

SECTION 2 DIAGNOSIS OF CARDIOVASCULAR DISORDERS

267 Physical Examination of the Cardiovascular System

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The approach to a patient with known or suspected cardiovascular disease begins with the time-honored traditions of a directed history and a targeted physical examination. The scope of these activities depends on the clinical context at the time of presentation, ranging from an elective ambulatory follow-up visit to a more focused emergency department encounter. There has been a gradual decline in physical examination skills over the last two decades at every level, from student to faculty specialist, a development of great concern to both clinicians and medical educators. Classic cardiac findings are recognized by only a minority of internal medicine and family practice residents. Despite popular perceptions, clinical performance does not improve predictably as a function of experience; instead, the acquisition of new examination skills may become more difficult for a busy individual practitioner. Less time is now devoted to mentored cardiovascular examinations during the training of students and residents. One widely recognized outcome of these trends is the progressive overutilization of noninvasive imaging studies to establish the presence and severity of cardiovascular disease even when the examination findings imply a low pretest probability of significant pathology. Educational techniques to improve bedside skills include repetition, patient-centered teaching conferences, and visual display feedback of auscultatory events with Doppler echocardiographic imaging.

The evidence base that links the findings from the history and physical examination to the presence, severity, and prognosis of cardiovascular disease has been established most rigorously for coronary artery disease, heart failure, and valvular heart disease. For example, observations regarding heart rate, blood pressure, signs of pulmonary congestion, and the presence of mitral regurgitation (MR) contribute importantly to bedside risk assessment in patients with acute coronary syndromes. Observations from the physical examination in this setting can inform clinical decision making before the results of cardiac biomarkers testing are known. The prognosis of patients with systolic heart failure can be predicted on the basis of the jugular venous pressure (JVP) and the presence or absence of a third heart sound (S_3). Accurate characterization of cardiac murmurs provides important insight into the natural history of many valvular and congenital heart lesions. Finally, the important role played by the physical examination in enhancing the clinician-patient relationship cannot be overestimated.

THE GENERAL PHYSICAL EXAMINATION

Any examination begins with an assessment of the general appearance of the patient, with notation of age, sex, height, weight, and

overall health status. Is the patient in pain or resting quietly, dyspneic or diaphoretic? Does the patient choose to avoid certain body positions to reduce or eliminate pain, as might be the case with suspected acute pericarditis? Are there clues indicating that dyspnea may have a pulmonary cause, such as a barrel chest deformity with an increased anterior-posterior diameter, tachypnea, and pursed-lip breathing? Skin pallor, cyanosis, and jaundice can be appreciated readily and provide additional clues. A chronically ill-appearing emaciated patient may suggest the presence of long-standing heart failure or another systemic disorder, such as a malignancy. Various genetic syndromes, often with cardiovascular involvement, can also be recognized easily, such as trisomy 21, Marfan's syndrome, and Holt-Oram syndrome. Height and weight should be measured routinely, and both body mass index and body surface area should be calculated. Knowledge of the waist circumference and the waist-to-hip ratio can be used to predict long-term cardiovascular risk. Mental status, level of alertness, and mood should be assessed continuously during the interview and examination.

Skin Central cyanosis occurs with significant right-to-left shunting at the level of the heart or lungs, allowing deoxygenated blood to reach the systemic circulation. Peripheral cyanosis or acrocyanosis, in contrast, is usually related to reduced extremity blood flow due to small vessel constriction, as seen in patients with severe heart failure, shock, or peripheral vascular disease; it can be aggravated by the use of β -adrenergic blockers with unopposed α -mediated constriction. Differential cyanosis refers to isolated cyanosis affecting the lower but not the upper extremities in a patient with a large patent ductus arteriosus (PDA) and secondary pulmonary hypertension with right-to-left shunting at the great vessel level. Hereditary telangiectasias on the lips, tongue, and mucous membranes, as part of the Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia), resemble spider nevi and can be a source of right-to-left shunting when also present in the lung. Malar telangiectasias also are seen in patients with advanced mitral stenosis and scleroderma. An unusually tan or bronze discoloration of the skin may suggest hemochromatosis as the cause of the associated systolic heart failure. Jaundice, which may be visible first in the sclerae, has a broad differential diagnosis but, in the appropriate setting, can be consistent with advanced right heart failure and congestive hepatomegaly or late-term "cardiac cirrhosis." Cutaneous ecchymoses are seen frequently among patients taking vitamin K antagonists or antiplatelet agents such as aspirin and thienopyridines. Various lipid disorders sometimes are associated with subcutaneous xanthomas, particularly along the tendon sheaths or over the extensor surfaces of the extremities. Severe hypertriglyceridemia can be associated with eruptive xanthomatosis and lipemia retinalis. Palmar crease xanthomas are specific for type III hyperlipoproteinemia. Pseudoxanthoma elasticum, a disease associated with premature atherosclerosis, is manifested by a leathery, cobblestoned appearance of the skin in the axilla and neck creases and by angiod streaks on

funduscopic examination. Extensive lentiginoses have been described in a variety of development delay–cardiovascular syndromes, including Carney's syndrome, which includes multiple atrial myxomas. Cutaneous manifestations of sarcoidosis such as lupus pernio and erythema nodosum may suggest this disease as a cause of an associated dilated cardiomyopathy, especially with heart block, intraventricular conduction delay, or ventricular tachycardia.

Head and Neck Dentition and oral hygiene should be assessed in every patient both as a source of potential infection and as an index of general health. A high-arched palate is a feature of Marfan's syndrome and other connective tissue disease syndromes. Bifid uvula has been described in patients with Loeys-Dietz syndrome, and orange tonsils are characteristic of Tangier disease. The ocular manifestations of hyperthyroidism have been well described. Many patients with congenital heart disease have associated hypertelorism, low-set ears, or micrognathia. Blue sclerae are a feature of osteogenesis imperfecta. An arcus senilis pattern lacks specificity as an index of coronary heart disease risk. The funduscopic examination is an often underused method by which to assess the microvasculature, especially among patients with established atherosclerosis, hypertension, or diabetes mellitus. A mydriatic agent may be necessary for optimal visualization. A funduscopic examination should be performed routinely in the assessment of patients with suspected endocarditis and those with a history of acute visual change. Branch retinal artery occlusion or visualization of a Hollenhorst plaque can narrow the differential diagnosis rapidly in the appropriate setting. Relapsing polychondritis may manifest as an inflamed pinna or, in its later stages, as a saddle-nose deformity because of destruction of nasal cartilage; granulomatosis with polyangiitis (Wegener's) can also lead to a saddle-nose deformity.

Chest Midline sternotomy, left posterolateral thoracotomy, or infraclavicular scars at the site of pacemaker/defibrillator generator implantation should not be overlooked and may provide the first clue regarding an underlying cardiovascular disorder in patients unable to provide a relevant history. A prominent venous collateral pattern may suggest subclavian or vena caval obstruction. If the head and neck appear dusky and slightly cyanotic and the venous pressure is grossly elevated without visible pulsations, a diagnosis of superior vena cava syndrome should be entertained. Thoracic cage abnormalities have been well described among patients with connective tissue disease syndromes. They include pectus carinatum ("pigeon chest") and pectus excavatum ("funnel chest"). Obstructive lung disease is suggested by a barrel chest deformity, especially with tachypnea, pursed-lip breathing, and use of accessory muscles. The characteristically severe kyphosis and compensatory lumbar, pelvic, and knee flexion of ankylosing spondylitis should prompt careful auscultation for a murmur of aortic regurgitation (AR). Straight back syndrome refers to the loss of the normal kyphosis of the thoracic spine and has been described in patients with mitral valve prolapse (MVP) and its variants. In some patients with cyanotic congenital heart disease, the chest wall appears to be asymmetric, with anterior displacement of the left hemithorax. The respiratory rate and pattern should be noted during spontaneous breathing, with additional attention to depth, audible wheezing, and stridor. Lung examination can reveal adventitious sounds indicative of pulmonary edema, pneumonia, or pleuritis.

Abdomen In some patients with advanced obstructive lung disease, the point of maximal cardiac impulse may be in the epigastrium. The liver is frequently enlarged and tender in patients with chronic heart failure. Systolic pulsations over the liver signify severe tricuspid regurgitation (TR). Splenomegaly may be a feature of infective endocarditis, particularly when symptoms have persisted for weeks or months. Ascites is a nonspecific finding but may be present with advanced chronic right heart failure, constrictive pericarditis, hepatic cirrhosis, or an intraperitoneal malignancy. The finding of an elevated JVP implies a cardiovascular etiology. In nonobese patients, the aorta typically is palpated between the epigastrium and the umbilicus. The sensitivity of palpation for the detection of an abdominal aortic aneurysm (pulsatile and expansile mass) decreases as a function of body size. Because palpation alone is not sufficiently accurate to establish

this diagnosis, a screening ultrasound examination is advised. The presence of an arterial bruit over the abdomen suggests high-grade atherosclerotic disease, although precise localization is difficult.

Extremities The temperature and color of the extremities, the presence of clubbing, arachnodactyly, and pertinent nail findings can be surmised quickly during the examination. Clubbing implies the presence of central right-to-left shunting, although it has also been described in patients with endocarditis. Its appearance can range from cyanosis and softening of the root of the nail bed, to the classic loss of the normal angle between the base of the nail and the skin, to the skeletal and periosteal bony changes of hypertrophic osteoarthropathy, which is seen rarely in patients with advanced lung or liver disease. Patients with the Holt-Oram syndrome have an unopposable, "fingerized" thumb, whereas patients with Marfan's syndrome may have arachnodactyly and a positive "wrist" (overlapping of the thumb and fifth finger around the wrist) or "thumb" (protrusion of the thumb beyond the ulnar aspect of the hand when the fingers are clenched over the thumb in a fist) sign. The Janeway lesions of endocarditis are nontender, slightly raised hemorrhages on the palms and soles, whereas Osler's nodes are tender, raised nodules on the pads of the fingers or toes. Splinter hemorrhages are classically identified as linear petechiae in the midposition of the nail bed and should be distinguished from the more common traumatic petechiae, which are seen closer to the distal edge.

Lower extremity or presacral edema in the setting of an elevated JVP defines volume overload and may be a feature of chronic heart failure or constrictive pericarditis. Lower extremity edema in the absence of jugular venous hypertension may be due to lymphatic or venous obstruction or, more commonly, to venous insufficiency, as further suggested by the appearance of varicosities, venous ulcers (typically medial in location), and brownish cutaneous discoloration from hemosiderin deposition (eburnation). Pitting edema can also be seen in patients who use dihydropyridine calcium channel blockers. A Homan's sign (posterior calf pain on active dorsiflexion of the foot against resistance) is neither specific nor sensitive for deep venous thrombosis. Muscular atrophy or the absence of hair along an extremity is consistent with severe arterial insufficiency or a primary neuromuscular disorder.

CARDIOVASCULAR EXAMINATION

Jugular Venous Pressure and Waveform JVP is the single most important bedside measurement from which to estimate the volume status. The internal jugular vein is preferred because the external jugular vein is valved and not directly in line with the superior vena cava and right atrium. Nevertheless, the external jugular vein has been used to discriminate between high and low central venous pressure (CVP) when tested among medical students, residents, and attending physicians. Precise estimation of the central venous or right atrial pressure from bedside assessment of the jugular venous waveform has proved difficult. Venous pressure traditionally has been measured as the vertical distance between the top of the jugular venous pulsation and the sternal inflection point (angle of Louis). A distance >4.5 cm at 30° elevation is considered abnormal. However, the actual distance between the mid-right atrium and the angle of Louis varies considerably as a function of both body size and the patient angle at which the assessment is made (30°, 45°, or 60°). The use of the sternal angle as a reference point leads to systematic underestimation of CVP, and this method should be used less for semiquantification than to distinguish a normal from an abnormally elevated CVP. The use of the clavicle may provide an easier reference for standardization. Venous pulsations above this level in the sitting position are clearly abnormal, as the distance between the clavicle and the right atrium is at least 10 cm. The patient should always be placed in the sitting position, with the legs dangling below the bedside, when an elevated pressure is suspected in the semisupine position. It should also be noted that bedside estimates of CVP are made in centimeters of water but must be converted to millimeters of mercury to provide correlation with accepted hemodynamic norms (1.36 cmH₂O = 1.0 mmHg).

The venous waveform sometimes can be difficult to distinguish from the carotid pulse, especially during casual inspection. Nevertheless, the venous waveform has several characteristic features, and its individual components can be appreciated in most patients (Fig. 267-1). The arterial pulsation is not easily obliterated with palpation; the venous waveform in patients with sinus rhythm is usually biphasic, while the carotid pulse is monophasic; and the jugular venous pulsation should change with changes in posture or inspiration (unless the venous pressure is quite elevated).

The venous waveform is divided into several distinct peaks. The *a* wave reflects right atrial presystolic contraction and occurs just after the electrocardiographic P wave, preceding the first heart sound (S_1). A prominent *a* wave is seen in patients with reduced right ventricular compliance; a cannon *a* wave occurs with atrioventricular (AV) dissociation and right atrial contraction against a closed tricuspid valve. In a patient with a wide complex tachycardia, the appreciation of cannon *a* waves in the jugular venous waveform identifies the rhythm as ventricular in origin. The *x* descent defines the fall in right atrial pressure after inscription of the *a* wave. The *c* wave interrupts this *x* descent and is followed by a further descent. The *v* wave represents atrial filling (atrial diastole) and occurs during ventricular systole. The height of the *v* wave is determined by right atrial compliance as well as the volume of blood returning to the right atrium either antegrade from the cavae or retrograde through an incompetent tricuspid valve. In patients with TR, the *v* wave is accentuated and the subsequent fall in pressure (*y* descent) is rapid. With progressive degrees of TR, the *v* wave merges with the *c* wave, and the right atrial and jugular vein waveforms become “ventricularized.” The *y* descent, which follows the peak of the *v* wave, can become prolonged or blunted with obstruction to right ventricular inflow, as may occur with tricuspid stenosis or pericardial tamponade. Normally, the venous pressure should fall by at least 3 mmHg with inspiration. Kussmaul’s sign is defined by either a rise or a lack of fall of the JVP with inspiration and is classically associated with constrictive pericarditis, although it has been reported in patients with restrictive cardiomyopathy, massive pulmonary embolism, right ventricular infarction, and advanced left ventricular systolic heart failure. It is also a common, isolated finding in patients after cardiac surgery without other hemodynamic abnormalities.

Venous hypertension sometimes can be elicited by performance of the abdominojugular reflex or with passive leg elevation. When these signs are positive, a volume-overloaded state with limited compliance of an overly distended or constricted venous system is present. The abdominojugular reflex is elicited with firm and consistent pressure over the upper portion of the abdomen, preferably over the right upper quadrant, for at least 10 s. A positive response is defined by a sustained rise of more than 3 cm in JVP for at least 15 s after release of the hand. Patients must be coached to refrain from breath holding or a Valsalva-like maneuver during the procedure. The abdominojugular reflex is useful in predicting a pulmonary artery wedge pressure in excess of 15 mmHg in patients with heart failure.

Although the JVP estimates right ventricular filling pressure, it has a predictable relationship with the pulmonary artery wedge pressure. In a large study of patients with advanced heart failure, the presence of a right atrial pressure >10 mmHg (as predicted on bedside examination) had a positive value of 88% for the prediction of a pulmonary artery wedge pressure of >22 mmHg. In addition, an elevated JVP has prognostic significance in patients with both symptomatic heart failure and asymptomatic left ventricular systolic dysfunction. The presence of an elevated JVP is associated with a higher risk of subsequent hospitalization for heart failure, death from heart failure, or both.

Assessment of Blood Pressure Measurement of blood pressure usually is delegated to a medical assistant but should be repeated by the clinician. Accurate measurement depends on body position, arm size, time of measurement, place of measurement, device, device size, technique, and examiner. In general, physician-recorded blood pressures are higher than both nurse-recorded pressures and self-recorded pressures at home. Blood pressure is best measured in the seated position with

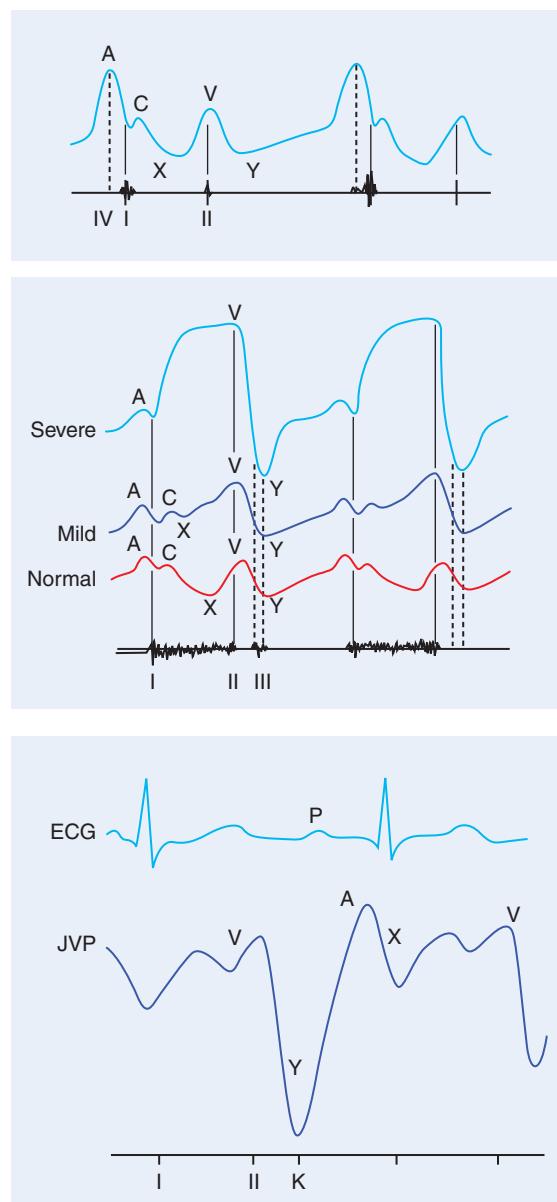


FIGURE 267-1 **A.** Jugular venous pulse wave tracing (top) with heart sounds (bottom). The *A* wave represents right atrial presystolic contraction and occurs just after the electrocardiographic P wave and just before the first heart sound (I). In this example, the *A* wave is accentuated and larger than normal due to decreased right ventricular compliance, as also suggested by the right-sided S_4 (IV). The *C* wave may reflect the carotid pulsation in the neck and/or an early systolic increase in right atrial pressure as the right ventricle pushes the closed tricuspid valve into the right atrium. The *x* descent follows the *A* wave just as atrial pressure continues to fall. The *V* wave represents atrial filling during ventricular systole and peaks at the second heart sound (II). The *y* descent corresponds to the fall in right atrial pressure after tricuspid valve opening. **B.** Jugular venous wave forms in mild (middle) and severe (top) tricuspid regurgitation, compared with normal, with phonocardiographic representation of the corresponding heart sounds below. With increasing degrees of tricuspid regurgitation, the waveform becomes “ventricularized.” **C.** Electrocardiogram (ECG) (top), jugular venous waveform (JVP) (middle), and heart sounds (bottom) in pericardial constriction. Note the prominent and rapid *y* descent, corresponding in timing to the pericardial knock (K). (From J Abrams: *Synopsis of Cardiac Physical Diagnosis*, 2nd ed. Boston, Butterworth Heinemann, 2001, pp 25–35.)

the arm at the level of the heart, using an appropriately sized cuff, after 5–10 min of relaxation. When it is measured in the supine position, the arm should be raised to bring it to the level of the mid-right atrium. The length and width of the blood pressure cuff bladder should be 80% and 40% of the arm's circumference, respectively. A common source of error in practice is to use an inappropriately small cuff, resulting in marked overestimation of true blood pressure, or an inappropriately large cuff, resulting in underestimation of true blood pressure. The cuff should be inflated to 30 mmHg above the expected systolic pressure and the pressure released at a rate of 2–3 mmHg/s. Systolic and diastolic pressures are defined by the first and fifth Korotkoff sounds, respectively. Very low (even 0 mmHg) diastolic blood pressures may be recorded in patients with chronic, severe AR or a large arteriovenous fistula because of enhanced diastolic "run-off." In these instances, both the phase IV and phase V Korotkoff sounds should be recorded. Blood pressure is best assessed at the brachial artery level, though it can be measured at the radial, popliteal, or pedal pulse level. In general, systolic pressure increases and diastolic pressure decreases when measured in more distal arteries. Blood pressure should be measured in both arms, and the difference should be less than 10 mmHg. A blood pressure differential that exceeds this threshold may be associated with atherosclerotic or inflammatory subclavian artery disease, supravalvular aortic stenosis, aortic coarctation, or aortic dissection. Systolic leg pressures are usually as much as 20 mmHg higher than systolic arm pressures. Greater leg-arm pressure differences are seen in patients with chronic severe AR as well as patients with extensive and calcified lower extremity peripheral arterial disease. The ankle-brachial index (lower pressure in the dorsalis pedis or posterior tibial artery divided by the higher of the two brachial artery pressures) is a powerful predictor of long-term cardiovascular mortality.

The blood pressure measured in an office or hospital setting may not accurately reflect the pressure in other venues. "White coat hypertension" is defined by at least three separate clinic-based measurements >140/90 mmHg and at least two non-clinic-based measurements <140/90 mmHg in the absence of any evidence of target organ damage. Individuals with white coat hypertension may not benefit from drug therapy, although they may be more likely to develop sustained hypertension over time. Masked hypertension should be suspected when normal or even low blood pressures are recorded in patients with advanced atherosclerotic disease, especially when evidence of target organ damage is present or bruits are audible.

