outcomes in Renal Artery Lesions) will hopefully provide insights into the treatment of this condition (7).

The endovascular management of RAS with percutaneous transluminal renal angioplasty (PTRA) and stenting (PTRS) was first described more than 20 years ago (8). While PTRA alone is generally effective for the treatment of FMD, PTRS has emerged in the modern era as the standard of care for patients with ARAS. As such, suboptimal prior clinical trial data comparing medical therapy to PTRA alone for the treatment of ARAS are not informative regarding clinical decision making at the current time (9). Despite extensive observational evidence of clinical benefits derived from PTRS in ARAS patients, adequately powered randomized studies comparing this technique to observation alone, contemporary medical management, and surgical bypass are lacking (10). These issues will clearly be the focus of further study in the years ahead.

Indications for Intervention
In most cases, intervention for an incidentally discovered RAS is not warranted, and established guidelines support the practice of screening for RAS only in individuals with clinical conditions supporting revascularization (Table 50.1) (11). Perhaps a single exception to this rule would be the identification of a severe (i.e., >80%) stenosis in an otherwise asymptomatic patient with a solitary functional kidney, due to an established risk of spontaneous arterial occlusion precluding subsequent endovascular management (12,13). In all cases, individual case assessment regarding the risks and merits of the procedure should be based on clinical, anatomic, hemodynamic, and comorbid factors. In patients with excessive procedural risk, an initial noninterventional strategy utilizing careful surveillance for progressive renal disease may be justified.

PTRA or PTRS is supported in patients with a hemodynamically significant RAS and an appropriate clinical condition for treatment (Table 50.1) (11,12). Intervention for accelerated, resistant, or malignant hypertension as well as hypertension with an unexplained unilateral small kidney or with intolerance to medication is considered by the ACC/AHA guidelines to be a Class IIa (Level of Evidence: B) treatment. Similarly, PTRS for RAS and progressive chronic kidney disease with bilateral RAS or RAS to a solitary functioning kidney is a Class IIa (Level of Evidence: B) treatment. Revascularization for patients with chronic renal insufficiency with unilateral RAS is a Class Ib (Level of Evidence: C) therapy. In contrast, stenting for significant RAS and recurrent, unexplained CHF or sudden, unexplained pulmonary edema is a Class I (Level of Evidence: C) intervention (12). Obviously, such guidelines will undergo periodic reevaluation as increasing data are accumulated regarding the role and relative outcomes of PTRS and other potential treatments (7,14).

Prognostic factors for both a favorable and unfavorable response to renal intervention have been described. Best responders for hypertension include hyperreninemia (either basal or angiotensin-converting enzyme stimulated), shorter hypertension duration, higher baseline diastolic blood pressure, more severe angiographic stenosis, measurable transstenotic gradient of at least 20 mmHg (15), and presence of FMD (16,17). Best responders for renal function preservation are patients with more severe stenosis and rapid declines in function prior to intervention (18). In general, worse outcomes are seen in patients with marked target kidney atrophy (i.e., <7 cm pole-to-pole length), advanced and long-standing renal failure, longer duration of hypertension, proteinuria, and the presence of bilateral disease (19). Microcirculatory evidence, as measured by a duplex renal resistive index of >0.80, was found in one study to be a negative outcome predictor for both hypertension and renal function (20), although a larger study did not confirm this finding (21). Finally, diabetes does not necessarily portend a lack of blood pressure or creatinine benefit, even in the presence of coexistent nephrosclerosis (22).

Several new prognostic tools have been recently proposed. An elevated serum biomarker level brain natriuretic peptide level >80 pg/mL has been identified in one study of 27 patients with multidrug-resistant hypertension and RAS as a predictor of good blood pressure response following revascularization (23). Renal fractional flow resistance (FFR) has also been correlated with reduced blood pressure after PTRS (24). Interestingly, it also appears that the FFR—defined as the intraprocedurally measured ratio of the mean pressure in the renal artery after maximum hyperemia (by intrarenally administered papaverine vasodilation) to the aortic mean...
pressure—is a better predictor of hemodynamic severity of RAS than angiographic measurements (24).

Anatomic Considerations for Renal Intervention

Several different variants of renal FMD have been described, the most common being medial fibroplasia (4). Since FMD typically involves the mid to distal portions of the renal artery, angioplasty alone is generally sufficient, with stenting reserved for dissections (de novo or post-PTRA) or suboptimal PTRA results (Fig. 50.1) (25). Balloon size is selected based on the normal diameter of the renal artery proximal to the FMD, rather than in areas of poststenotic dilation. Cases with complex associated aneurysm may require more complex management, including the use of stent grafts or selective embolization.

ARAS characteristically involves the ostium of the renal artery, and PTRS has been clearly proven to be more efficacious than PTRA alone (26). Consequently, most operators have adopted a practice of primary or direct stenting. Despite the fact that ostial calcification is often present, lesions are effaceable with direct stent implantation in almost all cases. Stents should be implanted so as to completely cover the culprit lesion, with 1 to 3 mm extension into the aorta in most cases. In scenarios in which remodeling of the aortorenal ostium proximal to the ARAS results in different medial positions of the upper and lower edges of the renal artery origin, complete stent coverage across the most medial edge is necessary.

Positioning of renal artery stents requires that the treated renal artery origin is seen in complete profile. Computed tomography (CT) studies demonstrate that the right renal artery is often best imaged from a straight anterior-posterior image. The left renal usually arises obliquely from the aorta and is best visualized with a 20° to 40° left anterior oblique (LAO) image (27). To accommodate these differences, initial angiographic imaging is often performed in the 15° LAO position. Review of prior CT or magnetic resonance (MR) angiographic images will often allow precise identification of the optimal imaging angulation needed for stenting.

The renal arteries can on occasion have a sharp caudal angulation. In cases in which this precludes successful lesion crossing or results in inadequate guide support for stenting, alternative approaches such as a brachial or radial puncture can be used (28). These techniques have been facilitated in recent

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**Table 50.1** Indications for Renal Intervention

I. Hypertension (86,88–90)

- Accelerated hypertension—sudden worsening of previously controlled hypertension
- Refractory hypertension—hypertension resistant to treatment with at least 3 medications of different classes including a diuretic
- Malignant hypertension—hypertension with coexistent evidence of end organ damage, including left ventricular hypertrophy, congestive heart failure, visual or neurological disturbance, and/or advanced (grade IV) retinopathy
- Hypertension with a unilateral small kidney
- Hypertension with intolerance to medication

II. Renal salvage

- Sudden unexplained worsening of renal function (91)
- Impairment of renal function secondary to antihypertensive treatment, particularly with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (92,95)
- Renal dysfunction not attributable to another cause

III. Cardiac disturbance syndromes

- Recurrent “flash” pulmonary edema out of proportion to left ventricular impairment (2,93,94)
- Unstable angina in the setting of significant RAS

IV. Medication flexibility

- Clinical need to use ACEI or ARB (i.e., for treatment of proteinuria or cardiac dysfunction) that would be otherwise contraindicated due to risk of inducing renal failure
- Intolerance to antihypertensive medications

Abbreviations: RAS, renal artery stenosis; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.
years by the routine use of low-profile stent systems that can be placed through smaller sheath introducers.

The use of distal embolic protection devices (DEP) imposes other anatomic considerations. CT studies have demonstrated a relatively short average length of the renal artery from origin to its first bifurcation, particularly on the left side (29). This has a considerable impact for DEP selection, since the distance of many filters from cone to base may leave insufficient space for stent positioning within the renal artery. Similarly, determinations of arterial diameter in the DEP “landing zone” can exceed the diameter of the protection device, rendering it ineffective, or necessitating a partial (segmental) protection strategy (29). The recent introduction of larger protection profile shorter span filters may be more anatomically suited for renal artery use (30).

Multiple renal arteries occur in up to 25% of patients. In patients with accessory RAS, the use of smaller profile devices is preferred. Although not yet defined, drug-eluting stents may play a role for the treatment of arteries <5 mm in diameter due to the higher restenosis rate of these lesions.

**Equipment and Techniques**

Renal interventions are most commonly performed via the common femoral artery approach, using shaped guides (advanced through a sheath) or guide sheaths (containing an inner introducer and integrated hemostatic valve). A variety of guide shapes can be utilized, with common shapes including the renal double curve, internal mammary, and multipurpose designs, with the objective of having a sheath tip that is directed toward and aligns with the angulation of the renal artery origin. Patients are routinely anticoagulated prior to treatment with either heparin or bivalirudin.

There are three critical steps involved in PTRA and PTRS: lesion traversal, treatment selection decision making (including determination of transstenotic pressures), and balloon/stent positioning and deployment.

**Lesion Traversal**

Crossing the lesion is often the most difficult component of percutaneous renal revascularization, particularly in cases of severe stenosis or occlusion. The selected guide should have sufficient breadth in its secondary curve to abut the contralateral aortic wall so that there is sufficient support for controlling and advancing the renal crossing wire. For horizontally oriented renal arteries, the guide is initially positioned immediately at or just above the renal artery. A floppy-tipped wire with a gentle curve on the tip is then directed toward the angiographically demonstrated remaining renal artery lumen; imaging is performed using small contrast injections through the sheath sidearm. Gently rotating the guide and/or wire tip may allow engagement of the true lumen when crossing eccentric lesions. With a properly shaped guide, primary lesion crossing is usually performed using a 2-cm floppy-tipped 0.014- or 0.018-in. guidewire. Care must be taken to avoid excessive pushing if there is resistance to wire advancement, and it is important that the wire remain visualized with its tip in first- or second-order branches during all phases of the procedure. Wires advanced too distally can result in cortical perforation and retroperitoneal hemorrhage (31). After crossing, the stiff portion of the guidewire should extend across the aortorenal angle to allow subsequent balloon and stent passage.

For more caudally directed renal arteries, the use of a reverse curve catheter (e.g., Sos Omni, AngioDynamics, Queensbury, New York, U.S.) can often be useful. With this technique, the reverse catheter is formed using a floppy-tipped 0.035-in. guidewire either in the aorta below the renal arteries or at the thoracic aortic arch. The catheter is initially positioned below the renal artery, with the tip facing the side to be treated. With approximately 5 mm of wire protruding from the catheter tip, the catheter is gently advanced cranially. When the renal artery is engaged, there will be a visible “quick flip” of the wire. The wire is then advanced into the artery while simultaneously retracting the reverse curve catheter across the lesion. The renal guide is then gently advanced and rotated until it engages the renal ostium, and exchange is made through the catheter for a stiffer stenting wire. The catheter is then removed and angioplasty or stenting performed.

**“Don’t touch” technique** This technique minimizes manipulation in the perirenal aorta, theoretically reducing the risk of plaque or cholesterol embolization into the kidney during lesion crossing. There are several different don’t touch techniques. The most commonly described method is to advance a “J” wire beyond the guide tip into the suprarenal aorta. This pushes the guide tip away from the aortic wall, preventing plaque disruption. A second curved 0.014-in. floppy tip wire is then used to cross the RAS, before removing the J wire, allowing the guide to engage the renal artery ostium, and proceeding with the procedure.

**“Buddy wire” technique** Although not a method for lesion crossing, the buddy wire technique represent a useful strategy to allow successful procedure completion in cases when the severity of the RAS impedes balloon or stent placement. After initial lesion crossing, the guide is aligned with the renal artery ostium, and a second short transition 0.014-in. guidewire is passed into the renal artery. Balloon or stent advancement is then performed over the stiff wire, with the buddy wire serving to stabilize the guide and allow more directed translation of pushing forces across the artery without recoiling the guide.

**Selecting the Interventional Strategy**

Uncomplicated FMD (without associated dissection) is treated with PTRA first, whereas ostial ARAS is usually approached with an intent to stent. Truncal or nonostial ARAS may be managed with an initial attempt at PTRA alone. In these cases, the plaque causing the stenosis is not in direct contiguity with the aorta, and there is a resulting proximal “normal” renal artery segment. Balloons and stents are sized to the normal diameter of the renal artery, either proximal to the stenosis or beyond any area of poststenotic dilatation. The contralateral renal artery may also be used for vessel sizing if necessary. Renal artery diameters are usually 5 to 6 mm in women, and 6 to 7 mm in men.

Intervention is not warranted for a <50% RAS. For stenoses causing 60% to 80% narrowing, determination of the transstenotic pressure gradient is recommended (13). After crossing the lesion, simultaneous dual-channel pressure measurements are obtained from the renal artery distal to the stenosis and from the aortic sheath. Renal pressures may be recorded either through a 4-Fr catheter or, more recently, by using a pressure-sensing wire (32). The latter has the advantage of preventing obturation of the renal artery resulting in speciously low-pressure measurements. Although there is no absolute gradient that is hemodynamically significant, a transstenotic gradient exceeding 20 mmHg and a >10% peak aortic systolic gradient [(aortic-renal)/aortic <0.90] are two criteria
frequently utilized to indicate a stenosis warranting intervention. Fractional flow reserve can also be obtained as a determination of stenosis severity prior to PTRS.

Balloon and Stent Positioning

The selected balloon should be limited to just slightly longer than the RAS treated. Dilatation more than 1 cm beyond the stenosis should be avoided to prevent distal dissection. Balloon inflation is performed over 20 to 30 seconds. After engaging the stenosis with partial balloon inflation, the balloon catheter shaft should be advanced slightly forward so that the balloon assumes a more horizontal course at the renal ostium; sharp downward angulation of the balloon at the aorta can result in an aortic tear (33). For ostial ARAS, the shortest possible stent that will completely cover the lesion and extend 1 to 3 mm into aorta should be used. When there is uncertainty as to the exact location of the ostium due to extensive aortic plaque, it is preferred to have complete coverage by assuring that a small amount of stent projects into the aorta. Ostial locators in clinical development have the potential to allow precise stent positioning in difficult cases (34).

Distal Embolic Protection

Cholesterol, platelet, and plaque embolization occurs in almost all cases of renal intervention (35). In ex vivo models, embolic debris has been recorded during each phase of the procedure, including wire traversal, balloon dilation, stent insertion, and stent deployment (35). One recent study suggested a high preponderance of platelet-rich embolic debris and suggested a role for a dual strategy of distal embolic protection and intravenous glycoprotein IIb/IIIa receptor antagonism (36). Several different types of DEP have been used in the renal artery, including wire mesh filters (37–39), fibrous mesh filters (30), and balloon occlusion devices (38,40). There are several technical and anatomic considerations that are unique to renal DEPs (Table 50.2). Principal among technical issues are device rigidity and crossing profile, which can affect the ability to position the DEP beyond the stenosis without injury, and characteristics of the landing zone (position of filter positioning), which may limit filter positioning or the ability for vessel wall apposition and complete protection.

With regard to device crossing as well as DEP length, fibrous mesh filters and balloon occlusion devices have more favorable characteristics, although occlusion balloons have restrictions in maximal capacity and ability for complete protection. Advancement of the occlusion balloon into upper or lower pole segmental arteries for partial renal protection has been described. While partial protection captures less measurable debris than complete protection, differences in renal function preservation between the two approaches have not been proven (41). Wire mesh filters have larger diameters, but generally are more rigid and longer devices, such that positioning requires at least 2 cm of normal artery beyond the planned distal end of a stent. If this is not possible, partial protection strategies can be employed. To facilitate lesion crossing, a buddy wire technique can be advantageous.

Outcomes After Renal Intervention

Patency and Reintervention

PTRA alone for patients with FMD is associated with very high patency rates and low rates of reintervention for recurrent stenosis. In contrast, PTAs for ARAS results in frequent stenosis recurrence; stent placement has considerably lower restenosis and is thus widely accepted as the standard of care for these lesions (42,43).

Restenosis after PTAs for ARAS occurs in 15% to 20% of cases and is more frequent with initial stent diameters <5 to 6 mm (44,45). Renal stent fracture has also been recently associated with restenosis in approximately 20% of cases (46) and is not surprising given the tremendous respiratory motion of the kidney and resulting “fulcrum-like” stress on ostially located stents (47). Not all patients with restenosis require target lesion revasculatization (TLR). In a large single-center experience by Bates et al. of 748 patients, revascularization was performed in 10% of patients at nearly four-year follow-up after renal artery stenting (48). The initial use of sirolimus drug-eluting stents has been associated with a reduction in late lumen loss but non-substantial differences in binary restenosis or TLR (46).

The management of in-stent renal artery restenosis is uncertain. Strategies have included balloon angioplasty alone (49), angioplasty with repeat stent placement (stent-in-stent angioplasty) (49,50), and covered stent placement (51). In a recent series of 34 patients with injection site reaction (ISR), a stent-in-stent angioplasty was superior to repeat PTAs alone, with recurrent ISR in 29% versus 71%, respectively (p = 0.02) (50).

Clinical Results

The results of PTFAs for hypertension are shown in Table 50.3 (52–60). Revascularization in most series results in reproducible and sustainable reductions in both systolic and diastolic blood pressure. In the largest published registry series to date, Dorros et al. reported on 1058 successfully stented patients, including 901 (85%) who were treated for poorly controlled hypertension. Follow-up data demonstrated a durable and statistically significant improvement in blood pressure control (at 4 years: systolic, 168 + 27 to 147 + 21 mmHg; diastolic 84 + 15 to 78 + 12 mmHg; p < 0.05) as well as a significant decrease in the number of antihypertensive medications (2.4 + 1.1 to 1.8 + 0.9 at 3 years; p = 0.05). Two recently published core laboratory adjudicated industry-sponsored prospective trials support these findings. In the ASPIRE-2 study, systolic/diastolic blood pressure was reduced from 168 ± 25/82 ± 13 mmHg at baseline to 149 ± 25/77 ± 12 mmHg at two years (p < 0.001) in 208 patients (56). The number of antihypertensive medications was changed from 2.8 ± 0.9 at baseline to 2.3 ± 1.5 at follow-up (p < 0.001). The RENAISSANCE study evaluated 100 patients for up to three
### Table 50.3 Hypertension Outcomes After Renal Artery Stenting

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Follow-up (mo)</th>
<th>Baseline</th>
<th>Postprocedure</th>
<th>Change</th>
<th>Baseline</th>
<th>Postprocedure</th>
<th>Change</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Dangas, 2001 (52)</td>
<td>131</td>
<td>Mean 15 ± 9 (n = 118)</td>
<td>170 ± 25</td>
<td>145 ± 20</td>
<td>–</td>
<td>84 ± 14</td>
<td>74 ± 12</td>
<td>–</td>
<td>48% improved</td>
</tr>
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<td>Doros, 2002 (53)</td>
<td>1058</td>
<td>12</td>
<td>168 ± 27</td>
<td>146 ± 24</td>
<td>–</td>
<td>84 ± 15</td>
<td>75 ± 12</td>
<td>–</td>
<td>–</td>
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<td>Zeller, 2004 (60)</td>
<td>340</td>
<td>6 (n = 278)</td>
<td>144 ± 19</td>
<td>136 ± 15</td>
<td>–</td>
<td>79 ± 11</td>
<td>72 ± 9</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td>12 (n = 211)</td>
<td>133 ± 15</td>
<td>–</td>
<td></td>
<td>75 ± 10</td>
<td>–</td>
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<td>–</td>
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<td>Sapoval, 2005 (58)</td>
<td>52</td>
<td>6 (n = 46)</td>
<td>172</td>
<td>152</td>
<td>–</td>
<td>92</td>
<td>85</td>
<td>–</td>
<td>5% cure, 61% improved</td>
</tr>
<tr>
<td>Tsao, 2005 (59)</td>
<td>34</td>
<td>6 (n = 33)</td>
<td>148 ± 4</td>
<td>130 ± 2</td>
<td>–</td>
<td>78 ± 3</td>
<td>70 ± 2</td>
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<td>85% cure/improved</td>
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<tr>
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<td>208</td>
<td>9 (n = 178)</td>
<td>168 ± 25</td>
<td>149 ± 24</td>
<td>–</td>
<td>82 ± 13</td>
<td>77 ± 12</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Ruchin, 2007 (57)</td>
<td>89</td>
<td>Mean: 28</td>
<td>161.7 ± 29.5</td>
<td>138.7 ± 17.9</td>
<td>–</td>
<td>78.4 ± 13.8</td>
<td>76.7 ± 10.8</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Goncalves, 2007 (54)</td>
<td>46</td>
<td>Median: 23</td>
<td>177 ± 30</td>
<td>135 ± 28</td>
<td>42.11 ± 37.8</td>
<td>98 ± 17</td>
<td>83 ± 8</td>
<td>15</td>
<td>43% improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean: 24.5 ± 15.2</td>
<td>–</td>
<td>–</td>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rocha-Singh, 2008 (55)</td>
<td>100</td>
<td>9 (n = 92)</td>
<td>156 ± 18</td>
<td>148 ± 22</td>
<td>9 ± 24</td>
<td>75 ± 12</td>
<td>75 ± 9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36</td>
<td>141 ± 22</td>
<td>16 ± 29</td>
<td>–</td>
<td>71 ± 9</td>
<td>4 ± 15</td>
<td>–</td>
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</tr>
</tbody>
</table>

**Abbreviation:** BP, blood pressure.
CARDIOVASCULAR CATHETERIZATION AND INTERVENTION

### Table 50.4 Renal Function Outcomes After Renal Artery Stenting

<table>
<thead>
<tr>
<th>First author, year</th>
<th>n</th>
<th>Follow-up (mo)</th>
<th>Mean serum creatinine (mg/dL)</th>
<th>Categorical outcomes (%)a</th>
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</thead>
<tbody>
<tr>
<td>Dorros, 2002 (53)</td>
<td>1058</td>
<td>1.7 ± 1.1</td>
<td>1.3 ± 0.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Rocha-Singh, 2002 (65)</td>
<td>51</td>
<td>2.3 ± 0.9</td>
<td>1.7 ± 0.7</td>
<td>&lt;0.001</td>
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<tr>
<td>Zeller, 2003 (21)</td>
<td>215</td>
<td>1.21</td>
<td>1.10</td>
<td>0.047</td>
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<tr>
<td>Zeller, 2004 (60)</td>
<td>354</td>
<td>34</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ramos, 2003 (63)</td>
<td>105</td>
<td>1.7 ± 0.9</td>
<td>1.4 ± 0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gill, 2003 (61)</td>
<td>100</td>
<td>25</td>
<td>–</td>
<td>10</td>
</tr>
<tr>
<td>Ilkay, 2004 (62)</td>
<td>13</td>
<td>2.6 ± 0.9</td>
<td>1.8 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rivolta, 2005 (64)</td>
<td>52</td>
<td>24</td>
<td>2.9 ± 1.8</td>
<td>–</td>
</tr>
<tr>
<td>Rocha-Singh, 2008</td>
<td>63b</td>
<td>9</td>
<td>–</td>
<td>16</td>
</tr>
<tr>
<td>(ASPIRE-2 Study) (55)</td>
<td></td>
<td></td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>Kashyap, 2007 (18)</td>
<td>125</td>
<td>2.2 ± 0.9</td>
<td>2.4 ± 1.5</td>
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<td>Bates, 2008 (77)</td>
<td>111b</td>
<td>36</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Rocha-Singh, 2008</td>
<td>100</td>
<td>36</td>
<td>1.3 ± 0.4</td>
<td>1.4 ± 0.6</td>
</tr>
<tr>
<td>(RENAISSANCE Trial) (55)</td>
<td></td>
<td></td>
<td>0.1038</td>
<td>–</td>
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</tbody>
</table>

**Notes:**
- Definitions for improvement and stabilization vary by report.
- Cohort of study patients with baseline serum creatinine ≥1.5 mg/dL.

years (55). Average systolic blood pressure was noted to be reduced by 15 ± 28 mmHg (p = 0.0003), with diastolic pressure lowered by 4 ± 15 mmHg (p = 0.0510).

The majority of patients undergoing RAST for renal insufficiency will have functional benefit, defined either as stabilization or improvement in either serum creatinine or calculated glomerular filtration rate (GFR) (Table 50.4) (18,22,53,55,60–65). Overall, between 50% and 90% of patients will benefit. Studies evaluating single kidney or total GFR after RAST have consistently demonstrated incremental positively directed changes when plotting the change in slope of inverse serum creatinine curves prior to and following intervention (66–68). Predictors of benefit include an absence of diabetes (69) or proteinuria (70), bilateral disease (71), recent rapid declines in renal function (18,72), and lower baseline serum creatinine (66,73,74). However, none of these is absolute, and benefit may still be observed in patients with measurable proteinuria (75), diabetes (22,70,76), and advanced renal insufficiency (53,77). Recent reports have even described renal recovery for dialysis-dependent patients after RAST (78).

There are several reasons attributed for continued renal decline in patients undergoing RAST for renal insufficiency. These include progression of underlying intrinsic renal pathology, immutable microcirculatory disturbance, contrast-induced nephropathy, and procedure-related embolization. A variety of strategies should be considered for nephroprevention when performing renal interventions in patients with baseline renal insufficiency. Useful approaches include vigorous hydration (79), alkaline (bicarbonate sodium) infusions (80), use of diluted and low-dose iso-osmolar nonionic contrast (81), CO2 angiography (82), periprocedural administration of oral N-acetylcysteine (83) alone or in combination with bicarbonated saline infusion (84), and the selective or routine use of distal embolic protection.

Several studies have evaluated outcomes of renal intervention utilizing DEP, with most showing improved results and a lower rate of subsequent renal failure when compared with historical controls (30,39,40,85). Capture of visible embolic debris occurs in 35% to 100% in reported series and appears to be more common with balloon occlusion techniques (Fig. 50.2) (37,39,40,85–87). However, the majority of liberated embolic particle may be <60 μm in size, and thus not macroscopically visible (88). The RESIST trial has demonstrated a propensity for small platelet-rich emboli (36) and suggested an advantage for concomitant antiplatelet therapy and DEP use also seen by Edwards (86). In an evaluation of 63 patients with ischemic nephropathy undergoing RAST with balloon occlusion embolic protection, Holden et al. noted stabilization or improvement of renal function after intervention in 97% of patients regardless of initial chronic kidney disease severity, although improvement was more likely in patients with less initial functional impairment (39). Of note, improvements in serum creatinine (SCr) were also more likely when visible debris was captured, although it is not clear whether this was due to technique or device failures or the occurrence of microemboli below the device filtration capacity. Sanjay and colleagues recently reported on protected PTRS using filter-type devices in 23 patients with baseline renal insufficiency. In this group, the collective mean modification of diet in renal disease equation (89) estimated GFR rose from 32.9 ± 0.9 mL/min prior to intervention to 41.3 ± 13.7 mL/min at last follow-up (8 ± 5 months). K-DQI stage (90) of chronic kidney disease improved in 26%, remained stable in 70%, and deteriorated in only 4% (86). In a series by Edwards et al., improvements in renal function were noted in 54% of 26 patients (32 lesions) with renal insufficiency (40). Randomized trials utilizing optimized renal protection devices will be necessary to clearly establish the value for this approach.

**Cardiovascular Events and Mortality**

There are a multitude of pathophysiological alterations that occur in RAS (91) beyond the classical Goldblatt model of hypertension (92). Neurohumoral activation results in diastolic dysfunction, which in addition to aldosterone-mediated volume overload and angiotensin II-stimulated peripheral vasoconstriction results in left ventricular hypertrophy, cardiovascular amplification, diastolic dysfunction, and RAS-related cardiac disturbance syndromes including “flash” pulmonary edema and precipitation of unstable angina. PTRS has been repeatedly shown to mitigate the subsequent risk of CHF and pulmonary edema in patients with RAS (93–95). In addition, at least one study has shown that revascularization of RAS in patients with coronary artery disease and angina reduces anginal severity even without coronary revascularization (2).

RAS is an independent risk factor for adverse cardiac events and cardiac mortality, with a graded risk correlation
Patients with RAS have higher mortality compared with matched individuals without renovascular disease that is not clearly related to degree of hypertension or concomitant existence of renal insufficiency (3). In a large study of 550 patients screened for renovascular disease during peripheral angiography, the presence of RAS was an independent risk factor for subsequent mortality (98). Death over a 3.8-year period of follow-up occurred in 27.6% of patients without RAS (n = 362), 54.3% of patients with RAS < 75% (n = 94), and 71.4% of patients with RAS ≥ 75% (n = 35) (p = 0.0001). Notably, differences in survival were observed at all levels of renal insufficiency (98). Patients with dialysis-dependent ischemic nephropathy have a particularly grim prognosis, with an annualized mortality rate in this cohort of almost 30% (99).