Orthostatic hypotension is defined by a fall in systolic pressure >20 mmHg or in diastolic pressure >10 mmHg in response to assumption of the upright posture from a supine position within 3 min. There may also be a lack of a compensatory tachycardia, an abnormal response that suggests autonomic insufficiency, as may be seen in patients with diabetes or Parkinson's disease. Orthostatic hypotension is a common cause of postural lightheadedness/syncope and should be assessed routinely in patients for whom this diagnosis might pertain. It can be exacerbated by advanced age, dehydration, certain medications, food, deconditioning, and ambient temperature.

Arterial Pulse The carotid artery pulse occurs just after the ascending aortic pulse. The aortic pulse is best appreciated in the epigastrium, just above the level of the umbilicus. Peripheral arterial pulses that should be assessed routinely include the subclavian, brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial. In patients in whom the diagnosis of either temporal arteritis or polymyalgia rheumatica is suspected, the temporal arteries also should be examined. Although one of the two pedal pulses may not be palpable in up to 10% of normal subjects, the pair should be symmetric. The integrity of the arcuate system of the hand is assessed by Allen's test, which is performed routinely before instrumentation of the radial artery. The pulses should be examined for their symmetry, volume, timing, contour, amplitude, and duration. If necessary, simultaneous auscultation of the heart can help identify a delay in the arrival of an arterial pulse. Simultaneous palpation of the radial and femoral pulses may reveal a femoral delay in a patient with hypertension and suspected aortic coarctation. The carotid upstrokes should never be examined simultaneously or before listening for a bruit. Light pressure

should always be used to avoid precipitation of carotid hypersensitivity syndrome and syncope in a susceptible elderly individual. The arterial pulse usually becomes more rapid and spiking as a function of its distance from the heart, a phenomenon that reflects the muscular status of the more peripheral arteries and the summation of the incident and reflected waves. In general, the character and contour of the arterial pulse depend on the stroke volume, ejection velocity, vascular compliance, and systemic vascular resistance. The pulse examination can be misleading in patients with reduced cardiac output and in those with stiffened arteries from aging, chronic hypertension, or peripheral arterial disease.

The character of the pulse is best appreciated at the carotid level (Fig. 267-2). A weak and delayed pulse (*pulsus parvus et tardus*) defines severe aortic stenosis (AS). Some patients with AS may also have a slow, notched, or interrupted upstroke (anacrotic pulse) with a thrill or shudder. With chronic severe AR, by contrast, the carotid upstroke has a sharp rise and rapid fall-off (Corrigan's or water-hammer pulse). Some patients with advanced AR may have a bifid or bisferiens pulse, in which two systolic peaks can be appreciated. A bifid pulse is also described in patients with hypertrophic obstructive cardiomyopathy (HOCM), with inscription of percussion and tidal waves. A bifid pulse is easily appreciated in patients on intraaortic balloon counterpulsation (IABP), in whom the second pulse is diastolic in timing.

Pulsus paradoxus refers to a fall in systolic pressure >10 mmHg with inspiration that is seen in patients with pericardial tamponade but also is described in those with massive pulmonary embolism, hemorrhagic shock, severe obstructive lung disease, and tension pneumothorax.

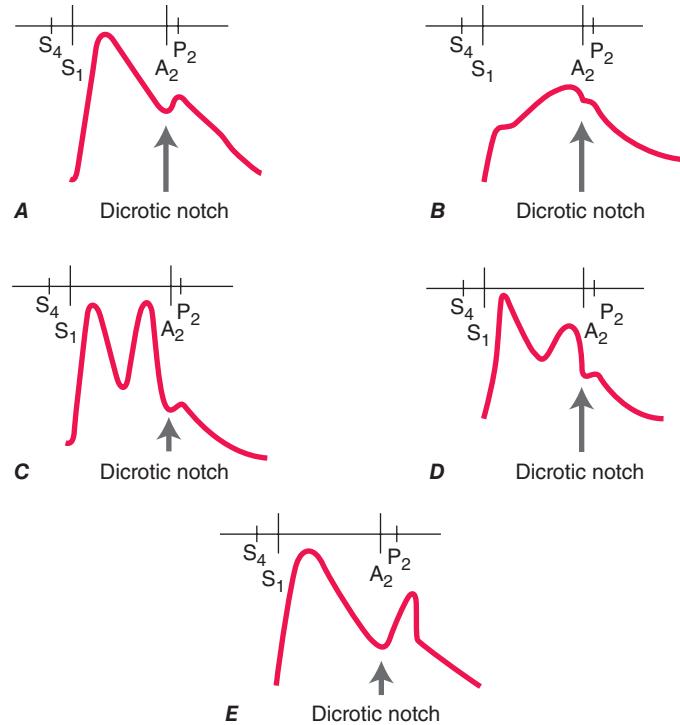


FIGURE 267-2 Schematic diagrams of the configurational changes in carotid pulse and their differential diagnoses. Heart sounds are also illustrated. **A.** Normal. S_4 , fourth heart sound; S_1 , first heart sound; A_2 , aortic component of second heart sound; P_2 , pulmonic component of second heart sound. **B.** Aortic stenosis. Anacrotic pulse with slow upstroke to a reduced peak. **C.** Bisferiens pulse with two peaks in systole. This pulse is rarely appreciated in patients with severe aortic regurgitation. **D.** Bisferiens pulse in hypertrophic obstructive cardiomyopathy. There is a rapid upstroke to the first peak (percussion wave) and a slower rise to the second peak (tidal wave). **E.** Dicrotic pulse with peaks in systole and diastole. This waveform may be seen in patients with sepsis or during intraaortic balloon counterpulsation with inflation just after the dicrotic notch. (From K Chatterjee, W Parmley [eds]: Cardiology: An Illustrated Text/Reference. Philadelphia, Gower Medical Publishers, 1991.)

1446 Pulsus paradoxus is measured by noting the difference between the systolic pressure at which the Korotkoff sounds are first heard (during expiration) and the systolic pressure at which the Korotkoff sounds are heard with each heartbeat, independent of the respiratory phase. Between these two pressures, the Korotkoff sounds are heard only intermittently and during expiration. The cuff pressure must be decreased slowly to appreciate the finding. It can be difficult to measure pulsus paradoxus in patients with tachycardia, atrial fibrillation, or tachypnea. A pulsus paradoxus may be palpable at the brachial artery or femoral artery level when the pressure difference exceeds 15 mmHg. This inspiratory fall in systolic pressure is an exaggerated consequence of interventricular dependence.

Pulsus alternans, in contrast, is defined by beat-to-beat variability of pulse amplitude. It is present only when every other phase I Korotkoff sound is audible as the cuff pressure is lowered slowly, typically in a patient with a regular heart rhythm and independent of the respiratory cycle. Pulsus alternans is seen in patients with severe left ventricular systolic dysfunction and is thought to be due to cyclic changes in intracellular calcium and action potential duration. When pulsus alternans is associated with electrocardiographic T-wave alternans, the risk for an arrhythmic event appears to be increased.

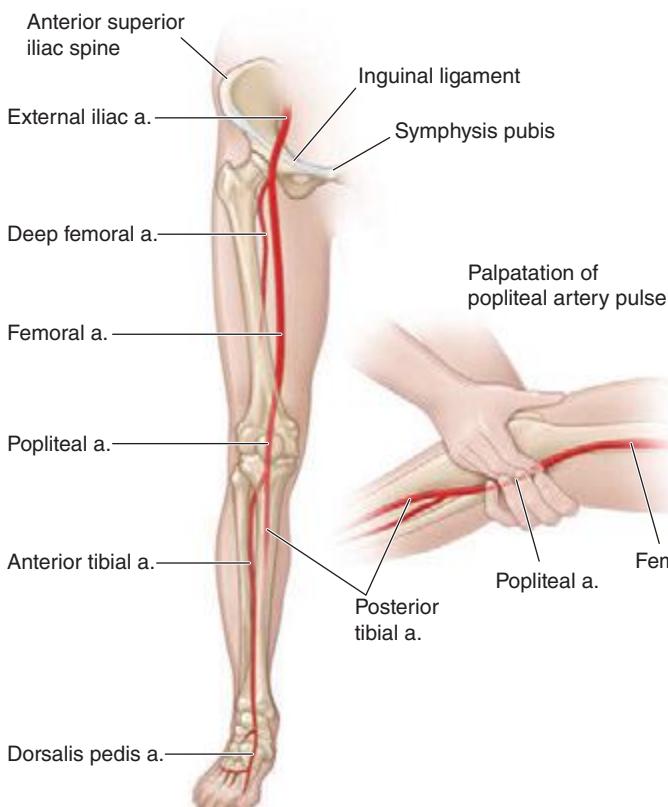
Ascending aortic aneurysms can rarely be appreciated as a pulsatile mass in the right parasternal area. Appreciation of a prominent abdominal aortic pulse should prompt noninvasive imaging for better characterization. Femoral and/or popliteal artery aneurysms should be sought in patients with abdominal aortic aneurysm disease.

The level of a claudication-producing arterial obstruction can often be identified on physical examination (Fig. 267-3). For example, in a

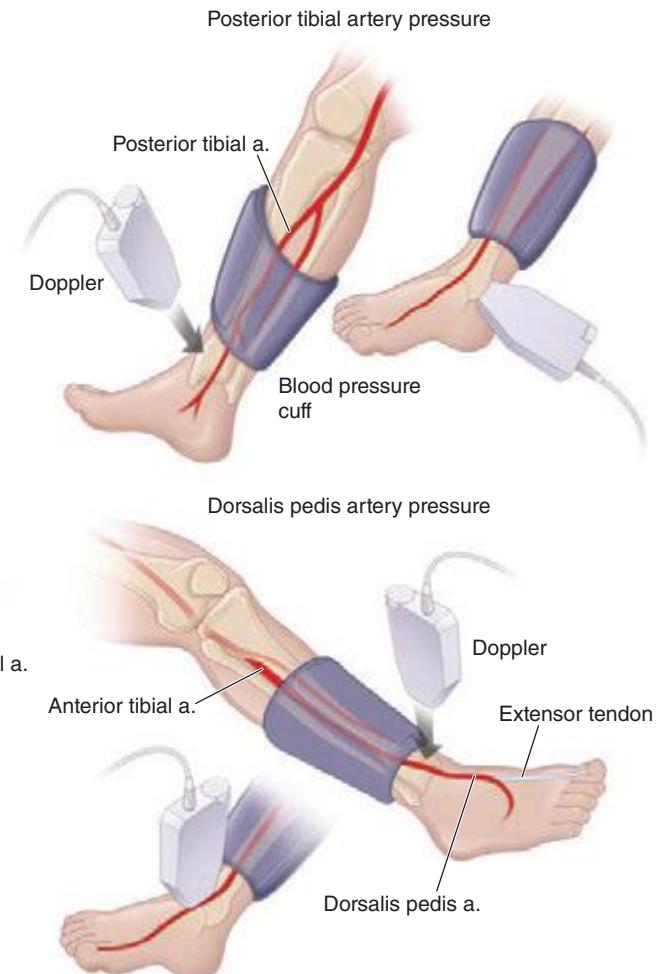
patient with calf claudication, a decrease in pulse amplitude between the common femoral and popliteal arteries will localize the obstruction to the level of the superficial femoral artery, although inflow obstruction above the level of the common femoral artery may coexist. Auscultation for carotid, subclavian, abdominal aortic, and femoral artery bruits should be routine. However, the correlation between the presence of a bruit and the degree of vascular obstruction is poor. A cervical bruit is a weak indicator of the degree of carotid artery stenosis; the absence of a bruit does not exclude the presence of significant luminal obstruction. If a bruit extends into diastole or if a thrill is present, the obstruction is usually severe. Another cause of an arterial bruit is an arteriovenous fistula with enhanced flow.

The likelihood of significant lower extremity peripheral arterial disease increases with typical symptoms of claudication, cool skin, abnormalities on pulse examination, or the presence of a vascular bruit. Abnormal pulse oximetry (a >2% difference between finger and toe oxygen saturation) can be used to detect lower extremity peripheral arterial disease and is comparable in its performance characteristics to the ankle-brachial index.

Inspection and Palpation of the Heart The left ventricular apex beat may be visible in the midclavicular line at the fifth intercostal space in thin-chested adults. Visible pulsations anywhere other than this expected location are abnormal. The left anterior chest wall may heave in patients with an enlarged or hyperdynamic left or right ventricle. As noted previously, a visible right upper parasternal pulsation may be suggestive of ascending aortic aneurysm disease. In thin, tall patients and patients with advanced obstructive lung disease and flattened



A Major arteries of the lower limb



B Measurement of ankle systolic pressure

FIGURE 267-3 **A.** Anatomy of the major arteries of the leg. **B.** Measurement of the ankle systolic pressure. (From NA Khan et al: JAMA 295:536, 2006.)

diaphragms, the cardiac impulse may be visible in the epigastrium and should be distinguished from a pulsatile liver edge.

Palpation of the heart begins with the patient in the supine position at 30° and can be enhanced by placing the patient in the left lateral decubitus position. The normal left ventricular impulse is less than 2 cm in diameter and moves quickly away from the fingers; it is better appreciated at end expiration, with the heart closer to the anterior chest wall. Characteristics such as size, amplitude, and rate of force development should be noted.

Enlargement of the left ventricular cavity is manifested by a leftward and downward displacement of an enlarged apex beat. A sustained apex beat is a sign of pressure overload, such as that which may be present in patients with AS or chronic hypertension. A palpable presystolic impulse corresponds to the fourth heart sound (S_4) and is indicative of reduced left ventricular compliance and the forceful contribution of atrial contraction to ventricular filling. A palpable third sound (S_3), which is indicative of a rapid early filling wave in patients with heart failure, may be present even when the gallop itself is not audible. A large left ventricular aneurysm may sometimes be palpable as an ectopic impulse, discrete from the apex beat. HOCM may very rarely cause a triple cadence beat at the apex with contributions from a palpable S_4 and the two components of the bisferiens systolic pulse.

Right ventricular pressure or volume overload may create a sternal lift. Signs of either TR (*cv* waves in the jugular venous pulse) and/or pulmonary arterial hypertension (a loud single or palpable P_2) would be confirmatory. The right ventricle can enlarge to the extent that left-sided events cannot be appreciated. A zone of retraction between the right and left ventricular impulses sometimes can be appreciated in patients with right ventricle pressure or volume overload when they are placed in the left lateral decubitus position. Systolic and diastolic thrills signify turbulent and high-velocity blood flow. Their locations help identify the origin of heart murmurs.

CARDIAC AUSCULTATION

Heart Sounds Ventricular systole is defined by the interval between the first (S_1) and second (S_2) heart sounds (Fig. 267-4). The first heart sound (S_1) includes mitral and tricuspid valve closure. Normal splitting can be appreciated in young patients and those with right bundle branch block, in whom tricuspid valve closure is relatively delayed. The intensity of S_1 is determined by the distance over which the anterior leaflet of the mitral valve must travel to return to its annular plane, leaflet mobility, left ventricular contractility, and the PR interval. S_1 is classically loud in the early phases of rheumatic mitral stenosis (MS) and in patients with hyperkinetic circulatory states or short PR intervals. S_1 becomes softer in the later stages of MS when the leaflets are rigid and calcified, after exposure to β-adrenergic receptor blockers, with long PR intervals, and with left ventricular contractile dysfunction. The intensity of heart sounds, however, can be reduced by any process that increases the distance between the stethoscope and the responsible cardiac event, including mechanical ventilation, obstructive lung disease, obesity, pneumothorax, and a pericardial effusion.

Aortic and pulmonic valve closure constitutes the second heart sound (S_2). With normal or physiologic splitting, the A_2-P_2 interval increases with inspiration and narrows during expiration. This physiologic interval will widen with right bundle branch block because of the further delay in pulmonic valve closure and in patients with severe MR because of the premature closure of the aortic valve. An unusually narrowly split or even a singular S_2 is a feature of pulmonary arterial hypertension. Fixed splitting of S_2 , in which the A_2-P_2 interval is wide and does not change during the respiratory cycle, occurs in patients with a secundum atrial septal defect. Reversed or paradoxical splitting refers to a pathologic delay in aortic valve closure, such as that which occurs in patients with left bundle branch block, right ventricular pacing, severe AS, HOCM, and acute myocardial ischemia. With reversed or paradoxical splitting, the individual components of S_2 are audible at end expiration, and their interval narrows with inspiration, the opposite of what would be expected under normal physiologic conditions. P_2 is considered loud when its intensity exceeds that of A_2 at the base, when it can be palpated in the area of the proximal main pulmonary

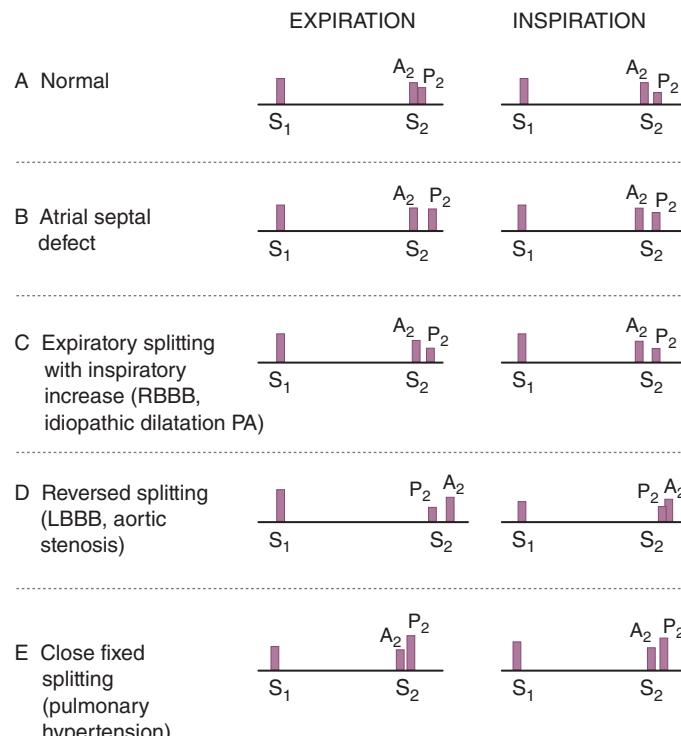


FIGURE 267-4 Heart sounds. **A.** Normal. S_1 , first heart sound; S_2 , second heart sound; A_2 , aortic component of the second heart sound; P_2 , pulmonic component of the second heart sound. **B.** Atrial septal defect with fixed splitting of S_2 . **C.** Physiologic but wide splitting of S_2 with right bundle branch block (RBBB). PA, pulmonary artery. **D.** Reversed or paradoxical splitting of S_2 with left bundle branch block (LBBB). **E.** Narrow splitting of S_2 with pulmonary hypertension. (From NO Fowler: *Diagnosis of Heart Disease*. New York, Springer-Verlag, 1991, p 31.)

artery (second left interspace), or when both components of S_2 can be appreciated at the lower left sternal border or apex. The intensity of A_2 and P_2 decreases with aortic and pulmonic stenosis, respectively. In these conditions, a single S_2 may result.

Systolic Sounds An ejection sound is a high-pitched early systolic sound that corresponds in timing to the upstroke of the carotid pulse. It usually is associated with congenital bicuspid aortic or pulmonic valve disease; however, ejection sounds are also sometimes audible in patients with isolated aortic or pulmonary root dilation and normal semilunar valves. The ejection sound that accompanies bicuspid aortic valve disease becomes softer and then inaudible as the valve calcifies and becomes more rigid. The ejection sound that accompanies pulmonic stenosis (PS) moves closer to the first heart sound as the severity of the stenosis increases. In addition, the pulmonic ejection sound is the only right-sided acoustic event that decreases in intensity with inspiration. Ejection sounds are often heard more easily at the lower left sternal border than they are at the base. Nonejection sounds (clicks), which occur after the onset of the carotid upstroke, are related to MVP and may be single or multiple. The nonejection click may introduce a murmur. This click-murmur complex will move away from the first heart sound with maneuvers that increase ventricular preload, such as squatting. On standing, the click and murmur move closer to S_1 .

Diastolic Sounds The high-pitched opening snap (OS) of MS occurs after a very short interval after the second heart sound. The A_2 -OS interval is inversely proportional to the height of the left atrial-left ventricular diastolic pressure gradient. The intensity of both S_1 and the OS of MS decreases with progressive calcification and rigidity of the anterior mitral leaflets. The pericardial knock (PK) is also high-pitched

and occurs slightly later than the OS, corresponding in timing to the abrupt cessation of ventricular expansion after tricuspid valve opening and to an exaggerated γ descent seen in the jugular venous waveform in patients with constrictive pericarditis. A tumor plop is a lower-pitched sound that rarely can be heard in patients with atrial myxoma. It may be appreciated only in certain positions and arises from the diastolic prolapse of the tumor across the mitral valve.

The third heart sound (S_3) occurs during the rapid filling phase of ventricular diastole. It can be a normal finding in children, adolescents, and young adults; however, in older patients, it signifies heart failure. A left-sided S_3 is a low-pitched sound best heard over the left ventricular (LV) apex. A right-sided S_3 is usually better heard over the lower left sternal border and becomes louder with inspiration. A left-sided S_3 in patients with chronic heart failure is predictive of cardiovascular morbidity and mortality. Interestingly, an S_3 is equally prevalent among heart failure patients with and without LV systolic dysfunction.

The fourth heart sound (S_4) occurs during the atrial filling phase of ventricular diastole and indicates LV presystolic expansion. An S_4 is more common among patients who derive significant benefit from the atrial contribution to ventricular filling, such as those with chronic LV hypertrophy or active myocardial ischemia. An S_4 is not present with atrial fibrillation.

Cardiac Murmurs Heart murmurs result from audible vibrations that are caused by increased turbulence and are defined by their timing within the cardiac cycle. Not all murmurs are indicative of structural heart disease, and the accurate identification of a benign or functional systolic murmur often can obviate the need for additional testing in healthy subjects. The duration, frequency, configuration, and intensity of a heart murmur are dictated by the magnitude, variability, and duration of the responsible pressure difference between two cardiac chambers, the two ventricles, or the ventricles and their respective great arteries. The intensity of a heart murmur is graded on a scale of 1 to 6; a thrill is present with murmurs of grade 4 or greater intensity. Other attributes of the murmur that aid in its accurate identification include its location, radiation, and response to bedside maneuvers. Although clinicians can detect and correctly identify heart murmurs with only fair reliability, a careful and complete bedside examination usually can identify individuals with valvular heart disease for whom transthoracic echocardiography and clinical follow-up are indicated and exclude subjects for whom no further evaluation is necessary.

Systolic murmurs can be early, mid, late, or holosystolic in timing (Fig. 267-5). Acute severe MR results in a decrescendo early systolic murmur, the characteristics of which are related to the progressive attenuation of the left ventricular to left atrial pressure gradient during systole because of the steep and rapid rise in left atrial pressure in this context. Severe MR associated with posterior leaflet prolapse or flail radiates anteriorly and to the base, where it can be confused with the murmur of AS. MR that is due to anterior leaflet involvement radiates posteriorly and to the axilla. With acute TR in patients with normal pulmonary artery pressures, an early systolic murmur that may increase in intensity with inspiration may be heard at the left lower sternal border, with regurgitant *cv* waves visible in the jugular venous pulse.

A midsystolic murmur begins after S_1 and ends before S_2 ; it is typically crescendo-decrescendo in configuration. AS is the most common cause of a midsystolic murmur in an adult. It is often difficult to estimate the severity of the valve lesion on the basis of the physical examination findings, especially in older hypertensive patients with stiffened carotid arteries or patients with low cardiac output in whom the intensity of the systolic heart murmur is misleadingly soft. Examination findings consistent with severe AS would include *parvus et tardus* carotid upstrokes, a late-peaking grade 3 or greater midsystolic murmur, a soft A_2 , a sustained LV apical impulse, and an S_4 . It is sometimes difficult to distinguish aortic sclerosis from more advanced degrees of valve stenosis. The former is defined by focal thickening and calcification of the aortic valve leaflets that is not severe enough to result in obstruction. These valve changes are associated with a Doppler jet velocity across the aortic valve of 2.5 m/s or less. Patients

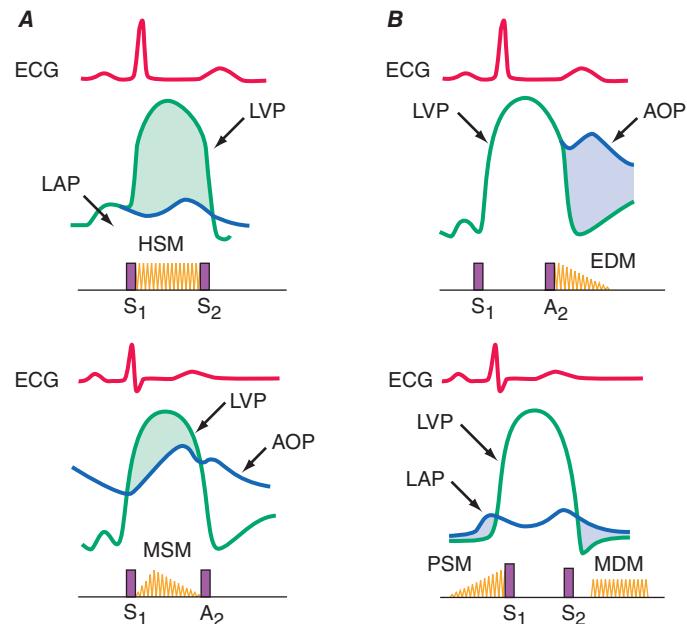


FIGURE 267-5 **A. Top.** Graphic representation of the systolic pressure difference (green shaded area) between left ventricle and left atrium with phonocardiographic recording of a holosystolic murmur (HSM) indicative of mitral regurgitation. ECG, electrocardiogram; LAP, left atrial pressure; LVP, left ventricular pressure; S_1 , first heart sound; S_2 , second heart sound. **Bottom.** Graphic representation of the systolic pressure gradient (green shaded area) between left ventricle and aorta in patient with aortic stenosis. A midsystolic murmur (MSM) with a crescendo-decrescendo configuration is recorded. AOP, aortic pressure. **B. Top.** Graphic representation of the diastolic pressure difference between the aorta and left ventricle (blue shaded area) in a patient with aortic regurgitation, resulting in a decrescendo, early diastolic murmur (EDM) beginning with A_2 . **Bottom.** Graphic representation of the diastolic left atrial-left ventricular gradient (blue areas) in a patient with mitral stenosis with a mid-diastolic murmur (MDM) and late presystolic murmurs (PSM).

with aortic sclerosis can have grade 2 or 3 midsystolic murmurs identical in their acoustic characteristics to the murmurs heard in patients with more advanced degrees of AS. Other causes of a midsystolic heart murmur include pulmonic valve stenosis (with or without an ejection sound), HOCM, increased pulmonary blood flow in patients with a large atrial septal defect and left-to-right shunting, and several states associated with accelerated blood flow in the absence of structural heart disease, such as fever, thyrotoxicosis, pregnancy, anemia, and normal childhood/adolescence.

The murmur of HOCM has features of both obstruction to LV outflow and MR, as would be expected from knowledge of the pathophysiology of this condition. The systolic murmur of HOCM usually can be distinguished from other causes on the basis of its response to bedside maneuvers, including Valsalva, passive leg raising, and standing/squatting. In general, maneuvers that decrease LV preload (or increase LV contractility) will cause the murmur to intensify, whereas maneuvers that increase LV preload or afterload will cause a decrease in the intensity of the murmur. Accordingly, the systolic murmur of HOCM becomes louder during the strain phase of the Valsalva maneuver and after standing quickly from a squatting position. The murmur becomes softer with passive leg raising and when squatting. The murmur of AS is typically loudest in the second right interspace with radiation into the carotids, whereas the murmur of HOCM is best heard between the lower left sternal border and the apex. The murmur of PS is best heard in the second left interspace. The midsystolic murmur associated with enhanced pulmonic blood flow in the setting of a large atrial septal defect (ASD) is usually loudest at the mid-left sternal border.

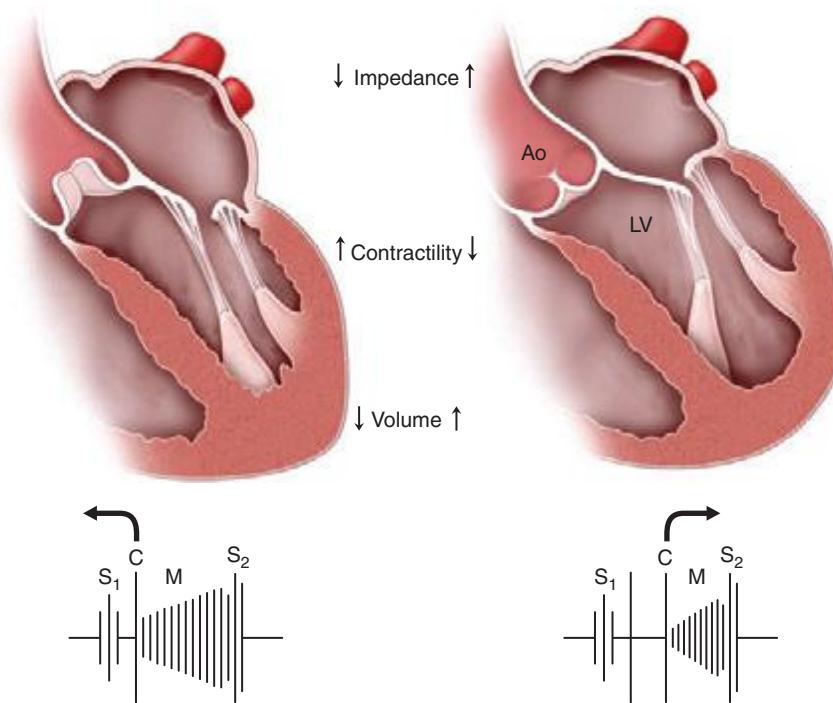


FIGURE 267-6 Behavior of the click (C) and murmur (M) of mitral valve prolapse with changes in loading (volume, impedance) and contractility. S_1 , first heart sound; S_2 , second heart sound. With standing (left side of figure), volume and impedance decrease, as a result of which the click and murmur move closer to S_1 . With squatting (right), the click and murmur move away from S_1 due to the increases in left ventricular volume and impedance (afterload). Ao, aorta; LV, left ventricle. (Adapted from RA O'Rourke, MH Crawford: Curr Prob Cardiol 1:9, 1976.)

A late systolic murmur, heard best at the apex, indicates MVP. As previously noted, the murmur may or may not be introduced by a nonejection click. Differential radiation of the murmur, as previously described, may help identify the specific leaflet involved by the myxomatous process. The click-murmur complex behaves in a manner directionally similar to that demonstrated by the murmur of HOCM during the Valsalva and stand/squat maneuvers (Fig. 267-6). The murmur of MVP can be identified by the accompanying nonejection click.

Holosystolic murmurs are plateau in configuration and reflect a continuous and wide pressure gradient between the left ventricle and left atrium with chronic MR, the left ventricle and right ventricle with a ventricular septal defect (VSD), and the right ventricle and right atrium with TR. In contrast to acute MR, in chronic MR the left atrium is enlarged and its compliance is normal or increased to the extent that there is little if any further increase in left atrial pressure from any increase in regurgitant volume. The murmur of MR is best heard over the cardiac apex. The intensity of the murmur increases with maneuvers that increase LV afterload, such as sustained hand grip. The murmur of a VSD (without significant pulmonary hypertension) is holosystolic and loudest at the mid-left sternal border, where a thrill is usually present. The murmur of TR is loudest at the lower left sternal border, increases in intensity with inspiration (Carvallo's sign), and is accompanied by visible *cv* waves in the jugular venous wave form and, on occasion, by pulsatile hepatomegaly.

Diastolic Murmurs In contrast to some systolic murmurs, diastolic heart murmurs always signify structural heart disease (Fig. 267-5). The murmur associated with acute, severe AR is relatively soft and of short duration because of the rapid rise in LV diastolic pressure and the progressive diminution of the aortic-LV diastolic pressure gradient. In contrast, the murmur of chronic severe AR is classically heard as a decrescendo, blowing diastolic murmur along the left sternal border in patients with primary valve pathology and sometimes along the right sternal border in patients with primary aortic root pathology.

With chronic AR, the pulse pressure is wide and the arterial pulses are bounding in character. These signs of significant diastolic run-off are absent in the acute phase. The murmur of pulmonic regurgitation is also heard along the left sternal border. It is most commonly due to pulmonary hypertension and enlargement of the annulus of the pulmonic valve. S_2 is single and loud and may be palpable. There is a right ventricular/parasternal lift that is indicative of chronic right ventricular pressure overload. A less impressive murmur of PR is present after repair of tetralogy of Fallot or pulmonic valve atresia. In this postoperative setting, the murmur is softer and lower-pitched, and the severity of the accompanying pulmonic regurgitation can be underestimated significantly.

MS is the classic cause of a mid- to late diastolic murmur, which is best heard over the apex in the left lateral decubitus position, is low-pitched or rumbling, and is introduced by an OS in the early stages of the rheumatic disease process. Presystolic accentuation refers to an increase in the intensity of the murmur just before the first heart sound and occurs in patients with sinus rhythm. It is absent in patients with atrial fibrillation. The auscultatory findings in patients with rheumatic tricuspid stenosis typically are obscured by left-sided events, although they are similar in nature to those described in patients with MS. "Functional" mitral or tricuspid stenosis refers to the generation of mid-diastolic murmurs that are created by increased and accelerated transvalvular diastolic flow, even in the absence

of valvular obstruction, in the setting of severe MR, severe TR, or a large ASD with left-to-right shunting. The Austin Flint murmur of chronic severe AR is a low-pitched mid- to late apical diastolic murmur that sometimes can be confused with MS. The Austin Flint murmur typically decreases in intensity after exposure to vasodilators, whereas the murmur of MS may be accompanied by an opening snap and also may increase in intensity after vasodilators because of the associated increase in cardiac output. Unusual causes of a mid-diastolic murmur include atrial myxoma, complete heart block, and acute rheumatic mitral valvulitis.

Continuous Murmur A continuous murmur is predicated on a pressure gradient that persists between two cardiac chambers or blood vessels across systole and diastole. The murmurs typically begin in systole, envelop the second heart sound (S_2), and continue through some portion of diastole. They can often be difficult to distinguish from individual systolic and diastolic murmurs in patients with mixed valvular heart disease. The classic example of a continuous murmur is that associated with a PDA, which usually is heard in the second or third interspace at a slight distance from the sternal border. Other causes of a continuous murmur include a ruptured sinus of Valsalva aneurysm with creation of an aortic-right atrial or right ventricular fistula, a coronary or great vessel arteriovenous fistula, and an arteriovenous fistula constructed to provide dialysis access. There are two types of benign continuous murmurs. The cervical venous hum is heard in children or adolescents in the supraclavicular fossa. It can be obliterated with firm pressure applied to the diaphragm of the stethoscope, especially when the subject turns his or her head toward the examiner. The mammary soufflé of pregnancy relates to enhanced arterial blood flow through engorged breasts. The diastolic component of the murmur can be obliterated with firm pressure over the stethoscope.

Dynamic Auscultation Diagnostic accuracy can be enhanced by the performance of simple bedside maneuvers to identify heart murmurs and characterize their significance (Table 267-1). Except for the pulmonic

TABLE 267-1 EFFECTS OF PHYSIOLOGIC AND PHARMACOLOGIC INTERVENTIONS ON THE INTENSITY OF HEART MURMURS AND SOUNDS

Respiration Right-sided murmurs and sounds generally increase with inspiration, except for the PES. Left-sided murmurs and sounds are usually louder during expiration.

Valsalva maneuver Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HOCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. After release of the Valsalva maneuver, right-sided murmurs tend to return to control intensity earlier than do left-sided murmurs.

After VPB or AF Murmurs originating at normal or stenotic semilunar valves increase in the cardiac cycle after a VPB or in the cycle after a long cycle length in AF. By contrast, systolic murmurs due to AV valve regurgitation do not change, diminish (papillary muscle dysfunction), or become shorter (MVP).

Positional changes With *standing*, most murmurs diminish, with two exceptions being the murmur of HOCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With *squatting*, most murmurs become louder, but those of HOCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results.

Exercise Murmurs due to blood flow across normal or obstructed valves (e.g., PS, MS) become louder with both isotonic and submaximal isometric (hand grip) exercise. Murmurs of MR, VSD, and AR also increase with hand grip exercise. However, the murmur of HOCM often decreases with nearly maximum hand grip exercise. Left-sided S_4 and S_3 sounds are often accentuated by exercise, particularly when due to ischemic heart disease.

Abbreviations: AF, atrial fibrillation; AR, aortic regurgitation; HOCM, hypertrophic obstructive cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PES, pulmonic ejection sound; PR, pulmonic regurgitation; PS, pulmonic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis; VPB, ventricular premature beat; VSD, ventricular septal defect.

ejection sound, right-sided events increase in intensity with inspiration and decrease with expiration; left-sided events behave oppositely (100% sensitivity, 88% specificity). As previously noted, the intensity of the murmurs associated with MR, VSD, and AR will increase in response to maneuvers that increase LV afterload, such as hand grip and vasopressors. The intensity of these murmurs will decrease after exposure to vasodilating agents. Squatting is associated with an abrupt increase in LV preload and afterload, whereas rapid standing results in a sudden decrease in preload. In patients with MVP, the click and murmur move away from the first heart sound with squatting because of the delay in onset of leaflet prolapse at higher ventricular volumes. With rapid standing, however, the click and murmur move closer to the first heart sound as prolapse occurs earlier in systole at a smaller chamber dimension. The murmur of HOCM behaves similarly, becoming softer and shorter with squatting (95% sensitivity, 85% specificity) and longer and louder on rapid standing (95% sensitivity, 84% specificity). A change in the intensity of a systolic murmur in the first beat after a premature beat or in the beat after a long cycle length in patients with atrial fibrillation suggests valvular AS rather than MR, particularly in an older patient in whom the murmur of the AS may be well transmitted to the apex (Gallavardin effect). Of note, however, the systolic murmur of HOCM also increases in intensity in the beat after a premature beat. This increase in intensity of any LV outflow murmur in the beat after a premature beat relates to the combined effects of enhanced LV filling (from the longer diastolic period) and postextrasystolic potentiation of LV contractile function. In either instance, forward flow will accelerate, causing an increase in the gradient across the LV outflow tract (dynamic or fixed) and a louder systolic murmur. In contrast, the intensity of the murmur of MR does not change in a postpremature beat, because there is relatively little change in the nearly constant LV to left atrial pressure gradient or further alteration in mitral valve flow. Bedside exercise can sometimes be performed to increase cardiac output and, secondarily, the intensity of both systolic and diastolic heart murmurs. Most left-sided heart murmurs decrease in intensity and duration during the strain phase of the Valsalva maneuver. The murmurs associated with MVP and HOCM are the two notable exceptions. The Valsalva maneuver also can be used to assess the integrity of the heart and vasculature in the setting of advanced heart failure.

Prosthetic Heart Valves The first clue that prosthetic valve dysfunction may contribute to recurrent symptoms is frequently a change in the quality of the heart sounds or the appearance of a new murmur. The heart sounds with a bioprosthetic valve resemble those generated by native valves. A mitral bioprosthetic usually is associated with a grade 2 or 3 midsystolic murmur along the left sternal border (created by turbulence across the valve struts as they project into the LV outflow tract) as well as by a soft mid-diastolic murmur that occurs with normal LV filling. This diastolic murmur often can be heard only in the left lateral decubitus position and after exercise. A high pitched or holosystolic apical murmur is indicative of pathologic MR due to a paravalvular leak and/or intra-annular bioprosthetic regurgitation from leaflet degeneration, for which additional imaging is usually indicated. Clinical deterioration can occur rapidly after the first expression of mitral bioprosthetic failure. A tissue valve in the aortic position is always associated with a grade 2 to 3 midsystolic murmur at the base or just below the suprasternal notch. A diastolic murmur of AR is abnormal in any circumstance. Mechanical valve dysfunction may first be suggested by a decrease in the intensity of either the opening or the closing sound. A high-pitched apical systolic murmur in patients with a mechanical mitral prosthesis and a diastolic decrescendo murmur in patients with a mechanical aortic prosthesis indicate paravalvular regurgitation. Patients with prosthetic valve thrombosis may present clinically with signs of shock, muffled heart sounds, and soft murmurs.

Pericardial Disease A pericardial friction rub is nearly 100% specific for the diagnosis of acute pericarditis, although the sensitivity of this finding is not nearly as high, because the rub may come and go over the course of an acute illness or be very difficult to elicit. The rub is heard as a leathery or scratchy three-component or two-component sound, although it may be monophasic. Classically, the three components are ventricular systole, rapid early diastolic filling, and late presystolic filling after atrial contraction in patients in sinus rhythm. It is necessary to listen to the heart in several positions. Additional clues may be present from the history and 12-lead electrocardiogram. The rub typically disappears as the volume of any pericardial effusion increases. Pericardial tamponade can be diagnosed with a sensitivity of 98%, a specificity of 83%, and a positive likelihood ratio of 5.9 (95% confidence interval 2.4–14) by a pulsus paradoxus that exceeds 12 mmHg in a patient with a large pericardial effusion.

The findings on physical examination are integrated with the symptoms previously elicited with a careful history to construct an appropriate differential diagnosis and proceed with indicated imaging and laboratory assessment. The physical examination is an irreplaceable component of the diagnostic algorithm and in selected patients can inform prognosis. Educational efforts to improve clinician competence eventually may result in cost saving, particularly if the indications for imaging can be influenced by the examination findings.

268 Electrocardiography

Ary L. Goldberger

An electrocardiogram (ECG or EKG) is a graphic recording of electric potentials generated by the heart. The signals are detected by means of metal electrodes attached to the extremities and chest wall and then are amplified and recorded by the electrocardiograph. ECG *leads* actually display the instantaneous *differences* in potential between the electrodes.

The clinical utility of the ECG derives from its immediate availability as a noninvasive, inexpensive, and highly versatile test. In addition to its use in detecting arrhythmias, conduction disturbances, and myocardial ischemia, electrocardiography may reveal findings related to life-threatening metabolic disturbances (e.g., hyperkalemia) or increased susceptibility to sudden cardiac death (e.g., QT prolongation syndromes).

(See also Chaps. 274 and 276) Depolarization of the heart is the initiating event for cardiac contraction. The electric currents that spread through the heart are produced by three components: cardiac pacemaker cells, specialized conduction tissue, and the heart muscle itself. The ECG, however, records only the depolarization (stimulation) and repolarization (recovery) potentials generated by the “working” atrial and ventricular myocardium.

The depolarization stimulus for the normal heartbeat originates in the *sinoatrial (SA) node* (Fig. 268-1), or *sinus node*, a collection of *pacemaker cells*. These cells fire spontaneously; that is, they exhibit *automaticity*. The first phase of cardiac electrical activation is the spread of the depolarization wave through the right and left atria, followed by atrial contraction. Next, the impulse stimulates pacemaker and specialized conduction tissues in the atrioventricular (AV) nodal and His-bundle areas; together, these two regions constitute the AV junction. The bundle of His bifurcates into two main branches, the right and left bundles, which rapidly transmit depolarization wavefronts to the right and left ventricular myocardium by way of Purkinje fibers. The main left bundle bifurcates into two primary subdivisions: a left anterior fascicle and a left posterior fascicle. The depolarization wavefronts then spread through the ventricular wall, from endocardium to epicardium, triggering ventricular contraction.