Neurohumoral activation appears to lessen after PTRS. Measurements of forearm vasoreactivity, serum endothelin, and left ventricular hypertrophy all improve after successful intervention (100–102). At least one retrospective study, conducted by Pizzolo et al., has demonstrated a survival advantage for patients with RAS treated with endovascular versus noninterventional therapy, with a mean 28-month cumulative probability of survival of 86.7% compared with 67.1% (101). Despite this, clear evidence of a survival benefit after RAST is lacking (10,103). Overall survival after RAST is to a large degree determined by baseline renal impairment (71,104), although

Figure 50.2 Treatment of atherosclerotic RAS using balloon occlusion distal embolic protection. (A) Digital subtraction abdominal aortography demonstrates severe bilateral ostial RAS. (B) After selective catheterization and crossing of the left renal artery with a Guardwire™ distal embolic protection device (Medtronic, Santa Rosa, California, U.S.), the balloon is inflated with resulting distal flow occlusion. (C) The selective catheter is reduced and removed (over the occluded distal balloon), advancing the renal double curve guide to the renal origin for stent positioning. Note the reflux of contrast into the aorta due to distal renal artery occlusion, facilitating stent positioning. The stent was initially inserted too deeply into the renal artery and was subsequently retracted for final positioning. (D) Completion angiography after stenting and deflation of the distal occlusion balloon shows a widely patent renal artery with preserved intrarenal flow. Filtration of aspirated blood showed visible captured embolic debris. Total renal artery occlusion time was 8.5 minutes. Abbreviation: RAS, renal artery stenosis.
recent evidence suggests that an improvement in renal function in initially azotemic RAS patients undergoing RAST may be associated with subsequent reduced mortality (105). The RENNAISSANCE study provides a contemporary prospective view of patients undergoing RAST, and found a three-year survival of almost 90% (55). Similar improved survival after renal revascularization has been demonstrated in both surgical (106) and stent (107) trials. The NIH-sponsored CORAL trial is currently underway and will collect data to definitively evaluate the occurrence of attributable cardiac and renal events in patients with RAS randomized to either optimal medical therapy alone or both medical therapy and RAST (7).

Complications of Renal Intervention

Renal intervention is generally safely performed. Risks of the procedure are related to puncture site complications, contrast-induced nephropathy, aortic or renal embolization including cholesterol embolization syndrome, and injury to the renal artery during lesion crossing, angioplasty, or stent placement. General procedural risks include periprocedural cardiac events and mortality, although both of these are distinctly uncommon. Complications may be either clinically relevant (e.g., major complications) or procedurally occurring events without anticipated clinical sequelae. Nonclinically important procedural events that increase the time or complexity of the procedure are termed “technical-procedural complications” (106) and would include small groin hematomas not increasing the level of care, minor arterial dissections, and suboptimcal stent positioning or need for a second stent placement. This last event is minimized by optimal profiling of ostial lesions before stent deployment.

The Society of Interventional Radiology has established guidelines delineating thresholds for major complications (108). On the basis of review of large meta-analyses, these established thresholds for 30-day mortality of 1%, periprocedural renal failure or exacerbation of 0% to 3%, access site hematoma requiring intervention of 3%, and symptomatic embolization or procedure-related renal artery occlusion of approximately 1% (108). Overall, major complications occur in approximately 5% (109,110). As noted earlier, renal embolic events may be minimized with the routine administration of antiplatelet agents and the use of distal embolic devices in selected cases.

Postprocedural Care

All patients undergoing renal intervention should be maintained on antiplatelet therapy for at least several months. While the optimal antiplatelet regimen has not been established, clopidogrel is the most commonly used agent and the de facto standard of care. Some investigators apply the coronary principle of dual antiplatelet therapy with aspirin and clopidogrel for one month followed by long-term aspirin alone, although this may be associated with a higher hemorrhagic risk. No additional anticoagulation is necessary postprocedurally. For patients with FMD, antihypertensive medication may be withheld following the procedure and the blood pressure closely monitored to determine the need for reinstitution of therapy. Since blood pressure in this scenario is frequently renin mediated, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are preferred. For patients with ARAS, blood pressure medications should be considered, although the most recently added or increased drug may sometimes be held pending an evaluation of clinical results.

However, abrupt hypotension is uncommon. Antihypertensive therapy should otherwise follow established guidelines (111). In patients with renal insufficiency, serum creatinine and GFR should be measured within one week of intervention as well as at other clinical follow-up appointments.

Due to the recognized risk of restenosis after stenting, duplex surveillance is recommended (55). Baseline studies obtained within one to two weeks of intervention provide a comparison for subsequent studies performed at three to six months, then annually for three to five years. Recurrent clinical events, particularly declining renal function or accelerated hypertension, warrant prompt evaluation. Since duplex criteria for restenosis within stents may be different than for de novo RAS (112), particularly in patient with aortic endografts (113), standards need to be developed and validated at local vascular laboratories. In questionable cases, CT angiography may be valuable for detecting in-stent restenosis (114).

Conclusions

RAS is a common clinical problem. The safety of renal interventions has improved with evolving techniques, and there is strong albeit predominantly observational data supporting clinical value for the treatment of associated hypertension, renal failure, or pulmonary edema. Demonstration of cardiovascular survival benefit will be a critical determinant of long-term acceptability and is currently the subject of a large international multicenter prospective trial.

CHRONIC MESENTERIC ISCHEMIA

Introduction

Chronic mesenteric ischemia (CMI) or mesenteric angina is an uncommon but not rare form of peripheral vascular disease. The disease usually develops after the age of 60 and is threefold more common in women than men. Patients commonly have prior vascular disease, affecting the lower extremities, coronary arteries, renal arteries, or cerebral arteries (115). Risk factors for atherosclerosis, including cigarette smoking, hypertension, and diabetes mellitus, are common. The classic symptomatic triad—which typically occurs with advanced disease—is postprandial pain, fear of eating, and involuntary weight loss. The characteristic pain is chronic and dull, begins 15 to 30 minutes after meals, and persists for 1 to 4 hours thereafter (116). As the disease progresses, the pain becomes progressively more severe and longer lasting and occurs after eating smaller amounts of food.

Physical examination often reveals an abdominal bruit (117). Signs of weight loss and malnutrition, such as temporal wasting, are common. Many patients have evidence of peripheral vascular disease, such as absent distal pulses and trophic changes in the feet, and of coronary artery disease, such as electrocardiographic abnormalities (118).

Anatomic Considerations

The abdominal viscera are supplied by the celiac axis, superior mesenteric artery (SMA), and inferior mesenteric artery (IMA). The occlusive disease progresses slowly in CMI permitting collaterals to develop to prevent bowel infarction. The celiac artery and SMA communicate by anastomoses between the superior pancreaticoduodenal branch of the gastroduodenal artery, which arises from the hepatic artery, and the inferior pancreaticoduodenal artery, which arises from the first part of
the SMA (Fig. 50.3). When the celiac artery is stenosed or occluded, blood flows from the SMA to branches of the celiac artery, and when the proximal SMA is occluded or stenosed, blood flows in the reverse direction. An anastomosis may also occur between the ascending division of the left colic branch of the IMA and the left division of the middle colic branch of the SMA in response to stenosis or occlusion of either the IMA or proximal SMA. This anastomosis is called the marginal artery or arc of Riolan (119). Occasionally, the IMA, which is usually small, may become enlarged and supply the entire abdominal viscera (Fig. 50.1) (120,121). Because of this rich collateral network, at least two of the three major mesenteric vessels must be diseased before symptoms of CMI occur (122).

Indications
The goals of revascularization in patients with symptomatic CMI are to improve symptoms and nutritional status and prevent intestinal infarction (123). Prophylactic mesenteric revascularization is rarely performed in the asymptomatic patient undergoing an aortic procedure for other indications (124).

Fundamentals and Equipment
Both the brachial and femoral approaches have been utilized in mesenteric angioplasty and stenting. The former appears to have a slight advantage in cases of acute angulation at the mesenteric vessel origin off the aorta. A 6-Fr sheath is inserted via the access vessel. If the brachial artery has been accessed, then early heparinization is advised to prevent thrombosis at the sheath insertion site. A pigtail catheter is advanced through the sheath into the abdominal aorta, and a diagnostic arteriogram is performed, first in the anterior-posterior direction to assess the SMA and celiac branches, and then in the lateral projection to assess the arterial orifices and confirm the presence and severity of stenosis. The pigtail is subsequently exchanged for a selective catheter. Our preference is to use a reverse curve catheter during femoral access and an angled multipurpose catheter during a brachial approach (Fig. 50.4). The catheter is navigated into the abdominal aorta and engages the target vessel, either celiac or SMA. If not already given, heparin (usually 5000 units) should be administered at that point. The lesion can then be crossed with a 0.035-in. guidewire. Alternatively, a 0.014-in. wire can be used if one plans to use a rapid exchange system. A 6- or 7-Fr guiding catheter or sheath is then placed just proximal to the lesion, and the balloon and/or stent is delivered to the lesion. Angiography through the guiding system is obtained to pinpoint the stenosis, and the angioplasty or stent placement follows. Alternatively, a no-touch technique has been described and can be used if the origin of the target vessel is very calcified or ulcerated. With this technique, the guide catheter is positioned in the aorta and is maintained straight by means of a 0.035-in. wire that keeps the catheter from engaging the takeoff of the target vessel. A 0.014-in. wire is then inserted in the guiding catheter, the 0.035-in. wire is removed, and the lesion is crossed with the finer 0.014-in. wire (125). The guiding catheter can at this point be advanced to engage the lesion and the intervention follows. After the procedure and if a stent has been deployed, the patient stays on clopidogrel and aspirin for at least six months.

The question of primary versus selective stenting has not been resolved. It appears to be a general consensus that an unsatisfactory result after angioplasty alone as evidenced by residual stenosis >30% or a >15-mmHg pressure gradient across the lesion, calcified ostial or high-grade eccentric stenoses, chronic occlusions, or the presence of dissection after angioplasty all constitute indications for stent placement. Balloon-expandable stents that offer precise placement are favored by most authors. Placement with 1- to 2-mm protrusion into the arterial lumen is advised. Postdilation is performed, and depending on the angiographic result, the pressure gradient across the lesion may be measured.

Complications
Access complications are by far the most common and can take the form of either hemorrhage or thrombosis. Hemorrhage is common in femoral and high brachial or axillary approaches. Bleeding into the axillary sheath has the potential to permanently compromise nerve function; therefore, early diagnosis and prompt evacuation are essential to minimize morbidity. Careful technique that involves an ultrasound-guided stick using a micropuncture needle is of paramount importance to prevent this complication. Thrombosis occurs almost exclusively in the brachial artery that is small in size and can be totally occluded by interventional sheaths. Rapid heparinization after sheath insertion is usually an adequate preventive measure. The status of the radial and ulnar circulation should be documented preoperatively, and any evidence of compromise after the completion of the endovascular procedure should be aggressively treated with thromboembolectomy of the brachial artery to avoid permanent ischemic sequelae.

Entering a subintimal plane while trying to cross a high-grade stenosis or occlusion causes dissection, which necessitates stent placement to avoid distal propagation and arterial occlusion. If reentry to the true lumen and successful wire advancement through the lesion are not possible, then conversion to an open operation may be necessary. Bowel ischemia is a related but infrequent complication that develops in cases of...
underestimated dissection after percutaneous transluminal angioplasty or as a result of distal embolization after crossing long occlusions. If intestinal malperfusion is suspected intra-operatively and confirmed angiographically, then standard catheter-based salvage techniques are available and should be implemented immediately. When these are not successful, or if abdominal symptoms from presumed intestinal ischemia have been established, abdominal exploration with bowel inspection and thromboembolectomy is indicated. Other complications that are common to all the endovascular procedures, such as renal failure and anaphylactic reaction, may also infrequently occur. One recognized pitfall of endovascular therapy of CMI is a relatively high restenosis and reintervention rate of 15% to 60% (Table 50.5) (123–125,132–135). This fact has led to our institution initiating an aggressive duplex surveillance protocol following mesenteric revascularization procedures to improve the primary patency of these procedures.

**Special Considerations**

**Acute Mesenteric Ischemia**

The role of endovascular therapy in acute mesenteric ischemia (AMI) remains controversial. In cases of AMI, assessment of intestinal viability is crucial and can be achieved only with abdominal exploration and direct bowel inspection. That point aside, it is worth mentioning that endovascular treatment is an
Table 50.5 Outcomes of Recent Series of Endovascular Treatment for Chronic Mesenteric Ischemia

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N</th>
<th>(technical/clinical)</th>
<th>Complications</th>
<th>30-Day mortality</th>
<th>Restenosis</th>
<th>No. of patients/mean follow-up</th>
<th>Reintervention</th>
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<tr>
<td>Lim, 2005 (131)</td>
<td>8</td>
<td>7/7</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>8/52</td>
<td>2</td>
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<td>Landis, 2005 (134)</td>
<td>29</td>
<td>28/26</td>
<td>4</td>
<td>2</td>
<td>10</td>
<td>29/28</td>
<td>10</td>
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<td>AbuRahma, 2003 (125)</td>
<td>22</td>
<td>21/21</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>18/26</td>
<td>5</td>
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<tr>
<td>Matsumoto, 2002 (135)</td>
<td>33</td>
<td>27/24</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>29/38</td>
<td>6</td>
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<td>Kasirajan, 2001 (124)</td>
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<td>5</td>
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<td>19/24</td>
<td>19</td>
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<td>Nyman, 1998 (133)</td>
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<td>4/4</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>5/24</td>
<td>3</td>
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<td>Rose, 1995 (123)</td>
<td>8</td>
<td>3/4</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>6/9</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>133</td>
<td>8/83</td>
<td>20</td>
<td>6</td>
<td>34</td>
<td>114/28</td>
<td>46</td>
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</table>

Comparison of Endovascular with Open Surgical Technique

Surgical intervention for mesenteric occlusive disease has traditionally been the treatment of choice. The number of vessels revascularized has often been reported to influence the long-term outcome. However, it has been noted that revascularization of the SMA is of paramount importance and provides optimal long-term symptomatic relief, even if revascularization of other compromised arteries is not possible (136,137). Open surgical techniques (SMA endarterectomy or aortomesenteric or celiac bypass grafting) have achieved an immediate clinical success that approaches 100%, surgical mortality rates from 0% to 17%, and operative morbidity rates that range from 19% to 54% in a number of different series (115,138–140). The median hospital stay has been reported to be 14 days (140). Recently, two reports of surgical revascularization for CMI revealed five-year survival rates of 61% to 64% and a nine-year assisted primary graft patency rate of 79% (138,139). However, overall patency rates as high as 93% have been reported (134).

In comparison to the above historical results and based on the data from a recent meta-analysis (141), mesenteric angioplasty and stenting demonstrate slightly inferior technical and clinical success rates (Table 50.5). Long-term patency rates appear to also be superior with the open technique. There is a general consensus, however, that the endovascular approach is associated with lower morbidity and mortality rates. Historically, open surgical repair of chronic mesenteric occlusion is associated with mean morbidity of 29% (range 19–54%) and a mean 30-day mortality of 7% (range 0–17%) (125). There is no randomized study comparing open versus endovascular intervention, and given the rarity of this condition, structuring such a study would be a challenging task. Current consensus is to reserve endovascular intervention for the high-risk and older patients or for the individual patient with unclear symptomatology and questionable diagnosis.

Median Arcuate Ligament Syndrome

The median arcuate ligament (MAL) syndrome results from compression of the celiac artery by the MAL. Compression by the adjacent sympathetic plexus may also contribute to the celiac axis compression. Most patients are asymptomatic. Symptoms, when present, mimic the clinical picture of CMI. Because of the extrinsic nature of the lesion, angioplasty or stenting in these patients is associated with high failure rates and is not recommended by most authors (133,134). The typical angiographic finding is that of a nonostial, eccentric, anterior, and superior lesion of the celiac artery that becomes more pronounced during deep expiration (Fig. 50.5) (142). The endovascular approach can be of benefit in the occasional patient.

appropriate alternative for the occasional patient who is a prohibitive operative risk and does not have frank peritoneal signs on physical examination as well as for those patients who have a contaminated peritoneal cavity and lack an autogenous conduit for the performance of a mesenteric or celiac bypass. Along these lines, Boley et al. (126) used arteriography and subsequent catheter-based interventions or transcatheter vasodilator therapy as the initial or sole therapy of AMI. Catheter-directed thrombolysis (127,128), as well as percutaneous angioplasty (129), has also been used with good results in the treatment of acute mesenteric embolism. Demirpolat et al. (130) reported three patients with increasing abdominal pain but without peritoneal findings who were treated percutaneously with good outcome. Lastly, Lim and colleagues (131,132) have reported the use of an endovascular approach in surgically unfit patients with good result. All these authors emphasized the importance of performing endovascular treatment in the absence of peritoneal signs and only when bowel viability can be assessed either clinically or with imaging techniques.

Total Occlusions

The presence of total occlusion implies a technically more demanding procedure, but it does not constitute a contraindication for endovascular intervention. Only a few attempts to cross occlusions were seen in the early studies, and Kasirajan et al. (124) noted that it was more common for their group to use an open procedure to treat patients with occluded vessels. A major concern at the time was the potential for plaque fragmentation, with subsequent distal embolization. This, however, has not been confirmed by authors who crossed and treated occluded mesenteric vessels (133). The length of the occlusion correlates with plaque burden and seems to be an important predictor of the likelihood for distal embolization; however, given the few patients studied, this has not been statistically confirmed. Low-profile systems and evolving expertise have now made successful treatment of occluded vessels feasible; Landis et al. (134) treated nine patients who had mesenteric occlusion and reported 100% technical success, clinical success, and primary one-year patency.

As a principle, treatment of SMA lesions takes priority over treatment of lesions in the celiac axis or the IMA. Even this rule, however, has an exception. In a study by Matsumoto et al. (135), four patients with occluded SMA had only their IMAs treated and remained asymptomatic in long-term follow-up. A patent meandering artery can assure collateral circulation in the event of a difficult-to-treat SMA occlusion. The feeding vessel of such important collateral should be visualized in detail, and any stenotic lesions found should be treated aggressively.
the superior mesenteric artery. There is moderate atherosclerotic plaque in this vessel as well as expiration, there is an extrinsic compression on the superior wall of gram in a patient with symptoms of chronic mesenteric ischemia. At Figure 50.5

REFERENCES


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INTRODUCTION
In Western countries, stroke is the third commonest cause of death, behind cardiac disease and cancer, and is the number one condition associated with serious, long-term disability (1). The yearly incidence of stroke approaches 0.2% of the Western population and the number of stroke-related deaths is expected to double over the next 30 years. In the United States, each year approximately 800,000 people experience a new or recurrent stroke and for the year 2009, the estimated direct and indirect costs of stroke are estimated at $69 billion (1). A stenosis of the internal carotid artery (ICA) is the underlying condition in 10% to 20% of patients presenting with ischemic stroke (2).

Large-scale randomized clinical trials have established the superiority of carotid endarterectomy (CEA) over medical management in patients with high-grade carotid stenosis, particularly in the presence of symptoms. However, these results were obtained by high-volume surgeons on selected patients and may therefore not be reproducible in clinical practice. Although balloon angioplasty of carotid stenosis was performed since the early 1980s, the use of stents in the mid-1990s and of emboli protection devices (EPDs) around the year 2000 have led to an exponential growth of carotid artery stenting (CAS) procedures performed worldwide. In the United States, a nationwide survey including over 130,000 Medicare patients undergoing carotid artery revascularization showed that the overall volumes of procedures decreased by 11% between 1998 and 2004 (3). In this period of time, while the number of CEA decreased by 17%, the number of CAS increased by 149% (Fig. 51.1). However, and possibly related to limited Medicare reimbursement for CAS, the overall proportion of patients treated by endovascular approach remained low (3.8% in 1998 and 10.5% in 2004).

A stenosis of the vertebral artery (VA) rarely causes symptoms and, as a consequence, revascularization is seldom required. While surgery is in most centers not considered a viable option for VA stenosis, the number of endovascular vertebral procedures remain limited compared to CAS procedures. Although the main focus of the chapter is on carotid artery interventions, the specifics of vertebral interventions will be mentioned.

ANATOMIC CONSIDERATIONS
Aortic Arch and Carotid Arteries
The details of carotid and cerebral angiography are described in detail in chapter 26. The present section recalls just the anatomic notions critical for the planning and the performance of CAS. The vertebral circulation, not covered elsewhere in the book, is addressed in more detail. Acquired abnormalities of the aortic arch are common and may increase the difficulty of carotid cannulation. Normally, all three great vessels arise from the apex of the aortic arch so that a horizontal line drawn perpendicular to the long axis of the human body at the apex of the arch will intersect the origin of all three vessels (type I arch) (Fig. 51.2). However, elongation and rostral migration of the distal aortic arch with increasing age, atherosclerotic burden, and hypertension may lead to a change in the relative positions of the great vessels: the left common carotid artery (CCA) and the left subclavian artery (SCA) migrate rostrally along with the distal arch, which takes on a narrowed and peaked appearance rather than a smooth convex shape. This leads to the brachiocephalic trunk (or innominate artery) arising “lower” and appearing to arise from the ascending aorta, followed by the left CCA and then the left SCA. This constellation makes cannulation of the brachiocephalic trunk and left CCA difficult if not impossible (so-called type III arch) (Fig. 51.2). The cannulation of the left CCA may also be challenging in the presence of the so-called “bovine arch.” In this configuration, only the brachiocephalic trunk and the left SCA arteries arise from the arch, while the left CCA originates from the brachiocephalic trunk (Fig. 51.2).

Once the CCA is cannulated, it is important to clearly differentiate the ICA from the external carotid artery (ECA). The most important difference between the two is that the ICA has no branches in the extracranial portion, while the ECA—smaller in caliber—has extensive early branching. Subsequently, baseline intracranial imaging of the carotid artery needs to be performed to assess the presence of collaterals, as described in chapter 26, and have a baseline angiographic status.

Cerebral Angiography
The fundamentals of cerebral angiography are reported in chapter 26. In the absence of contraindications—such as renal insufficiency, heart failure, or high-risk aortic arch anatomy—we encourage the performance of a four-vessel cerebral angiography—defined as the selective engagement of both CCA and the nonselective engagement of at least one VA prior to starting the CAS procedure. The purpose of a complete angiographic work-up is the assessment of the entire extra- and intracranial cerebrovascular vasculature to identify the collateral circulation and to exclude associated vascular conditions such as aneurysms or arteriovenous malformations. Finally, routine performance of cerebral angiography enhances the catheterization skills and the understanding of neurovascular anatomy.

The complication rates of diagnostic angiography have significantly decreased over the last two decades, likely due to improvements in equipment and operators’ skills. Important measures to increase safety include periprocedural anticoagulation and monitoring of the catheter-tip pressure throughout the procedure in order to prevent plaque dislodgement during catheter manipulation or dye injection. A recent prospective series of almost 3000 diagnostic cerebral angiographies astonishing low
rates of neurologic complications with 0.3% transient ischemic attacks (TIA) and no permanent deficit (4). Similarly, an analysis of over 19,000 consecutive patients detected a permanent neurologic deficit rate following cerebral angiography of 0.14% (5).

**The Vertebral Arteries**

The VA is usually the first branch off the SCA artery. On rare occasions, the left VA arises directly from the aortic arch, between the left CCA and left SCA or distally to the left SCA. The diameter of the VA is 3 to 5 mm, and in the same patient, the caliber may vary to a great extent between the left and the right side. The left and the right VA are dominant in over 50% and 25% of cases, respectively. In the remaining cases, the two vessels have similar caliber. In approximately 15% of the population one VA is atretic—that is, it has a diameter <2 mm—and supplies only the posterior inferior cerebellar artery (PICA) or gives only minimal contribution to the basilar system. The VA is divided into four segments (Fig. 51.3):

- The V1 segment extends from the VA origin to the transverse foramen of the sixth cervical (C6) vertebra; it has no branches.
- The V2 segment extends from the transverse foramen of C6 to C1; it gives off the meningeal, muscular, and radicular arteries.
The V4 segment extends from the entrance of the VA to V2 in the left panel and V2 to V4 in the right panel. Abbreviation: SCA, subclavian artery.

The left SCA and the brachiocephalic trunk are usually easily accessible with a variety of diagnostic catheters, including Judkins right 4, vertebral/Bernstein or headhunter. In more complex arches, the brachiocephalic trunk may be cannulated using catheter shapes such as Benson, Simmons/Sidewinder, or Vitek. A roadmap is then performed, and the catheter is advanced over a steerable 0.035-in. wire in the SCA.

Selective VA angiography requires gentle manipulation and for that purpose simple-shaped diagnostic catheters—such as the vertebral, Judkins right or headhunter—are preferred. Frequently, positioning the catheter at the ostium may allow selective angiography. If this is not the case and selective angiography is required, a steerable floppy 0.035-in. guidewire is positioned at the mid-distal third of the V2 segment avoiding hooking in small branches and then the catheter is advanced in the VA over the wire. For diagnostic purposes, the catheter should be kept in the V1 segment. In difficult anatomical situations, the selective catheterization of the VA should be discouraged because of the associated dissection risk. Vessel wall injury may be the result of catheter manipulations or forced contrast injection.

INDICATIONS
Carotid Artery Stenting
The presence of a carotid bruit is neither sensitive nor specific for the presence of a significant stenosis of the ICA. The imaging modality of choice in patients with suspected carotid stenosis is duplex ultrasound. If a significant stenosis of the ICA is detected, the finding should be confirmed either by CT angiography or MR angiography. At the same time, the brain should be imaged for the detection of silent ischemic lesions and to rule out associated intracranial pathologies such as brain tumors, arteriovenous malformations, or vascular aneurysms.

CAS is an appealing alternative to CEA because it is less invasive and it can potentially address lesions that may not be treated surgically. With respect to the degree of stenosis to be treated in asymptomatic and symptomatic patients, CAS and CEA share the same indications. The widely accepted guidelines of the American Heart Association support carotid revascularization—and specifically CEA—for patients with symptomatic carotid stenosis ≥50% and an estimated perioperative death or stroke risk <6% and for asymptomatic stenosis ≥60%, as long as the estimated perioperative death or stroke is <3% and life expectancy is ≥5 years (6). However, due to the usually benign course of asymptomatic carotid disease, in clinical practice, asymptomatic stenoses are frequently treated only beyond a stenosis grade of 80%.

Once the indication for revascularization is established, further steps in decision making should be based on the surgical and endovascular risk of the patient and on the locally available CAS expertise (Fig. 51.4). Importantly, the conditions associated with poor outcomes for CEA and CAS differ. Accordingly, while the outcomes of CEA are greatly influenced by the comorbidities of the patient, poor outcomes with CAS are related to challenging anatomies at the level of the aortic arch and of the carotid arteries. While advantages and disadvantages of CEA and CAS are listed in Table 51.1, the (relative) contraindications to CAS are reported in Table 51.2. The
The greatest advantage of CAS over CEA appears to be in patients with restenosis post-CEA, following neck radiation or neck dissection, contralateral carotid occlusion, or surgically poorly accessible carotid lesions. CAS may also be considered for patients who recently underwent coronary drug-eluting stent implantation, as any surgical procedure including CEA—even if performed under dual antiplatelet therapy with aspirin and clopidogrel—may be associated with an increased risk of coronary stent thrombosis.

Surgery should be preferred in the presence of severe peripheral arterial disease not allowing for femoral arterial access. Although CAS can be performed via the brachial or radial approach, the procedure is more demanding and likely associated with higher complication rates. Another challenging setting for CAS is the steep aortic arch with or without severe tortuosity of the common or ICA (Fig. 51.2). As a general rule, if unexpected difficulties are encountered during engagement of the CCA because of (underestimated) anatomic challenges, it is preferable to abort the procedure and to consider surgery. The inability to use an EPD, a rare occurrence based on the different modalities available, should also be considered a relative contraindication to CAS. Additional relative contraindications to CAS include severe circumferential calcification of the carotid bulb, which may limit the ability to dilate the lesion and the presence of a long (>15 mm), tubular lesions in the carotid bulb, which may increase the risk of distal embolization. Moreover, patients with renal insufficiency or a history of allergic reactions to angiographic contrast may not be appropriate for CAS.