Since the cardiac depolarization and repolarization waves have direction and magnitude, they can be represented by vectors. Vector analysis illustrates a central concept of electrocardiography: The ECG records the complex spatial and temporal summation of electrical potentials from multiple myocardial fibers conducted to the surface of the body. This principle accounts for inherent limitations in both ECG *sensitivity* (activity from certain cardiac regions may be canceled out or may be too weak to be recorded) and *specificity* (the same vectorial sum can result from either a selective gain or a loss of forces in opposite directions).

ECG WAVEFORMS AND INTERVALS

The ECG waveforms are labeled alphabetically, beginning with the P wave, which represents atrial depolarization (Fig. 268-2). The QRS complex represents ventricular depolarization, and the ST-T-U complex (ST segment, T wave, and U wave) represents ventricular repolarization. The J point is the junction between the end of the QRS complex and the beginning of the ST segment. Atrial repolarization ($S T_a$ and T_a) is usually too low in amplitude to be detected, but it may become apparent in conditions such as acute pericarditis and atrial infarction.

The QRS-T waveforms of the surface ECG correspond in a general way with the different phases of simultaneously obtained ventricular *action potentials*, the intracellular recordings from single myocardial

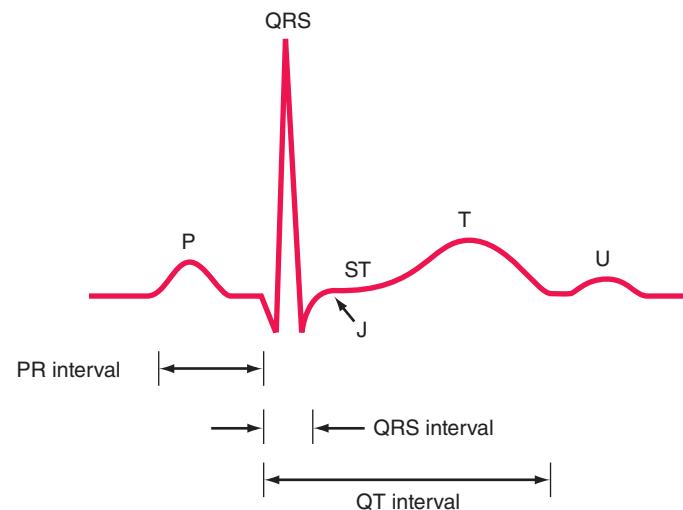


FIGURE 268-2 Basic ECG waveforms and intervals. Not shown is the RR interval, the time between consecutive QRS complexes.

fibers (Chap. 274). The rapid upstroke (phase 0) of the action potential corresponds to the onset of QRS. The plateau (phase 2) corresponds to the isoelectric ST segment, and active repolarization (phase 3) corresponds to the inscription of the T wave. Factors that decrease the slope of phase 0 by impairing the influx of Na^+ (e.g., hyperkalemia and drugs such as flecainide) tend to increase QRS duration. Conditions that prolong phase 2 (amiodarone, hypocalcemia) increase the QT interval. In contrast, shortening of ventricular repolarization (phase 2), such as by digitalis administration or hypercalcemia, abbreviates the ST segment.

The ECG ordinarily is recorded on special graph paper that is divided into 1-mm² gridlike boxes. Since the usual ECG paper speed is 25 mm/s, the smallest (1 mm) horizontal divisions correspond to 0.04 (40 ms), with heavier lines at intervals of 0.20 s (200 ms). Vertically, the ECG graph measures the amplitude of a specific wave or deflection (1 mV = 10 mm with standard calibration; the voltage criteria for hypertrophy mentioned below are given in millimeters). There are four major ECG intervals: RR, PR, QRS, and QT (Fig. 268-2). The heart rate (beats per minute) can be computed readily from the interbeat (RR) interval by dividing the number of large (0.20 s) time units between consecutive R waves into 300 or the number of small (0.04 s) units into 1500. The PR interval measures the time (normally 120–200 ms) between atrial and ventricular depolarization, which includes the physiologic delay imposed by stimulation of cells in the AV junction area. The QRS interval (normally 100–110 ms or less) reflects the duration of ventricular depolarization. The QT interval includes both ventricular depolarization and repolarization times and varies inversely with the heart rate. A rate-related (“corrected”) QT interval, QT_c , can be calculated as QT/\sqrt{RR} and normally is ≤ 0.44 s. (Some references give QT_c upper normal limits as 0.43 s in men and 0.45 s in women. Also, a number of different formulas have been proposed, without consensus, for calculating the QT_c .)

The QRS complex is subdivided into specific deflections or waves. If the initial QRS deflection in a particular lead is negative, it is termed a *Q wave*; the first positive deflection is termed an *R wave*. A negative deflection after an R wave is an *S wave*. Subsequent positive or negative waves are labeled *R'* and *S'*, respectively. Lowercase letters (qrs) are used for waves of relatively small amplitude. An entirely negative QRS complex is termed a *QS wave*.

ECG LEADS

The 12 conventional ECG leads record the difference in potential between electrodes placed on the surface of the body. These leads are divided into two groups: six limb (extremity) leads and six chest (precordial) leads. The limb leads record potentials transmitted onto the *frontal plane* (Fig. 268-3A), and the chest leads record potentials transmitted onto the *horizontal plane* (Fig. 268-3B).

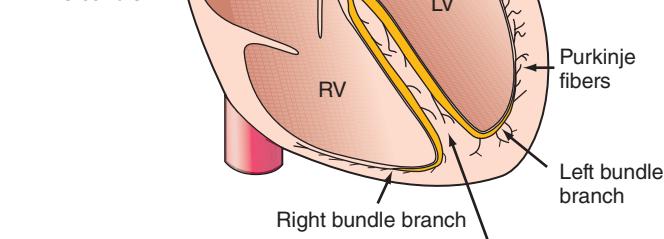


FIGURE 268-1 Schematic of the cardiac conduction system.

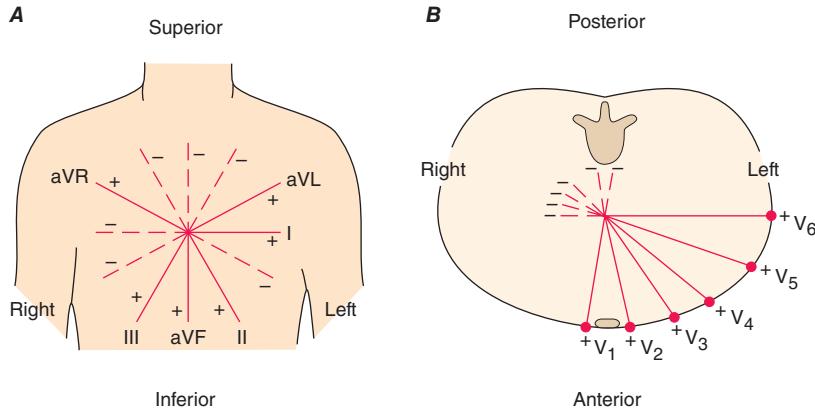


FIGURE 268-3 The six frontal plane (**A**) and six horizontal plane (**B**) leads provide a three-dimensional representation of cardiac electrical activity.

The spatial orientation and polarity of the six frontal plane leads is represented on the hexaxial diagram (Fig. 268-4). The six chest leads (Fig. 268-5) are unipolar recordings obtained by electrodes in the following positions: lead V_1 , fourth intercostal space, just to the right of the sternum; lead V_2 , fourth intercostal space, just to the left of the sternum; lead V_3 , midway between V_2 and V_4 ; lead V_4 , midclavicular line, fifth intercostal space; lead V_5 , anterior axillary line, same level as V_4 ; and lead V_6 , midaxillary line, same level as V_4 and V_5 . Additional posterior leads are sometimes placed on the same horizontal plane as V_4 to facilitate detection of acute posterolateral infarction (V_7 , midaxillary line; V_8 , posterior axillary line; and V_9 , posterior scapular line).

Together, the frontal and horizontal plane electrodes provide a three-dimensional representation of cardiac electrical activity. Each lead can be likened to a different video camera angle “looking” at the same events—atrial and ventricular depolarization and repolarization—from different spatial orientations. The conventional 12-lead ECG can be supplemented with additional leads in special circumstances. For example, right precordial leads V_3R , V_4R , etc., are useful in detecting evidence of acute right ventricular ischemia. Bedside monitors and

ambulatory ECG (Holter) recordings usually employ only one or two modified leads. **Intracardiac electrocardiography and electrophysiologic testing are discussed in Chaps. 274 and 276.**

The ECG leads are configured so that a positive (upright) deflection is recorded in a lead if a wave of depolarization spreads toward the positive pole of that lead, and a negative deflection is recorded if the wave spreads toward the negative pole. If the *mean* orientation of the depolarization vector is at right angles to a particular lead axis, a biphasic (equally positive and negative) deflection will be recorded.

GENESIS OF THE NORMAL ECG

P WAVE

The normal atrial depolarization vector is oriented downward and toward the subject’s left, reflecting the spread of depolarization from the sinus node to the right and then

the left atrial myocardium. Since this vector points toward the positive pole of lead II and toward the negative pole of lead aVR, the normal P wave will be positive in lead II and negative in lead aVR. By contrast, activation of the atria from an ectopic pacemaker in the lower part of either atrium or in the AV junction region may produce retrograde P waves (negative in lead II, positive in lead aVR). The normal P wave in lead V_1 may be biphasic with a positive component reflecting right atrial depolarization, followed by a small ($<1 \text{ mm}^2$) negative component reflecting left atrial depolarization.

QRS COMPLEX

Normal ventricular depolarization proceeds as a rapid, continuous spread of activation wave fronts. This complex process can be divided into two major sequential phases, and each phase can be represented by a mean vector (Fig. 268-6). The first phase is depolarization of the interventricular septum from the left to the right and anteriorly (vector 1). The second results from the simultaneous depolarization of the right and left ventricles; it normally is dominated by the more massive left ventricle, so that vector 2 points leftward and posteriorly. Therefore, a right precordial lead (V_1) will record this biphasic depolarization process with a small positive deflection (septal r wave) followed by a larger negative deflection (S wave). A left precordial lead, e.g., V_6 , will record the same sequence with a small negative deflection (septal q wave) followed by a relatively tall positive deflection (R wave). Intermediate leads show a relative increase in R-wave amplitude (normal R-wave progression) and a decrease in S-wave amplitude progressing across the chest from right to left. The precordial lead where

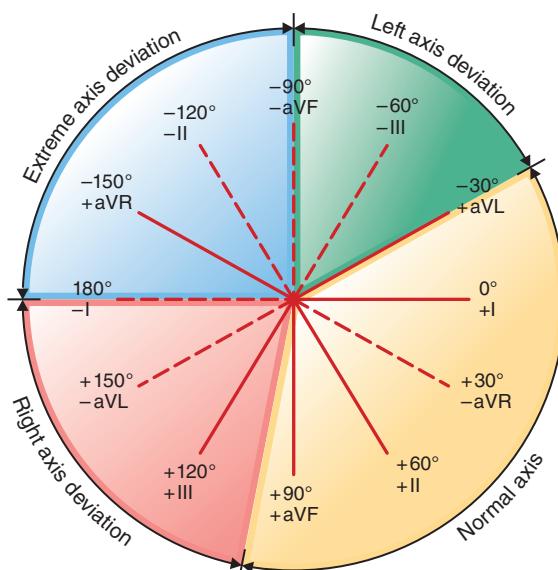


FIGURE 268-4 The frontal plane (limb or extremity) leads are represented on a hexaxial diagram. Each ECG lead has a specific spatial orientation and polarity. The positive pole of each lead axis (solid line) and the negative pole (hatched line) are designated by their angular position relative to the positive pole of lead I (0°). The mean electrical axis of the QRS complex is measured with respect to this display.

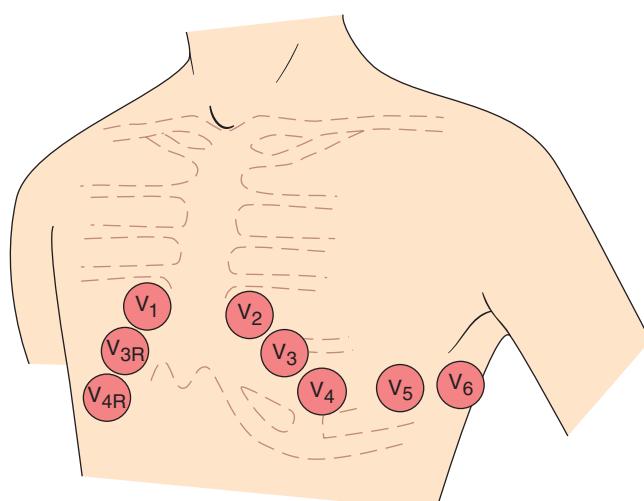


FIGURE 268-5 The horizontal plane (chest or precordial) leads are obtained with electrodes in the locations shown.

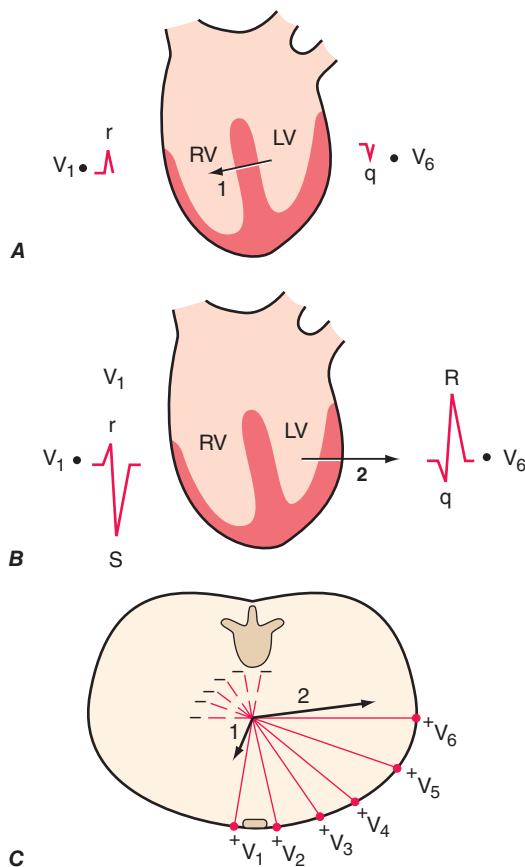


FIGURE 268-6 Ventricular depolarization can be divided into two major phases, each represented by a vector. **A.** The first phase (arrow 1) denotes depolarization of the ventricular septum, beginning on the left side and spreading to the right. This process is represented by a small “septal” r wave in lead V₁, and a small septal q wave in lead V₆. **B.** Simultaneous depolarization of the left and right ventricles (LV and RV) constitutes the second phase. Vector 2 is oriented to the left and posteriorly, reflecting the electrical predominance of the LV. **C.** Vectors (arrows) representing these two phases are shown in reference to the horizontal plane leads. (After AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia, Elsevier/Saunders, 2013.)

the R and S waves are of approximately equal amplitude is referred to as the *transition zone* (usually V₃ or V₄) (Fig. 268-7).

The QRS pattern in the extremity leads may vary considerably from one normal subject to another depending on the *electrical axis* of the QRS, which describes the mean orientation of the QRS vector with reference to the six frontal plane leads. Normally, the QRS axis ranges from -30° to $+100^\circ$ (Fig. 268-4). An axis more negative than -30° is referred to as *left axis deviation*, and an axis more positive than $+100^\circ$ is referred to as *right axis deviation*. Left axis deviation may occur as a normal variant but is more commonly associated with left ventricular hypertrophy, a block in the anterior fascicle of the left bundle system (left anterior fascicular block or hemiblock), or inferior myocardial infarction. Right axis deviation

also may occur as a normal variant (particularly in children and young adults), as a spurious finding due to reversal of the left and right arm electrodes, or in conditions such as right ventricular overload (acute or chronic), infarction of the lateral wall of the left ventricle, dextrocardia, left pneumothorax, and left posterior fascicular block.

T WAVE AND U WAVE

Normally, the mean T-wave vector is oriented roughly concordant with the mean QRS vector (within about 45° in the frontal plane). Since depolarization and repolarization are electrically opposite processes, this normal QRS-T-wave vector concordance indicates that repolarization normally must proceed in the reverse direction from depolarization (i.e., from ventricular epicardium to endocardium). The normal U wave is a small, rounded deflection (≤ 1 mm) that follows the T wave and usually has the same polarity as the T wave. An abnormal increase in U-wave amplitude is most commonly due to drugs (e.g., dofetilide, amiodarone, sotalol, quinidine) or to hypokalemia. Very prominent U waves are a marker of increased susceptibility to the *torsades de pointes* type of ventricular tachycardia (Chap. 276). Inversion of the U wave in the precordial leads is abnormal and may be a subtle sign of ischemia.

MAJOR ECG ABNORMALITIES

CARDIAC ENLARGEMENT AND HYPERTROPHY

Right atrial overload (acute or chronic) may lead to an increase in P-wave amplitude (≥ 2.5 mm) (Fig. 268-8), sometimes referred to as “P-pulmonale.” Left atrial overload typically produces a biphasic P wave in V₁ with a broad negative component or a broad (≥ 120 ms), often notched P wave in one or more limb leads (Fig. 268-8). This pattern, previously referred to as “P-mitrile,” may also occur with left atrial conduction delays in the absence of actual atrial enlargement, leading to the more general designation of *left atrial abnormality*.

Right ventricular hypertrophy due to a sustained, severe pressure load (e.g., due to tight pulmonic valve stenosis or certain pulmonary artery hypertension syndromes) is characterized by a relatively tall R wave in lead V₁ ($R \geq S$ wave), usually with right axis deviation (Fig. 268-9); alternatively, there may be a QR pattern in V₁ or V₃R. ST depression and T-wave inversion in the right-to-midprecordial leads are also often present. This pattern, formerly called right ventricular “strain,” is attributed to repolarization abnormalities in acutely or chronically overloaded muscle. Prominent S waves may occur in the left lateral precordial leads. Right ventricular hypertrophy due to ostium secundum-type atrial septal defects, with the accompanying

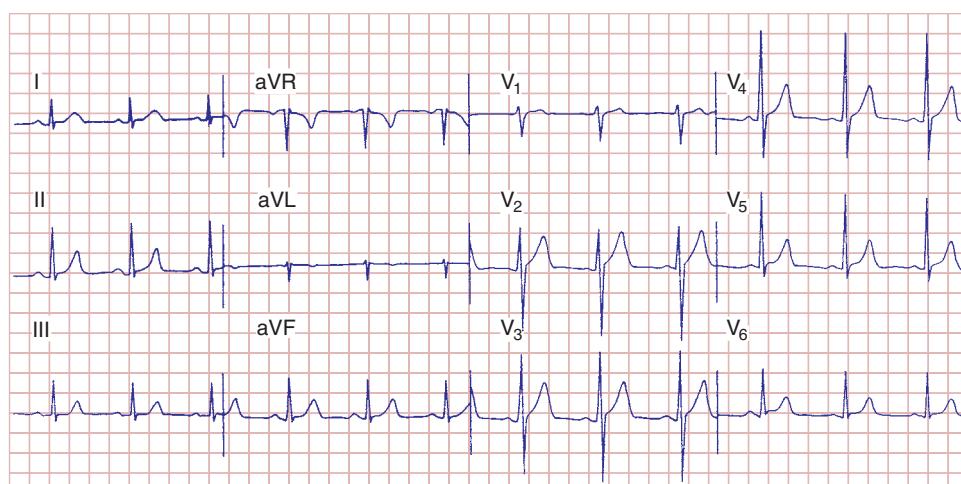


FIGURE 268-7 Normal electrocardiogram from a healthy subject. Sinus rhythm is present with a heart rate of 75 beats per minute. PR interval is 0.16 s; QRS interval (duration) is 0.08 s; QT interval is 0.36 s; QT_c is 0.40 s; the mean QRS axis is about $+70^\circ$. The precordial leads show normal R-wave progression with the transition zone (R wave = S wave) in lead V₃.

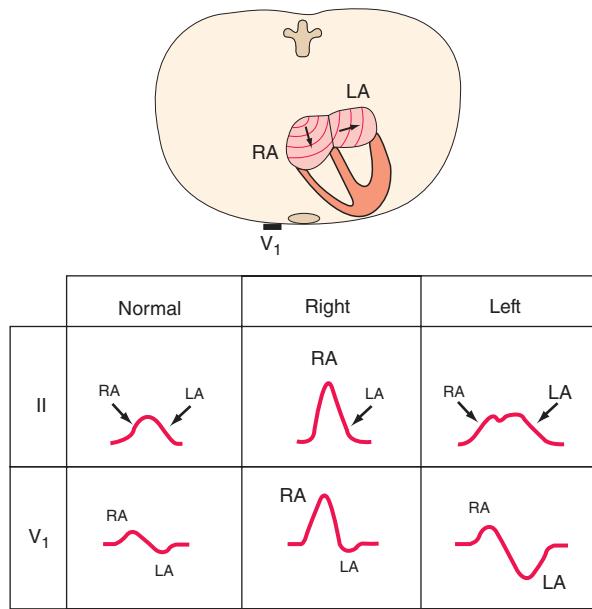


FIGURE 268-8 Right atrial (RA) overload may cause tall, peaked P waves in the limb or precordial leads. Left atrial (LA) abnormality may cause broad, often notched P waves in the limb leads and a biphasic P wave in lead V₁ with a prominent negative component representing delayed depolarization of the LA. (After MK Park, WG Guntheroth: How to Read Pediatric ECGs, 4th ed. St. Louis, Mosby/Elsevier, 2006.)