### Table 51.1 Pros and Cons of Carotid Revascularization Procedures

<table>
<thead>
<tr>
<th>Endarterectomy</th>
<th>Stenting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td>Outcome less influenced by comorbidities</td>
</tr>
<tr>
<td>Widely available</td>
<td>Local anesthesia</td>
</tr>
<tr>
<td>Excellent results for high-volume surgeons/hospitals in low-risk patients</td>
<td>No neck incision/scar</td>
</tr>
<tr>
<td>Frequently performed in general anesthesia</td>
<td>Usually next day discharge</td>
</tr>
<tr>
<td>Neck incision/scar</td>
<td>Fewer experienced operators</td>
</tr>
<tr>
<td>Neck complications, cranial nerve palsies</td>
<td>Risk of the procedure may increase in patients with</td>
</tr>
<tr>
<td>Not suitable for high or low carotid lesions</td>
<td>- severe peripheral vascular disease,</td>
</tr>
<tr>
<td>Longer hospital stay</td>
<td>- severely calcified, tortuous/steep aortic arch, and</td>
</tr>
<tr>
<td></td>
<td>- severe calcification or tortuosity of cervicocranial vessels</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td>Femoral access site complications</td>
</tr>
<tr>
<td>Outcome influenced by comorbidities</td>
<td>May not be performed if aspirin/clopidogrel intolerance</td>
</tr>
</tbody>
</table>

Source: From Ref. 8.
candidates for CAS. Finally, for patients who cannot tolerate dual antiplatelet therapy with aspirin and clopidogrel (e.g., in the presence of bleeding diathesis, intracerebral hemorrhage or cerebral arteriovenous malformation, documented intolerance to one of the agents, or noncompliance) surgery may be preferred. The locally available surgical and endovascular expertise are also important parameters in decision making. The term “dedicated CAS centers” defines hospitals with multidisciplinary programs for the management of patients with carotid artery stenosis, documented CAS expertise with a track record of complications within the guideline’s limits, and implemented prospective quality control programs. Hospitals not fulfilling these criteria should treat carotid patients with CEA and in case of high or prohibitive surgical risk, transfer them to a referral center. Reimbursement issues do influence the practice of CAS. While in Europe, CAS is reimbursed in most but not all countries, in the United States the Centers for Medicare and Medicaid Services (CMS) have concluded that CAS with EPD is reasonable and appropriate for symptomatic patients with carotid stenosis ≥ 70% at high risk for surgery (10). If performed within clinical trials or CAS postapproval studies, the procedure may be performed in high-risk symptomatic patients with 50% to 70% stenosis as well as in high-risk asymptomatic individuals with stenosis ≥ 80%. Carotid stenting is considered appropriate if performed in facilities and by operators complying with the set standards (10).

**Vertebral Interventions**

Treatment of atherosclerotic extracranial VA occlusive disease can consist of medical, surgical, or endovascular therapies. While the optimal antithrombotic therapy—aspirin, clopidogrel, or warfarin—in VA stenosis has not been defined, most patients are treated with low-dose aspirin. Surgery—including vertebral endarterectomy and bypass operations—is technically very challenging and is not considered a viable option in most centers. Accordingly, despite having favorable success rates in some series in terms of periprocedural stroke, surgery has been associated with a high frequency of non-stroke-related complications, such as Horner’s syndrome, lymphatic injury, VA thrombosis, and laryngeal nerve injury (11).

The most recent American Heart Association stroke prevention guidelines state that endovascular treatment of patients with symptomatic extracranial vertebral stenosis may be considered when patients remain symptomatic despite optimal medical management (Class IIb, Level of Evidence C) (12). As with any interventional procedure, the risk of the intervention must be outweighed by the potential benefits of revascularization. The need to intervene is tempered by the fact that the posterior circulation is supplied by the confluence of the two VA and a large proportion of patients remain asymptomatic despite occlusion of one extracranial VA. Patients with isolated stenosis of the extracranial VA > 50% confirmed on angiography and symptoms attributed to vertebrobasilar ischemia may benefit from stenting, especially if the vessel is dominant or the contralateral site occluded. The majority of patients with asymptomatic extracranial VA disease do not require treatment. Asymptomatic patients with high-grade (>70% stenosis) lesions may benefit from revascularization, especially if the severity of the lesion is progressive and the affected VA is dominant or is the only patent one.

**EQUIPMENT**

In addition to an appropriate angiography suite with digital subtraction and roadmap capabilities, the equipment required for CAS includes diagnostic catheters, sheath systems, guide catheters, guidewires, EPDs, balloons catheters, and stents. Since for every device manipulation there is a learning curve, it is recommended at the beginning of the CAS experience to be familiar with a limited basic armamentarium, which can be subsequently expanded (Table 51.3). The basic equipment should include few diagnostic catheters, a 8-Fr guiding catheter or 90-cm long sheath, three 0.035-in. wires (steerable, hydrophilic stiff, and stiff in exchange length), one balloon catheter type, one nitinol stent type, and one or two filter-based EPD systems. If a 8-Fr guiding catheter is used, we encourage advancing it over a 5-Fr, 125-cm long sheath and roadmap capabilities, the equipment required for CAS includes diagnostic catheters, sheath systems, guide catheters, guidewires, EPDs, balloons catheters, and stents. Since for every device manipulation there is a learning curve, it is recommended at the beginning of the CAS experience to be familiar with a limited basic armamentarium, which can be subsequently expanded (Table 51.3). The basic equipment should include few diagnostic catheters, a 8-Fr guiding catheter or 90-cm long sheath, three 0.035-in. wires (steerable, hydrophilic stiff, and stiff in exchange length), one balloon catheter type, one nitinol stent type, and one or two filter-based EPD systems. If a 8-Fr guiding catheter is used, we encourage advancing it over a 5-Fr, 125-cm long diagnostic catheter with Judkins right or multipurpose shapes (telescoping technique). Rarely, the filter EPD may get clogged during the procedure as a consequence of distal embolization, with subsequent no flow.
in the ICA. In these circumstances, a coronary aspiration catheter such as Export (Medtronic, Santa Rosa, California, U.S.) or Diver (Invatec, Roncadelle, Italy) should be used to aspirate the blood column in the internal carotid prior to EPD removal. With increasing CAS experience, the goal should be to tailor the equipment to the patient and the lesion. To prevent femoral access bleeding in those patients aggressively anticoagulated we encourage the use of closure devices.

Sheath Systems
Several sheath systems, usually 90-cm long, are available to access the CCA. Important features include kinking resistance and flexibility, a radiopaque band at the tip of the sheath to allow for accurate positioning, an atraumatic soft tip to reduce vessel trauma during engagement, and hydrophilic coating for enhanced trackability. Frequently used devices include the Cook Shuttle sheath (Cook Inc., Bloomington, Indiana, U.S.), the Avanti and the Brite Tip sheath systems (Cordis Corporation, Miami Lakes, Florida, U.S.), and the Pinnacle Destination guiding sheath (Terumo Medical Corporation, Somerset, New Jersey, U.S.). We recommend the use of 6-Fr sheath despite the fact that some of the stent systems may be 5-Fr sheath compatible. Accordingly, a tight fit of the stent system in the sheath bears the risk of air embolization at the time of device advancement.

Guide Catheters
Guide catheters may be used to cannulate the CCA as an alternative to long sheaths. The most frequently used shapes are the headhunter (H1, Cordis or Cook) and the multipurpose. For the same reasons as described above, we recommend 8-Fr guide catheters although some stent systems may be delivered through 7 Fr guides. The choice of performing CAS using a long sheath or a guide catheter is matter of personal preference and training. Overall, the guide catheter provides better torque control and stability and lesser chance of kinking but requires larger access size. In addition, during advancement of the guide catheter over a 0.035-in. guidewire, the abrupt transition at the tip may predispose to scraping the vessel wall with subsequent distal embolization. Therefore, we recommend to always advancing an 8-Fr guide over a 125-cm long 5-Fr diagnostic catheter (coaxial or telescoping technique). As a general rule, the more complex the anatomy at the level of the aortic arch and origin of the supra-aortic vessels, the more advantageous may be the use of a guide catheter over a sheath.

Guidewires
Several 0.035-in. guidewires are available for selective CCA cannulation for diagnostic and interventional purposes, including steerable guidewires with soft tip such as the Wholey (Mallinckrodt, St. Louis, Missouri, U.S.), Magic Torque (Boston Scientific, Natick, Massachusetts, U.S.), Storq (Cordis) wires, or hydrophilic wires such as the Glidewire (Terumo, Westwood, Massachusetts, U.S.). For excessively tortuous arteries and challenging aortic arches, a stiff hydrophilic wire (e.g., stiff Glidewire, Terumo) may be used to advance the diagnostic catheter. If the initial wire needs to be exchanged (over the diagnostic catheter) for an extrastiff one, then the options include the SupracoRe (Abbott Vascular, Redwood City, California, U.S.) and the Amplatz guidewires (Boston Scientific or Cook) in exchange length. Typically the stiff guidewire is placed in the ECA over a 5-Fr diagnostic catheter.

Once cannulation of the CCA is completed, the CAS procedure is continued over a 0.014-in. guidewire, usually incorporated in the EPD. For cases performed with proximal occlusion EPD or with filter systems that allow use of separate preferred guidewires, a variety of 0.014-in. coronary guidewires may be used, such as the Balanced Middle Weight or Balanced Heavy Weight (Abbott) or the Stabilizer (Cordis). The same wires can also be used as additional “buddy wires” in the presence of excessive tortuosity of the ICA. Unprotected CAS (not recommended) may also be performed over 0.018 in. peripheral guidewires such as Steelcore (Abbott), V18 Control (Boston Scientific), Roadrunner (Cook), and SV (Cordis).

Emboli Protection Devices
Three types of EPDs are currently on the market: filter-based, distal balloon occlusion, and the proximal occlusion (±flow reversal) EPD (Fig. 51.5). Additional details on EPDs are provided in chapter 37. A large prospective registry reported that filter-based EPD is the currently preferred method of emboli protection for CAS in clinical practice and both filter-based and distal occlusion EPD seem to be equally effective (13). Advantages and disadvantages of the different device types are

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**Figure 51.5 Strategies for emboli protection in carotid artery stenting.** On the left panel is demonstrated a filter device, in the middle a distal balloon occlusive device, and in the right panel a proximal occlusive device. Filter devices incorporate an angioplasty guidewire with a filter that expands and is placed distal to the lesion to capture and retrieve embolic debris that should get detached during the intervention. At the end of the procedure, the filter is collapsed and removed from the artery. Distal balloon occlusion devices (middle panel) result in complete occlusion of antegrade flow in the internal carotid artery (ICA) while balloon angioplasty and stenting are performed. The entire blood column—possibly containing embolic debris—is then aspirated before restoration of the circulation. The principle of proximal occlusion devices (right panel) is based on simultaneous occlusion of the external carotid artery (ECA) and of the common carotid artery (CCA). Depending on the devices used, during the stenting procedure, the flow in the ICA is either reversed (Gore Neuro Protection; Gore Medical, Flagstaff, Arizona, U.S.) or arrested and then aspirated (MO.MA, Invatec, Roncadelle, Italy).
Filter-based EPD usually incorporate a 0.014-in. guidewire with a filter that expands and is placed distal to the target lesion to capture and retrieve embolic debris that may get detached during balloon angioplasty and stenting. The filtering is performed by a polyurethane membrane with laser-drilled holes or a nitinol mesh (Fig. 51.6). At the end of the procedure, the filter is collapsed, trapping the embolic debris, and is removed from the artery. The major advantage of filter EPD is that the perfusion is maintained throughout the procedure. A variety of filter-based EPD is currently on the market, and the technical details are reported in Table 51.5. In the majority of the devices, the filter EPD is mounted directly on a wire (wire dependent). Few of them, such as the Emboshield Pro (Abbott) or Spider (ev3), allow for the advancement of a wire followed by the device (wire independent). This may be of advantage for complex lesions. In contrast to filter EPD, the use of balloon occlusive devices results in complete occlusion of antegrade flow while the device is deployed (Table 51.4). With distal balloon occlusion EPD (PercuSurge GuardWire, Medtronic), the wire can be used as an angioplasty guidewire and provides protection from distal embolization by means of an occlusion balloon. An inflation device allows controlled expansion of the balloon in the treated vessel. An aspiration catheter is used to remove the debris from the treated vessel before the balloon is deflated and antegrade flow in the treated vessel is restored. Another approach for EPD is to occlude the inflow to the brain by using a proximal occlusion balloon in the CCA. The proximal balloon occlusion systems include the MO.MA (Invatec) and the Gore Neuro Protection (Gore Medical, Flagstaff,

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**Table 51.4** Pros and Cons of Emboli Protection Devices

<table>
<thead>
<tr>
<th>Device type</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filters</td>
<td>Preserve antegrade flow throughout the procedure</td>
<td>May not capture debris smaller than pore size</td>
</tr>
<tr>
<td></td>
<td>Optimal visualization of the lesion</td>
<td>Not as steerable as coronary guidewires a</td>
</tr>
<tr>
<td></td>
<td>Lesion crossing with guidewire of choice possible</td>
<td>May cause spasm or dissection of the internal carotid artery</td>
</tr>
<tr>
<td></td>
<td>(with wire-independent systems)</td>
<td>Lesion crossing not protected</td>
</tr>
<tr>
<td></td>
<td>Can be deployed and captured rapidly</td>
<td>May cause flow obstruction</td>
</tr>
<tr>
<td></td>
<td>Easy to use</td>
<td>May not be placed in the presence of excessive ICA tortuosity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apposition in tortuous vessel may be suboptimal</td>
</tr>
<tr>
<td>Proximal balloon occlusion / flow reversal</td>
<td>All the steps of the procedures protected</td>
<td>Transient flow obstruction may be poorly tolerated b</td>
</tr>
<tr>
<td></td>
<td>Crossing of the lesion with guidewire of choice</td>
<td>Poor visualization of the lesion</td>
</tr>
<tr>
<td></td>
<td>Protection possible also in the presence of excessive tortuosity of the internal carotid artery</td>
<td>Handling more demanding than filter EPD</td>
</tr>
<tr>
<td></td>
<td>Protection independent of particle size</td>
<td>Larger sheath size required</td>
</tr>
<tr>
<td>Distal balloon occlusion</td>
<td>Protection independent of particle size</td>
<td>Occlusive balloons may cause dissection or spasm of the common or external carotid artery</td>
</tr>
<tr>
<td></td>
<td>Lower profile and less stiff than filter EPD</td>
<td>Time-consuming setup</td>
</tr>
<tr>
<td></td>
<td>More easily delivered in tortuous anatomy</td>
<td>Transient flow obstruction may be poorly tolerated b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor visualization of the lesion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crossing of the lesion not protected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use more cumbersome than filter EPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential for balloon-induced injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less steerable than coronary guidewires</td>
</tr>
</tbody>
</table>

*a*Does not apply for wire-independent systems.

*b*Problematic in patients with severe stenosis or occlusion of the contralateral ICA or isolated hemisphere.

**Abbreviations:** EPD, emboli protection devices; ICA, internal carotid artery.

**Source:** From Ref. 14.

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**Figure 51.6** Two examples of filter emboli protection devices. In the upper and lower panels are demonstrated the Spider (ev3, Plymouth, Minnesota, U.S.) and the Emboshield Pro (Abbott Vascular, Redwood City, California, U.S.), respectively.
Arkansas, U.S.) and are based on a guiding catheter with an occlusion balloon attached at its distal end that is inflated in the CCA. Protection is established by flow reversal (Gore Neuro Protection) or flow arrest (MO.MA) in the ICA. At the same time, the ECA is occluded to avoid retrograde collateral flow from the ECA into the ICA. With the MO.MA device, the particles are removed by aspiration of the blood column following stenting and before ECA and CCA balloon deflation.

Balloon Catheters

As a general rule, the balloon catheter used for predilatation (optional) should be greatly undersized and the one chosen for postdilatation (mandatory) should be shorter than the stent and also slightly undersized. To minimize the risk of distal embolization, a residual stenosis of up to 30% following postdilatation of the stent is acceptable. Typically, balloon catheters 3.0 to 4.0 mm in diameter and 20 mm in length are used for predilatation, while the balloon size for postdilatation of the stent is usually 5.0 to 5.5 mm in diameter and 20 mm in length. The use of 0.014-in. rapid exchange balloon catheters is recommended. For medical-legal reasons, it is preferable to use balloon catheters, which are labeled for carotid interventions, including Avion (Invatec), Aviator (Cordis), Ultra-Soft SV, and Sterling (Boston Scientific).

Stents

In order to prevent stent crushing, the devices used in the carotid territory are all self-expanding (Fig. 51.7). With the exception of the stainless steel Carotid Wallstent (Boston Scientific), all the devices are based on nitinol, an alloy allowing for excellent flexibility, conformability, and crush resistance. The properties of some of the carotid stents on the market are listed in Table 51.6. With respect to stent design, the most important differentiation is between open- and closed-cell designs. Closed-cell stents are characterized by fully connecting struts and may offer greater plaque coverage than open-cell stents—with both connecting and nonconnecting struts—potentially reducing the risk of delayed embolism due to plaque protrusion. Therefore, this type of stents may be preferred for soft or ulcerated plaques with high embolic potential. Finally, closed-cell stents have higher radial strength, an important feature in severely calcified lesions. Open-cell stents are more flexible, conform better to the artery, and result in better wall apposition. Therefore, this stent type may be preferred in tortuous arteries and in lesions extending into the CCA.

Table 51.5 Comparison of Selected Distal Emboli Protection Filters

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Spider</th>
<th>Filterwire</th>
<th>Angioguard</th>
<th>Accunet</th>
<th>Emboshield Pro</th>
<th>Interceptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>ev3</td>
<td>BSC</td>
<td>CJJ</td>
<td>GDT</td>
<td>ABT</td>
<td>MDT</td>
</tr>
<tr>
<td>Material</td>
<td>N</td>
<td>N, PU</td>
<td>N, PU</td>
<td>N, PU</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Guidewire (in.)</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
</tr>
<tr>
<td>RX</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Independent wire</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sheath (Fr)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Vessel size (mm)</td>
<td>3.0–7.0</td>
<td>3.5–5.5</td>
<td>4.0–8.0</td>
<td>4.5–7.5</td>
<td>4.0–7.0</td>
<td>4.5–6.5</td>
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<td>110</td>
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<td>150</td>
<td>140</td>
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<tr>
<td>FDA approval</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: ABT, Abbott Medical Corporation; BSC, Boston Scientific Corporation; CJJ, Cordis/Johnson & Johnson Inc.; FEP, fluorinated ethylene propylene; Fr, French; GDT, Guidant Corporation; GFS, Gore Filter System; MDT, Medtronic Corporation; N, nitinol; PTFE, polytetrafluoroethylene; PU, polyurethane; RX, rapid exchange; FDA, United States Food and Drug Administration.

Source: From Ref. 15.

Although differences in stent designs are interesting from a conceptual standpoint, their clinical impact remains to be demonstrated. Therefore, at the beginning of the learning curve, we recommend to be familiar with one device instead of tailoring the stent for a specific patient or lesion.

Equipment for Vertebral Interventions

Most vertebral interventions can be performed with coronary equipment using a 6-Fr guiding catheter, a medium or extra support 0.014-in. coronary guidewire, and a balloon-expandable coronary or peripheral stent (16). Guiding catheter shapes
Heparin as Anticoagulant

...winder or the Benson may be used. The handling of these aortic arches, shapes such as the Vitek or the Simmons/Sidewinder catheters can be used as routine. For more steep/tortuous catheters. Alternatively, the headhunter or the Benson diagnostic catheters. In the presence of a “friendly” aortic arch, CCA engagement can be achieved with catheter shapes such as the Judkins right coronary or the vertebral/Bernstein set.

**Intubation of the CCA may be achieved with a variety of EPD in the vertebral arteries may be associated with complications such as dissection or spasm (17).**

**TECHNIQUES**

**Carotid Angiography**

Intubation of the CCA may be achieved with a variety of diagnostic catheters. In the presence of a “friendly” aortic arch, CCA engagement can be achieved with catheter shapes such as the Judkins right coronary or the vertebral/Bernstein catheters. Alternatively, the headhunter or the Benson diagnostic catheters can be used as routine. For more steep/tortuous aortic arches, shapes such as the Vitek or the Simmons/Side-winder or the Benson may be used. The handling of these catheters is more challenging and may be associated with an increased risk of embolization. In the presence of a bovine arch, direct intubation of the left CCA may be achieved with a coronary Amplatz left catheter or a Simmons/Sidewinder or Benson catheter. The details of diagnostic angiography techniques are discussed in chapter 26. The intubation techniques with different catheters can be successfully learned at simulators (18).

**Carotid Artery Stenting**

On the basis of diagnostic angiography, the strategy and equipment should be determined and prepared to minimize the procedural time. Once diagnostic angiography is performed and it is assessed that the anatomy is suitable for CAS, additional unfractionated heparin should be administered, if needed, to achieve an activated clotting time of 250 to 300 seconds. Alternatively, bivalirudin has been used as anticoagulant for CAS. Patients not on chronic clopidogrel therapy, we recommend 300 mg of clopidogrel the day before the procedure. Documented aspirin or clopidogrel intolerance should be considered a contraindication for CAS, and patients should be referred for surgery. To allow for assessment of alertness, speech, and communication, preprocedural sedation should be limited to low-dose benzodiazepines to alleviate anxiety, if necessary.

Particularly in the early phase of the learning curve, CAS should be performed in a standardized way using limited and familiar equipment (Table 51.3). Lesion length and vessel size to guide equipment choice are usually estimated visually. A step-by-step description of the procedure is summarized in Table 51.7. Over a 0.035-in. long steerable wire, a 125-cm 5-Fr diagnostic catheter is inserted inside an 8-Fr guide catheter or a 90-cm, 6-Fr sheath (Fig. 51.8). The origin of the left CCA or the brachiocephalic trunk is intubated with the diagnostic catheter. Under roadmap, a steerable 0.035-in. guidewire advanced into the distal CCA or, if necessary, into the ECA. The diagnostic catheter is advanced over the guidewire into the distal CCA. Subsequently, the 8-Fr guide catheter or the 6-Fr sheath is...

<table>
<thead>
<tr>
<th>Stent type</th>
<th>Name</th>
<th>Company</th>
<th>FDA approval</th>
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<tr>
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<td>Abbott</td>
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<tr>
<td>nitinol</td>
<td>Exponent</td>
<td>Medtronic</td>
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</tr>
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<td>Cordis</td>
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<td>ev3</td>
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<td>✓</td>
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<tr>
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<td>NexStent</td>
<td>Boston</td>
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<tr>
<td>steel</td>
<td>Scientific</td>
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<td></td>
</tr>
</tbody>
</table>

*aHybrid design since in part open cell in part closed cell. Abbreviation: FDA, United States Food and Drug Administration.*

**Table 51.7** Carotid Artery Stenting Protocol Using Telescopng Technique, Filter-Based Distal Embol Protection, and Unfractionated Heparin as Anticoagulant

- **Patient pretreated with aspirin and clopidogrel**
- **Common femoral arterial access in local anesthesia with a 5-Fr sheath**
- **Intravenous unfractionated heparin to achieve activated clotting time 250–300 seconds**
- **5-Fr pigtail catheter → aortic arch angiography (LAO 30° –40°)**
- **Insert a 125-cm, 5-Fr diagnostic catheter (e.g., JR4) inside a 100-cm, 8-Fr guide catheter (e.g., H1)**
- **Intubation of the CCA with the diagnostic catheter**
- **Under roadmap, 0.035-in. guidewire advanced into the distal CCA or ECA, then diagnostic catheter advanced into the distal CCA, then 8-Fr guide catheter advanced over the diagnostic catheter into the mid/distal CCA**
- **Diagnostic catheter and 0.035-in. guidewire are retrieved**
- **DSA angiography of the carotid bifurcation and of the intracranial circulation**
- **ICA lesion passed with filter EPD under roadmap, filter deployed**
- **0.5 to 1.0 mg of IV atropine**
- **Balloon predilatation (if required) with a 3.0–4.0 × 20 mm, 0.014-in rapid exchange balloon catheter**
- **Stenting with a nitinol, self-expanding, rapid exchange, 8.0–9.0 × 30–40 mm stent**
- **Postdilation (always) with a 5.0–5.5 × 20 mm, 0.014-in. rapid exchange balloon catheter**
- **Filter retrieved**
- **DSA angiography carotid bifurcation and intracranial circulation**
- **Non-DSA angiography of the CCA during retrieval of guiding catheter/sheath**
- **Femoral closure device if patient hemodynamically stable**

*Abbreviations: LAO, left anterior oblique projection; CCA, common carotid artery; DSA, digital subtraction angiography; ECA, external carotid artery; ICA, internal carotid artery stenosis; EPD, emboli protection device.*
advanced over the diagnostic catheter. This step should be performed under lower magnification in order to have control of both the guidewire in the distal CCA or ECA and the catheter advancement in the aortic arch.

As an alternative to the telescoping technique, the steerable 0.035-in. guidewire such as Wholey (Mallinckrodt), Magic Torque (Boston Scientific), or Storq (Cordis) can be advanced under roadmap into the ECA and then the diagnostic 5-Fr catheter can be advanced over the wire into the ECA. Subsequently, the steerable guidewire is exchanged for a stiff 0.035-in. guidewire such as the Supracore (Abbott) or the Amplatz superstiff (Boston Scientific). With the stiff guidewire in place in the ECA, the short 5-Fr sheath is exchanged for a 90-cm, 6-Fr sheath, which is advanced into the distal CCA. This type of engagement is applicable in the presence of a friendly anatomy of the aortic arch and the CCA and has the advantage of requiring a smaller femoral access. However, it may not be used in the presence of severe ECA or distal CCA disease. In patients with bovine arch, direct intubation of the left CCA with a guiding catheter (e.g., AL1 8 Fr) may be considered.

Following intubation of the CCA with the guiding catheter or sheath, the lesion, usually located at the origin of the ICA, is crossed under roadmap with the filter EPD. The device should be placed in a straight segment of the ICA and filter apposition to the vessel wall should be verified with angiography. On rare occasions, primary crossing of the lesion with the EPD may not be possible because of lesion complexity. In these cases, a wire-independent EPD system or a proximal occlusion type of EPD should be considered. Alternatively, a buddy wire or predilatation with an undersized balloon (e.g., 2.0 mm) may be used in order to be able to advance the EPD. To prevent bradycardia and hypotension associated with balloon angioplasty and stenting, atropine 0.5 to 1.0 mg IV is administered routinely. Balloon predilatation should be considered when it is anticipated that advancement of the stent may be problematic, and in particular, in the presence of high-grade and/or severely calcified stenosis. Advancement of the stent within the guiding catheter should be performed slowly, as air may be entrapped during the procedure. With respect to stent length, it is recommended to be generous, since the whole diseased segment should be covered and, unlike in the coronary arteries, restenosis is a minor concern in CAS. As a consequence, almost invariably the stent will cover the carotid bifurcation (Fig. 51.9). Even if the ECA seems compromised following ICA stenting, the patients will invariably remain asymptomatic and the ECA stenosis does not need to be treated. Postdilatation of the stent is mandatory, but a residual stenosis up to 30% is acceptable. Finally, the EPD is retrieved using the retrieval sheath. Should the flow be compromised during the procedure because of filling of the filter EPD with

Figure 51.8  Sheath system (90 cm, 6 Fr) for carotid artery stenting (Cook shuttle sheath, Cook Inc., Bloomington, Indiana, U.S.).

Figure 51.9  Carotid artery stenting procedure. Following engagement of the common carotid artery (CCA) with a guiding catheter or long sheath, the lesion in the internal carotid artery (ICA) is passed with a wire or with the filter emboli protection device (Panel A). Subsequently, a self-expanding stent is deployed, usually covering the carotid bifurcation (Panels B and C). Thereafter, a balloon postdilatation is performed to achieve a good stent expansion (Panel D). Abbreviation: ECA, external carotid artery. Source: From Ref. 9.
debris, then the blood column in the ICA should be aspirated with an aspiration catheter such as the Export (Medtronic) or Diver (Invatec) catheters prior to EPD removal to prevent distal embolization.

If a distal balloon occlusion EPD is used (PercuSurge GuardWire, Medtronic), then the wire containing a central lumen that communicates with a low-pressure distal occlusion balloon incorporated into the tip is advanced through the lesion under roadmap. Following inflation of the balloon distally to the lesion, the procedure is performed and at the end, prior to balloon deflation, an aspiration catheter is used to remove the debris suspended in the blood column from the treated vessel. If a proximal balloon occlusion system is used (MO.MA or Gore Neuro Protection System), then the device is advanced over a stiff guidewire previously placed in the ECA. The procedure can be performed following occlusion of the ECA and CCA balloon. While in the Gore system there is flow reversal in the ICA during occlusion time, the MO.MA system requires aspiration of 60 mL of blood at the end of the procedure prior to restoration of blood flow. The handling of occlusive EPD is technically more demanding than the one of filters EPD and should be introduced later in the CAS learning curve.

Following retrieval of the EPD, the patient is examined on the catheterization table to detect major neurologic deficits and final DSA angiography of the carotid bifurcation and the intracranial vasculature are performed (Fig. 51.10). In the absence of neurologic or angiographic abnormalities, the guide catheter/sheath is retrieved into the descending aorta at the time of contrast injection to exclude complications at the level of the CCA such as catheter-induced dissections. If the patient is hemodynamically stable, the sheath may be removed and hemostasis may be achieved with a femoral closure device such as Starclose or Perclose (Abbott) or Angioseal (St. Jude Medical, St. Paul, MN, U.S.). Alternatively, the sheath can be pulled few hours following the procedure to allow for the effect of heparin to dissipate, and hemostasis can be achieved by manual compression. Antihypertensive medications are discontinued post-CAS and resumed gradually. Aspirin 100 to 325 mg/day is given indefinitely and clopidogrel 75 mg/day is administered for at least one month.

Vertebral Stenting

Similar to CAS, endovascular treatment of extracranial VA stenosis is usually performed under local anesthesia and conscious sedation allowing for early detection of neurologic symptoms. After arterial access is obtained, unfractionated heparin is administered to achieve an activated clotting time of 250 to 300 seconds. Access is usually obtained at the common femoral artery. Occasionally, the radial or brachial artery access may be preferred based on an unfavorable anatomy at the level of the aortic arch or in the presence of excessive angulation between the subclavian and the vertebral arteries. A 6-Fr guide catheter is advanced over a 0.035-in. wire to obtain a stable position in the SCA. Usual curves include the vertebral, Judkins right, and the multipurpose one. If additional stability is needed, the use of a 7-Fr guide catheter or 7-Fr, 90-cm sheath may be helpful because it allows the advancement of 0.014- or 0.018-in. buddy wire into the distal SCA. If the long sheath approach is chosen, then a 0.035-in. exchange length wire is advanced over a diagnostic catheter positioned in the SCA in the axillary artery and the long sheath is then advanced over the wire. Angiographic runs are performed to visualize the extracranial and intracranial VA and to obtain accurate views defining the VA lesions and its relation to the SCA.

The use of EPD for VA stenosis is controversial. The absence of neurologic or angiographic abnormalities, the guide catheter/sheath is retrieved into the descending aorta at the time of contrast injection to exclude complications at the level of the CCA such as catheter-induced dissections. If the patient is hemodynamically stable, the sheath may be removed and hemostasis may be achieved with a femoral closure device such as Starclose or Perclose (Abbott) or Angioseal (St. Jude Medical, St. Paul, MN, U.S.). Alternatively, the sheath can be pulled few hours following the procedure to allow for the effect of heparin to dissipate, and hemostasis can be achieved by manual compression. Antihypertensive medications are discontinued post-CAS and resumed gradually. Aspirin 100 to 325 mg/day is given indefinitely and clopidogrel 75 mg/day is administered for at least one month.

Vertebral Stenting

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The use of EPD for VA stenosis is controversial. The smaller caliber of the VA, the frequently marked angulation between the VA origin and the SCA, the tortuosities of the proximal VA segments, and the tendency to develop spasms are all factors that may cause difficulties in the advancement of the EPD device. In addition, recovery of the system may also be difficult in the presence of spasm or unfavorable angulation of the VA origin, angulation that may be more pronounced following stent deployment. The use of EPD may be considered for VA with diameters exceeding 3.5 mm, favorable geometric orientation of the VA origin, and the presence of with ulcerated target lesions (19).

Under roadmap guidance, the VA lesion is crossed with a 0.014-in. medium-support or extraluminal coronary wire. In order to obtain stable guiding catheter position, the wire should be positioned far enough distally in the VA. The tip of the wire should be visualized during the entire procedure to reduce the risk of perforation. Stent selection (either self-expanding or balloon mounted) is based mainly on lesion location. Ostial VA lesion are treated preferably with balloon-expandable coronary stents because of high radial force, lack of foreshortening, and low crossing profile. For true ostial lesions, the stent should protrude 1 to 2 mm into the SCA to allow for optimal lesion coverage, and a second balloon inflation at high pressure.

**Figure 51.10** Digital subtraction angiography of the carotid bifurcation showing in the left panel a severe stenosis of the internal carotid artery (ICA) and in the right panel the result following stenting. **Abbreviations**: ECA, external carotid artery; CCA, common carotid artery.
should be performed following partial balloon retrieval to optimize the apposition of the stent struts at the vessel wall, the so-called “flaring of the ostium.” Self-expanding stents are reserved nonostial lesions in vessels with larger diameters (i.e., >5.5 mm) (19). In the presence of a severe or calcified lesion, balloon dilatation prior to stenting may be appropriate. The balloon selected should be undersized and shorter than the stent placed thereafter (Fig. 51.11).

**CLINICAL ASPECTS**

**Randomized Trials of CEA Vs. CAS**

Five major—that is, including over 300 patients—randomized trials have compared endovascular and surgical carotid revascularization. While the SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial (20) focused on patients—both symptomatic and asymptomatic—at high risk for surgery, CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study) (21), SPACE (Stent-protected Percutaneous Angioplasty of the Carotid artery vs. Endarterectomy) (22), EVA-3S (Endarterectomy vs. Angioplasty in patients with Symptomatic Severe carotid Stenosis) (23), and ICSS (International Carotid Stenting Study) (24) enrolled exclusively symptomatic patients.

The CAVATAS, performed in the late 1990s, randomized 504 symptomatic patients at low to moderate risk for surgery to CEA or carotid angioplasty (21). The incidence of death or stroke at 30 days was 10.0% in the endovascular group and 9.9% in the surgical group. The outcomes between the two groups remained comparable at three years.

The SAPPHIRE study is the only randomized trial comparing CEA and CAS performed with the systematic use of EPD (20). The trial included symptomatic and asymptomatic patients at high risk for surgery and was designed to prove the noninferiority of the endovascular approach. The study was terminated prematurely because of slow enrollment due to competing CAS registries. Among the 334 patients randomized (29% of them being symptomatic), major adverse events at one year occurred in 12.2% in the CAS group and in 20.1% in the CEA group (P = 0.053). In the actual treatment analysis, the observed difference reached statistical significance (P = 0.048). The difference was mainly driven by a reduction in the rate of myocardial infarction (at 30 days 0.6% in the CAS group vs. 4.3% in the CEA group; P = 0.04). No cranial nerve injury was observed in the CAS group while this complication occurred in 5.3% of the CEA patients (P < 0.01). The durability of CAS was documented by a comparable cumulative percentage of major (1.5% for CAS vs. 3.3% for CEA) and minor (6.1% for CAS vs. 3.0% for CEA) ipsilateral strokes at three years as well as by a low rate of repeat revascularization during the same period of time (3.0% for CAS vs. 7.1% for CEA) (25).

The SPACE study sought to prove the noninferiority of CAS compared with CEA among symptomatic patients. The use of EPD in the CAS arm was left at the discretion of the treating physician and was used in 27% of cases. Although the required sample size based on interim analysis was >2400 patients, the trial had to be terminated following the inclusion of 1200 patients because of slow enrollment and lack of funding. The incidence of ipsilateral stroke or death at 30 days was the primary endpoint of the study and did not differ between the groups, occurring in 6.8% of cases in the endovascular group and in 6.3% of patients in the surgical arm (22). At two-year follow-up, no difference in adverse events between the two groups could be detected (26).

The EVA-3S was a randomized noninferiority trial comparing CAS with CEA in patients with a ≥60% symptomatic carotid artery stenosis. The primary end point was the cumulative incidence of any stroke or death within 30 days after treatment (23). The protocol did not mandate the use of EPD. The performance of CAS without EPD protection in the study was rapidly halted following the observation that 4/15 patients treated without protection suffered a stroke, while the proportion of patients treated with protection was 5/58 (OR 3.9; 95% CI, 0.9–16.7) (27). The entire trial was then stopped prematurely after the inclusion of 527 patients because of significant increased event rates in the CAS arm (death or stroke 9.6% in the CAS arm and 3.9% in the CEA arm; P = 0.01). At six months, the incidence of any stroke or death was 11.7% in the CAS group and 6.1% in the CEA group (P = 0.02). At 4-year follow-up, the death or stroke rate still favored CEA, driven by the 30-day events. Beyond 30 days, no difference was observed (28).

The ICSS randomized 1710 symptomatic patients to CAS or CEA (24). The primary end point is the long-term survival free of disabling stroke. The use of EPD was not mandatory. While follow-up is ongoing and expected to be completed in 2011, the 30-day safety results were recently presented (29). The incidence of death, stroke, or periprocedural myocardial infarction was 8.5% in the CAS group and 5.1% in the CEA group (P = 0.004). No difference was observed in the survival free of disabling stroke at 120 days.

A meta-analysis of 10 trials published or presented up to May 2009 and reporting 30-day death or stroke has been published. The study included a total of 4648 patients and
showed that patients undergoing CAS has a significant increase in 30-day death or stroke compared to patients treated surgically (OR 1.60, 95% CI 1.26–2.02) (Fig. 51.12). Statistical tests showed significant heterogeneity in outcomes among the trials (heterogeneity; $P = 0.02$) (9).

Limitations of the CAS vs. CEA Randomized Trials

Current randomized data comparing CAS and CEA have several limitations. First of all, the data on asymptomatic patients are limited since all but one trial included only symptomatic patients. Second, the use of EPD was mandatory in just one trial (SAPPHIRE). Third, the minimal endovascular experience required per protocol was in most of the trials incredibly low and four of the five large randomized trials (i.e., enrolling over 300 patients) allowed endovascular treatment in the presence of a tutor for interventionalists with insufficient experience (Table 51.8). Other than SAPPHIRE, none of the randomized trials would have satisfied the minimum recommended endovascular experience according to a multispecialty CAS clinical competence statement (31).

The trials missed the main purpose of randomized testing of a new procedure, namely to show that the novel therapy is efficacious in the hands of the most skilled operators on selected (favorable) patients. In this respect, early testing of CEA against medical therapy was properly conducted. In the ACAS trial, for example, patients at high risk for surgery were excluded from the trial and both the centers and the individual surgeons had to demonstrate a 30-day death or stroke rate of $<3.0\%$ to be able to enroll. In addition, during the study the surgeons were audited in the presence of more than one complication and were allowed to continue enrollment only if no operator-related problem was observed (32,33).

Large-Scale CAS Registries

The results of seven CAS registries enrolling over 1000 patients have been published, for a total of 20,105 patients (Table 51.9). All but one were performed in the United States, included patients at high risk for surgery, and the majority of patients included were asymptomatic. The good quality of the studies is demonstrated by the high proportion of mandatory neurologic

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**Table 51.8** Minimal Requirements in Terms of Endovascular Expertise in Large-Scale CAS Vs. Endarterectomy Randomized Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>CAS Training</th>
<th>CEA periprocedural death or stroke rate had to be $&lt;6%$</th>
<th>No tutor-assisted procedures allowed</th>
<th>At least 10 cases of endovascular treatment of supra-aortic trunks. Tutor-assisted CAS allowed for centers not fulfilling minimal requirements</th>
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</thead>
<tbody>
<tr>
<td>CAVATAS (21)</td>
<td>Training in neuroradiology and angioplasty (but not necessarily in the carotid artery) required. Tutor-assisted procedures allowed</td>
<td>Procedures submitted to an executive review committee</td>
<td>No tutor-assisted procedures allowed</td>
<td>A minimum of 50 total stenting procedures, of which at least 10 should be in the carotid artery. Tutor-assisted procedures allowed for interventionalists with insufficient experience</td>
</tr>
<tr>
<td>SAPPHIRE (20)</td>
<td>Procedures submitted to an executive review committee; CAS periprocedural death or stroke rate had to be $&lt;6%$</td>
<td>No tutor-assisted procedures allowed</td>
<td>At least 10 cases of endovascular treatment of supra-aortic trunks. Tutor-assisted CAS allowed for centers not fulfilling minimal requirements</td>
<td></td>
</tr>
<tr>
<td>SPACE (22, 30)</td>
<td>Procedures submitted to an executive review committee; CAS periprocedural death or stroke rate had to be $&lt;6%$</td>
<td>No tutor-assisted procedures allowed</td>
<td>At least 10 cases of endovascular treatment of supra-aortic trunks. Tutor-assisted CAS allowed for centers not fulfilling minimal requirements</td>
<td></td>
</tr>
<tr>
<td>EVA-3S (23)</td>
<td>A minimum of 50 total stenting procedures, of which at least 10 should be in the carotid artery. Tutor-assisted procedures allowed for interventionalists with insufficient experience</td>
<td></td>
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**Abbreviation:** CAS, carotid artery stenting.  
*Source:* From Ref. 9.
Table 51.9 Thirty-Day Event Rates in Carotid Artery Stenting Registries Enrolling Over 1000 Patients

<table>
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<tr>
<th>Name</th>
<th>Year</th>
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<th>Industry sponsored</th>
<th>Surgical high-risk</th>
<th>EPD</th>
<th>Sympt patients (%)</th>
<th>Neurologist&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CEC adjud. (%)</th>
<th>D/S</th>
<th>D/S/MI (%)</th>
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<td>Yes</td>
<td>Mandatory</td>
<td>14</td>
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<td>5.7</td>
<td>6.3</td>
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<td>1493</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>4.5</td>
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<td>No</td>
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<td>55</td>
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<td>Yes</td>
<td>3.6&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>2.7&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>28</td>
<td>No&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>SVS (38)</td>
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<td>1450</td>
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<td>95</td>
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<tr>
<td>EXACT (39)</td>
<td>2009</td>
<td>2145</td>
<td>Yes</td>
<td>Yes</td>
<td>Mandatory</td>
<td>10</td>
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<td>4.1</td>
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<td>CAPTURE 2 (39)</td>
<td>2009</td>
<td>4175</td>
<td>Yes</td>
<td>Yes</td>
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<td>13</td>
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<td>Yes</td>
<td>3.4</td>
<td>NA</td>
<td>6.2</td>
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<sup>a</sup>Neurologist, independent pre- and postprocedural assessment by a neurologist.

<sup>b</sup>Refers to in-hospital events; EPD = emboli protection devices.

<sup>c</sup>Neurologic assessment performed by stroke scale certified staff member.

Abbreviations: sympt, symptomatic; asympt, asymptomatic; CEC adjud., clinical event committee adjudication; D, death; S, stroke; MI, myocardial infarction.

Source: From Ref. 9.
assessment pre- and postprocedure (4/7) and clinical event committee adjudication of adverse events (5/7). The use of EPD was mandatory in five studies and used in the majority of patients in the remaining two.

The PRO-CAS registry enrolled in German patients with variable risk for surgery and reported an in-hospital death or stroke rate of 3.6% (36). Symptomatic and asymptomatic patients had an event rate of 4.3% and 2.7%, respectively. In the CAPTURE registry, the 30-day stroke/mortality rate was 5.7% among 3500 patients, with symptomatic individuals experiencing a stroke rate of 8.9% and asymptomatic patients a rate of 4.1% (34). The CASES-PM registry recorded outcomes in 1493 high-risk patients treated with CAS utilizing EPD reported a stroke/mortality rate of 4.5%, with a stroke rate of 5.3% in symptomatic patients and 3.4% in asymptomatic individuals (35). The SAPPHIRE Worldwide registry reported a 30-day stroke or death rate of 4.0% in 2001 among high-risk patients, with higher event rates in symptomatic compared to asymptomatic patients (adjusted OR 2.4) (37).

The SVS registry reported 30-day outcomes among 1450 patients who underwent CAS and 1368 patients treated with surgery (38). In this analysis, the CAS group had significantly higher event rates than CEA (death, stroke, or myocardial infarction rate 6.4% vs. 2.6%). This analysis was limited by the marked imbalances among the groups, the <50% collection of 30-day events, the lack of systematic neurologic assessment and event adjudication as well as the different definition of myocardial infarction among the centers.

The results of two large-scale registries enrolling patients at high risk for surgery, the EXACT (N = 2145) and the CAPTURE 2 (N = 4175) studies were recently reported (39). The overall 30-day death and stroke rate in the two studies were 4.1% and 3.4%, respectively. In the population comparable to AHA guidelines (age <80 years), the pooled analysis of the two registries denoted a death or stroke rate within current recommendations for CEA, namely 5.3% for symptomatic patients and 2.9% for asymptomatic patients. In patients ≥80 years of age, the death and stroke rates in symptomatic and asymptomatic patients were 10.5% and 4.4%, respectively.

### Data on Vertebrobasilar Interventions

The data on vertebrobasilar interventions are virtually limited to single-center series, most of them retrospective. Table 51.10 reports the results of the larger series. Although in most series, the technical success is greater than 95% and the occurrence of periprocedural stroke is a rare event, the placement of a bare metal stent in the VA is associated with restenosis. The true incidence of restenosis is unknown because the follow-up of most series was not systematic and the reported results varied considerably (between 3% and 52%). Although the placement of drug-eluting stents has proven to be highly efficacious in restenosis prevention in the coronary artery, the results in the VA are still sparse. The only two series published with more than 25 patients undergoing drug-eluting stent implantation in the VA have reported a promising low restenosis rate of 7% and 12% (51,52).

The CAVATAS included also 16 patients with symptomatic VA stenosis that were randomized in equal proportions to receive endovascular therapy (balloon angioplasty or stenting) or best medical treatment alone. An independent neurologist followed up the patients for as long as eight years. The trial failed to show a benefit of endovascular treatment of VA stenosis, but the number of patients included was small. The authors of this study concluded that larger randomized trials are required to determine whether VA stenting is justified in patients at higher risk of vertebrobasilar stroke (53).

### LIMITATIONS AND COMPLICATIONS

In addition to the limitation of the randomized comparison against CEA just described, the main limitation of CAS is that it has not been studied prospectively in specific patient populations. Specifically, randomized data compared to CEA in asymptomatic patients are lacking. In addition, for surgical high-risk patients with asymptomatic carotid disease (e.g., SAPPHIRE population), it remains to be demonstrated that carotid revascularization (both stenting and surgery) is of benefit over best medical management. As previously mentioned, adequately powered randomized trials in vertebral

<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th>Vessel treated, N</th>
<th>Type of stent</th>
<th>Technical success (%)</th>
<th>Periprocedural stroke</th>
<th>Follow-up (mo)</th>
<th>Significant restenosis (%)</th>
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<tr>
<td>Higashida et al. (40)</td>
<td>1993</td>
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<td>2003</td>
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<td>BMS</td>
<td>97</td>
<td>3.3%</td>
<td>16</td>
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<td>Lin et al. (44)</td>
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<td>BMS</td>
<td>100</td>
<td>4.1%</td>
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<td>38</td>
<td>BMS</td>
<td>100</td>
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<td>11</td>
<td>36</td>
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<td>93</td>
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<td>38</td>
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<td>2009</td>
<td>29</td>
<td>BMS</td>
<td>100</td>
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<td>77</td>
<td>BMS</td>
<td>99</td>
<td>3.9%</td>
<td>8</td>
<td>48</td>
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<td>29</td>
<td>BMS</td>
<td>100</td>
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<td>32</td>
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<td>52</td>
<td>DES</td>
<td>100</td>
<td>0</td>
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</table>

*Usually defined as stent successfully placed and residual stenosis <50%.

bUsually defined as restenosis >50% on angiography and refers to the percentage of patients who underwent follow-up.

*Related to other lesions treated at the same time.

Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent.
revascularization are lacking. Complications of endovascular procedures not specific to carotid or vertebral interventions include access site vascular compromise, bleeding events, allergic reactions to contrast, heart failure, contrast-induced nephropathy, and athereoembolism. While less data are available on the complication related to vertebral revascularization—mainly distal embolization with the associated neurologic symptoms, spasms, or dissections—the complications related to CAS are described in details.

**Bradyadria and Hypotension**

Hemodynamic instability, characterized by hypotension and sinus bradycardia, is fairly common during CAS (54). A dysfunction of adventitious stretch baroreceptors in the carotid sinus following balloon catheter dilatation and stent deployment, leading to sympathetic fibers inhibition and parasympathetic pathway stimulation, has been postulated as the trigger mechanism (35). Although benign, this hemodynamic response may rarely lead to asystole or profound hypotension. While in the early days of the procedure, a temporary transvenous pacemaker was inserted to prevent bradycardia; this rhythm disturbance can be effectively prevented with atropine (0.5 to 1.0 mg intravenously) administered routinely prior to balloon inflation/stenting. To treat hypotension, large volumes of normal saline and at times vasopressors (e.g., noradrenaline 5 to 10 mcg as repeated bolus and, if needed, 1 to 5 mcg/min as an infusion) may be required.

**Spasm, Dissection, and Slow or No Flow**

Some degree of spasm of the ICA may be frequently observed at the level of the placement of the filter EPD. Spasms are usually asymptomatic, do not compromise flow, and resolve mostly spontaneously. If needed, nitroglycerin 50 to 200 mcg may be administered in the CCA through the guiding catheter or sheath. However, patients are frequently hypotensive during the procedure and, whenever possible, spontaneous resolution of the spasms should be awaited in order not to exacerbate hypotension. Vessel dissection is a rare event in CAS. It can happen in the ICA distally to the treated area, as propagation of a previously unrecognized dissection following angioplasty or as an injury occurring at the time of stent postdilatation. Measures to prevent dissection include the use of undersized balloons for predilatation, the coverage of the lesion with a nitinol stent having a safety margin of several millimeters distally and proximally to the lesion, and, more importantly, the performance of postdilatation with a slightly undersized balloon placed well within the limits of the stent.

In the occurrence of a dissection distal to the stent, an additional self-expanding nitinol stent should be placed prior to retrieval of the EPD. As an alternative, the dissection may be treated with a 0.014-in. balloon-expandable bare metal coronary stent, since the risk of crushing in this distal location for a short stent is minimal. A dissection of the CCA may be caused by the guide catheter or sheath. This is usually prevented by avoiding pushing in case of difficult advancement and by advancement of the guiding catheter over a diagnostic catheter (telescoping technique) or over the introducer if a sheath is used. In order to detect injuries to the CCA, it is recommended to perform a final angiogram while retrieving the guiding catheter or sheath. In the presence of dissection of the CCA, an additional nitinol self-expanding stent should be used to cover it.

Temporary flow obstruction in the ICA may be due to spasm, dissection, or obstruction of the blood flow at the level of the filter EPD in case of debris embolization; in the latter case, aspiration of the ICA blood column with an aspiration catheter such as Export (Medtronic) or Diver (Invatec) should be performed prior to EPD removal in order to prevent distal embolization.

**Hypertension and Hyperperfusion Syndrome**

Rarely, patients may be hypertensive following CAS. Strict blood pressure control is mandatory because severe hypertension following carotid revascularization (both with CEA and with CAS) may be associated with hyperperfusion syndrome (56). The clinical presentation is characterized by headache, alteration of consciousness, or seizure. The pathophysiologic mechanism underlying hyperperfusion syndrome is an alteration of the blood-brain barrier with free extravasation and cerebral edema. The more severe forms may lead to intracranial hemorrhage. Therefore, any persistent severe headache post-CAS should be investigated with an emergent CT scan. High-risk features associated with the development of hyperperfusion syndrome include peri- and postprocedural hypertension and the revascularization of a severe stenosis supplying a poorly collateralized cerebral area (e.g., isolated hemisphere) or the revascularization of a stenosis in the presence of a contralateral severe carotid stenosis or occlusion (57).

Intracranial hemorrhage may occur in <1% of carotid revascularization cases (both with CEA and CAS) and is associated with high morbidity and mortality. In addition to hyperperfusion syndrome, bleeding may be the results of hemorrhagic conversion of a previously infarcted region or of severe small vessel intracranial disease and is favored by dual antiplatelet therapy and periprocedural anticoagulation. Patients with hyperperfusion syndrome and intracranial hemorrhage should be monitored in an intensive care unit with neurologic or neurosurgical evaluation, careful fluid and blood pressure management, and mannitol or hyperventilation for treatment of increased intracranial pressure.

**Periprocedural Stroke**

In patients with focal periprocedural neurologic deficits occurring during CAS, the presumptive diagnosis is ischemic stroke and not intracranial hemorrhage. Therefore, these patients should not be primarily transferred for CT scan but instead should receive emergent cerebral angiogram. If a patient develops focal neurologic symptoms during the procedure, it is generally best to complete the intervention, retrieve the EPD, and reassess the patient clinically and angiographically. Once problems at the level of the ICA such as spasms or dissections are excluded, the intracranial angiogram should be carefully examined and compared with the baseline images. Findings suggestive of distal embolization include vessel filling defects or cutoffs and delayed vessel filling.

The decision to perform neurorescue should be based on the in-house expertise with intracranial interventions, the localization of the vessel closure, and the clinical course of the patient. As a general rule, pharmacologic (i.e., with glycoprotein IIb/IIIa receptor inhibitors or local or systemic fibrinolytic agents) or mechanical neurorescue is reserved to major strokes involving the middle cerebral artery or its main branches. In fact, it is important to remember that a bleeding complications...
following rescue may be far more devastating than the ischemic stroke one intended to treat.

SPECIAL ISSUES OR CONSIDERATION

There are three groups of patients at high risk for whom the best approach (CAS vs. CEA) remains to be determined. The first group includes patients with evidence of thrombus in a symptomatic carotid lesion. On angiography thrombus appears as intraluminal filling defect, although the differentiation with a severe but focal calcification or a ruptured eccentric plaque may not always be possible. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), these patients carried an 18% to 22% risk of perioperative stroke. With respect to CAS, such patients have been excluded from the trials, but it is generally agreed that the stroke risk is also high with the endovascular treatment. In these patients, a short period of anticoagulation in addition to aspirin may be considered, followed by CEA or CAS once the thrombus resolves. In patients experiencing ongoing ischemia despite anticoagulation, endovascular therapy may be an option if it can be performed with flow reversal/blockage to prevent embolization during EPD placement.

Similarly, the best revascularization strategy for patients over the age of 80 years remains undefined. Octogenarians were excluded from the CEA randomized trials but are known to have a higher perioperative complication rate than younger patients. Recent evidence suggests that even with CAS the complication rate is high. In the CREST lead-in phase in octogenarians, the 30-day stroke and death rate among octogenarians is 12.2% (58). In the more recent CAPTURE registry, the 30-day event rate in octogenarians ranged according to the level of expertise of the treating interventionalists ranged between 6.3% and 10.3% (34). Since octogenarian are also at increased risk for CEA, the optimal management of octogenarians with symptomatic carotid stenosis remains unknown. Since the benefit from revascularization of asymptomatic patients becomes evident at ~5 years, revascularization of asymptomatic patients older than 80 years of age should be discouraged.

The third group of patients for whom the best strategy needs to be defined includes those with recent (<6 weeks), large and disabling strokes. These patients were also excluded from both the CEA and the CAS randomized trials. The primary concern is that in patients with stroke, especially large strokes, revascularization predispose to intracerebral hemorrhage due to the cerebral hyperperfusion syndrome. This complication is well described after CEA but has also been reported following CAS (57). Predisposing conditions for cerebral hyperperfusion syndrome include recent ischemia, perioperative hypertension, revascularization of a severe stenosis with poor collateral blood flow, and the presence of bilateral severe stenoses or contralateral occlusion. In this setting, intracerebral hemorrhage may have devastating consequences and carries nearly 80% mortality rate. Therefore, if only a small territory of viable cortex fed by the symptomatic carotid remains at risk of ischemia, the risk of revascularization, both in terms of peri-procedural ischemic stroke and intracerebral hemorrhage, should be weighed against the risk of recurrent ischemia, which may be as high as 10% to 14% over four to six weeks. If it is decided to proceed to revascularization, then peri-procedural strict blood pressure control is mandatory. If peri-procedural hypertension can be aggressively controlled then revascularization may be considered (56).

CONCLUSIONS

CAS has emerged as less invasive alternative to surgery for patients with stenosis of the ICA. In patients at high risk for surgery, one randomized trial has shown that CAS is equivalent of not superior to CEA. In symptomatic patients, a meta-analysis suggests that CAS is inferior to CEA in terms of 30-day death or stroke rate, while beyond 30 days current evidence supports the equivalence of both revascularization strategies in stroke prevention. As a limitation, the majority of the randomized studies had inadequate requirements in terms of endovascular expertise and did not mandate the use of EPD. Contrary to the randomized data, large-scale high-quality registries have reported CAS results in the range of current recommendation for CEA even in patients at high risk for surgery. Until further data become available, the performance of CAS should be limited to dedicated CAS centers and targeted especially to patients at high risk for surgery. Independently of the revascularization strategy used, patients with carotid artery stenosis remain at risk of cardiovascular events and require aggressive secondary cardiovascular prevention.

With respect to vertebral revascularization, data remains very limited. Surgery is in most centers not considered a viable option. Percutaneous revascularization, currently limited to symptomatic patients, appears to be associated with high technical success and low complication rates, but in-stent restenosis remains a concern. Preliminary data on drug-eluting stents appear promising. Also, in patients with VA stenosis, the focus of treatment should be the global reduction of vascular risk, including pharmacologic prevention of stroke and myocardial infarction.

REFERENCES


Intracranial stenosis and acute stroke interventions

Alex Abou-Chebl

INTRODUCTION
Acute ischemic stroke (AIS) is a major public health issue that is preventable, but until recently was not treatable. Major advances in the past 10 years have made treatment a reality. Intracranial large vessel occlusion is the most common cause of severe AIS and is most amenable to endovascular therapy; this is analogous to an acute coronary syndrome (ACS) presenting as ST-segment elevation myocardial infarction. However, unlike an ACS, which is most often caused by an atherosclerotic plaque rupture, AIS and transient ischemia (TIA) may be caused by several different mechanisms including embolism (cardiac or artery to artery), intracranial atherosclerotic thrombosis, perforator occlusion (due to lipohyalinosis, atherosclerosis, or embolism), spontaneous dissection, vasculitis, and hypoperfusion. Therefore, no single therapy will be effective in all cases. Also, factors such as patient’s age, duration of ischemia, presence of early infarct signs, presenting blood pressure, serum glucose level, and presence of collaterals have to be taken into account because they determine the risk of intracerebral hemorrhage (ICH)—the most feared and devastating complication associated with all treatments for AIS (1).