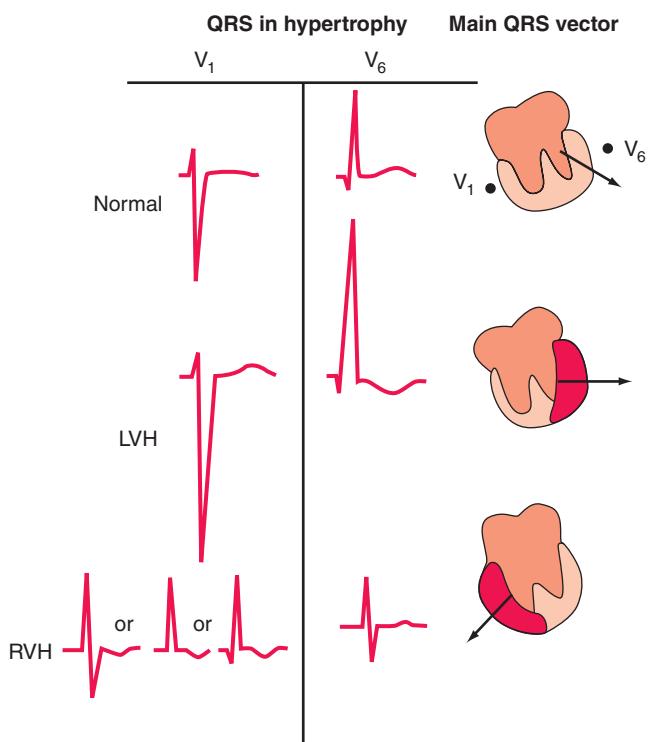


FIGURE 268-9 Left ventricular hypertrophy (LVH) increases the amplitude of electrical forces directed to the left and posteriorly. In addition, repolarization abnormalities may cause ST-segment depression and T-wave inversion in leads with a prominent R wave. Right ventricular hypertrophy (RVH) may shift the QRS vector to the right; this effect usually is associated with an R, RS, or qR complex in lead V₁. T-wave inversions may be present in right precordial leads.

right ventricular volume overload, is commonly associated with an incomplete or complete right bundle branch block pattern with a rightward QRS axis.

Acute cor pulmonale due to pulmonary embolism (Chap. 300), for example, may be associated with a normal ECG or a variety of abnormalities. Sinus tachycardia is the most common arrhythmia, although other tachyarrhythmias, such as atrial fibrillation or flutter, may occur. The QRS axis may shift to the right, sometimes in concert with the so-called S₁Q₃T₃ pattern (prominence of the S wave in lead I and the Q wave in lead III, with T-wave inversion in lead III). Acute right ventricular dilation also may be associated with slow R-wave progression and ST-T abnormalities in V₁ to V₄ simulating acute anterior infarction. A right ventricular conduction disturbance may appear.

Chronic cor pulmonale due to obstructive lung disease (Chap. 279) usually does not produce the classic ECG patterns of right ventricular hypertrophy noted above. Instead of tall right precordial R waves, chronic lung disease more typically is associated with small R waves in right-to-midprecordial leads (slow R-wave progression) due in part to downward displacement of the diaphragm and the heart. Low-voltage complexes are commonly present, owing to hyperaeration of the lungs.

A number of different voltage criteria for *left ventricular hypertrophy* (Fig. 268-9) have been proposed on the basis of the presence of tall left precordial R waves and deep right precordial S waves (e.g., SV₁ + [RV₅ or RV₆] >35 mm). Repolarization abnormalities (ST depression with T-wave inversions, formerly called the left ventricular “strain” pattern) also may appear in leads with prominent R waves. However, prominent precordial voltages may occur as a normal variant, especially in athletic or young individuals. Left ventricular hypertrophy may increase limb lead voltage with or without increased precordial voltage (e.g., RaVL + SV₃ >20 mm in women and >28 mm in men). The presence of left atrial abnormality increases the likelihood of underlying left ventricular hypertrophy in cases with borderline voltage criteria. Left ventricular hypertrophy often progresses to incomplete or complete left bundle branch block. The sensitivity of conventional voltage criteria for left ventricular hypertrophy is decreased in obese persons and smokers. ECG evidence for left ventricular hypertrophy is a major noninvasive marker of increased risk of cardiovascular morbidity and mortality rates, including sudden cardiac death. However, because of false-positive and false-negative diagnoses, the ECG is of limited utility in diagnosing atrial or ventricular enlargement. More definitive information is provided by echocardiography (Chap. 270e).

BUNDLE BRANCH BLOCKS AND RELATED PATTERNS

Intrinsic impairment of conduction in either the right or the left bundle system (intraventricular conduction disturbances) leads to prolongation of the QRS interval. With complete bundle branch blocks, the QRS interval is ≥120 ms in duration; with incomplete blocks, the QRS interval is between 100 and 120 ms. The QRS vector usually is oriented in the direction of the myocardial region where depolarization is delayed (Fig. 268-10). Thus, with right bundle branch block, the terminal QRS vector is oriented to the right and anteriorly (rSR' in V₁ and qRS in V₆, typically). Left bundle branch block alters both early and later phases of ventricular depolarization. The major QRS vector is directed to the left and posteriorly. In addition, the normal early left-to-right pattern of septal activation is disrupted such that septal depolarization proceeds from right to left as well. As a result, left bundle branch block generates wide, predominantly negative (QS) complexes in lead V₁ and entirely positive (R) complexes in lead V₆. A pattern identical to that of left bundle branch block, preceded by a sharp spike, is seen in most cases of electronic right ventricular pacing because of the relative delay in left ventricular activation.

Bundle branch block may occur in a variety of conditions. In subjects without structural heart disease, right bundle branch block is seen more commonly than left bundle branch block. Right bundle branch block also occurs with heart disease, both congenital (e.g., atrial septal defect) and acquired (e.g., valvular, ischemic). Left bundle branch block is often a marker of one of four underlying conditions associated with increased risk of cardiovascular morbidity and mortality rates: coronary heart disease (frequently with impaired left ventricular

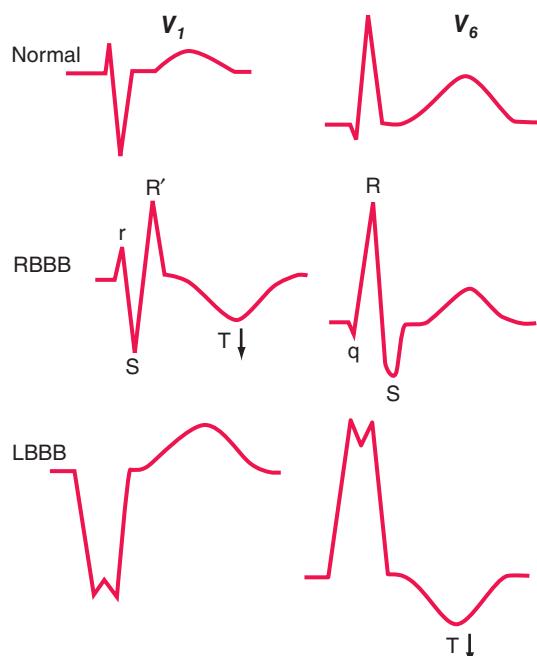


FIGURE 268-10 Comparison of typical QRS-T patterns in right bundle branch block (RBBB) and left bundle branch block (LBBB) with the normal pattern in leads V_1 and V_6 . Note the secondary T-wave inversions (arrows) in leads with an $r'R'$ complex with RBBB and in leads with a wide R wave with LBBB.

function), hypertensive heart disease, aortic valve disease, and cardiomyopathy. Bundle branch blocks may be chronic or intermittent. A bundle branch block may be rate-related; for example, it often occurs when the heart rate exceeds some critical value.

Bundle branch blocks and depolarization abnormalities secondary to artificial pacemakers not only affect ventricular depolarization (QRS) but also are characteristically associated with *secondary repolarization* (ST-T) abnormalities. With bundle branch blocks, the T wave is typically opposite in polarity to the last deflection of the QRS (Fig. 268-10). This discordance of the QRS-T-wave vectors is caused by the altered sequence of repolarization that occurs secondary to altered depolarization. In contrast, *primary repolarization* abnormalities are independent of QRS changes and are related instead to actual alterations in the electrical properties of the myocardial fibers themselves (e.g., in the resting membrane potential or action potential duration), not just to changes in the sequence of repolarization. Ischemia, electrolyte imbalance, and drugs such as digitalis all cause such primary ST-T-wave changes. Primary and secondary T-wave changes may coexist. For example, T-wave inversions in the right precordial leads with left bundle branch block or in the left precordial leads with right bundle branch block may be important markers of underlying ischemia or other abnormalities.

A distinctive abnormality simulating right bundle branch block with ST-segment elevations in the right chest leads is seen with the Brugada pattern (Chap. 276).

Partial blocks (fascicular or “hemiblocks”) in the left bundle system (left anterior or posterior fascicular blocks) generally do not prolong the QRS duration substantially but instead are associated with shifts in the frontal plane QRS axis (leftward or rightward, respectively). Left anterior fascicular block (QRS axis more negative than -45°) is probably the most common cause of marked left axis deviation in adults. In contrast, left posterior fascicular block (QRS axis more

rightward than $+110\text{--}120^\circ$) is extremely rare as an isolated finding and requires exclusion of other factors causing right axis deviation mentioned earlier.

More complex combinations of fascicular and bundle branch blocks may occur that involve the left and right bundle system. Examples of *bifascicular block* include right bundle branch block and left posterior fascicular block, right bundle branch block with left anterior fascicular block, and complete left bundle branch block. Chronic bifascicular block in an asymptomatic individual is associated with a relatively low risk of progression to high-degree AV heart block. In contrast, new bifascicular block with acute anterior myocardial infarction carries a much greater risk of complete heart block. Alternation of right and left bundle branch block is a sign of *trifascicular disease*. However, the presence of a prolonged PR interval and bifascicular block does not necessarily indicate trifascicular involvement, since this combination may arise with AV node disease and bifascicular block. Intraventricular conduction delays also can be caused by extrinsic (toxic) factors that slow ventricular conduction, particularly hyperkalemia or drugs (e.g., class 1 antiarrhythmic agents, tricyclic antidepressants, phenothiazines).

Prolongation of QRS duration does not necessarily indicate a conduction delay but may be due to *preexcitation* of the ventricles via a bypass tract, as in Wolff-Parkinson-White (WPW) patterns (Chap. 276) and related variants. The diagnostic triad of WPW consists of a wide QRS complex associated with a relatively short PR interval and slurring of the initial part of the QRS (delta wave), with the latter effect being due to aberrant activation of ventricular myocardium. The presence of a bypass tract predisposes to reentrant supraventricular tachyarrhythmias.

MYOCARDIAL ISCHEMIA AND INFARCTION

(See also Chap. 295) The ECG is a cornerstone in the diagnosis of acute and chronic ischemic heart disease. The findings depend on several key factors: the nature of the process (reversible [i.e., ischemia] versus irreversible [i.e., infarction]), the duration (acute versus chronic), the extent (transmural versus subendocardial), and localization (anterior versus inferoposterior), as well as the presence of other underlying abnormalities (ventricular hypertrophy, conduction defects).

Ischemia exerts complex time-dependent effects on the electrical properties of myocardial cells. Severe, acute ischemia lowers the resting membrane potential and shortens the duration of the action potential. Such changes cause a voltage gradient between normal and ischemic zones. As a consequence, current flows between those regions. These currents of injury are represented on the surface ECG by deviation of the ST segment (Fig. 268-11). When the acute ischemia is *transmural*, the ST vector usually is shifted in the direction of the outer (epicardial) layers, producing ST elevations and sometimes, in the earliest stages of ischemia, tall, positive so-called hyperacute T waves over the ischemic zone. With ischemia confined primarily to the *subendocardium*, the ST vector typically shifts toward the subendocardium and ventricular cavity, so that overlying (e.g., anterior precordial) leads show ST-segment depression (with ST elevation in lead aVR). Multiple factors affect the amplitude of acute ischemic ST deviations. Profound ST elevation or depression in multiple leads usually indicates very severe ischemia.

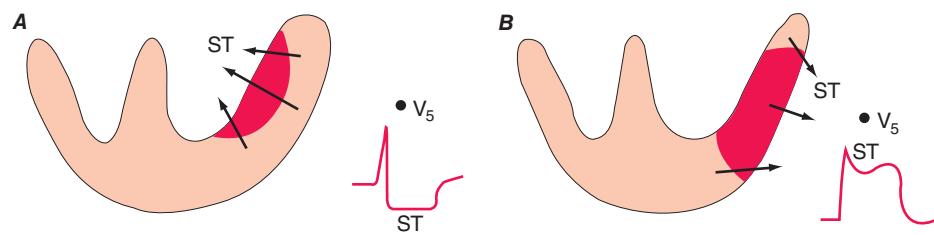


FIGURE 268-11 Acute ischemia causes a current of injury. With predominant subendocardial ischemia (**A**), the resultant ST vector will be directed toward the inner layer of the affected ventricle and the ventricular cavity. Overlying leads therefore will record ST depression. With ischemia involving the outer ventricular layer (**B**) (transmural or epicardial injury), the ST vector will be directed outward. Overlying leads will record ST elevation.

- 1456** From a clinical viewpoint, the division of acute myocardial infarction into ST-segment elevation and non-ST elevation types is useful since the efficacy of acute reperfusion therapy is limited to the former group.

The ECG leads are usually more helpful in localizing regions of ST elevation than non-ST elevation ischemia. For example, acute transmural anterior (including apical and lateral) wall ischemia is reflected by ST elevations or increased T-wave positivity in one or more of the precordial leads (V_1-V_6) and leads I and aVL. Inferior wall ischemia produces changes in leads II, III, and aVF. "Posterior" wall ischemia (usually associated with lateral or inferior involvement) may be indirectly recognized by *reciprocal* ST depressions in leads V_1 to V_3 (thus constituting an ST elevation "equivalent" acute coronary syndrome). Right ventricular ischemia usually produces ST elevations in right-sided chest leads (Fig. 268-5). When ischemic ST elevations occur as the earliest sign of acute infarction, they typically are followed within a period ranging from hours to days by evolving T-wave inversions and often by Q waves occurring in the same lead distribution. Reversible transmural ischemia, for example, due to coronary vasospasm (Prinzmetal's variant angina and possibly the Tako-tsubo "stress" cardiomyopathy syndrome), may cause transient ST-segment elevations without development of Q waves, as may very early reperfusion in acute coronary syndromes. Depending on the severity and duration of ischemia, the ST elevations may resolve completely in minutes or be followed by T-wave inversions that persist for hours or even days. Patients with ischemic chest pain who present with deep T-wave inversions in multiple precordial leads (e.g., V_1-V_4 , I, and aVL) with or without cardiac enzyme elevations typically have severe obstruction in the left anterior descending coronary artery system (Fig. 268-12). In contrast, patients whose baseline ECG already shows abnormal T-wave inversions may develop T-wave normalization (*pseudonormalization*) during episodes of acute transmural ischemia.

With infarction, depolarization (QRS) changes often accompany repolarization (ST-T) abnormalities. Necrosis of sufficient myocardial

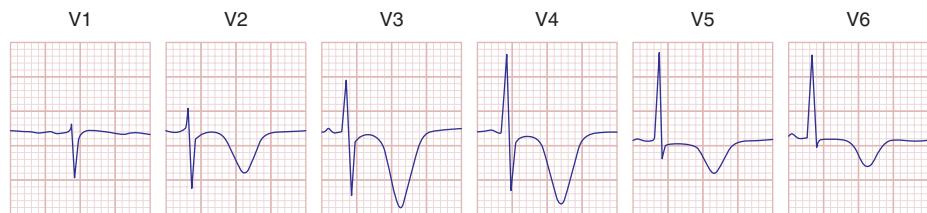


FIGURE 268-12 Severe anterior wall ischemia (with or without infarction) may cause prominent T-wave inversions in the precordial leads. This pattern (sometimes referred to as Wellens T waves) is usually associated with a high-grade stenosis of the left anterior descending coronary artery.

tissue may lead to decreased R-wave amplitude or abnormal Q waves (even in the absence of transmurality) in the anterior or inferior leads (Fig. 268-13). Previously, abnormal Q waves were considered markers of transmural myocardial infarction, whereas subendocardial infarcts were thought not to produce Q waves. However, careful ECG-pathology correlative studies have indicated that transmural infarcts may occur without Q waves and that subendocardial (nontransmural) infarcts sometimes may be associated with Q waves. Therefore, infarcts are more appropriately classified as "Q-wave" or "non-Q-wave." The major acute ECG changes in syndromes of ischemic heart disease are summarized schematically in Fig. 268-14. Loss of depolarization forces due to posterior or lateral infarction may cause reciprocal increases in R-wave amplitude in leads V_1 and V_2 without diagnostic Q waves in any of the conventional leads. Atrial infarction may be associated with PR-segment deviations due to an atrial current of injury, changes in P-wave morphology, or atrial arrhythmias. In the weeks and months after infarction, these ECG changes may persist or begin to resolve. Complete normalization of the ECG after Q-wave infarction is uncommon but may occur, particularly with smaller infarcts. In contrast, ST-segment elevations that persist for several weeks or more after a Q-wave infarct usually correlate with a severe underlying wall motion disorder (akinetic or dyskinetic zone), although not necessarily a frank ventricular aneurysm. ECG changes due to ischemia may occur spontaneously or may be provoked by various exercise protocols (stress electrocardiography; Chap. 293).

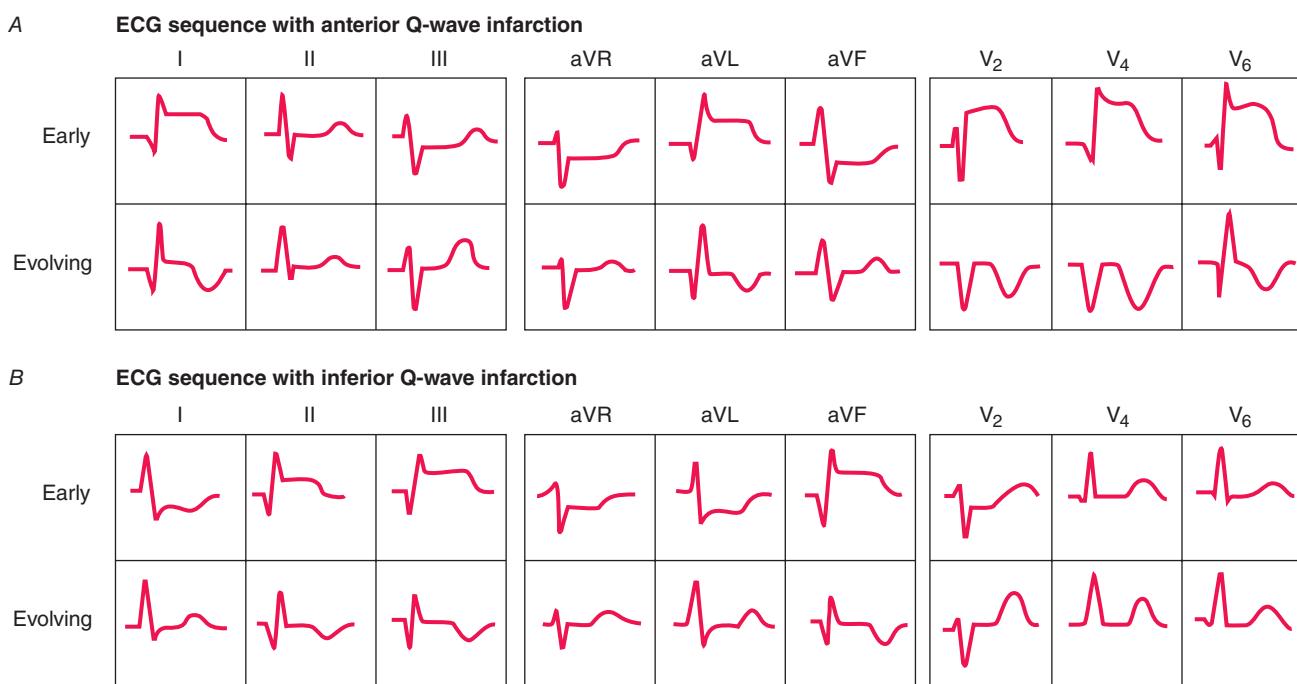


FIGURE 268-13 Sequence of depolarization and repolarization changes with (A) acute anterior and (B) acute inferior wall Q-wave infarctions. With anterior infarcts, ST elevation in leads I and aVL and the precordial leads may be accompanied by reciprocal ST depressions in leads II, III, and aVF. Conversely, acute inferior (or posterolateral) infarcts may be associated with reciprocal ST depressions in leads V_1 to V_3 . (After AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia, Elsevier/Saunders, 2013.)

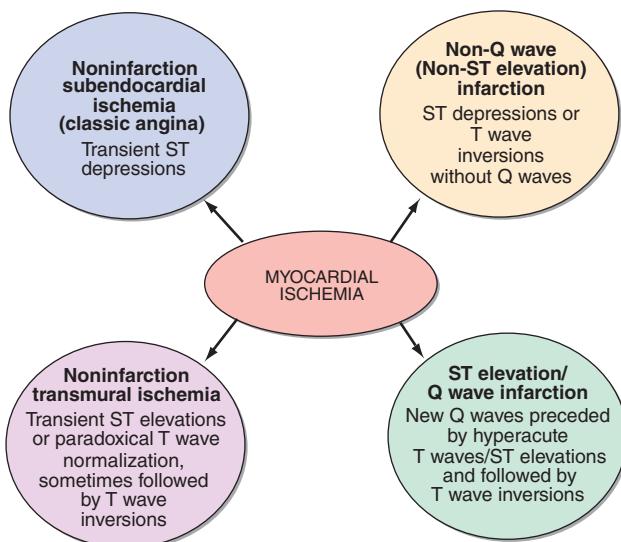


FIGURE 268-14 Variability of ECG patterns with acute myocardial ischemia. The ECG also may be normal or nonspecifically abnormal. Furthermore, these categorizations are not mutually exclusive. (After AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia, Elsevier/Saunders, 2013.)