On the other hand, patients who have symptomatic intracranial atherosclerotic stenoses and who have failed medical therapy can be treated by endovascular means, much like the patient with symptomatic coronary artery disease. These patients often present with TIA or small strokes and have brain tissue at risk. Medical therapy is relatively ineffective and surgical bypass is associated with worse outcomes than medical therapy. Endovascular therapy has emerged as a viable treatment option, but as with treatment for AIS, the risk of ICH is a major obstacle, as are the lack of clinical efficacy data and a paucity of brain-specific devices.

ANATOMIC CONSIDERATIONS
There are many similarities between the intracranial vessels and atherosclerotic stroke and other acute vascular events, but in particular, ACS. For the most part, the vessels of the circle of Willis, which are the vessels that are most often associated with AIS and intracranial atherosclerosis, are comparable in size to the coronary arteries. The vessels include the

- paired intracranial internal carotid arteries (ICA, 3–4 mm),
- middle cerebral arteries (MCA, 2–3 mm),
- anterior cerebral arteries (ACA, 1.5–2 mm),
- intracranial vertebral arteries (VA, 2–3 mm),
- posterior cerebral arteries (PCA, 1.5–2 mm), and
- singular basilar artery (BA, 2.75–3.5 mm).

The atherosclerotic process that affects the coronary arteries is the same process that affects the cerebral vessels with the same dynamism for plaque progression, rupture, and regression. Furthermore, the fundamental principle of ACS treatment—that early revascularization leads to reduced tissue injury and therefore reduced disability and mortality—applies to the brain. Additionally, vessel revascularization to improve flow and reduce thrombosis and embolization is the most effective means of preventing recurrent events. The medical treatments are interventions that are effective for the treatment of coronary artery disease (both symptomatic and asymptomatic) are also effective for AIS and intracranial atherosclerotic disease.

Despite these similarities, there are major differences between the cerebral vessels and the coronary arteries or other muscular arteries. The cerebral vessels are histologically different: they have no external elastic lamina and they have a thinner tunica media and trivial adventitia; this makes these vessels quite fragile. They also differ from the coronary arteries in being partly (i.e., the petrous and cavernous carotids) surrounded by bone or rigid and fibrous tissue (i.e., the dura mater). Combined with significant tortuosity in their proximal segments, this makes the navigation of endovascular devices to the intracranial vessels extremely difficult, if not impossible at times, which greatly increases the risk of vessel injury and perforation during endovascular therapy. The most tortuous and rigid segments of artery are the petrous and cavernous segments of the ICA. As a consequence, access to the MCA may be difficult. This makes the endovascular AIS approach problematic because approximately 80% of large-vessel AISs involve the MCA.

Perforation or dissection of intracranial vessels is often a catastrophic event and is fatal in up to 80% of cases because the vessels course in the subarachnoid space, which is surrounded by the noncompliant skull. As a result, intracranial pressure often rapidly increases, leading to cessation of cerebral blood flow and death. Neurosurgical rescue is rarely, if ever, beneficial, and in the presence of anticoagulants, antiplatelets, or fibrinolytics, surgery is often contraindicated. Another unique characteristic of the brain is that it is very sensitive to embolic debris, even if the debris is nearly microscopic in size.

Finally, a unique anatomical characteristic of the cerebral vasculature is the circle of Willis. This potentially robust source of collateral blood flow can completely restore flow to the territory of an occluded ICA or VA. The circle of Willis consists of the two posterior communicating arteries (PCom) connecting the terminal ICAs and the PCA and the anterior communicating artery connecting the two ACAs. Unfortunately, the circle of Willis is fully developed in only 25% of humans and anatomical variants are numerous. Pial collaterals, connections between the distal branches of the MCA, ACA, and PCA and the cerebellar arteries over the surface of the brain, are less robust potential collaterals.
ACUTE ISCHEMIC STROKE

Fundamentals

Access is obtained rapidly via the femoral artery. A 5-Fr diagnostic catheter is used for diagnostic angiography of the suspected culprit vessel as well as any sources of collateral blood supply. If the ICA or MCA are the symptomatic vessels, ipsilateral common carotid artery angiography should be performed with cervical (i.e., carotid bifurcation and ICA-origin imaging) as well as intracranial views in both an anteroposterior image (with slight, 10°–15°, cranial angulation) and a lateral image. For vertebralbasilar circulation ischemia, a left subclavian artery—usually more easily cannulated than the right—angiogram should be performed and the ostium of the VA visualized. Of note, many individuals have a dominant VA on one side with the other, smaller VA, ending in the PICA, which does not contribute significant flow to the BA and the brainstem, so if the BA is not the culprit vessel as well as any sources of collateral blood supply. If the ICA or MCA are the symptomatic vessels, ipsilateral common carotid artery angiography should be performed with cervical (i.e., carotid bifurcation and ICA-origin imaging) as well as intracranial views in both an anteroposterior image (with slight, 10°–15°, cranial angulation) and a lateral image. For vertebralbasilar circulation ischemia, a left subclavian artery—usually more easily cannulated than the right—angiogram should be performed and the ostium of the VA visualized. Of note, many individuals have a dominant VA on one side with the other, smaller VA, ending in the PICA, which does not contribute significant flow to the BA and the brainstem, so if the BA is not the culprit vessel. Of note, many individuals have a dominant VA on one side with the other, smaller VA, ending in the PICA, which does not contribute significant flow to the BA and the brainstem, so if the BA is not the culprit vessel.

When the decision to treat has been made, stable access to the culprit vessel becomes critical. To achieve this, a short femoral sheath is adequate as described above, but if there is marked tortuosity, the placement of a long (typically 80 cm) 6- to 8-Fr sheath in the corresponding common carotid or subclavian artery is recommended. The tortuosity and sharp angles of the cervical and cranial vessels can make distal wire and catheter navigation impossible, and an added benefit of a long sheath is that if needed the guide catheter can be rapidly exchanged. Prior to sheath placement in the carotid or subclavian a 2000-U bolus of heparin is given and is followed by a 500-U/hr infusion. Higher doses may be used but with greater risk of ICH (2). A 100-cm, 6-Fr guide catheter with a soft tip and a simple hockey stick curve is then advanced into the distal cervical ICA or distal cervical VA (just proximal to the C2 loop). Of note, these vessels have a high proclivity to spasm, particularly in younger patients and can be easily dissected.

Interventionalists must also be aware of the presence of multiple small perforating branches from both the MCA and VA, which originate superiorly and posteriorly, respectively, to avoid inadvertent cannulation. These are end arteries that have poor collaterals. Their ostia can be occluded by angioplasty and stenting, leading to ischemia. Other essential branches to be aware of are the ophthalmic artery arising anteriorly from the cavernous ICA, the PCom arising posteriorly from the carotid siphon, and the very small anterior choroidal artery arising just distal to the PCom. Occlusion of this vessel causes infarction of the internal capsule with a resultant severe contralateral hemiplegia. The VA has several muscular branches in its distal cervical segments and the posterior inferior cerebellar artery (PICA) can often arise extracranially at the C1 level. Intracranially, the VA gives off the PICA dorsally and just before the vertebralbasilar junction each VA gives off the very small anterior spinal artery to the spinal cord, dorsomedially.

A variation of this approach is to place a balloon occlusion guide catheter rather than a conventional neuroguide as it may facilitate mechanical embolectomy by allowing aspiration through the guide and occlusion of antegrade blood flow. This approach can increase the risk of arterial dissection and the available guide catheters are not curved and are not as stable as the conventional guide catheters.

Following guide insertion, a 0.014-in. hydrophilic, soft-tipped wire should be carefully passed through the occluded segment and placed distally remembering the presence of perforators and that the intracranial vessels have no adventitia and are easily perforated. If there is a high likelihood of underlying atherosclerotic plaque as the cause of the vessel occlusion, the wire may be advanced with the aid of a small, 1.5- to 2.5-mm diameter balloon catheter that will allow for more rapid angioplasty. On the other hand, if thrombolysis or embolectomy is the first planned treatment because of a high likelihood of angioplasty, a microcatheter may be more appropriate so that thrombolysis can be immediately begun.

Intra-arterial Thrombolysis

Most clinical experience has been with the slow infusion of a thrombolytic agent (tissue plasminogen activator or tPA primarily, but urokinase and others have also been used) over 30 minutes to 2 hours (2–4). In the author’s opinion, waiting two hours for a fibrinolytic to take effect is too long; more rapid recanalization techniques such as multimodal therapy or mechanical clot extraction should be considered, particularly if the thrombus burden is high. If distal branch occlusions are the problem, microcatheter fibrinolytic infusions are appropriate and they are more likely than M1 or BA occlusions to recanalize quickly in this way. Depending on the clinical circumstances (see later in text) the dosage and rate of infusion can be adjusted, but 30 to 45 minutes is appropriate infusion duration (based on personal experience and preference). In the PROACT II (Prolyse in Acute Cerebral Thromboembolism) trial, the fibrinolytic was infused over two hours. The total dose of fibrinolytic used is generally 20% to 25% of the intra-venous dose (3–7). Typically, fibrinolytic infusions are performed primarily within and just proximal to the thrombus; however, some advocate infusion of a small amount of lytic immediately distal to the thrombus.

Multimodal Approach

Increasingly, the use of a combination of pharmacological agents with both thrombolitics and platelet glycoprotein (GP) IIb/IIIa antagonists has been described (4,8,9). Use of these agents seems appropriate in the setting of atherosclerotic occlusions or artery-to-artery emboli, but less so in the setting of cardioembolism in which fibrin-rich clots are expected. The fundamental principle of AIS therapy is that revascularization must be rapid and timely, but it must not come at the cost of ICH. Therefore, when adding GPIIb/IIIa receptor antagonists to either fibrinolytics or angioplasty and stenting procedures, the interventionist must weigh the definite increased risk of ICH versus the potential benefit. No randomized or large trial data are available to guide the choice of route and dosage of additional GPIIb/IIIa receptor antagonists, but the same guidelines that guide fibrinolytic use apply to GPIIb/IIIa antagonist use as well: use the smallest dose possible of the shortest acting drug and avoid use in high-risk patients (see sect. “Clinical Aspects”). The author will typically begin with 20% to 25% of the usual loading dose given directly within the thrombus
alternating with small aliquots of fibrinolytic. The maximum dose of GPIIb/IIIa antagonist is unknown, but 50% to 75% of the usual bolus dose appears to be effective in most cases and certainly no more than the usual IV loading dose should be used. There is no indication for continuous infusion of these, or any fibrinolytic or antithrombotic (even heparin) for that matter, following the procedure. The brain is not like the peripheral vasculature, and prolonged infusions are associated with very high rates of ICH and death (10).

**Mechanical Clot Disruption and Extraction**

Purely mechanical approaches using balloons, snares, or the embolectomy devices have been described (11–13). Angioplasty, especially in the presence of underlying atherosclerotic stenotic lesions, has been shown to be highly effective in several large Japanese series (14,15). Recanalization rates of 91% have been described with lower risks of ICH compared to fibrinolysis (3% vs. >10%). However, such high success with angioplasty may be unique to the Japanese population, characterized by a high incidence of intracranial atherosclerosis—unlike the 8% to 10% incidence in the United States—as a cause of ischemia. Nevertheless, angioplasty is sometimes effective even if there is no underlying stenosis. Stenting of an underlying stenosis or occlusion may also be effective and should be considered in select patients (7,8). Stenting of the intracranial vessels has a nearly 100% recanalization efficacy but comes at a cost of higher complication rates and the need for dual antplatelet therapy, which is potentially very hazardous in individuals who have large infarcts or are treated with fibrinolytics. The author reserves stenting for patients with definite atherosclerotic intracranial or extracranial occlusions and who have no or minimal ischemic changes on initial CT. Angioplasty and stenting are particularly effective for atherosclerotic, acute, and cervical ICA-origin occlusions (16). The exception is in the relatively young patient with a cardioembolism who has not recanalized with other approaches and has a large territory at risk (i.e., without recanalization, there is a high risk of malignant MCA syndrome or persistent BA occlusion). These two situations are associated with 40% to 90% mortality and <10% probability of good outcome, so desperate measures may be justifiable even if they would necessitate dual antplatelet therapy.

As described below (in sect. “Intracranial Stenting”), all balloons must be undersized for the smallest segment they are to be placed in. Stents should be slightly undersized or sized one to one if focal type A lesions are encountered. Oversizing of a balloon or stent is associated with a high rate of vessel rupture and death and should never be performed in cerebral vessels.

**Mechanical embolectomy with the MERCI™** (Mechanical Embolus Removal in Cerebral Ischemia) Clot Retriever™ (Concentric Medical Inc., Mountain View, California, U.S.) was approved by the U.S. Food and Drug Administration (FDA) in August 2005 for the removal of “blood clots from the brain in patients experiencing an ischemic stroke.” With the aid of negative pressure applied through a balloon occlusion guide catheter, the device can be used to extract clots (Fig. 52.1) with a 45% to 58% efficacy (13). The single arm study of the device showed feasibility and safety but failed to show efficacy in terms of stroke outcomes or mortality compared with historical controls; this has been used by many as an argument that mechanical embolectomy is not an effective stroke treatment. None of the studies conducted with the MERCI retriever, nor its recent competitor the Penumbra™ (Penumbra Medical, Inc., Alameda, California, U.S.) system, were intended or powered to show efficacy. Therefore, it is a valid argument that these devices are not proven effective in stroke treatment. However, it is clear that recanalization, when appropriately timed, is the most effective treatment for stroke and these devices do recanalize vessels. Therefore, clinical benefit will be dependent on appropriate patient selection and safe endovascular technique. The main disadvantages of the MERCI and Penumbra clot retrieval devices are that they can cause vessel injury (<5%), and lesion wire access is lost with every attempt potentially requiring multiple wire passes through the lesion. Nevertheless, this approach may be the preferred therapeutic option in patients with presumed cardioembolic stroke or those in whom thrombolytics may be contraindicated.

The MERCI retrieval technique consists of placing a wire distal to the occlusion as described above. The microcatheter is then removed and the appropriately sized MERCI microcatheter is advanced over the wire just past the site of occlusion. The site of occlusion can be found in several ways. The safest way is to simply film late when injecting the parent vessel and observe for retrograde pial collateral flow that often reaches the distal aspect of the occlusion. If collateral flow is so poor that no retrograde pial flow is seen, the interventionalist should reconsider treating the patient since the complete absence of collaterals on angiography is a good predictor of inevitable infarction with little chance of neurological recovery (17). The other technique is to place the microcatheter past the typical site of occlusion—in the MCA, this is usually the MCA bifurcation, and in the BA, it is usually the proximal PCAs—and then to withdraw the wire for a gentle microcatheter-contrast injection with digital subtraction angiography. This technique clearly defines the distal face of the thrombus but it carries the risk of causing distal embolization as well as vessel perforation and ICH (18). Once the distal aspect is defined, the MERCI microcatheter can be advanced just beyond it. The microguidewire is removed and the appropriate MERCI retriever is slowly deployed, by unsheathing it from the microcatheter, with the first one to two loops just distal to the thrombus and the remainder of the loops within the thrombus. After complete deployment and documenting that the retriever has assumed its fully deployed configuration, the microcatheter is readvanced until it reaches the proximal loop. Both devices are then slowly withdrawn as a unit over two to four minutes, all the while making sure not to pull back too quickly so the retriever does not stretch and lose its shape. When the retriever reaches the terminal ICA or comes proximal to the vertebral-similar junction, the balloon on the guide catheter should be inflated and gentle suction applied on the guide catheter central lumen. The retriever and microcatheter are continuously withdrawn under suction until they exit the guide catheter. The guide catheter is then vigorously back-bled and control angiography is performed. If the first pass is unsuccessful—and it almost always will be—the lesion is recrossed with the microguidewire and microcatheter, which are then exchanged for the MERCI system and the process is repeated. On average, three passes are needed for clot retrieval. Multiple retrievers are often needed and often require downsizing as the thrombus moves distally.

The Penumbra clot-extraction system is the second FDA-approved device for the removal of clot from the brain. It was tested in much the same way as the MERCI system in a single arm registry (11). In a 125-patient study, nearly 82% of vessels were recanalized. This system has the benefit that complete access to the lesion is not always lost. Much like the MERCI
system the Penumbra microcatheter of choice is advanced into the lesion with an exchange-length wire. The MERCI and Penumbra microcatheters are in general too stiff to be navigated primarily with the microguidewire except in young patients with straight arteries. Once the Penumbra microcatheter is placed at the proximal aspect of the thrombus—the author has actually found it best to advance the microcatheter to the distal aspect, but the instructions for use and company literature state that the device is to be used from proximal to distal—the microwire is exchanged for the appropriate Separator Wire™ (Penumbra Medical, Inc, Alameda, California, U.S.). The suction apparatus is then activated, applying 1 atm of continuous suction through the microcatheter. The separator wire is moved in and out of the microcatheter as the microcatheter is advanced forward. In this way, the thrombus is removed one small fragment at a time. The separator wire acts to break up any thrombus sucked into the microcatheter to maintain flow within the catheter. The drawback to proximo-distal motion is that neither the separator wire nor the microcatheter is shaped, and as a result, they often cannot be advanced beyond the straight segments of the MCA or BA. Unfortunately, most emboli tend to lodge at the MCA bifurcation or BA apex. By starting distal to proximal, the catheter and separator “fall back” into the straight segment hopefully after removing the distal thrombus. In practice, multiple passes are required with this device as with the MERCI retriever, and as with that system, multiple devices are often needed per case. The largest Penumbra catheter, the 041 device, has the most efficacy but is too large for most MCA trunks and all MCA and BA branches.

Both the MERCI and Penumbra devices have been associated with subarachnoid hemorrhage and vessel perforation. In most cases, the perforations occur at the M2 and M3 branches of the MCA and the P1 and P2 segments of the PCA. Great care must be taken when smaller branches are cannulated with these devices, and it is reasonable to assume that in most cases any branch <2 mm in diameter should be avoided.

In clinical practice, significant differences in technique remain, and until a randomized trial shows benefit of one approach over another, the interventional treatment of ischemic stroke is likely to remain variable among institutions.

**Indications**

The indications for endovascular treatment (also known as intra-arterial therapy or IAT) of AIS are evolving. Since IAT for stroke is not FDA approved, a great deal of variability exists among experts in the field in regard to the indications. In general, however, any patient with AIS presenting <3 hours (and soon perhaps 4.5 hours if FDA labeling changes for IV tPA based on the recently published ECASS III trial results) 19 should be offered IV tPA if they meet the criteria for it. IAT may be offered to these patients with the understanding that the
including cerebral blood volume maps, which are likely to define any salvageable brain tissue. Assistance of a stroke neurologist is necessary to decide which modalities to use and how to select patients appropriately is mandatory.

**Equipment**

In selecting equipment for AIS intervention, the operator must be aware that the majority of devices used do not have FDA labeling for intracranial use, including those discussed here. As a consequence, a frank and honest discussion with all involved, from administrators to institutional review board members to patients and families regarding the off-label use of devices is mandatory. AIS interventions are typically performed with 6-Fr guide catheter-compatible equipment with the exception of the MERCI clot-extraction devices that sometimes are performed with 8- or 9-Fr guide catheters. The most common guide catheter used is the Envoy™ 6-Fr guide catheter (Cordis Neurovascular, Inc., Miami Lakes, Florida, U.S.) with a multipurpose-shaped tip. A 90-cm length is usually sufficient but in taller individuals or those with severe tortuosity longer guides in the 100 cm range are preferred. Many other guide catheters are on the market with many new devices that have exceptional trackability (e.g., Neuron™ guide catheter by Penumbra Inc.), but the author’s experience with some of these devices is less favorable than with the reliable Envoy. These devices come in various lengths up to 125 cm and can allow intracranial placement of the guide catheter tip to facilitate navigation of devices.

Numerous microcatheters are also available and most interventions are performed with 2.3-Fr end-hole microcatheters; the author’s workhorse is a Rapid Transit™ (Cordis). In general, smaller catheters are easier to navigate but their inner lumen size makes microcatheter injections difficult. The author performs all of his cases with 0.04-in. microwires. Smaller wires have less support and a greater risk of artery perforation, and the larger wires are not as steerable through the tortuous cerebral vessels. As a rule, hydrophilic wires are needed to access the branches of the MCA or PCA and due to their fragility, the wire tips are always the softest possible. Middleweight wires may rarely be placed intracranially by microcatheter exchange to give support, but they are not used primarily and stiff wires are never used; the risk of perforation is simply too great to permit anything, but the softest tipped wires are to be navigated to the brain. Numerous microwires are available, each with different purported benefits. The best wire is, in general, the one that the interventionalist has the most experience with. Examples of good wires are the Whisper™ (Abbott Vascular/Guidant, Santa Clara, California, U.S.), Transcend Floppy or Extra-Floppy™ (Boston Scientific, Inc., Natick, Massachusetts, U.S.), Synchro (Boston Scientific, Inc., etc.).

For balloon angioplasty, the best balloons are the coronary balloon systems particularly the Maverick™ (Boston Scientific, Inc.). Another good rule of thumb is that only over-the-wire systems should be used for several reasons. First, rapid exchange (RX) devices are difficult to navigate to the brain. Second, if wire or catheter exchanges are needed they are not possible with RX systems. Third, an over-the-wire balloon may be used as a microcatheter if needed to inject contrast, lysics, or exchange equipment. Therefore, the author exclusively uses exchange-length wires for all acute stroke interventions.

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**Table 52.1 Contraindications to Acute Ischemic Stroke Intervention**

<table>
<thead>
<tr>
<th>Contraindication</th>
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<tbody>
<tr>
<td>ICH (lobar, subdural, intraventricular)</td>
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<tr>
<td>Subarachnoid hemorrhage</td>
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<tr>
<td>History of ICH</td>
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<tr>
<td>Cerebral arteriovenous malformation or giant thrombosed cerebral aneurysm</td>
</tr>
<tr>
<td>CT evidence of &gt; 1/3 MCA territory infarct</td>
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<tr>
<td>Uncontrolled hypertension &gt; 185/110 mmHg</td>
</tr>
<tr>
<td>Unknown stroke duration or duration &gt; 6 hr</td>
</tr>
<tr>
<td>Thrombocytopenia &lt; 100,000</td>
</tr>
<tr>
<td>Bleeding diathesis</td>
</tr>
<tr>
<td>International normalized ratio &gt; 1.7</td>
</tr>
<tr>
<td>History of Alzheimer’s disease or amyloid angiopathy</td>
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</tbody>
</table>

*Unruptured, incidental, nonthrombosed aneurysms are not a contraindication.*

Abbreviations: CT, computerized tomography; ICH, intracerebral hemorrhage; MCA, middle cerebral artery.

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The standard of care in AIS < 3 hours is treatment with IV tPA. Patients who do not meet the IV tPA criteria due to time window or some other factor may be offered IAT. The standard time window for IAT is up to six hours and for mechanical embolectomy is eight hours. All patients should be evaluated clinically with laboratory tests and cerebral imaging before an intervention is contemplated. In general, the time window for treatment is six hours from stroke onset or the last time the patient was known to be normal. The duration of ischemia is a leading predictor of neurological outcome. The patient must also have a clinical deficit severe enough to warrant intervention both to avoid the risk of the procedure and to ensure that an intervention is likely to be of benefit since patients with mild strokes (National Institutes of Health Stroke Score or NIHSS < 4) are unlikely to have a vascular arterial occlusion and are likely to have a good outcome without therapy, in contrast to patients with the most severe strokes (NIHSS > 20) (2). The primary contraindication to AIS intervention is any history or propensity for ICH (Table 52.1). Therefore, all patients being considered for a cerebrovascular intervention must have a baseline CT scan of the brain to differentiate ischemic from hemorrhagic stroke. This is the current standard of care and no stroke revascularization therapy may be initiated without a baseline CT scan of the brain to exclude ICH or other contraindications.

Patients are best selected for IAT with the help of perfusion imaging. This technique permits assessment of the ischemic penumbra and thus can define any salvageable brain tissue as well as the size of the necrotic, and irrevocably injured, core of the stroke. The ideal patient is one with no or little necrotic core and a large area of penumbra. These patients have the most to gain with the least risk, whereas the patient with a large necrotic core, even with a large penumbra, has much to risk because revascularization of necrotic tissue is the presumed mechanism of hemorrhagic conversion following ischemic stroke. The patient with no penumbra, even if there is no necrotic core, in general, has nothing to gain by an intervention, which simply exposes the patient to risk without benefit. The penumbra and ischemic core can be assessed noninvasively with magnetic resonance imaging and CT imaging. The former produces diffusion-weighted images that define the areas of dead tissue and perfusion images that define the hypoperfused regions. CT perfusion provides several possible types of images including cerebral blood volume maps, which are likely the best marker of necrotic core, cerebral blood flow maps, mean transit time, and time to peak. Many controversies exist regarding these techniques and much is still undefined including the exact definition of penumbra. Assistance of a stroke neurologist is necessary to decide which modalities to use and how to select patients appropriately is mandatory.
In some cases, acute stenting is indicated. For extracranial ICA stenoses leading to occlusion, the same devices used for elective carotid stenting should be used, including emboli prevention devices if possible. The author performs all emergent carotid stenting procedures with either filter type or proximal flow arrest emboli prevention devices. The latter are preferred because they can facilitate clot extraction if needed. For intracranial stenting, the same devices used for elective stenting are preferred. The more flexible coronary cobalt-chromium stent platforms are ideal, for example Vision™ (Abbott Vascular, Inc.) or Driver™ (Medtronic, Inc., Santa Rosa, California U.S.). The stainless steel devices are very difficult to deliver in all cases and greatly increase the risks of complications (see the discussion on elective stenting below for details). In the acute setting, the author prefers to avoid drug-eluting stents because of the need for prolonged dual antiplatelet therapy as well as the increased risk of stent thrombosis associated with off-label use.

The only other devices typically used are the clot-extraction devices approved by the FDA, namely the MERCI (Concentric Medical, Inc.) and the Penumbra systems. Each of these systems consists of several sizes of microcatheter and wire combinations and the MERCI system also includes a balloon occlusion guide catheter. The MERCI clot-extraction device is a corkscrew-shaped nitinol wire that has four configurations (X, L, V, and K-mini) as well as different stiffness (soft vs. stiff) and sizes (2, 2.5, and 3 mm). Depending on the wire chosen, one of two microcatheters is required to deploy the device. With this system, clot extraction is most efficient if proximal occlusion can be achieved. Concentric, Inc. manufactures three balloon occlusion guide catheter sizes: 7, 8, or 9 Fr. Larger guides are less likely to be occluded by extracted clot but at the cost of greater risk of vessel injury and access sheath size.

The Penumbra system currently consists of three microcatheter sizes (2.6, 3.2, and 4.1 Fr) each with its own Separator wire and the universal suction apparatus. The devices are chosen based on vessel size and tortuosity. The larger catheters are more efficient at clot extraction but are more difficult to deliver and have a tendency to kick back at genus, especially the MCA bifurcation and BA apex.

Clinical Aspects
It is valuable to determine the likely etiology of a stroke prior to intervention. As an example, a lesion likely to be due to atherosclerotic occlusion can be approached differently than one due to cardioembolism (8). A CT scan of the brain is mandatory in all patients and is the standard means of differentiating AIS from ICH. Any sign of ICH is an absolute contraindication to intervention regardless of their size or the severity of the deficit. Other modalities such as diffusion weighted and perfusion imaging may be useful in selecting the optimal patient for intervention since the patient with a large penumbra (brain tissue that is ischemic but not irreversibly injured) but a small ischemic core (irreversibly infarcted tissue) may be the most likely to benefit from revascularization therapy with a lower risk of ICH (20,21).

Although, ICA is the most widely used agent for intraarterial lysis, it may not be the ideal choice because it has some neurotoxic effects and results in higher rates of ICH (22). Based on the PROACT II data, a 10% rate of symptomatic ICH following interventional treatment of ischemic stroke is considered acceptable (2). The optimal dose of each thrombolytic is unknown. As a rule of thumb, however, lower doses of all thrombolytics are preferred to minimize the risk of ICH taking into account the unique characteristics of each patient that may increase the risk of ICH (e.g., age >80 years, hypertension >185/110 mmHg, elevated serum glucose, duration of ischemia >4 hours, absence of collateral blood flow, underlying infarct size, large clot burden, anticoagulant use or coagulopathy, or the intended use of other agents or aggressive mechanical manipulation during the intervention) (1).

Periprocedural Medical Management
Although most patients are able to breathe spontaneously (patients with diffuse brainstem ischemia not withstanding), those with a depressed level of consciousness may hypoventilate or be at risk for aspiration. These patients should be intubated and mechanically ventilated. Most others will not need mechanical ventilation and intubation may inappropriately delay revascularization. Stroke patients receiving intervention are by definition cognitively impaired and will often have difficulty following commands and holding still. Stroke interventionists need to be familiar with how to manage these patients while keeping them awake. It is the author’s belief that all cerebrovascular interventions, with rare exception, are safest when performed while the patient is awake so neurological changes can be monitored and potentially guide the aggressiveness of revascularization and avoid devastating complications. The cerebral vessels are densely innervated and any excessive dilation or mechanical force often results in patient discomfort. The astute interventionist can use this information to reassess device sizing, wire tip position, etc. and make appropriate changes.

Other neurointerventionists argue that all such interventions should be performed under general anesthesia to make them safer by avoiding inadvertent wire perforation due to patient motion. Since no randomized trials of local versus general anesthesia have been performed, the issue cannot be definitively solved. However, the author and others have observed the same or lower complication rates under local anesthesia than those reported in the literature with general anesthesia, suggesting that the procedures can in fact be performed safely under local anesthesia. However, operator comfort is key in these matters.

Peri- and postprocedural strict blood pressure control is the most important factor influencing outcomes of endovascular stroke treatment. Under ischemic conditions, the cerebral arteries maximally vasodilate to maintain cerebral blood flow due to cerebral autoregulation. As a consequence, cerebral blood flow becomes linearly proportional to the mean arterial pressure and a decrease in the latter can exacerbate cerebral ischemia. Conversely, excessive elevations of mean arterial pressure may lead to marked elevations of cerebral blood flow following recanalization, which may result in reperfusion injury and ICH. The American Heart Association guidelines for the management of ischemic stroke recommend not treating systolic pressures acutely until values exceed 220 mmHg except in patients receiving thrombolytics (1,23). For this latter group, the ideal range for blood pressure varies, but as a general guide, mean arterial pressure should be kept <135 mmHg (<185/110 mmHg). Also, it is preferable not to lower arterial blood pressures prior to recanalization. Following complete recanalization, pressures can (and should) be lowered into the normal or below normal ranges since the prevention of ICH is the single most important task following any cerebral
intervention. In cases of incomplete recanalization, some mild degree of hypertension may be desired to maintain collateral flow to the nonperfused regions. If ICH is observed or suspected, immediate and aggressive lowering of blood pressure should begin—the lower the better.

Postprocedural Management
Following successful intervention, there is no clear indication for continuing a heparin or GPIIb/IIIa antagonist infusion. Although PROACT II data suggested that a four-hour infusion of 500 U/hr of heparin may be of benefit, no data support its use following in the setting of other thrombolytic regimen (2). Other antithrombotics including aspirin should not be given for at least 24 hours except in situations where a stent was placed, in which case aspirin and clopidogrel may be given weighing the risk of ICH. Neurological checks should be performed every 15 minutes. The occurrence of any headache with or without worsening of deficits should be considered as a possible sign of ICH warranting immediate clinical evaluation and emergent CT scan of the brain. Should an ICH be found, reversal of all antithrombotic agents and thrombolytics in the patient’s system should be carried out if at all possible along with emergent neurosurgical consultation. All these procedures are done despite the fact that it is unclear whether any of these interventions, including neurosurgical intervention, are lifesaving or of any clinical benefit.

Many important aspects to the postoperative care of acute stroke patients are beyond the scope of this chapter, including monitoring of intracranial pressure, fluid management and shifts, temperature management, seizure prophylaxis, neuroimaging surveillance, head-of-bed elevation, and feeding. Needless to say, inexperienced or poor postprocedural management can make a great technical outcome a clinical tragedy. Experienced stroke neurologists and neurocritcal care specialists are essential partners in the management of these patients. Accordingly, patients treated by stroke neurologists in stroke units fair better than those not treated in this way. A multidisciplinary approach is the most effective means of treating AIS patients, and the interventionalist embarking on an AIS treatment program must have all of the components of the team ready prior to initiating therapy.

Limitations
Only one randomized trial of an endovascular acute stroke treatment has been performed, and, although the study was positive, the drug tested (recombinant pro-urokinase) is not commercially available (2). In addition, although FDA-approved devices are available for mechanical clot removal from the cerebral vessels, clinical efficacy has not been demonstrated (13). As a consequence, AIS interventions remain essentially “investigational” and unregimented. Much of the above discussion and much of the literature represent little more than anecdotal experience, albeit somewhat scientifically based.

Another major limitation is that recanalization efficacy is relatively poor compared with that achieved with ACS interventions. As a result, in the best series, only about 50% of patients have major neurological improvement to the point of having no disability or minimal disability (2,8,24). The remainder of patients either have minimal to no recovery or die as a result of the stroke, brain edema, ICH, or as a direct complication of the procedure. The latter is occurring less commonly than it used to, but still complication rates of 10% to 15% are to be expected. Furthermore, many patients will have complete recanalization but will still do poorly either due to ICH or due to reperfusion injury and cytotoxicity—these patients are likely better off not receiving recanalization therapy. Unfortunately, those patients are difficult to identify in advance. Currently, no effective treatments or preventive measures exist other than appropriate patient selection through penumbral imaging and blood pressure control. Interventions such as neuroprotectant drugs and hypothermia are promising potential therapies but remain investigational at this time.

Special Issues
Potential contraindications to intervention include factors such as patient age >80 years; elevated serum glucose >200 mg/dL; profound or difficult to control hypertension >185/110 mmHg; active treatment with warfarin, heparin, or a heparinoid therapy with high-dose aspirin and clopidogrel, or platelet GPIIb/IIIa receptor antagonists; other coagulopathies; or thrombocytopenia <100K (1). The presence of an area of early infarct measuring >1/3 of the MCA territory is generally considered to be a contraindication for intervention as these patients tend to have very poor collateral flow and poor neuronal viability with a high propensity for hemorrhagic conversion following intervention (17). Underlying poor neuronal reserve (i.e., dementia, especially Alzheimer’s type with or without known amyloid angiopathy) should be considered a strong contraindication for pharmacological recanalization because of a very high risk of ICH, and such patients tend not to do well even with successful recanalization.

INTRACRANIAL ATHEROSCLEROSIS—ANGIoplasty and Stenting
Fundamentals
Intracranial atherosclerosis causes 8% to 10% of all ischemic strokes and involves the vessels of the circle of Willis (25). Stenoses of these vessels cause cerebral ischemia primarily by limiting flow as well as by leading to vessel thrombosis and occlusion with or without embolization. The pathophysiology of most intracranial stenoses is atherosclerosis. However, other causes such as noninfectious and infectious vasculitis, dissection, recanalized occlusion following embolism, moyamoya, and post-radiation arteriopathies have to be considered. Importantly, since few pathological studies have correlated specimens with angiographic or modern noninvasive imaging modalities, the specificity of all vascular imaging techniques—including catheter angiography—for atherosclerotic disease is unknown.

Endovascular therapy has emerged as a feasible and potentially highly effective means of treating patients with intracranial vascular disease. Improving flow through the stenosis should be the primary goal of endovascular therapy. A moderate increase in the lumen may be sufficient since flow is proportional to the fourth power of the radius. The angiographic end point of a smooth, normal caliber lumen, while desirable, is not necessary since the cerebral vessels are so fragile and the pursuit of such a goal may lead to arterial rupture or dissection and ICH. This concept is of paramount importance and in opposition to the aggressive strategy in coronary interventions, since the coronary arteries are more forgiving.

Interventional Approach
The approach for intracranial angioplasty and stenting is very similar to that of acute stroke treatment but pretreatment with
dual antiplatelet agents is critical. A femoral approach is preferred, especially for MCA and ICA procedures. Heparin is given to achieve an activated clotting time of 250 to 300 seconds. In addition to anticoagulants, treatment for vasospasm should be considered during every stage of the procedure, although there are no data to support this approach except that the cerebral vessels are prone to spasm much like the coronary arteries, and since proper stent sizing is essential, antispasm treatments may help improve device sizing. As described above, a long stent (except in the rare patient with no tortuosity and a relatively proximal stenosis in whom a short stent may be sufficient) should be placed in the ipsilateral common carotid artery or subclavian and a 6-Fr guide should be placed distally in the cervical ICA or VA. The lesion should then be crossed with a hydrophilic, soft microwire with an atraumatic tip as described above. The tip of the guidewire should be placed distal to the stenosis with great care to avoid placing the wire in small branches or perforators. For terminal ICA and MCA treatment, the wire should be passed into the second or proximal third-order branches. In the posterior circulation, the wire should be placed in a PCA if possible.

Although no randomized data are available to support stenting over angioplasty alone, stenting is generally considered superior (26,27). The author’s approach is to predilate the lesion with a short, undersized, over-the-wire balloon keeping in mind that vessel rupture or dissection with subarachnoid hemorrhage are often fatal in this setting. This permits adequate sizing of the vessel, observation of lesion response to angioplasty as well as the patient’s response. A headache with submaximal balloon inflation portends that the patient’s vessel may not tolerate a stent much larger than the predilation balloon or that inflation rates need to be slower (28,29). Postangioplasty angiography should be performed and unless an excellent result with <30% residual stenosis is seen, stenting should be performed with a stent sized not larger than the smallest normal segment into which the stent will be placed. Stent length should be kept to the minimum needed to cover the lesion or angioplasty segment, particularly, since stents longer than 12 to 13 mm are very difficult to deliver. Poststenting dilation is rarely needed except if a self-expanding stent is used. If a large branch or perforator emanates from the lesion, a frank discussion about the risk of branch occlusion and consequent stroke should be done a priori. If this occurs, the author has found, anecdotally, that GPIib/IIIa intra-arterial infusion may recanalize the occluded branch. This is less of a problem than one would expect considering the large number of perforators that arise from the MCA and BA, but it does occur especially in patients with perforator syndromes (see later in text).

Coronary Devices in the Brain

Stent delivery is the most challenging single aspect of intracranial interventions, particularly delivery to the terminal ICA and MCA. The newer generation coronary stents, for example, Multilkink Vision™ (Guidant Corp.) and Driver (Medtronic, Inc.), have proven to be highly deliverable but in 8% to 10% of patients even these stents cannot be delivered safely, especially through the cavernous carotid artery (28). Better guide catheter support is often the most effective maneuver to improve delivery but has to be weighed against the risk of dissection. Maneuvers such as exchanging for medium support wires may sometimes be effective, but these wires may actually make tracking of the stent even more difficult since they push the stent against the vessel wall in the rigid, angulated segments (e.g., cavernous carotid). Very stiff wires should never be used in the intracranial vessels for fear of vessel rupture. Vasodilators, buddy wires, and other maneuvers may be attempted but are of variable benefit (30). Throughout, close observation of the patient and monitoring for headache should be carried out (28).

The complication rates with balloon-expandable coronary stents have been highly variable because of differences in patient selection and techniques as well as operator experience. Most studies have revealed 30-day stroke, ICH, death rates of 8% to 20%, but some have had rates as high as 50% (28,31–33). The author and others have reported on the use of drug-eluting stents for intracranial stenoses with fairly good success, but the ultimate safety of this approach is unclear (34). The same limitations that apply to their use in the coronaries apply to the intracranial vessels but even more so in the brain since prolonged dual antiplatelet therapy has been associated with markedly higher rates of ICH in patients with stroke (35,36). There are theoretical concerns of neurotoxicity with these devices, but in some preliminary work they appeared to be safe (37). Similarly, there is the potential for vessel wall toxicity since the wall thickness is less than that of the coronary tree. Also, until recently, the available drug-eluting stents were very stiff and difficult to navigate to the brain.

Brain-Specific Devices

Two stents developed for the cerebral vasculature have been tested in humans. The first, the balloon-expandable Neuralink™ (Guidant and Abbott Corp.) stent, was evaluated in the 43-patient SSYLVIA (Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries) trial and although it was highly deliverable with a low complication rate (6.6% stroke at 30 days), it was associated with a high restenosis rate of 32.4% (38). This result is not unexpected given that the Neuralink was a bare-metal stent and was placed in arteries 2 to 3 mm in diameter on average. That stent is not commercially available. The more recent device, the Wingspan™ (Boston Scientific Corp.) self-expanding nitinol stent was tested in a 45-patient study and was approved by the FDA under a humanitarian device exemption (39). Wingspan is highly deliverable, with flexibility comparable to a balloon catheter, and was associated with a low complication rate of 4.5% stroke or death at 30 days. However, the long-term durability of this device is questionable because postmarketing studies have shown a high early thrombosis rate (4.1% thrombosis at mean of 4.7 months) and a high rate of restenosis (25–45%) (40–43). One issue with the Wingspan stent is that the instructions for use do not allow for poststenting angioplasty. The stent itself has very little radial force and the notion that it will keep expanding like the much more robust extracranial carotid stents and prevent restenosis has not held to be true. Therefore, an excellent preangioplasty result is needed prior to delivery of the device or poststenting angioplasty should be performed.

Although the latter raises medical-legal issues, leaving a significant residual following stenting is inappropriate, and it was this that in the authors’ opinion led to the very high restenosis rates observed with this device. The ideal device for the treatment of intracranial stenosis is yet to be developed so the clinician must decide on a case-by-case basis which device to use. There is a pressing need for prospective clinical trials of intracranial angioplasty and stenting with standardized patient and lesion selection criteria, standardized...
perioperative medical management, balloons and stents designed for the cerebral vasculature, and comprehensive postoperative management criteria and follow-up.

**Indications**

As with the treatment of AIS, appropriate patient selection is the first and most crucial step in ensuring success. The major indication is the presence of a symptomatic atherosclerotic stenosis. In patients with symptomatic, angiographically proven >50% intracranial stenoses measured via the WASID (Warfarin vs. Aspirin for Symptomatic Intracranial Disease) method, the risk of recurrent stroke is approximately 12% annually regardless of treatment with aspirin or warfarin (44). In patients who have a >70% stenosis, the risk of stroke is approximately 22% annually (45). The risk of TIA or stroke in patients who have incidentally found intracranial stenoses but are asymptomatic is unknown but is thought to be low. Therefore, the ideal candidate for intracranial intervention is the patient with a symptomatic 70% to 99% stenosis, who has failed antithrombotic therapy (Fig. 52.2). The mandate that patients fail medical therapy stems from the fact that the risk of intervention is relatively low.

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**Figure 52.2** A 55-year-old man with diabetes mellitus, hypertension, coronary artery disease, and cigarette smoking developed recurrent, crescendo left MCA infarcts and transient ischemic attacks despite treatment with aspirin and clopidogrel. He was found to have a >90% left ICA terminus stenosis extending into the MCA. He underwent endovascular therapy with a coronary balloon but a balloon-expandable stent could not be advanced beyond an acute 90° bend in the cavernous ICA [long arrow, B (lateral common carotid angiogram)]. Since the angioplasty result was adequate, the procedure was terminated, which kept the patient symptom-free for six months before he returned with recurrent left MCA, TIAs, and stroke despite aspirin. An AP view left common carotid angiogram (A) shows a severe terminal ICA restenosis extending into the MCA (long arrow). The stenosis was severely flow limiting; compare the extent of MCA filling (short arrow) with that of the occipital artery (double arrow). The terminal ICA proximal to the stenosis measured 3 mm in diameter and the MCA distally measured 2.3 mm. A 0.014-in. microwire was advanced into the inferior division of the left MCA that resulted in severe, symptomatic vasospasm [note the absence of contrast surrounding the wire (arrow, C)]. The spasm resolved partially and only temporarily with nitroglycerin with continued symptoms of aphasia. A 2 × 9 mm² balloon was rapidly advanced into the lesion and angioplasty was performed. An AP angiogram revealed significant lesion recoil (long arrow, D) with slow flow into the ACA (short arrow, D). Although a drug-eluting stent might have been a good choice to prevent restenosis in such a small vessel, the previous failure to deliver a balloon-mounted stent and the persistent vasospasm necessitated a rapid revascularization, therefore a 3 × 15 mm² Wingspan™ stent was chosen. Despite its flexibility, the stent was difficult to deliver beyond the cavernous ICA. The patient required continuous boluses of nitroglycerin, induced hypertension, and slow withdrawal of the wire to a more proximal position to maintain MCA perfusion while the stent was delivered. Eventually the stent was deployed with a good but not perfect result (AP angiogram in E). Given the continued symptoms from the vasospasm the procedure was terminated without postdilation even though to decrease the risk of restenosis, it would have been optimal to do so. From a hemodynamic point of view, the result was adequate: compare the MCA flow with that of the external carotid artery branches on the final lateral angiogram (F). The patient’s symptoms resolved completely, and at one-year follow-up, he has an asymptomatic 50% stenosis that will be observed. Abbreviations: ACA, anterior cerebral artery; anteroposterior; ICA, internal carotid artery; MCA, middle cerebral artery; TIA, transient ischemia.
high and endovascular therapy is not yet validated as an effective treatment for this disease. The reasoning, therefore, is that if patients fail medical therapy they have no other recourse. Furthermore, the FDA humanitarian device exemption approval of the Wingspan system requires that patients fail medical therapy. Although patients with stenoses that measure 50% to 69% are also at an increased risk of stroke, that risk is relatively low compared to the risk of intervention so it is not obvious that the risk of intervention is warranted in those patients. It may be appropriate in selected patients who have multiple stenoses, poor collaterals, poor cerebrovascular reserve, or those who continue to have ischemic events despite aggressive medical therapy (see limitations and controversies below).

In addition, the patient’s symptoms should be attributable to the territory distal to the stenotic segment rather than due to the territory of a perforator arising from the stenosis. In those latter cases, angioplasty and stenting has a high likelihood of causing complete occlusion of and subsequent infarction in the territory of the perforator (28,46). Recently symptomatic patients, especially those with a large or disabling infarct, may have an increased risk of ICH (31); unless the need is pressing, some have advocated delaying treatment for six weeks or more in these patients (29).

Another important selection criterion is the feasibility of the intervention in terms of vascular access. The patient must also be able to tolerate dual antiplatelet therapy for at least 30 days but preferably for at least 6 months. Some patients will have multiple lesions or their symptoms may be vague or nonlocalizable or they may have some factor that increases the risk of the intervention. For such patients, the assessment of cerebrovascular reserve may be very helpful in delineating the symptomatic territory or in qualifying the risk of recurrent events as either high or low and may assist in clinical decision making. The author prefers acetazolamide single photon emission computed tomography and breath-holding transcranial Doppler, but acetazolamide CT perfusion or even positron emission tomography scanning may also be used. All of these studies aim to qualify the hemodynamic significance of a lesion and the risk of recurrent stroke. There are many unresolved issues with these modalities, not the least of which is their ability to predict stroke recurrence. Each interventionist must be familiar with one or two of these modalities and know when to use them and how to interpret the results. Colleagues in neuroradiology and stroke neurology are helpful resources. A systematic approach to the evaluation of patients with intracranial atherosclerosis is needed.

**Equipment**

For the most part, the equipment used for intracranial angioplasty and stenting is the same as that used for AIFS treatment. In terms of guide catheters, sheaths, and microwires, the devices are exactly the same. The only new tools are the balloons and stents, the majority of which are coronary devices and intracranial use is off-label. The Maverick coronary balloon is the author’s preferred percutaneous transluminal angioplasty balloon. Any similar, low profile and highly trackable coronary balloon may be used. Only compliant balloons should be used intracranially and noncompliant and cutting balloons should never be used. In regard to stents, the cobalt-chromium platforms have proven to be much more deliverable than the stainless steel platforms. Complication rates with attempted delivery of the stiffer stainless steel stents were significantly higher than that with the cobalt-chromium devices (unpublished data). Stent and balloon sizes are variable depending on the vessel being treated, keeping in mind that balloons should be undersized by roughly 20% and balloon-expandable stents should be sized to the smallest segment being treated—and as a rule, neither should ever be oversized. Over-the-wire systems are preferred for both balloon and stent systems as mentioned above. In regard to drug-eluting stent use, delivery is the major obstacle that has greatly limited intracranial use of the Cypher™ (Cordis, Inc.) stent (34). The Taxus Express2 (Boston Scientific) has proven to be more deliverable than the Cypher but only marginally so. The latest generation of drug-eluting stents based on cobalt-chromium are more deliverable, but the author and others have less experience with these devices.

Currently, the most commonly used stent for intracranial stenosis treatment is the Wingspan (Boston Scientific, Inc.) stent system. This device is the only device that has FDA approval for intracranial stenting for atherosclerotic lesions. The FDA approval is under a humanitarian device exemption and therefore its use and availability are somewhat limited. It is a highly flexible, nitinol stent that is delivered through a microcatheter. It comes in a variety of sizes from 2.5 to 4.5 mm in 0.5 mm increments with lengths of 9, 15, and 20 mm. The actual unconstrained stent diameter ranges from 2.8 to 4.9 mm. The stent system includes (separate packaging and cost) the Gateway™ (Boston Scientific) balloon system, which is in actuality a slightly modified Maverick balloon that has intracranial indications. As approved by the FDA, the instructions for use state that predilation with the Gateway balloon, sized to 80% of the target vessel diameter, should be performed followed by stent deployment with the stent sized approximately 0.5 mm larger than target vessel diameter. No postdilation is permitted per the instructions for use. This stent system is not compatible with guide catheter lengths >90 cm and requires a minimum of a 6-Fr guide catheter diameter.

**Clinical Aspects**

Certainty in the diagnosis is essential since cerebral vasculitis, which can often mimic atherosclerosis and vice versa, increases the friability of the cerebral vessels and angioplasty and stenting of the affected vessels can often result in devastating arterial rupture or early, rapid restenosis (unpublished data). Also in up to 20% of patients with arterial stenoses, there is another cause of stroke and failure to treat a cardioembolic source could increase the risk of stroke (47). A thorough evaluation must, therefore, be performed for every patient being considered for intracranial angioplasty and stenting to ensure that atherosclerosis is the most likely etiology. A full discussion of the evaluation of patients with stroke is beyond the scope of this chapter and as stressed above a stroke neurologist should be involved in the care of all patients being considered for intracranial interventions and is invaluable in patient evaluation and selection.

The medical therapy of patients with large-vessel atherosclerosis is well known, and the same treatments that are appropriate for coronary or peripheral vascular disease are appropriate for patients with intracranial atherosclerosis. The major difference is that dual antiplatelet therapy, specifically aspirin and clopidogrel, has been shown to be associated with an increased risk of ICH (35,36). Although the combination has been shown to be highly effective in patients with ACS and in those undergoing coronary stenting, dual antiplatelet therapy
has never been evaluated in patients with intracranial atherosclerosis. The only treatments tested in a randomized trial were aspirin 1300 mg/day versus warfarin to an international normalized ratio of 2 to 3 (WASID). In that study, aspirin was equally efficacious at ischemia prevention but was associated with reduced mortality and hemorrhagic events. Therefore, the standard medical treatment for intracranial atherosclerosis is aspirin. Since the dose of aspirin used in the trial is not a standard dose, very few physicians use it at those high doses. There is also no consensus on what the definition of failure of medical therapy should mean. The author defines failure of medical therapy as any recurrent ischemic event attributable to the stenotic territory while a patient is receiving aspirin (of any dose) along with a high-dose statin and an angiotensin-renin system if antihypertensive. Furthermore, the patient must have an adequate platelet inhibitory response to aspirin. If the above applies and the symptomatic lesion is treatable then the patient is offered endovascular therapy.

Besides medical therapy and endovascular surgery, surgical bypass has been used to treat patients with intracranial stenoses. Unfortunately, in a randomized trial of surgery versus medical therapy, surgery was markedly inferior to medical therapy and should not be considered as a viable option except in patients with complete occlusions who continue to have hemodynamic events and who have radiographically proven impairment of cerebrovascular reserve (48).

Periprocedural Management
After every maneuver and before removing the equipment, the patient should be assessed neurologically. If a deficit is found then angiography of the appropriate vessel should be immediately performed. Vasospasm, embolization, and dissection are the most likely causes of intraoperative deficits. If a significant or worsening deficit is noted but angiography is normal, then an expanding ICH should be considered and appropriate measures taken. If there is frank extravasation of contrast on angiography then immediate lowering of blood pressure, reversal of heparin, and even temporary balloon occlusion should be considered. Under these circumstances, the author has seen only a few survive despite all of these measures. If all is well then the heparin may be discontinued but not reversed unless the patient is at high risk for hyperperfusion syndrome or ICH. Routine use of GPIIb/IIa antagonists is discouraged except in those who are inadequately pretreated with oral antiplatelet drugs because of an increased risk of ICH.

Postoperative Care
Care of these patients is similar to that of patients treated with acute thrombolysis as described above. Close observation and monitoring of blood pressure are the critical issues. There is a risk of hyperperfusion syndrome, and intracranial hemorrhage and blood pressures should be monitored frequently while in hospital and daily after discharge and kept in the low normal range for at least 14 days following the procedure (49,50). Dual antiplatelet therapy is continued for at least 30 days for uncomplicated bare-metal stent procedures, but prolonged therapy for up to 6 months may be reasonable and up to 1 to 2 years of treatment should be considered when drug-eluting stents are utilized. It is critical to keep in mind that there have been no randomized or prospective data on the safety of dual antiplatelet agents in the setting of intracranial interventions and the author’s approach is to follow cardiac recommendations since the vessels are comparable in size.

Patients should have follow-up at 30 days with a neurological evaluation and a transcranial Doppler. At six months, another follow-up is indicated and unless the stented segment is easily evaluated by transcranial Doppler then angiography should be considered to reassess stent patency. An argument against angiography can be made because if the patient has a high-grade restenosis, but which is asymptomatic, repeat revascularization is not indicated. The author finds it useful to know if there is early, severe neointimal proliferation so that more frequent clinical assessment can be initiated and dual antiplatelet therapy continued, although the benefit of it still needs to be demonstrated. Also reassessment of cerebrovascular reserve should be considered in such patients to help quantify the risk of recurrent stroke.

Limitations
The major limitation of intracranial angioplasty and stenting is the lack of efficacy data and long-term durability data. Few prospective studies have been done, and they have varied greatly in patient selection criteria, treatment algorithms, medical management, definitions of outcomes, and follow-up data. Confounding this is the lack of agreement on what constitutes optimal medical therapy, making patient selection from site to site highly variable. At this time, therefore, intracranial angioplasty and stenting remain investigational and should be used only in selected patients by highly experienced operators. The complication rates remain relatively high with stroke, ICH, death rates of around 10% to 15% but as high as 50% (28,31-33). A major limitation is that, should hemorrhagic complications occur, there is often no surgical rescue.

Another limitation is that the sole FDA-approved device can only be used as part of a humanitarian device exemption and requires institutional review board approval and allows only a small number of patients to be treated annually. This device, along with the bare-metal coronary stents that are often used, is associated with high restenosis rates, which is often symptomatic (40,42,43,51). While drug-eluting stents may be promising, they are, in general, not as deliverable and no long-term safety data are available regarding potential neurotoxicity of the antiproliferative drugs and the prolonged use of dual antiplatelet agents. Follow-up imaging of the stents is difficult because, as with coronary stents, the noninvasive imaging modalities are quite limited in their ability to image the lumen of the stent, making catheter-based angiography necessary in most cases. Since catheter cerebral angiography has up to 1% stroke risk, particularly in inexperienced hands, the limitations of this technique are self-evident.

Special Issues
The treatment of intracranial atherosclerosis requires thoughtful evaluation and consideration of all of the clinical and radiological factors before deciding on an intervention. As stressed above, the mere presence of a stenosis is not a sufficient indication for an intervention. The global view of the patient’s health needs to be considered when making a decision to intervene or not. The very old are less tolerant of endovascular interventions due to either underlying dementia or severe calcification of their vessels, and unless compelled by an extraordinarily active and healthy octogenarian with major territory at risk, the author does not generally advocate stenting in these patients. In addition, young women with carotid terminus and proximal MCA stenoses appear to have very high rates of restenosis and stenting should be reconsidered in those locations (40). One absolute
contraindication to intracranial angioplasty and stenting is chronic complete occlusion. Such lesions have been shown to be associated with a high morbidity and mortality approaching 60% with endovascular therapy (52). As mentioned above, asymptomatic lesions should never be treated even if incidentally found before a coronary bypass surgery.

REFERENCES


Training program guidelines, case numbers, and maintenance of certification

Gregory W. Barsness and Charanjit S. Rihal

BACKGROUND
Developed by Dr. Andreas Gruentzig in the 1970s, coronary angioplasty training originally occurred through observation, proctorship, and attending live-demonstration courses, which were often run by Dr. Gruentzig himself. Training was an apprenticeship, expertise passed down from mentor to colleague, and experience was gained “on the job.”

The continued growth of interventional cardiology ultimately resulted in the development of formal training programs and nationally accepted standards for training and certification. The Core Cardiology Training Symposium (COCATS) consensus statements (1–4) by the American College of Cardiology (ACC) reflected the need for common standards at a national level for fellowship training in cardiology. This chapter reviews the links between training program accreditation and professional certification, as guided by national organizations with a stake in professional training.