The ECG has important limitations in both sensitivity and specificity in the diagnosis of ischemic heart disease. Although a single normal ECG does not exclude ischemia or even acute infarction, a normal ECG *throughout* the course of an acute infarct is distinctly uncommon. Prolonged chest pain without diagnostic ECG changes therefore should always prompt a careful search for other noncoronary causes of chest pain (Chap. 19). Furthermore, the diagnostic changes of acute or evolving ischemia are often masked by the presence of left bundle branch block, electronic ventricular pacemaker patterns, and Wolff-Parkinson-White preexcitation. However, clinicians continue to over-diagnose ischemia or infarction based on the presence of ST-segment elevations or depressions; T-wave inversions; tall, positive T waves; or Q waves *not* related to ischemic heart disease (pseudoinfarct patterns). For example, ST-segment elevations simulating ischemia may occur with acute pericarditis or myocarditis, as a normal variant (including the typical "early repolarization" pattern), or in a variety of other conditions (Table 268-1). Similarly, tall, positive T waves do not invariably represent hyperacute ischemic changes but may also be caused by normal variants, hyperkalemia, cerebrovascular injury, and left ventricular volume overload due to mitral or aortic regurgitation, among other causes.

ST-segment elevations and tall, positive T waves are common findings in leads V₁ and V₂ in left bundle branch block or left ventricular hypertrophy in the absence of ischemia. The differential diagnosis of Q waves includes physiologic or positional variants, ventricular hypertrophy, acute or chronic noncoronary myocardial injury, hypertrophic cardiomyopathy, and ventricular conduction disorders. Digoxin, ventricular hypertrophy, hypokalemia, and a variety of other factors may cause ST-segment depression mimicking subendocardial ischemia. Prominent T-wave inversion may occur with ventricular hypertrophy, cardiomyopathies, myocarditis, and cerebrovascular injury (particularly intracranial bleeds), among many other conditions.

METABOLIC FACTORS AND DRUG EFFECTS

A variety of metabolic and pharmacologic agents alter the ECG and, in particular, cause changes in repolarization (ST-T-U) and sometimes QRS prolongation. Certain life-threatening electrolyte disturbances may be diagnosed initially and monitored from the ECG. *Hyperkalemia* produces a sequence of changes (Fig. 268-15), usually beginning with narrowing and peaking (tenting) of the T waves. Further elevation of extracellular K⁺ leads to AV conduction disturbances, diminution in P-wave amplitude, and widening of the QRS interval. Severe hyperkalemia

TABLE 268-1 DIFFERENTIAL DIAGNOSIS OF ST-SEGMENT ELEVATIONS

Ischemia/myocardial infarction
Noninfarction, transmural ischemia (Prinzmetal's angina, and probably Tako-tsubo syndrome, which may also exactly simulate classical acute infarction)
Acute myocardial infarction
Postmyocardial infarction (ventricular aneurysm pattern)
Acute pericarditis
Normal variants (including benign "early repolarization" patterns)
Left ventricular hypertrophy/left bundle branch block ^a
Other (rarer)
Acute pulmonary embolism ^a
Brugada patterns (right bundle branch block-like pattern with ST elevations in right precordial leads) ^a
Class 1C antiarrhythmic drugs ^a
DC cardioversion
Hypercalcemia ^a
Hyperkalemia ^a
Hypothermia (J [Osborn] waves)
Nonischemic myocardial injury
Myocarditis
Tumor invading left ventricle
Trauma to ventricles

^aUsually localized to V₁–V₂ or V₃.

Source: Modified from AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia, Elsevier/Saunders, 2013.

eventually causes cardiac arrest with a slow sinusoidal type of mechanism ("sine-wave" pattern) followed by asystole. *Hypokalemia* (Fig. 268-16) prolongs ventricular repolarization, often with prominent U waves. Prolongation of the QT interval is also seen with drugs that increase the duration of the ventricular action potential: class 1A antiarrhythmic agents and related drugs (e.g., quinidine, disopyramide, procainamide, tricyclic antidepressants, phenothiazines) and class III agents (e.g., amiodarone [Fig. 268-16], dofetilide, dronedarone, sotalol, ibutilide). Marked QT prolongation, sometimes with deep, wide T-wave inversions, may occur with intracranial bleeds, particularly subarachnoid hemorrhage ("CVA T-wave" pattern) (Fig. 268-16). Systemic *hypothermia* also prolongs repolarization, usually with a distinctive convex elevation of the J point (Osborn wave). *Hypocalcemia* typically prolongs the QT interval (ST portion), whereas *hypercalcemia* shortens it (Fig. 268-17). Digitalis glycosides also shorten the QT interval, often with a characteristic "scooping" of the ST-T-wave complex (*digitalis effect*).

Many other factors are associated with ECG changes, particularly alterations in ventricular repolarization. T-wave flattening, minimal T-wave inversions, or slight ST-segment depression ("nonspecific ST-T-wave changes") may occur with a variety of electrolyte and acid-base disturbances, a number of infectious processes, central nervous system disorders, endocrine abnormalities, many drugs, ischemia, hypoxia, and virtually any type of cardiopulmonary abnormality. Although subtle ST-T-wave changes may be markers of ischemia, transient nonspecific repolarization changes may also occur after a meal or with postural (orthostatic) change, hyperventilation, or exercise in healthy individuals.

LOW QRS VOLTAGE

Low QRS voltage is arbitrarily defined as peak-to-trough QRS amplitudes of ≤ 5 mm in the six limb leads and/or ≤ 10 mm in the chest leads. Multiple factors may be responsible. Among the most serious include pericardial (Fig. 268-18) or pleural effusions, chronic obstructive pulmonary disease, infiltrative cardiomyopathies, and anasarca.

ELECTRICAL ALTERNANS

Electrical alternans—a beat-to-beat alternation in one or more components of the ECG signal—is a common type of nonlinear cardiovascular response to a variety of hemodynamic and electrophysiologic

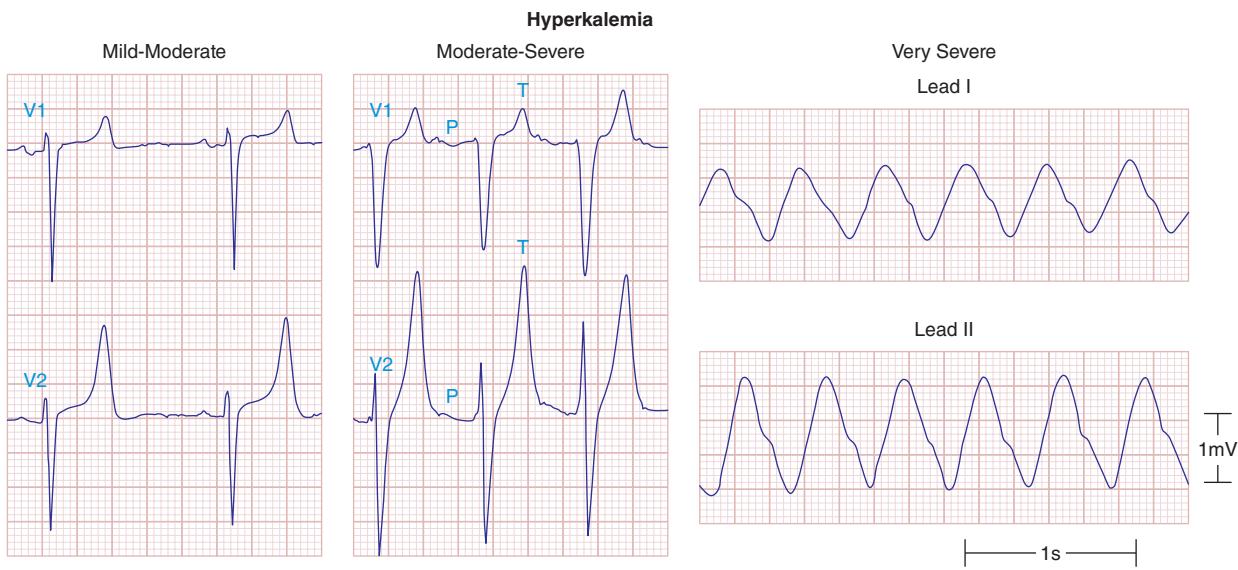


FIGURE 268-15 The earliest ECG change with hyperkalemia is usually peaking (“tenting”) of the T waves. With further increases in the serum potassium concentration, the QRS complexes widen, the P waves decrease in amplitude and may disappear, and finally a sine-wave pattern leads to asystole unless emergency therapy is given. (After AL Goldberger *et al*: Goldberger’s Clinical Electrocardiography: A Simplified Approach, 8th ed. Philadelphia, Elsevier/Saunders, 2013.)

perturbations. Total electrical alternans (P-QRS-T) with sinus tachycardia is a relatively specific sign of pericardial effusion, usually with cardiac tamponade (Fig. 268-18). The mechanism relates to a periodic swinging motion of the heart in the effusion at a frequency exactly one-half the heart rate. In contrast, pure repolarization (ST-T or U wave) alternans is a sign of electrical instability and may precede ventricular tachyarrhythmias.

CLINICAL INTERPRETATION OF THE ECG

Accurate analysis of ECGs requires thoroughness and care. The patient’s age, gender, and clinical status should always be taken into account. Many mistakes in ECG interpretation are errors of omission. Therefore, a systematic approach is essential. The following 14 points should be analyzed carefully in every ECG: (1) standardization (calibration) and technical features (including lead placement and artifacts), (2) rhythm, (3) heart rate, (4) PR interval/AV conduction, (5) QRS interval, (6) QT/QT_c intervals, (7) mean QRS electrical axis, (8) P waves, (9) QRS voltages, (10) precordial R-wave progression,

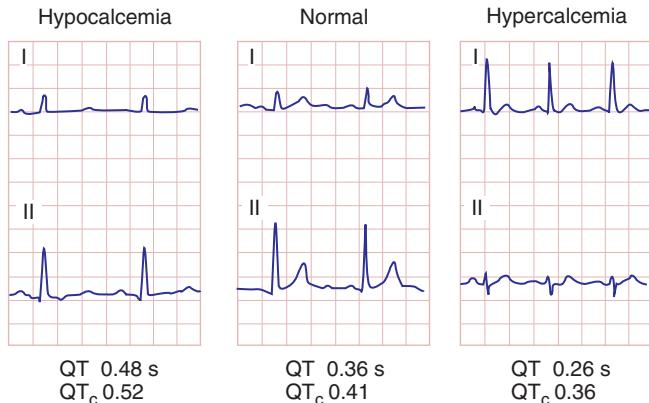


FIGURE 268-17 Prolongation of the Q-T interval (ST-segment portion) is typical of hypocalcemia. Hypercalcemia may cause abbreviation of the ST segment and shortening of the QT interval.

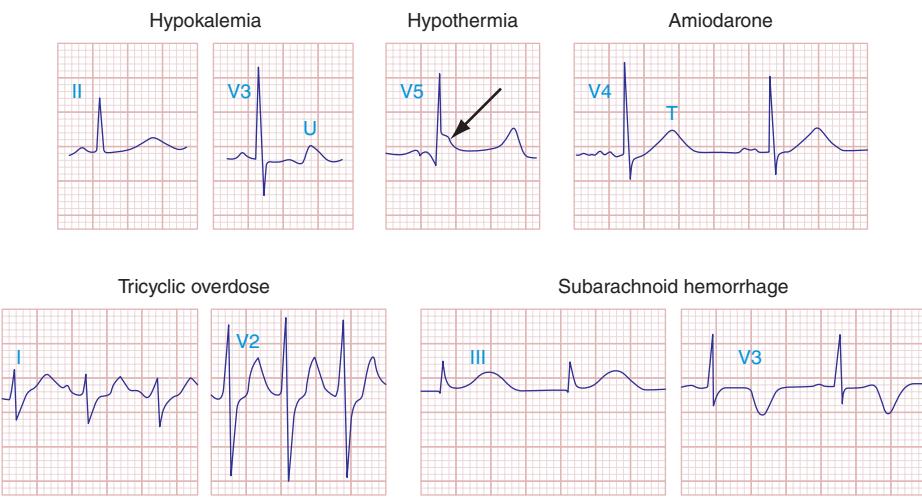


FIGURE 268-16 A variety of metabolic derangements, drug effects, and other factors may prolong ventricular repolarization with QT prolongation or prominent U waves. Prominent repolarization prolongation, particularly if due to hypokalemia, inherited “channelopathies,” or certain pharmacologic agents, indicates increased susceptibility to *torsades des pointes*-type ventricular tachycardia (Chap. 277). Marked systemic hypothermia is associated with a distinctive convex “hump” at the J point (Osborn wave, arrow) due to altered ventricular action potential characteristics. Note QRS and QT prolongation along with sinus tachycardia in the case of tricyclic antidepressant overdose.

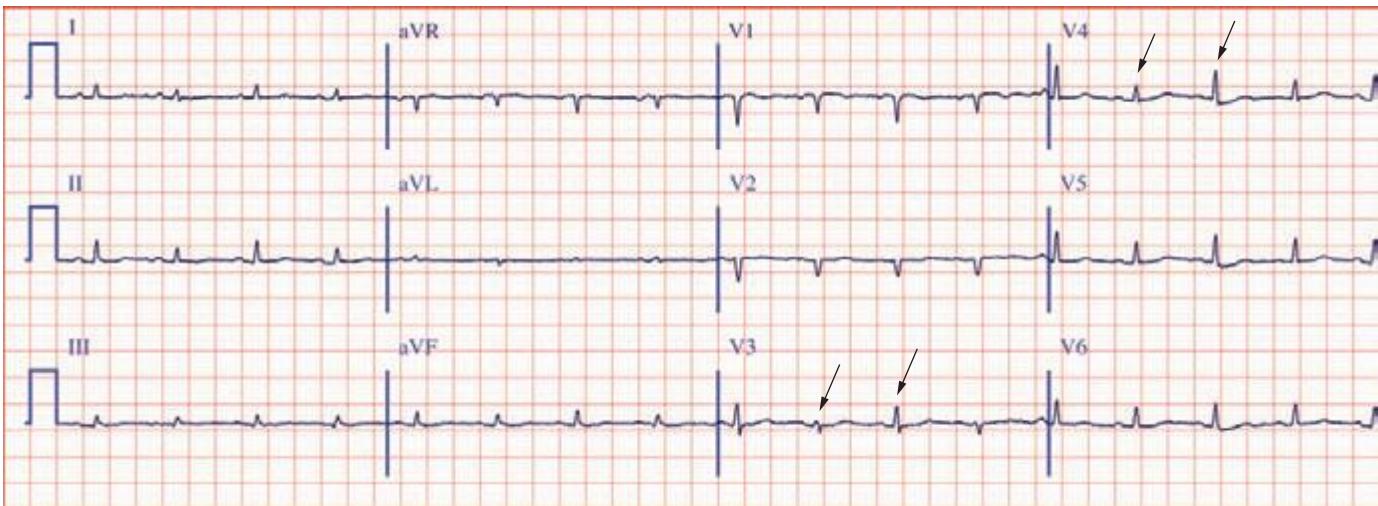


FIGURE 268-18 Classic triad of findings for pericardial effusion with cardiac tamponade: (1) sinus tachycardia; (2) low QRS voltages; and (3) electrical alternans (best seen in leads V_3 and V_4 in this case; arrows). This triad is highly specific for pericardial effusion, usually with tamponade physiology, but of limited sensitivity. (Adapted from LA Nathanson et al: ECG Wave-Maven. <http://ecg.bidmc.harvard.edu/>.)

(11) abnormal Q waves, (12) ST segments, (13) T waves, and (14) U waves. Comparison with any previous ECGs is invaluable. **The diagnosis and management of specific cardiac arrhythmias and conduction disturbances are discussed in Chaps. 274 and 276.**

COMPUTERIZED ELECTROCARDIOGRAPHY

Computerized ECG systems are widely used for immediate retrieval of thousands of ECG records. Computer interpretation of ECGs still has major limitations. Incomplete or inaccurate readings are most likely with arrhythmias and complex abnormalities. Therefore, computerized interpretation (including measurements of basic ECG intervals) should not be accepted without careful clinician review.

269e Atlas of Electrocardiography

Ary L. Goldberger

The electrocardiograms (ECGs) in this atlas supplement those illustrated in **Chap. 268**. The interpretations emphasize findings of specific teaching value.

All of the figures are from ECG Wave-Maven, Copyright 2003, Beth Israel Deaconess Medical Center, <http://ecg.bidmc.harvard.edu>.

The abbreviations used in this chapter are as follows:

- AF—atrial fibrillation
- HCM—hypertrophic cardiomyopathy
- LBBB—left bundle branch block
- LVH—left ventricular hypertrophy
- MI—myocardial infarction
- RBBB—right bundle branch block
- RV—right ventricular
- RVH—right ventricular hypertrophy
- SR—sinus rhythm

MYOCARDIAL ISCHEMIA AND INFARCTION

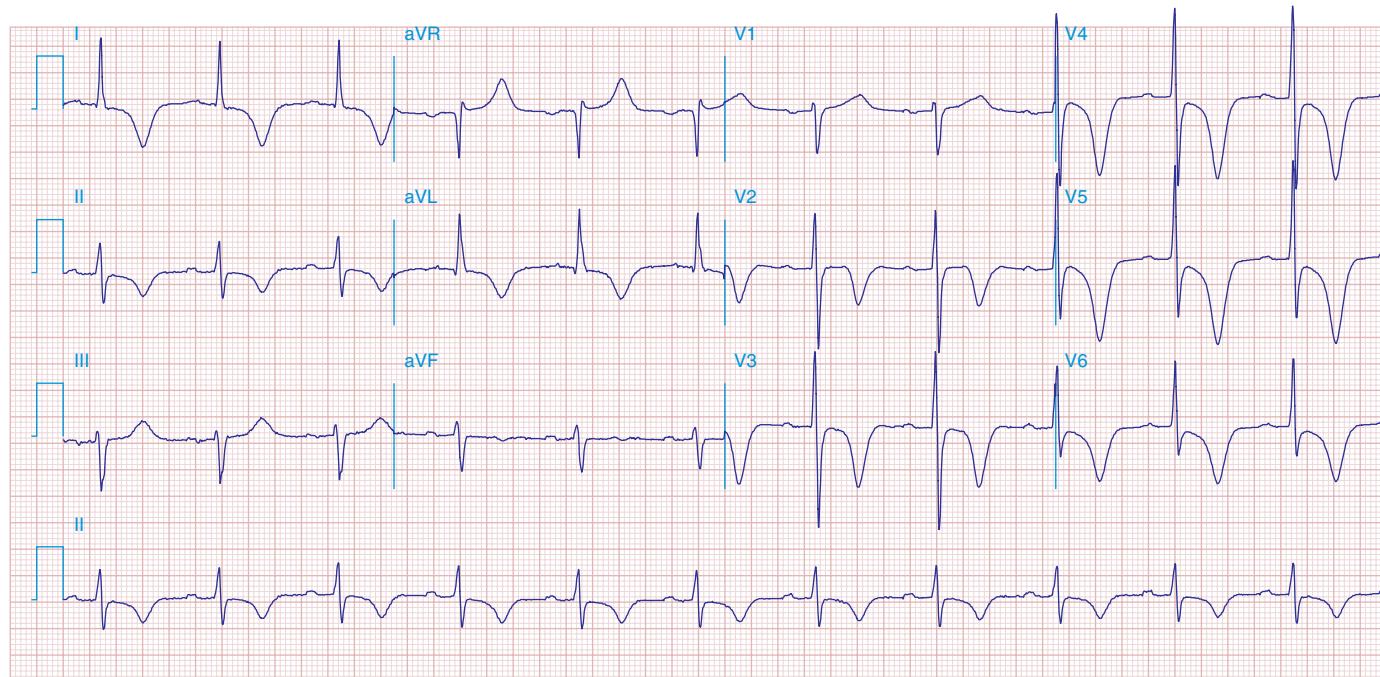


FIGURE 269e-1 Anterior wall ischemia (deep T-wave inversions and ST-segment depressions in I, aVL, V₃-V₆) in a patient with LVH (increased voltage in V₂-V₅).