TRAINING PROGRAM REQUIREMENTS
Training Program Structure
Numerous not-for-profit nongovernmental organizations oversee the structure, content, and evaluation of medical training. The primary accrediting body is the American College of Graduate Medical Education (ACGME), which inspects training programs through its Residency Review Committees (RRC). The content of the program is guided by the COCATS Taskforce 3 document promulgated by the ACC and endorsed by the Society for Cardiovascular Angiography and Interventions (SCAI). Trainees are tested and certified by the American Board of Internal Medicine (ABIM), which is in turn affiliated with the American Board of Medical Specialties (ABMS).

To gain or maintain accreditation through the ACGME, training programs must adhere to a set of program guidelines applicable to all ACGME-approved institutions (5). ACGME accreditation is required for program graduates to be eligible to sit for the ABIM-added qualification certifying examination in interventional cardiology, an essential step toward certification.

A sponsoring institution must take responsibility for all aspects of each program and abide by the requirements set forth in the ACGME Institutional Requirements (6). Primary of these requirements is the assurance that programs at sponsoring and participating institutions are based on “clear educational rationale” with “clearly stated activities and objectives.” Each interventional cardiology training program must have a single program director who is accountable for all aspects of the program operation. The program director must maintain certification in interventional cardiology by the ABIM and is expected to “possess the requisite specialty expertise” along with “documented educational and administrative abilities” at the primary teaching site. In addition to the program director, sufficient core educational faculty with sufficient clinical experience, academic productivity, and procedural expertise are also mandated to be present within the program to maintain a ratio of 1 core faculty for every 1.5 trainees.

Institutions and individual operators involved in education must maintain sufficient case volume to assure that quality is maintained in procedural instruction. Supervising faculty must perform at least 75 percutaneous interventional procedures annually at sponsoring institutions that perform at least 400 procedures each year. The availability of on-site cardiac surgical support is a required component of all interventional training programs.

COCATS and ACGME Specifications
The goals and standards for interventional cardiology training are established by the ACGME and the COCATS training statements (1–4). COCATS is a multisociety series of consensus documents developed by the ACC and SCAI and reviewed by the American Heart Association (AHA). COCATS 3 (1,2) was published in 2008 and represents the most recent iteration of the governing document for interventional cardiology training program requirements.

While the COCATS recommendations are consistent with the requirements of the ACGME, training program, review, and accreditation are strictly based on ACGME principles. To gain and maintain accreditation, interventional training programs must adhere to published ACGME standards. These standards include the common program requirements (7) that apply uniform outcome-oriented or competency-based standards to all programs (Table 53.1), encompassing the outcome-oriented basis for medical education across medical specialties. These competencies promote development of skills in lifelong learning, professionalism, and quality assessment and improvement.

CERTIFICATION AND CREDENTIALING
Training and Procedural Requirements for Certification
Certification is the process of individual quality assurance and recognition developed and implemented by the ABIM, which oversees certification through training requirements and assessment, including the administration of examinations. The ABIM is the largest member of the ABMS, currently certifying one of every three certified practicing physicians in the United States, and has as its stated mission, the goal of “enhancing the quality of health care” by certifying medical...
internists and subspecialists who demonstrate the knowledge and skills commensurate with excellent patient care (8). Although not developed as a requirement for employment or a measure of excellence, ABIM certification is a public affirmation of achievement of a minimal standard of competence and is a criterion used by many hospital privilege and credentialing committees. The ABIM grants certificates in internal medicine and 18 subspecialties. The pathway to certification in interventional cardiology involves a series of sequential steps, from initial credentialing in internal medicine, to credentialing in cardiovascular diseases and, ultimately, interventional cardiology.

Initial credentialing in the field of internal medicine is open to graduates of accredited medical schools in the United States or Canada as well as international graduates with a standard certificate from the Educational Commission for Foreign Medical Graduates (ECFMG). To be eligible for admission to the secure Certification Examination in Internal Medicine, candidates must complete 36 months of internal medicine training at a program accredited by the ACGME, the Royal College of Physicians and Surgeons of Canada, or the Professional Corporation of Physicians of Quebec and possess a valid and unrestricted medical license in their practice region. Documentation of successful training and competence in the six core competencies (Table 53.1) and basic procedural techniques in interpretation of results is required. Once these requirements are met and a passing grade achieved on the certification examination administered by the ABIM, certification is granted. The ABIM certification examination for internal medicine and the specialties and subspecialities may be taken any number of times to secure a passing score, as long as other appropriate licensure and professional standing requirements continue to be met.

Certification in cardiovascular disease requires prior certification in internal medicine and an additional 36 months of training, which must include 24 clinical months. Specific procedural and knowledge requirements include advanced cardiac life support, cardioversion, electrophysiology, exercise testing, echocardiography, atrial catheter placement, right heart catheterization, and temporary pacemaker insertion and management. Documentation of procedural competence, satisfactory mastery of the core competencies, and adequate scores on the secure ABIM examination in cardiovascular disease are required.

Certification in interventional cardiology requires prior certification in cardiovascular disease and an additional 12 continuous months of clinical training in coronary intervention at an ACGME-accredited institution. The ACGME requires demonstration of mastery of specific procedural and cognitive aspects of interventional practice (Table 53.2). Again, documentation of mastery of the core competencies and passing the secure ABIM examination are required for certification.

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<tr>
<th>Table 53.1</th>
<th>The Six Accreditation Councils for Graduate Medical Education Core Competencies in Medical Education</th>
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<tr>
<td>1. Medical knowledge</td>
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<td>2. Patient care</td>
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<td>3. Practice-based learning and improvement</td>
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<tr>
<td>Evidence-based medicine</td>
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<td>Quality improvement</td>
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<td>4. Systems-based practice</td>
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<td>Cost effectiveness</td>
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<tr>
<td>5. Interpersonal and communications skills</td>
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<tr>
<td>6. Professionalism</td>
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**Source:** From Ref. 5.

Institutional Credentialing

Credentialing is the responsibility of local hospital bodies. According to Joint Commission mandates, the medical staff has the responsibility to develop appropriate practice and competency standards and to document these principles in medical staff bylaws. These bylaws provide documentation and guidance for initial credentialing and periodic review (recredentialing) to assure maintenance of standards and the professional competence of all active hospital staff. Many hospitals require board certification, as a recognized minimal standard, for granting privileges and credentialing. Supportive of this policy, recent data have suggested some association between ABIM certification and improved health care delivery (9,10), although more research is needed to confirm or refute an association between certification and markers of quality outcomes. Physician scores in the highest quartile on ABIM Maintenance of Certification (MOC) testing were associated with improved quality care measures among their Medicare patients with diabetes after adjustment for patient and physician covariates (OR 1.17; 95% CI, 1.08–1.27) (9). Further suggestion of a relationship between performance on certification testing and
physician quality includes findings of better ratings by program directors (11) and colleagues (12) for physicians who score higher on the initial certification examinations.

MAINTENANCE OF CERTIFICATION

Overview
In an effort to encourage lifelong learning and promote excellence in health care, certification is time limited. All certification obtained since 1990 has been valid for a 10-year period, requiring renewal through the MOC program administered by the ABIM. There are three components for eligibility for maintenance of (re-)certification: holding a valid and unrestricted licensure to practice medicine, completion of self-evaluation and education components, and achieving a passing score on the secure recertification examination. For candidates in the subspecialties of interventional cardiology, successful maintenance of certification in cardiovascular disease is also required, although it is not necessary to maintain certification in internal medicine. These certificates are also valid for 10 years.

Self-Evaluation Modules
Self-evaluation of medical knowledge and practice performance are central features of the ABIM pathway to recertification (Table 53.3). Self-evaluation medical knowledge modules are available through the ABIM as web-based, open book exercises that can be completed individually or in groups. The practice performance self-evaluation is an opportunity for physicians to evaluate and reflect on the medical care they provide. A total of 100 “points” in self-evaluation is required for successful recertification and must include 20 points in medical knowledge self-assessment, 20 points in practice performance self-evaluation, and 60 points from either or both categories. These points can be earned through a variety of approved exercises, may be eligible for additional continuing medical education (CME) credit, and are valid for both cardiovascular disease and interventional cardiology recertification eligibility. Subspecialty societies, including the SCAI and the ACC, frequently review and provide guidance to the ABIM as appropriate to address the scope and further the benefit of these exercises.

The recertification process is meant to be performed throughout the 10-year recertification period, and candidates are encouraged to enroll with ABIM by the fourth year of the recertification cycle. By the end of the 10-year cycle, candidates who have successfully passed the secure examination and secured a sufficient number of self-evaluation module points will be granted recertification valid for another 10 years.

Specific Training Requirements in Interventional Cardiology

Training in invasive cardiology can be achieved to three levels of expertise (Table 53.4):

- Level 1 is intended for trainees planning a career in non-invasive cardiology and who may perform bedside procedures such as central line insertion.
- Level 2 is intended for trainees planning on performing diagnostic angiography but not interventional procedures.
- Level 3 is for full certification in interventional cardiology.

Interventional expertise requires mastery of a broad depth and breadth of literature, and technical and cognitive skills. The components of this skill set have been outlined in COCATS (Table 53.4) and the requirements for the ABIM board examination in interventional cardiology (Fig. 53.1; Table 53.5). All aspects of care associated with the procedure, including preprocedural case selection, recognition and management of intra procedural complications, and postprocedural care, are covered. Specific programmatic requirements include spending 12 continuous months of training in interventional cardiology as part of a structured fourth year of training in an ACCME-accredited program. Of note, neither clinical research experience nor vascular, carotid, or congenital interventions are part of core interventional cardiology training program requirements as currently constructed; however, many interventional cardiology trainees are interested in attaining certification in vascular interventions as well. Requirements for levels 1 to 3 training in vascular medicine and interventions are given in Table 53.6.

CONCLUSION

Interventional cardiology is a mature field with requirements for mastery of a specialized knowledge base of astounding breadth and depth, mastery of complex technical skills requiring hundreds of cases to obtain, and integration with judgment and experience. Training is guided by the COCATS document, programs overseen by the ACGME, and evaluation performed
by the ABIM. Trainees planning a career in invasive cardiology need to be thoroughly familiar with programmatic requirements to assure proficiency and eligibility for credentialing at their institution.

TRAINING IN EUROPE

Training standards in Europe are evolving rapidly. Both national and pan-European standards exist or are under development. The European Board of the Specialty of Cardiology (EBSC) and European Society of Cardiology (ESC) have promulgated guidelines for training in cardiology including subspecialty training in Interventional Cardiology. The efforts include accreditation. Formal training programs do not exist in most countries; however, concentrated experiences in interventions are provided. Board examinations similarly do not exist in most other countries, including Canada, Europe, and Asia. A Diploma of European Cardiology was established by the EBSC to facilitate quality standards and mobility across Europe.

FUTURE DIRECTIONS

Interventional cardiology continues to grow as the pace of innovation quickens. New procedures are constantly being developed and introduced into practice. As such, training requirements will need to evolve to keep pace with practice changes. This evolution demands frequent reassessment of the training pathway to assure adequate exposure to critical components of modern intervention. Expansion of the field of interventional cardiology into noncoronary, especially noncardiac, interventions has become common, and ensuring adequate training and certification is a challenge. Enhanced training pathways to assure proficiency in noncoronary cardiac and vascular interventions are in nascent stages of development. Continued trainee exposure to these disease entities will likely be followed by further educational initiatives, the expectation of competency, and expansion of training and certification requirements to document mastery. Whether training standards for peripheral vascular disease and interventions should remain distinct from those established for cardiovascular interventional training remains a point of debate.

Endovascular Training

Since the development of the ABIM process for Interventional Cardiology Training Pathway and Curriculum (13), endovascular procedures and techniques have continued to rapidly evolve with expanding implications for interventional training. While specific training in vascular medicine, carotid or peripheral vascular intervention, or structural heart disease intervention is not required as part of the Coronary Interventional Cardiology Training Program (13) requirements as currently constructed, many interventional cardiology trainees now demand the opportunity to obtain certification in these

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<th>Table 53.4 Specific Requirements for Training in Invasive Cardiology as Outlined by the COCATS of the American College of Cardiology</th>
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<tr>
<td><strong>Level 1</strong></td>
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<td>- Minimum four months performing at least 100 diagnostic procedures, including both hemodynamic and angiographic procedures</td>
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<td>- Technical skills include vascular access, right heart catheterization, temporary pacing, and coronary and left ventricular angiography</td>
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<tr>
<td>- Cognitive knowledge base includes coronary anatomy and physiology, hemodynamics, indications and contraindications, complications, treatment selection for coronary disease, pacing, radiation safety, adjunctive pharmacotherapy, hemodynamic assist devices, and vascular closure devices</td>
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<tr>
<td><strong>Level 2</strong></td>
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<td>- An incremental four months performing at least 200 procedures</td>
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<tr>
<td>- Technical skills include proficiency to an independent level in vascular access, left and right heart catheterization, coronary, graft, aortic, and femoral angiography, hemodynamic catheterization, pericardiocentesis, endomyocardial biopsy, vascular closure device use, and balloon pump insertion</td>
</tr>
<tr>
<td>- Cognitive skills include understanding X-ray imaging systems and recording equipment, coronary physiology, transseptal catheterization, and peripheral vascular anatomy</td>
</tr>
<tr>
<td><strong>Level 3</strong></td>
</tr>
<tr>
<td>- Must be a fourth year of advanced training performing at least 250 coronary interventional procedures</td>
</tr>
<tr>
<td>- Technical skills include PCI and its complications, transseptal catheterization, atherectomy devices, distal protection devices, IVUS, and coronary physiology. Familiarity with noncoronary intervention is encouraged. Technical skills do not include peripheral PTA, carotid stenting, valvuloplasty, or congenital intervention</td>
</tr>
<tr>
<td>- Cognitive and technical skills as outlined in Figure 53.1 and Table 53.5</td>
</tr>
</tbody>
</table>

**Figure 53.1** Breakdown of ABIM skills required for examination in interventional cardiology. Source: From Ref. 13. Abbreviation: ABIM, American Board of Internal Medicine.
Table 53.5  American Board of Internal Medicine Technical and Cognitive Skill Set Required for Examination in Interventional Cardiology

<table>
<thead>
<tr>
<th>Case selection and management (25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Angioplasty, stent placement, and related catheter-based interventions in management of chronic ischemic heart disease, including case selection</td>
</tr>
<tr>
<td>2. Urgent catheterization in management of acute coronary syndromes and acute myocardial infarction, including case selection</td>
</tr>
<tr>
<td>3. Interventional approaches to management of hemodynamic compromise, including pharmacologic agents, balloon counterpulsation, emergency pacing, pericardiocentesis, and stent placement</td>
</tr>
<tr>
<td>4. Catheter-based management in valvular disorders (mitral, aortic, and pulmonary) and in hypertrophic cardiomyopathy, including clinical, invasive, and case selection</td>
</tr>
<tr>
<td>5. Catheter-based interventions in management of congenital heart disease in adults</td>
</tr>
<tr>
<td>6. Interventional approaches to peripheral vascular disease, focusing primarily on diagnosis and patient selection</td>
</tr>
</tbody>
</table>

Procedural techniques (25%)

| 1. Planning and execution of interventional procedures, including knowledge of options, limitations, outcomes, and complications as well as alternatives |
| 2. Selection and use of guiding catheters, guidewires, balloon catheters, and other FDA-approved interventional devices, including atherectomy, thrombectomy, brachytherapy, and embolic protection devices and coronary stents |
| 3. Use of antithrombotic agents in interventional procedures |
| 4. Management of complications in interventional procedures |

Basic science (15%)

| 1. Vascular biology, including the processes of plaque formation, vascular injury, vasoreactivity, vascular healing, restenosis, reperfusion injury, and effects of diabetes |
| 2. Hematology, including the clotting cascade, platelet function, thrombolysis, and methods of altering clot formation |
| 3. Coronary anatomy, including angiographic data such as distribution of vascular segments, lesion characteristics, and their importance in interventions |
| 4. Coronary physiology and myocardial function, including alterations in coronary flow due to obstructions in vessels; assessment and effect of flow dynamics on myocardial perfusion; function of collateral circulation; effect of arterial spasm or microembolization on coronary flow; and left ventricular function, including stunning and hibernation |

Pharmacology (15%)

| 1. Biologic effects and appropriate use of vasoactive drugs, antiplatelet agents, thrombolytics, anticoagulants, antiarrhythmics, lipid-lowering agents, sedating agents, and local anesthetic agents |
| 2. Biologic effects and appropriate use of angiographic contrast agents |

Imaging (15%)

| 1. Specific applications of imaging to interventional cardiology, including identification of anatomic features and visualization of lesion morphology by angiography and by intravascular and intracardiac ultrasonography. |
| 2. Radiation physics, radiation risks and injury, and radiation safety, including methods to control radiation exposure for patients, physicians, and technicians |

Miscellaneous (5%)

| 1. Ethical issues and risks associated with diagnostic and therapeutic techniques |
| 2. Statistics, epidemiologic data, and economic issues related to interventional procedures |

Source: From Ref. 13.
Abbreviation: FDA, food and drug administration.

Table 53.6  Summary of Training Requirements for Vascular Medicine and Peripheral Catheter-Based Interventions

<table>
<thead>
<tr>
<th>Level</th>
<th>Duration of training (months)</th>
<th>Components of training</th>
<th>Cumulative number of procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>• Evaluation and management of arterial, venous, and lymphatic disease, atherosclerotic risk factors, and hypercoagulable states</td>
<td>Noninvasive vascular laboratory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Noninvasive vascular laboratory and vascular imaging (i.e., ultrasound, MRA, and CTA)</td>
<td>100 Venous ultrasounds</td>
</tr>
<tr>
<td>2 Vascular medicine</td>
<td>12</td>
<td>• Outpatient vascular medicine clinic</td>
<td>100 Carotid artery ultrasounds</td>
</tr>
<tr>
<td>specialist</td>
<td></td>
<td>• Inpatient vascular medicine consultation service</td>
<td>100 Limb artery ultrasounds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Noninvasive vascular laboratory, examinations MRA/CTA</td>
<td>75 Renal/mesenteric vascular ultrasounds</td>
</tr>
<tr>
<td>3 Peripheral vascular</td>
<td>12</td>
<td>• Peripheral vascular catheterization and vascular surgery</td>
<td>100 Physiologic arterial examinations</td>
</tr>
<tr>
<td>intervention</td>
<td></td>
<td>• Outpatient vascular medicine clinic</td>
<td>Peripheral vascular interventions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Inpatient medical consultation service</td>
<td>100 Diagnostic peripheral angiograms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vascular imaging, including ultrasound, MRA, CTA (1–2 mo)</td>
<td>50 Peripheral angioplasties/lentors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Peripheral vascular catheterization and intervention</td>
<td>10 Peripheral thrombolytic infusions/thrombectomy</td>
</tr>
</tbody>
</table>

Source: From Ref. 14.
Abbreviations: CTA, computed tomography angiography; MRA, magnetic resonance angiography.
disciplines as well. As physicians with specialized skills in the recognition and treatment of vascular disease, interventional cardiologists are ideally suited for gaining expertise in the practice of interventional vascular disease management. Indeed, while current interventional cardiologist fellows often achieve exposure to peripheral vascular intervention, imaging, and complex structural heart interventional procedures during interventional cardiology training, this is usually without the benefit of a fixed and organized schedule or program. This exposure also often occurs within the single year of dedicated coronary training, although it is not the focus of this dedicated year. This decentralization limits the institutional awareness of current potential offerings and expertise, reducing access, demand, and limiting training opportunities for fellows. Moreover, there is potential for distraction and dilution of the core coronary interventional training experience.

It bears emphasis that dedicated training in interventional coronary procedures over a continuous 12-month period is not only desirable but critical in the development of sufficient skills, knowledge base, and procedural awareness to become proficient in this area alone. Current training guidelines, however, do not require exposure or any measure of competence in peripheral vascular, structural, or invasive imaging techniques during the one-year fellowship. This is based on the principle that adequate skills in coronary intervention, the primary goal of training, require a full year of fellowship training with adequate case volume and training in coronary interventions.

The current training program structure mandated by ACGME guidelines, while providing adequate exposure to coronary interventions, is generally inadequate to provide sufficient exposure to skills and techniques demanded in today’s marketplace and, indeed, by patients presenting for care to an interventional cardiologist. Indeed, where a second year of training is not provided by an interventional program, fellows often elect to pursue additional training elsewhere after formal training in interventional cardiology in order to develop skills in peripheral and structural heart intervention.

In recognition of this deficit in current training standards and regulations, a second year of interventional cardiology training is proposed during which time fellows may achieve exposure and competence in a variety of areas including peripheral intervention within the carotid, renal, subclavian, and lower extremity territories as well as structural heart disease interventions including valvular intervention, and advanced hemodynamic training. Training in vascular medicine should be a central component of this experience, with a growing national emphasis marking for establishment of clinical performance measures to include parameters of appropriate diagnosis and established care patterns for those physicians involved in the treatment of patients with peripheral vascular disease. This training would be delivered within the prescribed recommendations of the ACC Task Force 11 documentation (14), which advocates training of vascular medicine specialists with the requisite skills in recognition and treatment of vascular disease. We propose that this year be divided into four quarters with the trainee rotating through vascular medicine (where it exists), vascular surgery, vascular radiology, and interventional cardiology services in order to gain a broad base of knowledge, experience, and competence. Obviously only trainees dedicated to achieving excellence in the endovascular management of vascular diseases would be interested in such a program. We strongly feel that practitioners interested in performing vascular procedures must have an interest and expertise in the care and management of vascular patients.

Trainees in a comprehensive interventional cardiology training program are ideally suited to gain the additional expertise in the practice of vascular medicine and endovascular care. Key to the successful integration of these new disciplines, however, will be maintenance of a balance between appropriate duration and scope of training to avoid limiting the breadth or quality of the overall cardiovascular training experience.

**Structural Heart Disease Training**

Alongside endovascular interventions, the development of percutaneous and minimally invasive approaches to the treatment of structural cardiac pathology is being rapidly developed. For years, structural heart disease has been treated in catheterization laboratories by congenital interventionalists, the vast majority of whom come from a pediatric training background. In adult catheterization laboratories, structural heart disease has been generally limited to percutaneous balloon valvuloplasties of the mitral and, less commonly, the aortic valve. These are well-established procedures, but given case volumes only a small minority of practitioners develop expertise in performance. More recently, the realization that patent foramen ovale (PFO) may be causally linked to neurologic events has lead to a surge in percutaneous PFO closure. Although not approved by the FDA, this has been largely accomplished through the use of off-label devices approved for other indications such as atrial septal defect. Although controversy continues about the indications and contraindications for this procedure, a large number of interventional cardiologists are now offering it.

Perhaps what has spurred the development of structural heart disease interventions as an important area of future growth has been the development of percutaneous techniques to treat aortic and mitral valve disease. Percutaneously implantable aortic valves are now approved in Europe, and undergoing clinical trials in the United States. Similarly, approaches for direct clipping of the mitral valve as well as percutaneous mitral annuloplasty for mitral regurgitation are undergoing rapid development. It is likely that the pace of innovation and development will continue to accelerate, and that the demand for lesser invasive procedures will accelerate from patients, and from interventional colleagues and cardiovascular surgeons who wish to learn these procedures.

Central to the training of structural specialists, we believe a defined body of knowledge, procedural building blocks, and specific skill sets should be defined that would allow the safe and effective application of structural heart disease techniques. These would include, but not be limited to, training in normal and abnormal cardiac anatomy as well as cardiac imaging, including planar, tomographic three-dimensional (3D), and real-time techniques. Echocardiography for procedural guidance can include transesophageal, transthoracic (including 3D), intervascular, or intracardiac approaches, all of which must be mastered by the structural interventionalist. Familiarity with unusual and complex invasive procedures such as percutaneous femoral artery suturing, transseptal puncture, direct left or right ventricular puncture, endovascular snaring, and various embolization techniques are all essential to the structural interventionalist. It is our contention that formal training programs in structural heart disease, therapeutics should be developed and consist both of cognitive and procedural aspects. Training ideally will be adapted to the background of the individual trainee, be it interventional cardiology or cardiovascular surgery (as training
needs will be different). We believe a dedicated year of structural interventional training, typically after a first year of interventional training, or as part of a comprehensive cardiovascular surgical program, is needed. Specialty societies should define the cognitive and procedural base, and then develop evaluative measures for these requirements.

Learning in Practice
Even if all of the above are done, novel procedures will continue to be developed. Thus, a broader question is how does an experienced practicing interventionalist continue to acquire new skills, techniques, and knowledge? In many ways, we are back to the days of Andreas Gruentzig—observation and proctorship. Supplementing this, medical simulation is poised to play an important role in all aspects of the training process and may be particularly important in acquiring new skills. As yet, medical simulation is not a required component of interventional cardiology training programs, but prospective studies have been conducted by the ABIM and others to assess the impact of simulation on procedural training. The Centers for Medicare and Medicaid Services (CMS) have taken the lead in requiring simulation training for carotid stenting as evidence of competency prior to reimbursement. Continued evolution of simulation devices and incorporation into expanded training experiences will provide a strong foundation for continued enhancement of the lifelong learning process and, ultimately, improve patient care and outcomes.

REFERENCES
INTRODUCTION
Percutaneous coronary intervention (PCI) is the preferred method of reperfusion for patients with ST-elevation myocardial infarction (STEMI), when it can be performed in a timely manner at an experienced center (1–4). Transfer from non-PCI hospitals to PCI-capable facilities has also been shown to be superior to fibrinolysis (5,6). The American Heart Association/ American College of Cardiology (AHA/ACC) guidelines currently recommend a door-to-balloon time of ≤90 minutes for primary PCI (1). Though the evidence supporting rapid reperfusion of STEMI patients using PCI is ample, consistently achieving rapid treatment of patients with STEMI on a national scale is a challenging problem (7–9).

Treating STEMI patients in a timely manner requires the cooperation of multiple disciplines, including emergency medical services (EMS), emergency department physicians, and cardiologists, often at multiple locations including community hospitals and tertiary care centers. The significant collaboration required to treat a STEMI patient has led to the development of regional STEMI systems.

This chapter focuses on data supporting the formation of STEMI systems of care, the measures used to assess the quality of a STEMI system, the essential components of STEMI systems of care, evidence-based strategies to optimize treatment times, and real-world models demonstrating improved outcomes in STEMI patients.

THE IMPORTANCE OF TIME TO TREATMENT
“Time is muscle” has served as the mantra for programs focused on the rapid treatment of STEMI patients. This was initially supported in animal models in the late 1970s (10) and was later confirmed in clinical trials of fibrinolytic therapy and primary PCI, demonstrating that a delay in time to treatment led to increased mortality (11,12). The degree of reperfusion also plays a role in outcome, with the establishment of normal TIMI 3 coronary flow improving outcomes compared to those achieving suboptimal (TIMI 2) flow and minimal (TIMI 1) flow (13).

While time to treatment is an essential component of STEMI care, it may be less critical for PCI compared with fibrinolytic therapy. Results from a Swedish registry have shown that the benefit of fibrinolytic therapy declines after a two-hour time delay, a limitation not seen when evaluating PCI. At every time point, PCI was better than fibrinolysis, and PCI mortality did not reach the lowest fibrinolytic mortality (door-to-needle 0–60 minutes) until time to reperfusion exceeded five hours (Fig. 54.1) (14). In high-risk patients (Killip class 3 or 4, age >70 or anterior myocardial infarction) treated with primary PCI, Brodie et al. demonstrated that a door-to-balloon time >2 hours was associated with higher mortality rates [32.5% for >2 hours vs. 21.5% for <2 hours; HR 1.53 (1.22–1.9); p = 0.0002; median 83-month follow-up]. In contrast, time to treatment with PCI was less critical in low-risk (all other) patients [10.8% for >2 hours vs. 9.2% for <2 hours; HR 1.13 (0.78–1.64); p = 0.53] (15). Patients presenting within 3 hours of symptom onset with door-to-balloon times >2 hours also had higher mortality, but door-to-balloon was less critical in patients presenting after 3 hours of symptom onset (15).

Although time to treatment may be less critical in primary PCI than fibrinolytic therapy, delays in door-to-balloon times have consistently correlated with increased mortality (16–18). Cannon et al. demonstrated a linear association between mortality and door-to-balloon times, with a relative risk of mortality increasing from 1 (door-to-balloon time <60 minutes) to 1.15 (door-to-balloon time 60–120 minutes) to 1.41 (door-to-balloon time 120–150 minutes) to >1.6 for patients with a door-to-balloon time >150 minutes (Fig. 54.2) (16). De Luca et al. demonstrated similar results, showing a 7.5% increase per 30 minutes delay in time to treatment (Fig. 54.3) (17).

Given the vital nature of time to reperfusion, it is of utmost importance to develop strategies that increase both access to primary PCI and improve door-to-balloon times in STEMI patients (19–22). To highlight the importance of improving treatment times in STEMI patients, the Joint Commission (JC) includes door-to-balloon time as a core quality assurance measure. The ACC “D2B Alliance” (23) was designed to improve time to treatment in PCI hospitals and the AHA has established “Mission: Lifeline” (22,24) to develop STEMI systems of care that will improve timely access to PCI.

DOOR-TO-BALLOON TIME: THE IDEAL MEASURE OF A STEMI SYSTEM?
The total ischemic time (symptom onset to reperfusion) is the most critical factor in the treatment of STEMI, but symptom-to-door times are patient dependent and difficult to objectively measure on a consistent basis. The door-to-needle and door-to-balloon times have been the most measurable treatment times and therefore the focus of quality performance measures. However, there are limitations to focusing on only the door-to-balloon time to measure the quality of a STEMI system.

The ideal performance measure for STEMI patients continues to be the focus of discussion (25,26). Door-to-first angiogram, door-to-wire, and door-to-first device have all been raised as alternatives to door to balloon. A strong argument can be made for door to reperfusion being the most appropriate
definition to gauge the quality and rapidity of STEMI treatment. For example, if a patient has TIMI 3 flow on the first angiogram, it may not only be reasonable but better patient care to provide more complete assessment or stabilization in the cardiac catheterization laboratory rather than a rush to inflate the balloon. On the other hand, TIMI 0 or 1 flow following balloon inflation should not really be considered successful. Recently published guidelines acknowledge the complexity of performance measures in the treatment in STEMI patients. With the increasing use of stents and thrombectomy devices, “balloon” time is frequently a misnomer. Therefore, the work group developing the recommendations for these performance measures advocates the use of time-to-first device as the end point for assessing treatment time (25,26). A major limitation of door to balloon as the primary performance measure is that it excludes patients who do not receive PCI. A more comprehensive look at the care of patients in a STEMI system should involve all STEMI patients including those who are “eligible but untreated,” treated with fibrinolysis or a pharmacoinvasive approach, and patients not receiving PCI (patients receiving CABG, medical therapy, or those with no clear culprit artery).

The door-to-balloon quality improvement initiatives and reporting requirements have primarily focused on PCI centers. Patients who require transfer for primary PCI are currently not included in JC’s core measure of a door-to-balloon time of 90 minutes. These patients represent a substantial portion of the STEMI population (7,9). The new quality improvement strategies include transferred patients and focus on measures beyond door-to-balloon time (25,26). Another example of a system measure is false-positive catheterization laboratory activation. Larson et al. reported a false-positive catheterization laboratory activation rate of 9.5% to 14% (depending on the definition) in a regional STEMI care system (27). Clearly a false-positive catheterization laboratory activation rate of 25% would introduce a significant resource and economic stress on the STEMI system. Finally, at the present time, there is considerable variability in the patients included in quality improvement programs. In a series of 501 consecutive STEMI patients treated in the Minneapolis Heart Institute Level 1 MI program, only 282 (56%) met criteria for the ACC-National Cardiovascular Data Registry (NCDR) and only 66 (63%) for JC reporting (28). These are important factors to consider as we enter the pay-for-performance era.

**KEY COMPONENTS OF A STEMI SYSTEM**

Every STEMI system needs to include three key components: (i) prehospital identification and cardiac catheterization laboratory activation, (ii) triage to PCI-capable hospitals (STEMI-receiving centers), and (iii) interhospital transfer of STEMI patients.
Prehospital Identification
Utilization of prehospital EKGs for early diagnosis of STEMI patients is essential but will only be effective if it includes prehospital notification and cardiac catheterization laboratory activation. In a recent pooled analysis of 10 separate STEMI systems, the use of prehospital EKGs in 2712 consecutive patient resulted in 86% of patients being treated with a door-to-balloon time <90 minutes, a substantial improvement over the reported national average of 42% (29).

Data supporting the use of prehospital EKGs has led to a consensus statement from the AHA supporting the integration of prehospital EKGs into STEMI systems of care (30). Despite these recommendations, only roughly 25% of STEMI patients who utilize EMS received a prehospital EKG (31).

Triage
Prehospital EKGs would be of limited benefit if the information they provide are not utilized. This includes early activation of the cardiac catheterization laboratory as well as triage of patients directly to PCI centers. Le May et al. implemented a citywide protocol for STEMI patients, which included (i) prehospital EKG, (ii) activation of the catheterization laboratory directly from the field, and (iii) direct triage to the PCI center. With this combination, they reported achieving a door-to-balloon time of <90 minutes in 80% of patients. In comparison, only 12% of patients achieved a door-to-balloon time of <90 minutes when they were taken to the nearest emergency department for evaluation prior to activation of the catheterization laboratory and transfer to the PCI center (32). Nallamothu et al. reported data from a cross-sectional study examining the feasibility of prehospital triage from the standpoint of driving times and distances to PCI-capable hospitals (33). The results indicate 79% of the adult population in the United States in the year 2000 lived within 60 miles of a PCI-capable hospital. For adults whose closest hospital was not PCI capable, 74% would require additional transport times of <30 minutes to reach a PCI-capable hospital. This provides strong evidence for including prehospital triage directly to PCI centers as a key strategy to increase timely access to PCI.

Interhospital Transfer
A major limitation of both prehospital identification and triage to a PCI center is the underuse of EMS. Unfortunately, 50% to 75% of patients with chest pain either drive themselves or ride with family or friends to the emergency department (34,35). In addition, only 25% of United States hospitals are PCI capable, and an estimated two-thirds of patients with STEMI present to non-PCI-capable hospitals (36). Therefore, interhospital transfer of STEMI patients who present to non-PCI-capable centers is another critical factor to increase timely access to PCI.

Several randomized, controlled trials have demonstrated that transfer for primary PCI improves outcomes compared to fibrinolytic therapy. The DANAMI-2 study randomized 1527 Danish patients to primary PCI versus fibrinolytic therapy, including 1129 patients who were transferred from community hospitals to PCI centers (37). The primary end point (death, reinfarction, or disabling stroke at 30 days) occurred in 8.5% of the transfer groups compared to 14.2% in the fibrinolytic group. The majority of this benefit was from a reduction in the rate of reinfarction (1.6% vs. 6.3%, p < 0.001), with nonsignificant reductions in mortality (6.6% vs. 7.8%, p = 0.35) and stroke (1.1% vs. 2.0%, p = 0.15) (37). Dalby et al. subsequently performed a meta-analysis of six trials involving 3750 patients comparing transfer for PCI versus fibrinolytic therapy in patients with STEMI. A 42% reduction (95% CI, 29–53%; p < 0.001) was seen in the end point of death/reinfarction/stroke in favor of transfer for primary PCI, with a trend toward improvement in all-cause mortality by a reduction of 19% (95% CI, -3% to 36%; p = 0.08) (5). A more recent meta-analysis involving 11 randomized trials comparing transfer for primary angioplasty to fibrinolyis showed a significant reduction in 30-day mortality in addition to reduced reinfarction and stroke for patients transferred for PCI (6).

In general, the data supporting transfer for primary PCI has come from trials in Europe, in which countries are small and organized transfer systems are already in place. The only randomized trial in the United States to date (Air PAMI) had a mean total door-to-balloon time of 155 minutes and was stopped prematurely due to poor enrollment (38). The significant challenge of transferring patients for primary PCI in the United States was verified by Nallamothu et al., who reported national averages from the National Registry of Myocardial Infarction (NRMI) database of patients transferred for primary PCI. They found that only 4% of patients were treated with a door-to-balloon time of <90 minutes and only 15% were treated within 120 minutes. The average door-to-balloon time was 180 minutes with over one-quarter of patients treated in >240 minutes (9). The most recent data from the ACC NCDR in 2006 reported only 36% of transferred STEMI patients were treated with door-to-balloon times of <120 minutes (7).

Based on these data, many have questioned the feasibility of transporting STEMI patients for primary PCI in the United States. The development of successful regional STEMI systems that have substantially improved treatment times as well as clinical outcomes has clearly established the transfer of STEMI patients to PCI centers as a key strategy to increase timely access to PCI (34-44). Largely based on these models, the AHA has developed recommendations for “STEMI-receiving” hospitals to help facilitate transfer in future STEMI systems (45). Examples of regional STEMI systems are discussed in more detail later in this chapter. As noted, patients transferred for primary PCI are currently not included in JC’s quality performance measure but the recent ACC/AHA Task Force on Performance Measures recommend they be included (25,26).

The 2007 Focused Update of the ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (46) state that if the patient presents to a non-PCI-capable hospital, it is appropriate to consider emergency inter-hospital transfer of the patient to a PCI-capable hospital if:

- Fibrinolysis is contraindicated.
- PCI can be initiated within 90 minutes of patient presentation to the initial receiving hospital or within 60 minutes of when fibrinolysis with a fibrin-specific agent could be initiated at the initial receiving hospital.
- Fibrinolysis is administered and is unsuccessful (i.e., “rescue PCI”).

In addition to the above criteria for transferring patients for primary PCI, the 2009 Focused Update of the ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (47) states that all high-risk patients with STEMI receiving fibrinolytic therapy should be considered for immediate transfer to a PCI-capable facility (Class 2a recommendation). This recommendation is largely based on results from the CARESS-in-AMI and TRANSFER-AMI (48,49) trials.
that showed improved outcomes in STEMI patients immediately transferred for angiography after receiving fibrinolytic therapy compared to those transferred only if fibrinolysis was unsuccessful (Rescue PCI). The 2009 update also includes the class 1 recommendation that every community establishes a STEMI system of care.

EVIDENCE-BASED STRATEGIES TO REDUCE DOOR-TO-BALLOON TIMES

Recently, with a collaborative endorsement from multiple associations, including EMS, nursing, emergency physicians, and cardiologists, a multidisciplinary advisory working group was formed to develop recommendations for strategies to increase the number of STEMI patients with timely access to PCI (42). For the purposes of STEMI care, a system is “an integrated group of separate entities within a region providing specific services for the system that could include EMS providers, a community hospital(s), a tertiary center(s), and others.” A center is defined as “an entity such as a community or tertiary hospital that provides patient care services for a specific specialty or service (24,42).” The AHA has established the Mission: Lifeline Program to facilitate the development of STEMI systems (24). Ideally every hospital in the United States should be part of a STEMI system with an established reperfusion strategy for STEMI patients including standardized protocols and standing orders.

Despite the recent initiatives and published data showing the benefit of regional STEMI systems, disparities between guidelines and clinical performance still exist as national treatment times are improving, but still less than one-half of STEMI patients achieve a door-to-balloon time of 90 minutes or less (8). The ACC’s D2B alliance has encouraged the implementation of evidenced-based strategies to improve nationwide treatment times in PCI centers (23). The majority of these recommendations come from a cross-sectional survey of 362 hospitals in the United States that provide primary PCI for STEMI (19). After multivariate analysis, the following six strategies were identified as being independently associated with producing significantly faster treatment for STEMI patients:

- An attending cardiologist always on site
- The emergency department and catheterization laboratory staff giving real-time feedback
- An attending cardiologist always on site
- The emergency department and catheterization laboratory staff giving real-time feedback
- Real-world models

Several regional transfer programs have published data demonstrating the real-world viability of implementing the aforementioned strategies. Their success serves as a model for the initiation of regional STEMI programs across the country.

The Minneapolis Heart Institute at Abbott Northwestern Hospital initiated a regional STEMI system utilizing a standardized protocol and integrated transfer system in 2003 (40,41). Currently, 36 hospitals without PCI capability are participating with Abbott Northwestern Hospital serving as the PCI center. Implementing all six of the key guidelines later determined by Bradley et al., the Level 1 program has demonstrated excellent treatment times, even for patients transferred from as far as 210 miles to the PCI center (Fig. 54.4). For patients presenting directly to the PCI center, door-to-balloon times were well within guidelines, with a median of 65 minutes (n = 297; interquartile range (IQR) 47–84). For patients transferred ≤60 miles (zone 1 on Fig. 54.4), median door-to-balloon times were 95 minutes (n = 620; IQR 82–116), and for patients transferred 60 to 120 miles (zone 2 on Fig. 54.4), the median door-to-balloon time was 120 minutes (n = 396; IQR 100–145) (44). Despite up to 55 minutes longer total door-to-balloon time in zone 2, no significant differences in mortality were seen.
between the PCI center and patients transferred from zones 1 and 2. These results demonstrate that the benefits of primary PCI can be provided to patients up to 210 miles from a PCI center.

The Reperfusion of Acute Myocardial Infarction in North Carolina Emergency (RACE) investigators implemented a statewide system to improve the quality of care and increased access to timely reperfusion for STEMI patients (43). Compared with treatment times prior to implementation of the STEMI system, treatment times improved for patients presenting directly to the PCI center (median 85–74 minutes, \( p < 0.001 \)) as well as for those transferred from non-PCI hospitals (median 165–128 minutes). Other programs have reported similar success initiating STEMI systems, including interhospital transfer as well (39,44). The design of the STEMI system should incorporate all three key components (prehospital identification and activation, triage, and transfer for PCI centers), but the details will depend on local needs and resources.

CONCLUSION

As data demonstrating the importance of timely access to PCI for STEMI patients has grown, the importance of optimizing STEMI systems of care has been magnified. In recent years, we have witnessed modest improvements in time to reperfusion due to the efforts of several regional STEMI systems and national quality improvement initiatives. Yet gaps and barriers remain to implementation of regionalized systems for STEMI care on a national level in the United States (8,21,22,50). We remain to implementation of regionalized systems for STEMI care on a national level in the United States (8,21,22,50). We need to focus our continuing efforts in several key areas:

- Increasing utilization of EMS by STEMI patients through public education
- Increasing utilization of prehospital EKGs through funding and education for EMS systems
- Continuing to recruit and provide incentives for all hospitals to participate in voluntary quality improvement initiatives such as the ACC’s D2B alliance and the AHA’s Mission: Lifeline programs.

Organizing regional systems of STEMI care along with continuing improvement efforts will result in timely access to reperfusion for more STEMI patients thus leading to improved clinical outcomes.

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Figure 8.4  Computed tomographic angiogram showing relationship of the iliac and common femoral arteries to the bony structures of the pelvis and the femoral head. Note that the distance from the artery to a bony support structure (that can serve as an anvil against which compression forces can be applied) is shortest (green arrow) over the common femoral artery. The lower red arrow shows the increased distance between the shaft of the femur and the distal common femoral artery if punctures are below the femoral head; this requires compression through additional soft tissue including muscle, fat and cartilage with associated increased risk of pseudoaneurysm. Puncture into the superficial femoral artery is associated with increased risk of arteriovenous fistulae. The upper red arrow shows the extensive distance between the external iliac artery, which descends toward the retroperitoneum, and the deep pelvis; high puncture has odds ratios up to 18 to 1 for RPH in fully anticoagulated patients. 

Abbreviation: RPH, retroperitoneal hemorrhage. 
Source: From Ref. 17 (see page 70).

Figure 18.10  Three-dimensional representation of a “modeled” coronary tree with the subsequent optimal view map generation of the proximal left anterior descending artery. Please note the potential angiographic views on the map with the respective color representing foreshortening. White represents least amount of foreshortening, whereas red represent the most amount of foreshortening. The current LAO 1 CAUD 1 view angiographically has a 47% degree of foreshortening visually and on the optimal view map. 

Abbreviations: LAO, left anterior oblique; RAO, right anterior oblique; CRAN, cranial; CAUD, caudal; Fore., foreshortening; MAGN, magnification; Min, minimum; Max, maximum (see page 221).

Figure 18.11  Computed tomography angiography rendering with subsequent image reconstruction (see page 221).

Figure 18.12  Computed tomography angiography of the LAD (A, B, C, D) and the RCA (E, F, G, H). The initial image on the left (A) shows a MIP image of the LAD followed by a volume rendering (B) contiguous to it. The same applies for the RCA on the right panel that has a MIP image of the RCA (E) followed by its respective volume rendering (F). The lower panel shows for each vessel a stretched MIP image displaying each vessel lumen (D, H) in a longitudinal fashion with its respective “intravascular ultrasound” like cut of the lumen (C, G). The LAD shows moderate calcification in the proximal segment (A, D) with a moderate to severe obstruction that was also seen on standard angiography. The RCA has very mild proximal calcification (E, H) followed by a widely patent lumen with no significant disease on the regular MIP (E) image or the stretched MIP (H). 

Abbreviations: MIP, maximum intensity projection; LAD, left anterior descending artery; RCA, right coronary artery (see page 223).
Figure 23.9  (A) Three-dimensional echocardiography to demonstrate apposition of the transseptal apparatus with tenting of the septum and (B) the appearance after needle and sheath entry into the LA. Intracardiac or transesophageal echo is used for echo guidance by most operators. **Abbreviations**: CS, coronary sinus; FO, foramen ovale; LA, left atrium; RA, right atrium. **Source**: From Ref. 55 by permission of the Oxford University Press and the European Heart Rhythm Association (see page 283).

Figure 27.5  Typical example of simultaneous aortic pressure ($P_a$) and distal coronary pressure ($P_d$) recordings at rest and during maximal steady-state hyperemia as induced by an intravenous infusion of adenosine. Soon after starting the infusion, the decrease in distal pressure is preceded by a transient increase in aortic pressure. **Abbreviation**: FFR, fractional flow reserve (see page 345).
Figure 27.6  Example of the influence of collaterals on FFR measurements in a 76-year-old man with a critical stenosis in the proximal RCA (A) and collaterals supplied by the left coronary artery (B). The FFR in the distal LAD was measured first (A and D) before recanalization of the RCA and (C and E) after recanalization of the RCA. When antegrade flow was restored in the RCA, the LAD had no longer to supply blood to the territory of the RCA. Therefore, hyperemic flow in the LAD was lower than before and the FFR increased from 0.76 to 0.82. This example also illustrates the relationship between FFR and the myocardial mass supplied by the artery: the larger the myocardial mass, the greater the hyperemic flow, and the lower the FFR for a given stenosis. 

Abbreviations: FFR, fractional flow reserve; RCA, right coronary artery; LAD, left anterior descending artery (see page 347).
Figure 27.9 Example of two patients in whom FFR measurements in an “intermediate” ostial left main stenosis changed the therapeutic strategy. The first (upper panel) represents a 67-year-old man with massive mitral regurgitation who was scheduled for minimally invasive (port access) mitral valvuloplasty. The coronary angiogram showed an intermediate ostial left main stenosis. The FFR of the left main stenosis was 0.69. Accordingly, this patient underwent conventional bypass surgery and mitral valvuloplasty via a median sternotomy. The second (lower panel) represents an 89-year-old man with critical aortic stenosis, referred for aortic valve replacement and bypass surgery because of the presence of an ostial left main stenosis. FFR of the left main stem was 0.83. Accordingly, only a percutaneous aortic valve implantation was performed and the left main stenosis was left alone. Abbreviation: FFR, fractional flow reserve (see page 349).
Figure 27.11  Example of two patients with multivessel disease. (A) A 46-year-old man with stable angina and angiographic three-vessel disease but functional two-vessel disease (LAD, RCA). (B) A 69-year-old man with severe angina. MPI showed a reversible defect in the inferolateral segments. From the angiogram it is obvious that the RCA and the LCx are significantly narrowed (no pressure measurements are needed). However, the mid-LAD stenosis, considered “nonsignificant” on the angiogram, appears to be hemodynamically significant. This LAD stenosis was undetected by MPI because the uptake of tracer is notably worse in the LCx territory than in the LAD territory.

Abbreviations: LAD, left anterior descending artery; RCA, right coronary artery; MPI, myocardial perfusion imaging; LCx, left circumflex artery; FFR, fractional flow reserve (see page 350).
Figure 27.13 A 73-year-old man with angina related to a tight stenosis in the proximal right coronary artery. The distal $P_d/P_a$ ratio in the LAD artery is 0.74. The pressure pullback tracing under steady-state maximal hyperemia shows that the distal pressure increases progressively in three or four “steps.” This indicates that the abnormal FFR value is due to diffuse disease, rather than to one focal stenosis that was the intended target of percutaneous coronary intervention. Abbreviations: LAD, left anterior descending artery; FFR, fractional flow reserve (see page 352).

Figure 28.14 Plaque composition and atherosclerotic plaque classification by VH-IVUS. (A) fibrotic, (B) fibrocalcific, (C) pathological intimal thickening (D) thick cap fibroatheromas, and (E) thin cap fibroatheromas (see page 365).
Figure 28.15  Examples of conventional IVUS image and VH-IVUS side by side. (Left) Lesion with acute coronary syndrome with positive remodeling. In this segment, notice the presence of thin cap fibroatheromas (i.e., necrotic core representing >10% of the plaque burden without overlying fibrous tissue). (Right) Lesion with stable angina with negative remodeling. In this segment the plaque is predominantly fibrotic. Abbreviations: IVUS, intravascular ultrasound; VH-IVUS, virtual histology IVUS (see page 366).

Figure 35.1  (A) CTO, soft plaque (hematoxylin-eosin stain; magnification 1×). (B) Magnified view of A, showing cholesterol clefts and loose fibrous tissue (hematoxylin-eosin stain; magnification 10×). (C) CTO, hard plaque, dense fibrous tissue, and calcium (elastic van Gieson stain; magnification 1×). Abbreviation: CTO, chronic total occlusion. Source: From Ref. 8 (see page 454).
Figure 35.2  (A) A single large channel is seen in this CTO (elastic van Gieson stain; magnification 1×). (B) Traversing capillaries connect with the small recanalization channels in the center of this CTO (elastic van Gieson stain; magnification 1×). (C) Small recanalization vascular channels are seen in the center of this CTO (elastic van Gieson stain; magnification 1×). (D) Inflammation is found adjacent to vascular channels of the adventitia in this vessel (hematoxylin-eosin stain; magnification 25×). (E) Adventitial capillaries have grown to large size in this CTO (hematoxylin-eosin stain; magnification 40×). **Abbreviation:** CTO, chronic total occlusion. **Source:** From Ref. 8 (see page 454).

Figure 37.3  Different views of particulates obtained from filters and panoramic views of a recent thrombus. An extensive thrombus (A) is compared with very small particles (D). Some areas stained light pink (B, C) are suspicious of being plaque remnants. Hematoxylin and eosin stain, 40×. **Source:** Courtesy of Dr Jose Milei and From Ref. 41 (see page 485).
Figure 37.14  Amount of clot mass removal with mechanical versus manual thrombectomy devices (see page 489).

Figure 40.4  (D) Doppler flow delineates the flow across PFO during a Valsalva maneuver. Abbreviations: IAS, interatrial septum; LA, left atrium; RA, right atrium; PFO, patent foramen ovale (see page 519).
Figure 40.8  (A) After acquisition of an ECG-gated ultrasound image, the endocardial contours (green) of the LA and pulmonary veins are manually traced and are thereafter assigned to a corresponding map. (B) By systematically collecting images of the whole LA and marking the endocardial borders, a registered 3-D reconstruction of the LA anatomy is created. (C) The acquired 3-D geometry can be used to guide radiofrequency catheter ablation for atrial fibrillation. Abbreviation: LA, left atrium (see page 521).

Figure 41.1  Reconstruction of the “true” size and geometry of a secundum atrial septal defect derived from postprocessing of a 3D transesophageal echocardiography acquisition (bottom right). Abbreviations: LA, left atrium; RA, right atrium (see page 528).
Figure 41.2 A 61-year-old patient with a large superior sinus venosus defect. Panel A: Mid-esophageal four-chamber view, showing enlarged right-sided heart chambers. Panel B: Standard bicaval view of interatrial septum does not demonstrate superior sinus venosus defect. Panel C: Only further withdrawing and slight clockwise rotation of the echo probe shows the large superior sinus venosus defect (white arrow). Panel D: After injection of agitated saline into left antecubital vein immediate opacification of both atrial chambers from the SVC (arrowheads). Abbreviations: RV, right ventricle; LV, left ventricle; LA, left atrium; RA, right atrium; SVC, superior vena cava (see page 529).
Figure 41.4  Large atrial septal defect II (secundum) with small posterior tissue rim (arrowhead) and good rim toward the AV valve level (arrow) (see page 530).

Figure 41.5  Panels A to C depict transesophageal echocardiography images of a large secundum-type atrial septal defect at an angle of 0°, 109°, and 29°. From 2D images the impression arises that there are two defects, but only the 3D reconstruction (view from left atrium shows the true extent of the defect, being a common atrium with a narrow tissue bridge (arrow in panel D) across the atrium, rather than two separate defects (arrowheads). Abbreviations: RA, right atrium; LA, left atrium (see page 532).
Figure 41.6 An 84-year-old patient in cardiogenic shock due to subacute postmyocardial infarction ventricular septal defect. The arrow points to the left ventricular disc of an Amplatzer® ventricular septal defect occluder (white arrow), entangling the subvalvular mitral valve apparatus, leading to severe mitral regurgitation (arrowhead). Abbreviations: LA, left atrium; LV, left ventricle (see page 534).

Figure 41.7 Catheter-based aortic valve implantation. Panels A to D depict long-axis views of the aortic root. Panel A: Placement of the valved stent (arrowheads mark edges of stent balloon; double-headed arrows mark the actual length of the valved stent). Panel B: Valve implantation, balloon inflated. Panel C: Immediate post-valve deployment with thin prosthetic valve cusps visible. Panel D: Short-axis view through base of the heart, depicting mild valvular and three small paravalvular jets (white stars) of aortic regurgitation. Abbreviations: LA, left atrium; LVOT, left ventricular outflow tract; AO, aorta. (see page 535).
Figure 41.8  Device closure of fistula from aorta to left atrium after bioprosthetic aortic valve replacement. Panel A: Mid-esophageal short-axis view through aortic root. The arrowhead points to the aortic valve prosthesis, the large arrow to the shunt. Panel B: Angiographic view of sizing balloon (white star) measuring defect size. Panel C: Small residual left shunt after deployment of an Amplatzer duct occluder (arrow).

Abbreviations: LA, left atrium; RA, right atrium; RV, right ventricle (see page 536).
**Figure 41.9** Attempted device closure of ruptured sinus valsalva aneurysm. Panel A and B: Mid-esophageal short-axis view through aortic root without and with color Doppler. The arrow points to the perforation of the sinus valsalva aneurysm toward the right atrium. Panel C: Angiographic view of the sinus valsalva aneurysm. Panel D: Balloon sizing of the defect (white star). Panel E: Amplatzer duct occluder sealing the perforation of the sinus valsalva aneurysm (not released). The device seals only one of three communications between the aorta and the right ventricle, leaving a large residual shunt. The device was therefore retrieved and the patient was referred for surgical repair. *Abbreviations:* LA, left atrium; RA, right atrium; RV, right ventricle; AO, aorta *(see page 537).*
Figure 47.2  Transesophageal echocardiographic images during balloon aortic valvuloplasty in a teenage boy. (A) Longitudinal view demonstrating the domed stenotic aortic valve; (B) same view as A with color Doppler showing the stenotic mosaic color jet; (C) balloon inflation; (D) after the valvuloplasty showing complete opening of the valve; (E) with color during systole showing improved opening of valve; and (F) diastolic frame showing no aortic insufficiency. Abbreviations: LA, left atrium; LV, left ventricle; RV, right ventricle; AO, aorta (see page 596).

Figure 41.10  Device closure of paravalvular mitral leak (bioprosthesis). Panels A and B: 74° Mid-esophageal transesophageal echocardiography views demonstrating paravalvular mitral regurgitation (arrow). Panel C: Live 3D image of the mitral valve prosthesis, seen from the left atrium demonstrating a large inferomedial paravalvular leak (arrow). The arrowhead points to the delivery sheath crossing the leak. Panel D: Live 3D image after device closure of paravalvular leak with two Amplatzer duct occluder (white stars). Abbreviations: LA, left atrium; LVOT, left ventricular outflow tract; AO, aorta (see page 537).
About the book

The field of invasive and interventional cardiology is dynamic with frequent advances in both technique and technology. An internationally renowned team of editors and over 100 contributors have shaped this textbook to provide clinicians with a thorough guide that covers the procedural and peri-procedural aspects of coronary, peripheral, and structural heart disease diagnostics and interventions.

The comprehensive and highly illustrated textbook presents critical information for anyone active in the field of cardiovascular interventions, including:

- Practical suggestions on how to set up a cardiovascular catheterization laboratory, choose the right equipment and minimize radiation exposure.
- A careful analysis of the general principles of percutaneous coronary interventions, the specific knowledge needed in different clinical scenarios, as well as the patient selection criteria for each invasive procedure.
- In-depth coverage of non-coronary interventions, including 13 chapters on peripheral vascular interventions, including carotid artery stenting, as well as newer procedures for intracranial stenosis treatment, septal defect repair, and left atrial appendage closure.
- An incorporation of emerging procedures in structural heart disease, such as percutaneous aortic valve replacement and mitral valve repair – that although not presently mainstream, will likely become an important domain of interventional cardiologists.

Given the importance of appropriate training and credentialing for clinicians, the textbook also includes current national guidelines and policies on the performance of the various procedures.

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