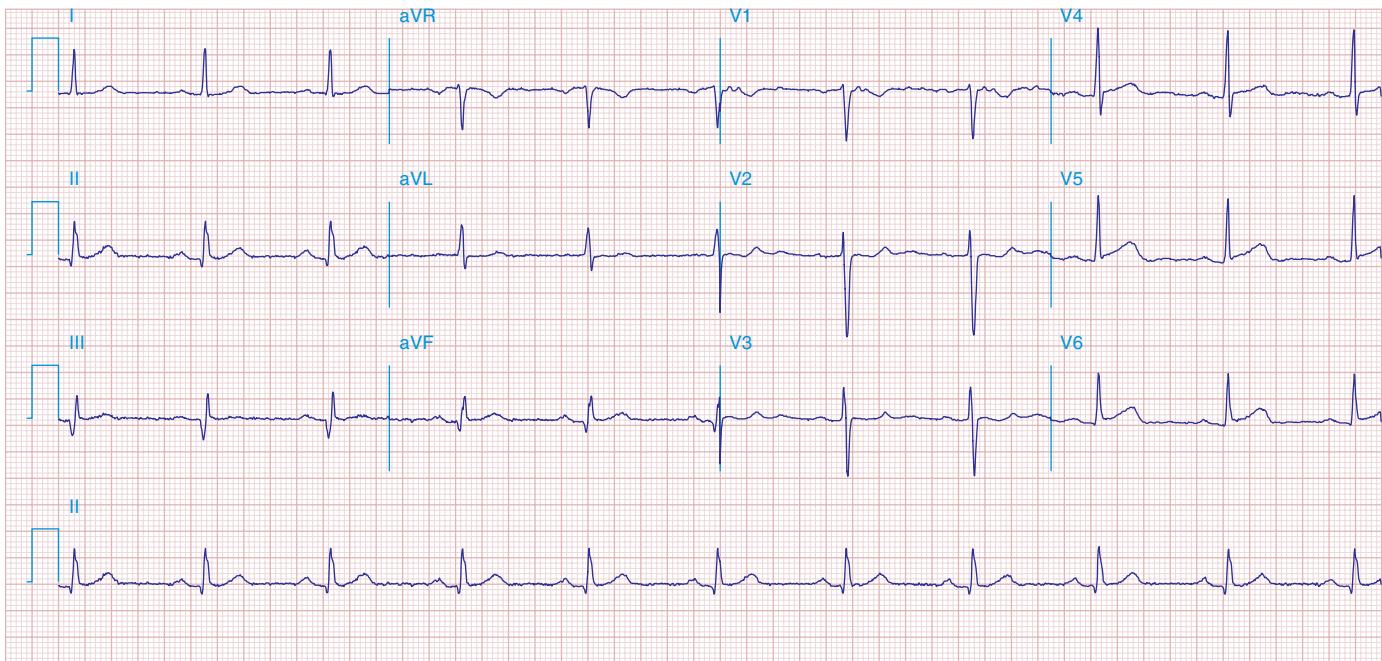


FIGURE 269e-2 Acute anterolateral wall ischemia with ST elevations in V_4 – V_6 . Probable prior inferior MI with Q waves in leads II, III, and aVF.

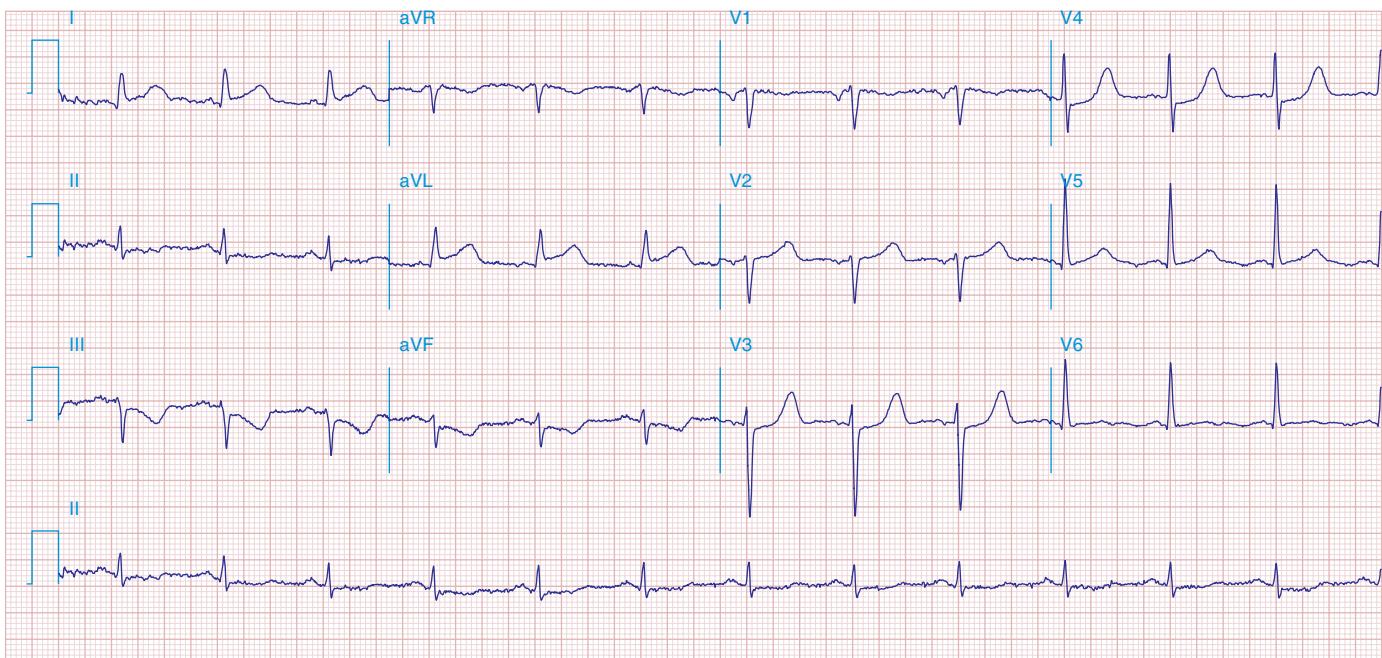


FIGURE 269e-3 Acute lateral ischemia with ST elevations in I and aVL with probable reciprocal ST depressions inferiorly (II, III, and aVF). Ischemic ST depressions also in V_3 and V_4 . Left atrial abnormality.

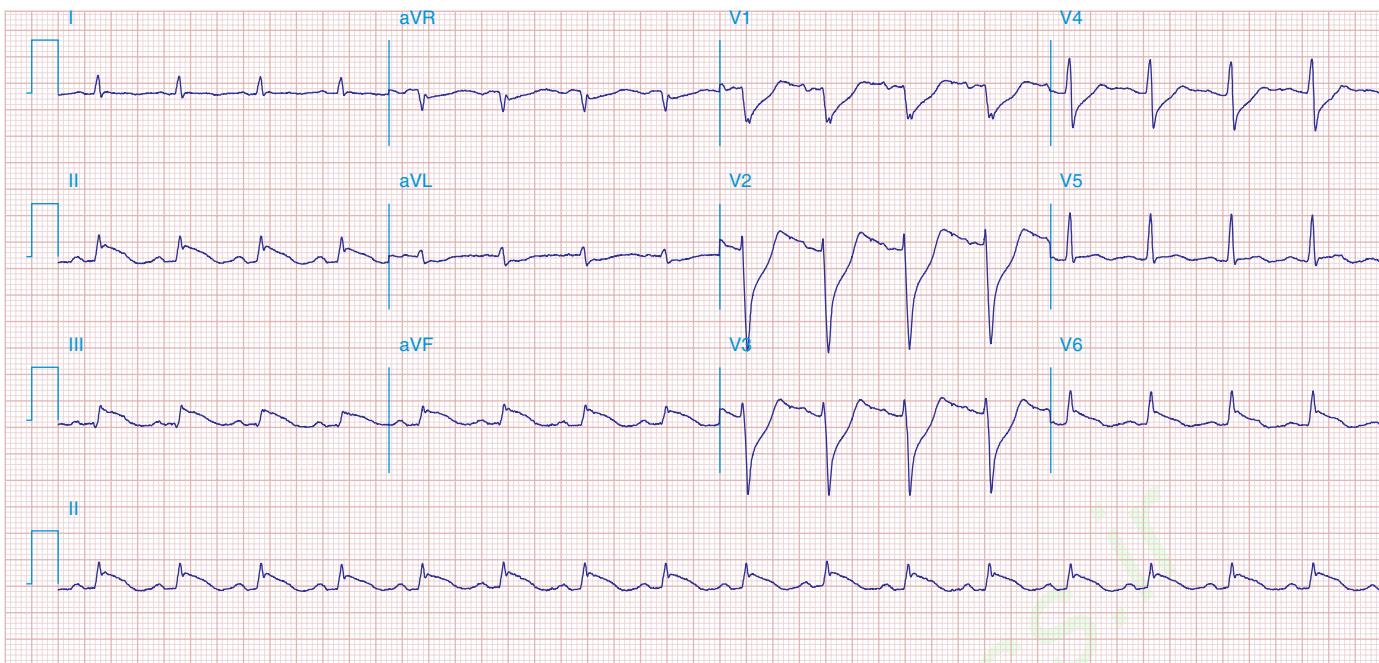


FIGURE 269e-4 Sinus tachycardia. Marked ischemic ST-segment elevations in inferior limb leads (II, III, aVF) and laterally (V₅) suggestive of acute inferolateral MI, and prominent ST-segment depressions with upright T waves in V₁-V₄ are consistent with associated acute posterior MI.

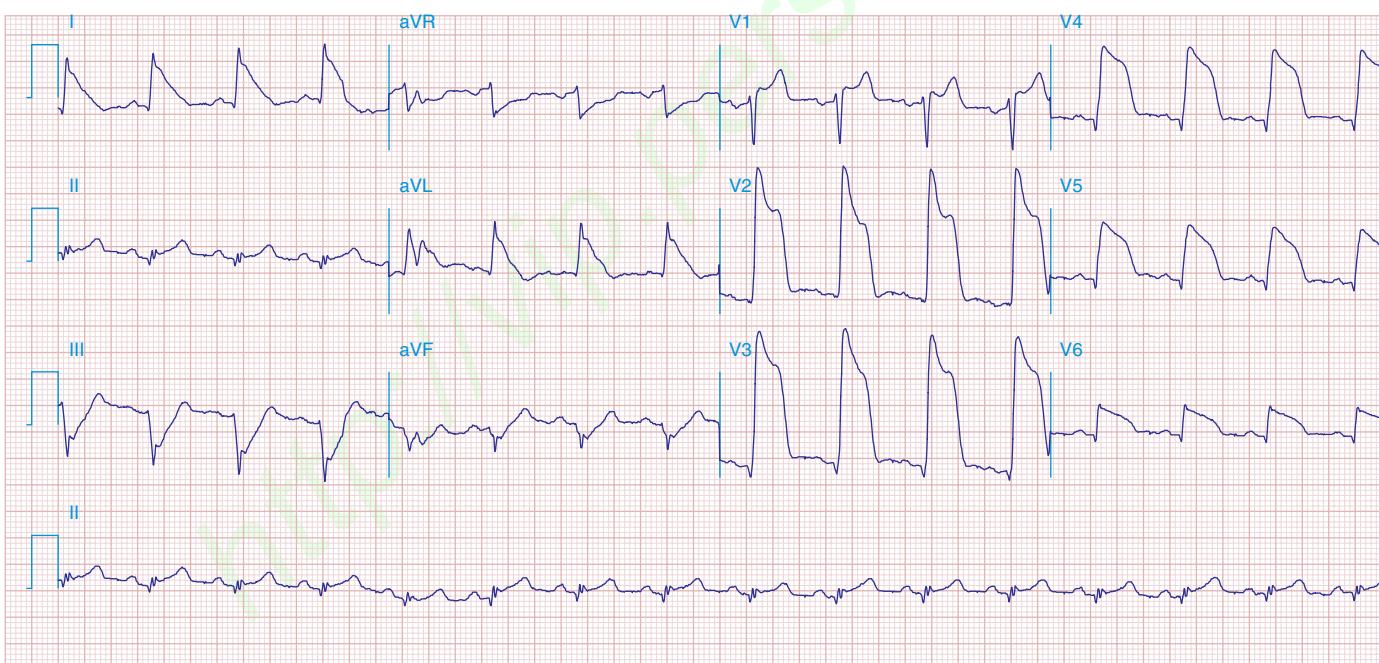


FIGURE 269e-5 Acute, extensive anterior MI with marked ST elevations in I, aVL, V₁-V₆ and low amplitude pathologic Q waves in V₃-V₆. Marked reciprocal ST-segment depressions in III and aVF.

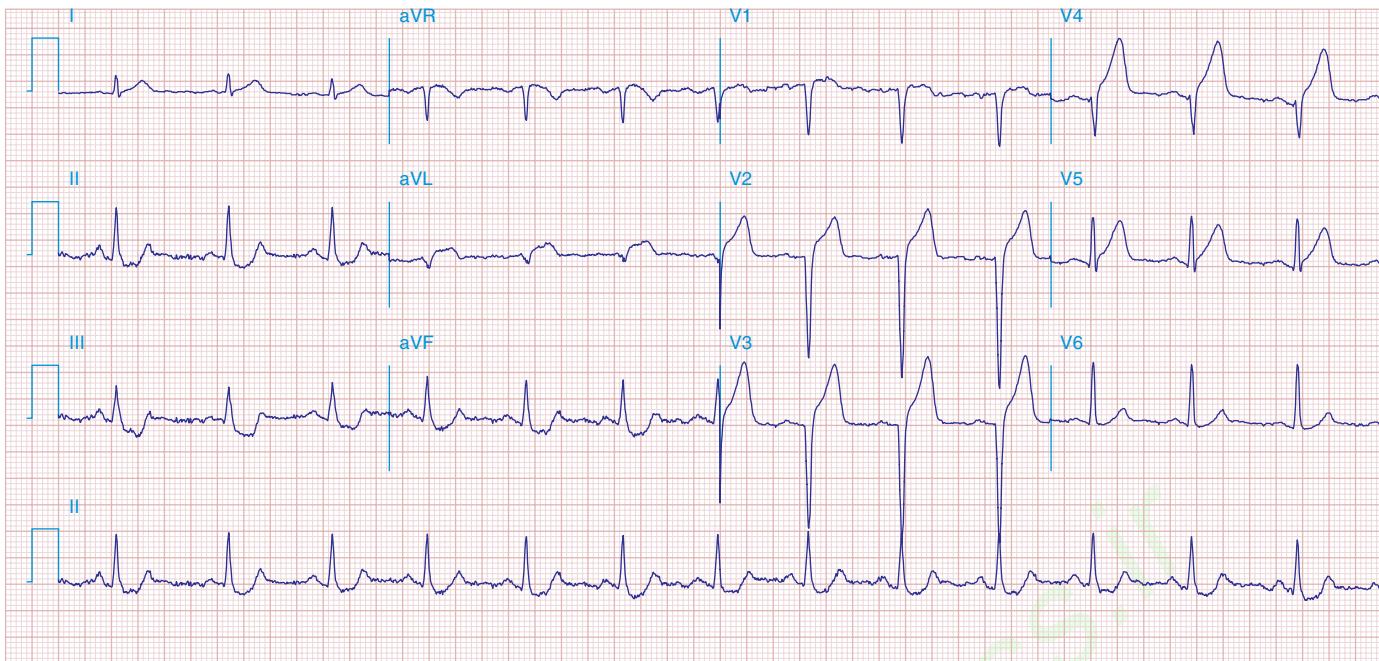


FIGURE 269e-6 Acute anterior wall MI with ST elevations and Q waves in V_1 - V_4 and aVL and reciprocal inferior ST depressions.

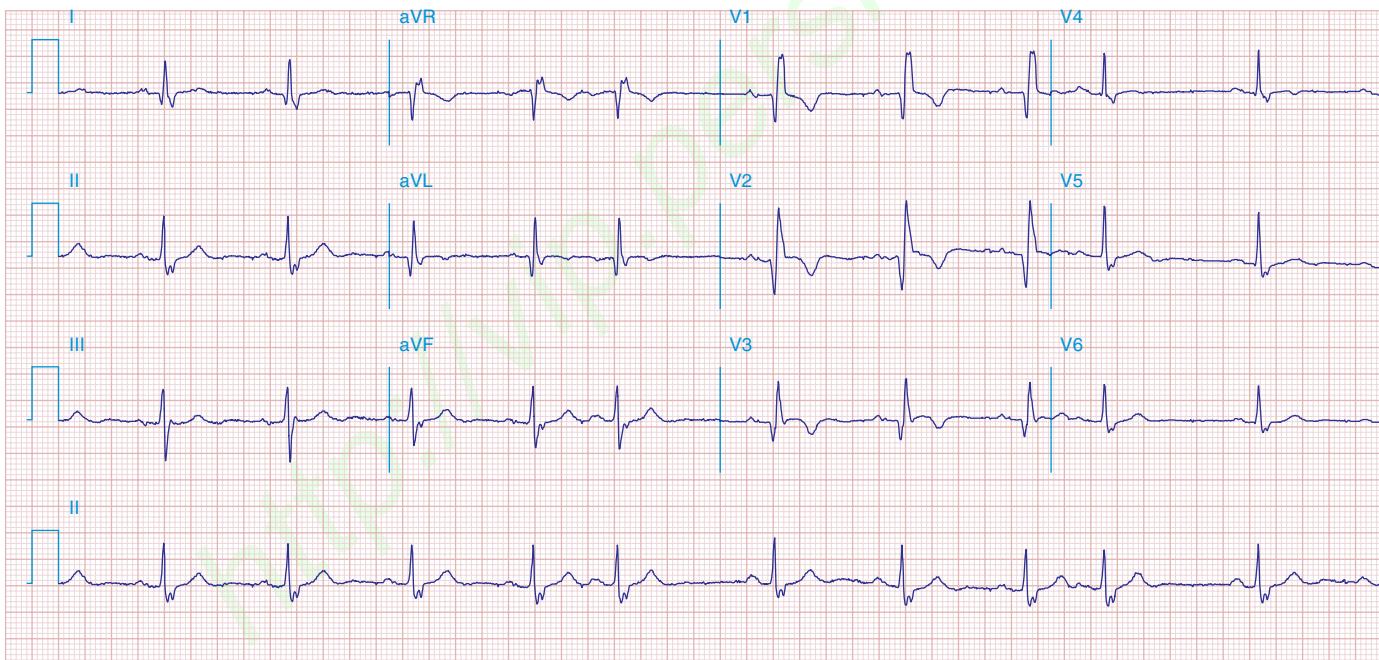


FIGURE 269e-7 SR with premature atrial complexes. RBBB; pathologic Q waves and ST elevation due to acute anterior/septal MI in V_1 - V_3 .

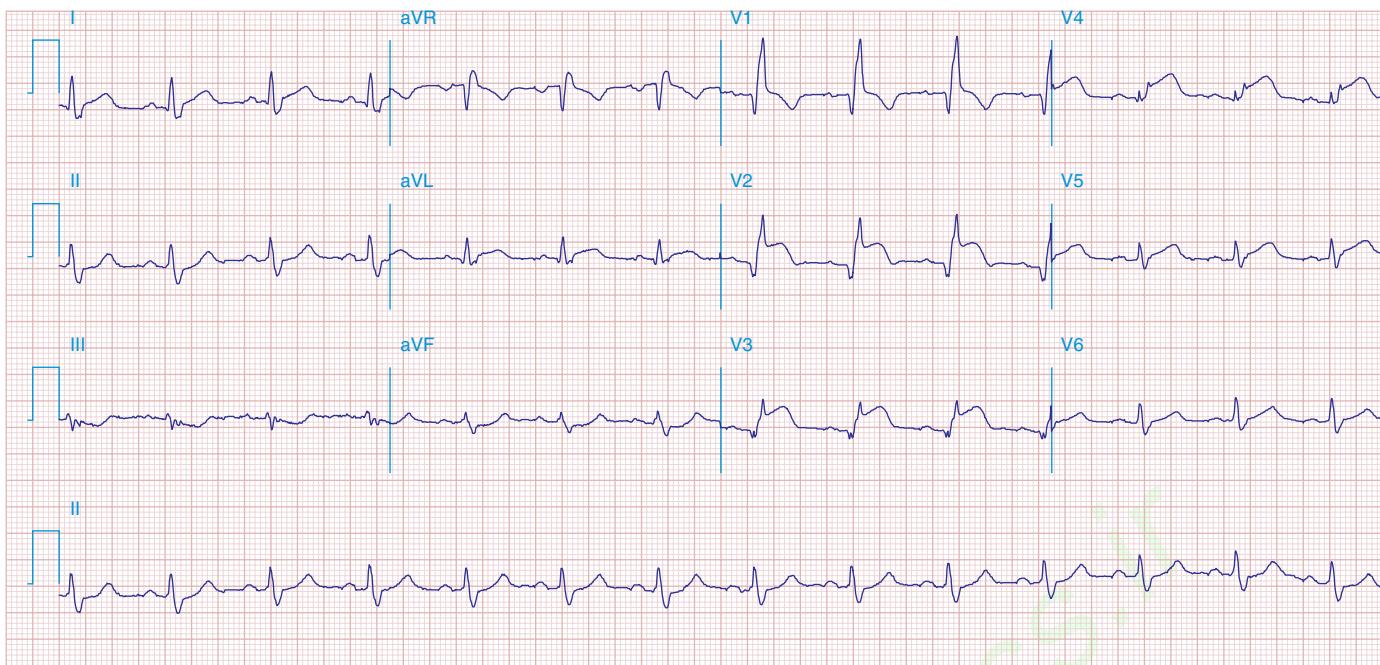


FIGURE 269e-8 Acute anteroseptal MI (Q waves and ST elevations in V_1-V_4) with RBBB (note terminal R waves in V_1).

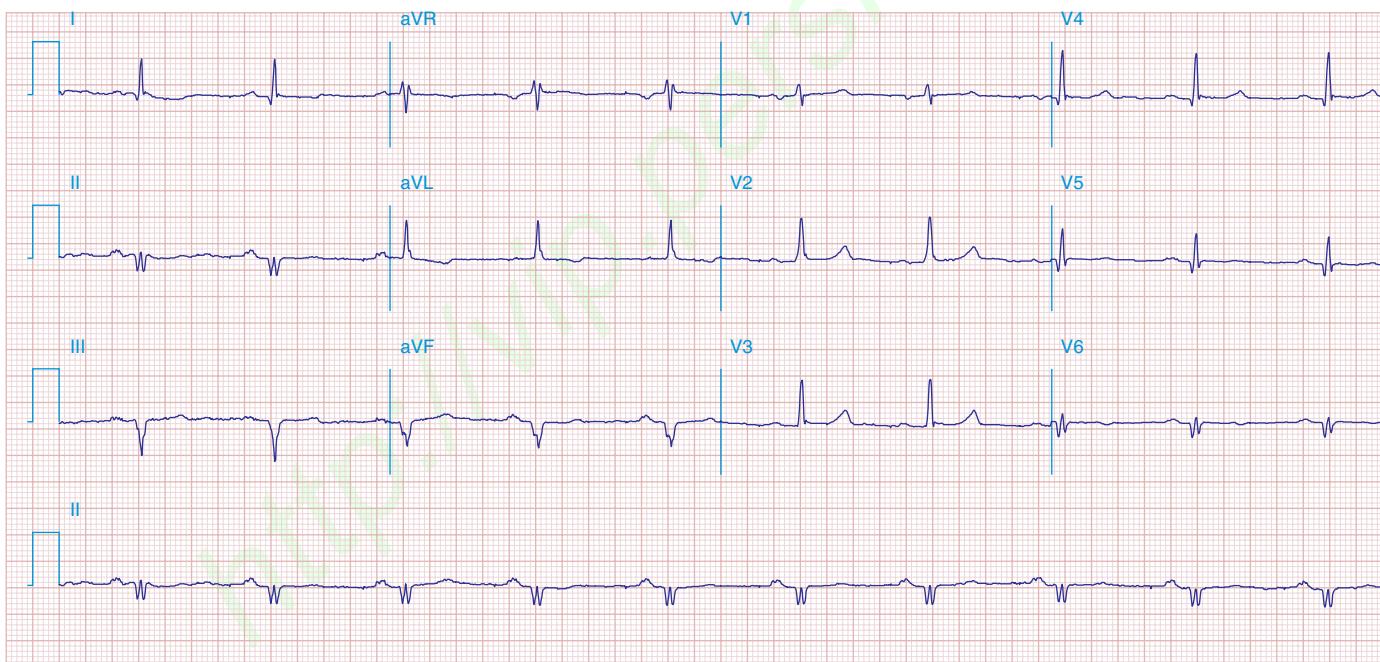


FIGURE 269e-9 Extensive prior MI involving inferior-posterior-lateral wall (Q waves in leads II, III, aVF, tall R waves in V_1 , V_2 , and Q waves in V_5 , V_6). T-wave abnormalities in leads I and aVL, V_5 , and V_6 .

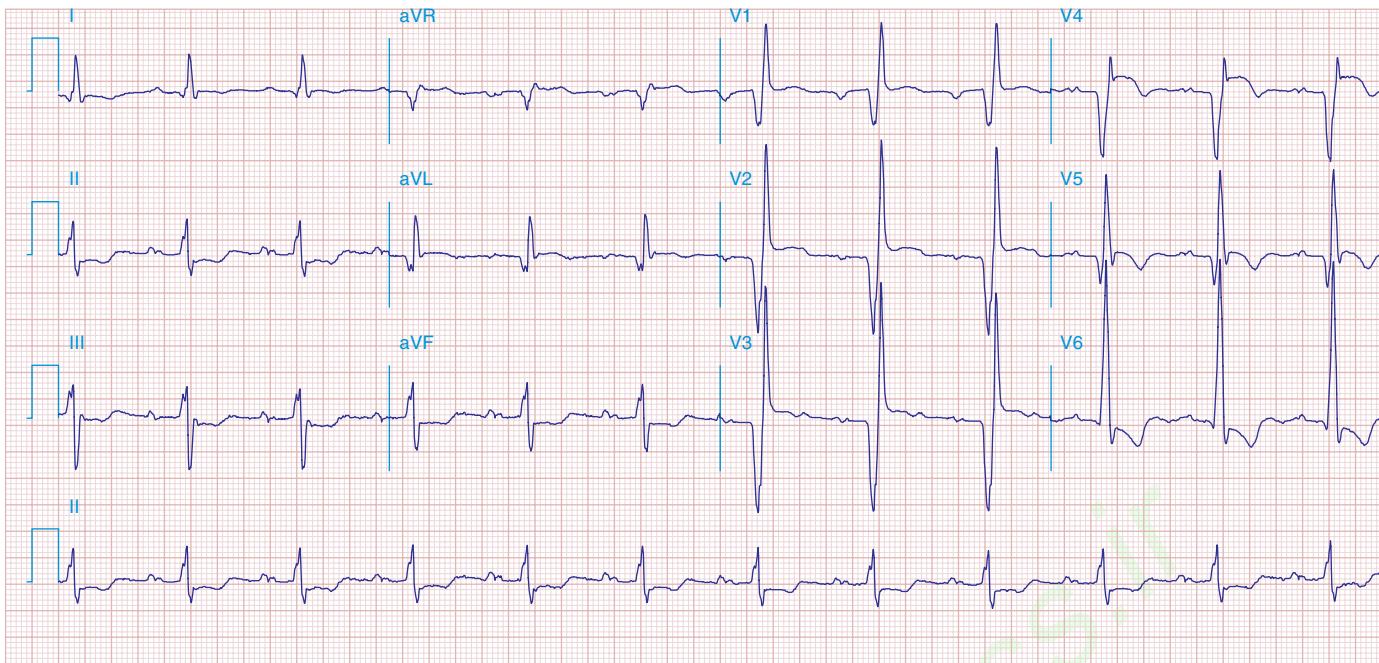


FIGURE 269e-10 SR with PR prolongation (“first-degree AV block”), left atrial abnormality, LVH, and RBBB. Pathologic Q waves in V_1 – V_5 and aVL with ST elevations (a chronic finding in this patient). Findings compatible with prior anterolateral MI and left ventricular aneurysm.

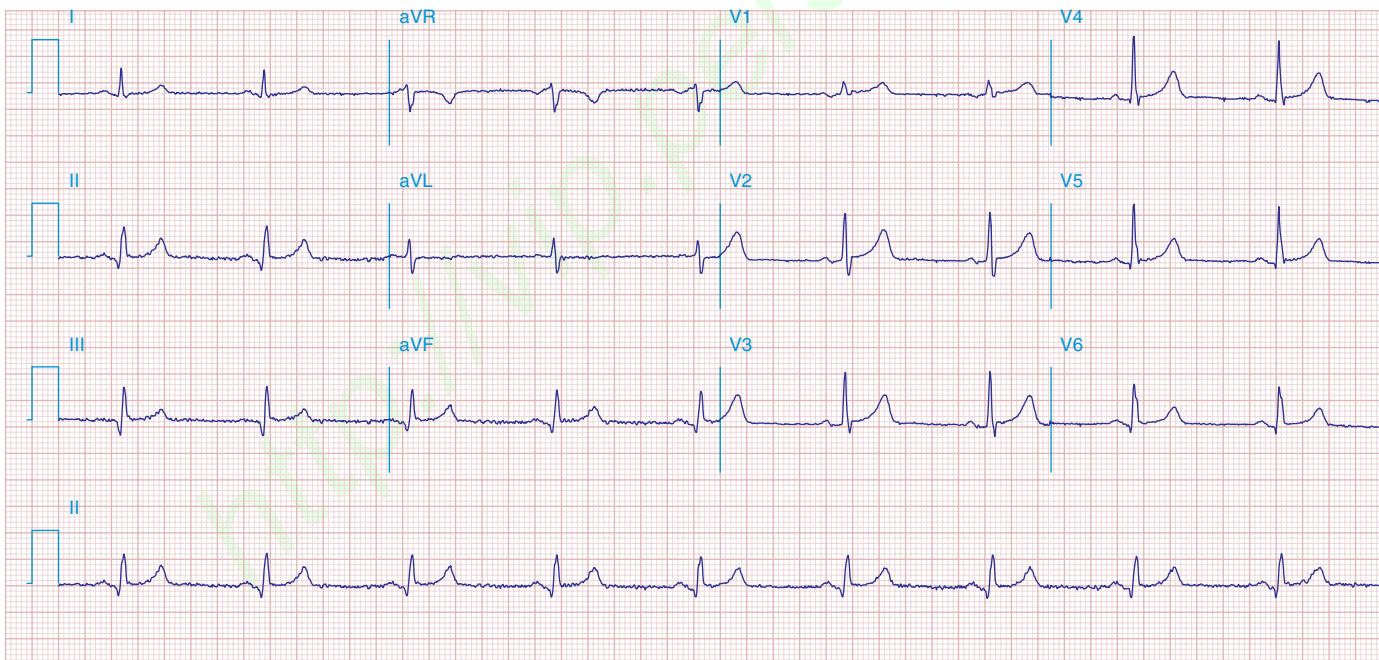


FIGURE 269e-11 Prior inferior-posterior MI. Wide (0.04 s) Q waves in the inferior leads (II, III, aVF); broad R wave in V_1 (a Q wave “equivalent” here). Absence of right-axis deviation and the presence of upright T waves in V_1 – V_2 are also against RVH.

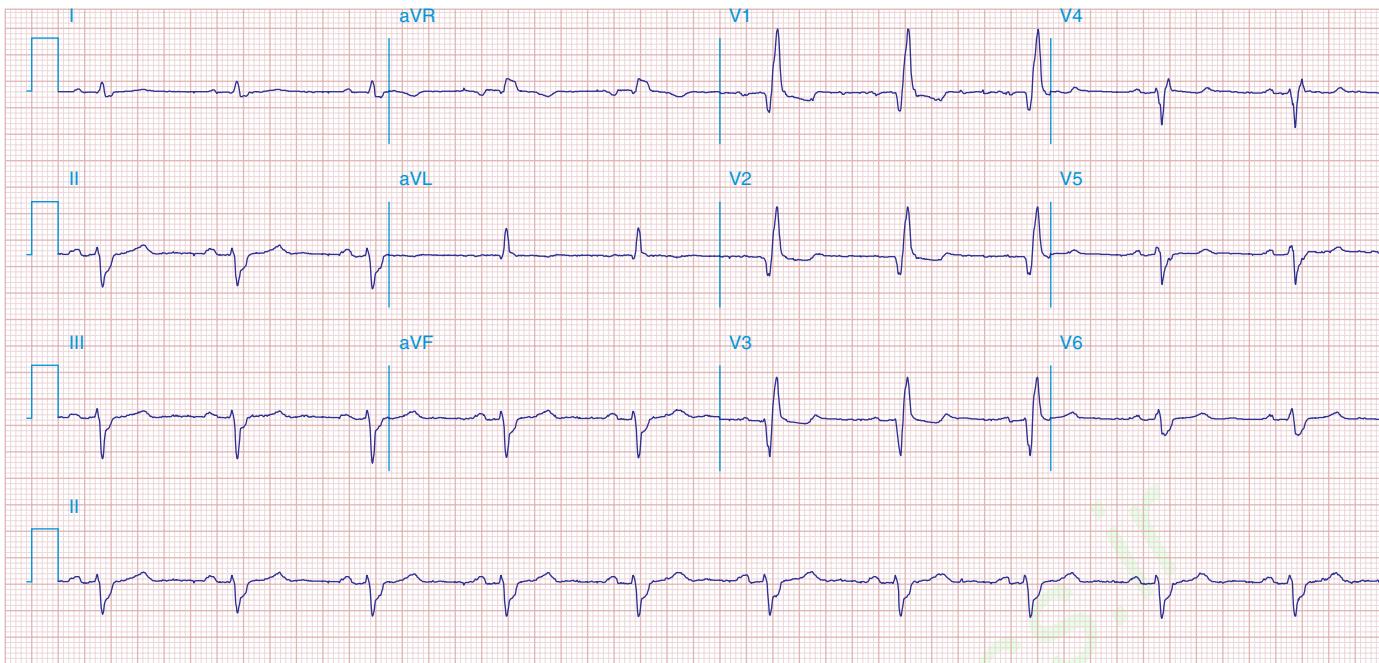


FIGURE 269e-12 SR with RBBB (broad terminal R wave in V_1) and left anterior fascicular block (hemiblock) and pathologic anterior Q waves in V_1 - V_3 . Patient had severe multivessel coronary artery disease, with echocardiogram showing septal dyskinesis and apical akinesis.

PERICARDITIS

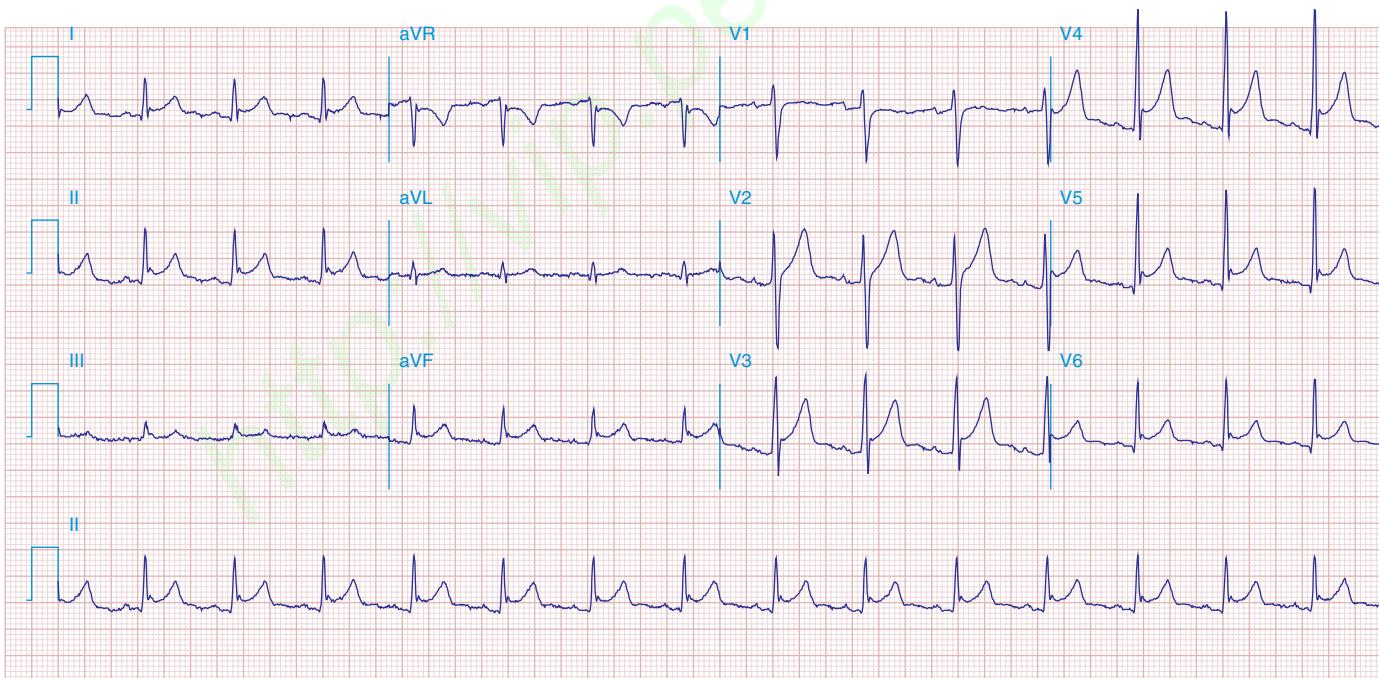


FIGURE 269e-13 Acute pericarditis with diffuse ST elevations in I, II, III, aVF, V_3 - V_6 , without T-wave inversions. Also note concomitant PR-segment elevation in aVR and PR depression in the inferolateral leads.

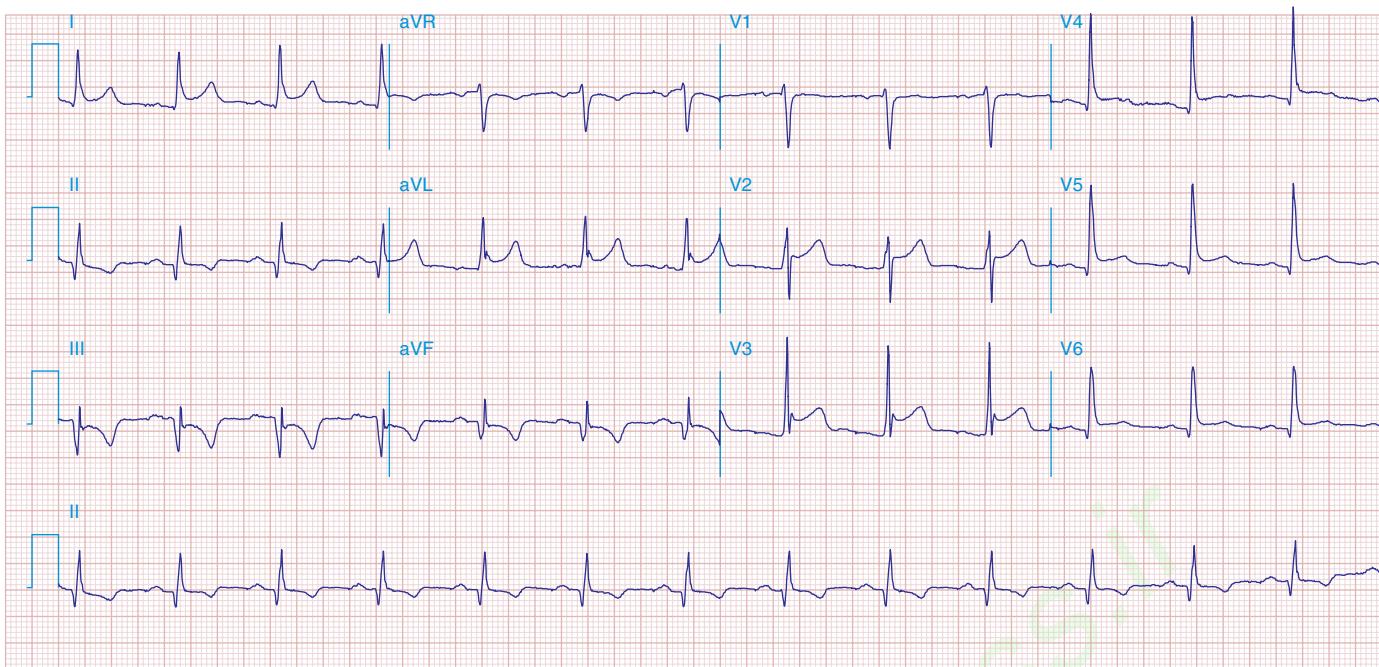


FIGURE 269e-14 SR; diffuse ST elevations (I, II, aVL, aVF, V₂-V₆) with associated PR deviations (elevated PR in aVR; depressed in V₄-V₆); borderline low voltage. Q-wave and T-wave inversions in II, III, and aVF. Diagnosis: acute pericarditis with inferior Q-wave MI.

VALVULAR HEART DISEASE AND HYPERTROPHIC CARDIOMYOPATHY

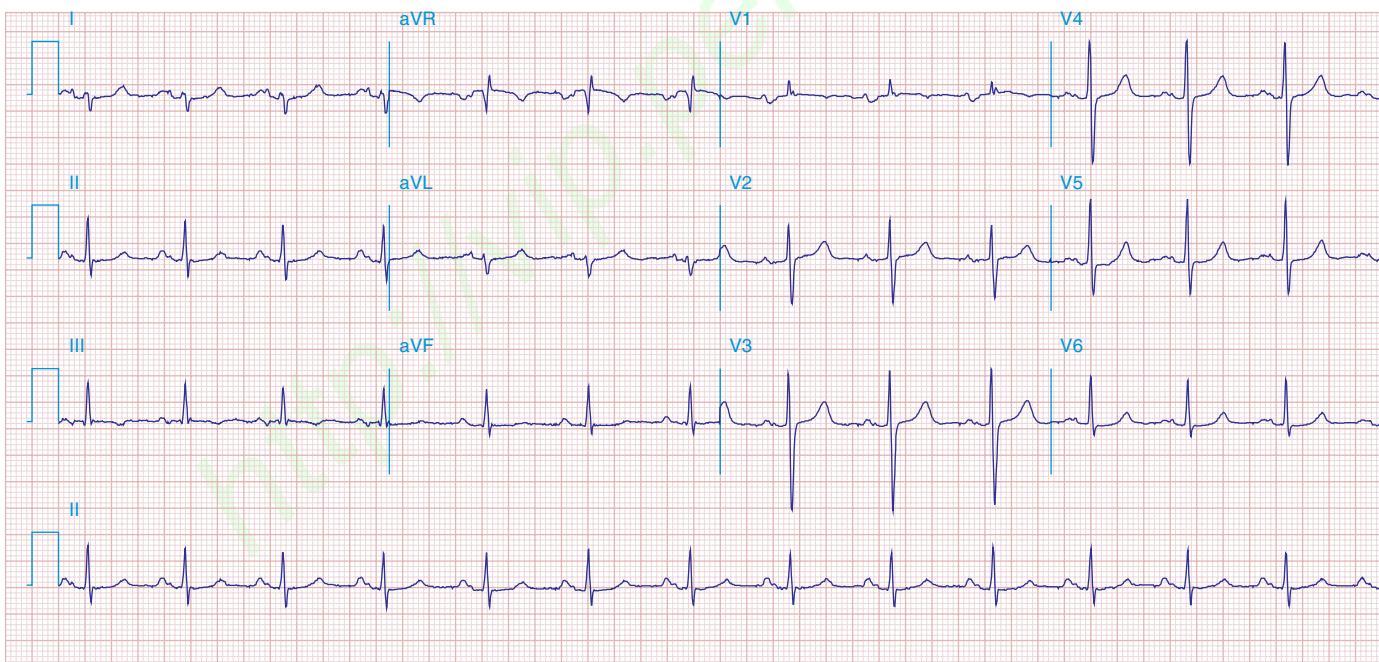


FIGURE 269e-15 SR, prominent left atrial abnormality (see I, II, V₁), right-axis deviation, and RVH (tall, relatively narrow R wave in V₁) in a patient with mitral stenosis.

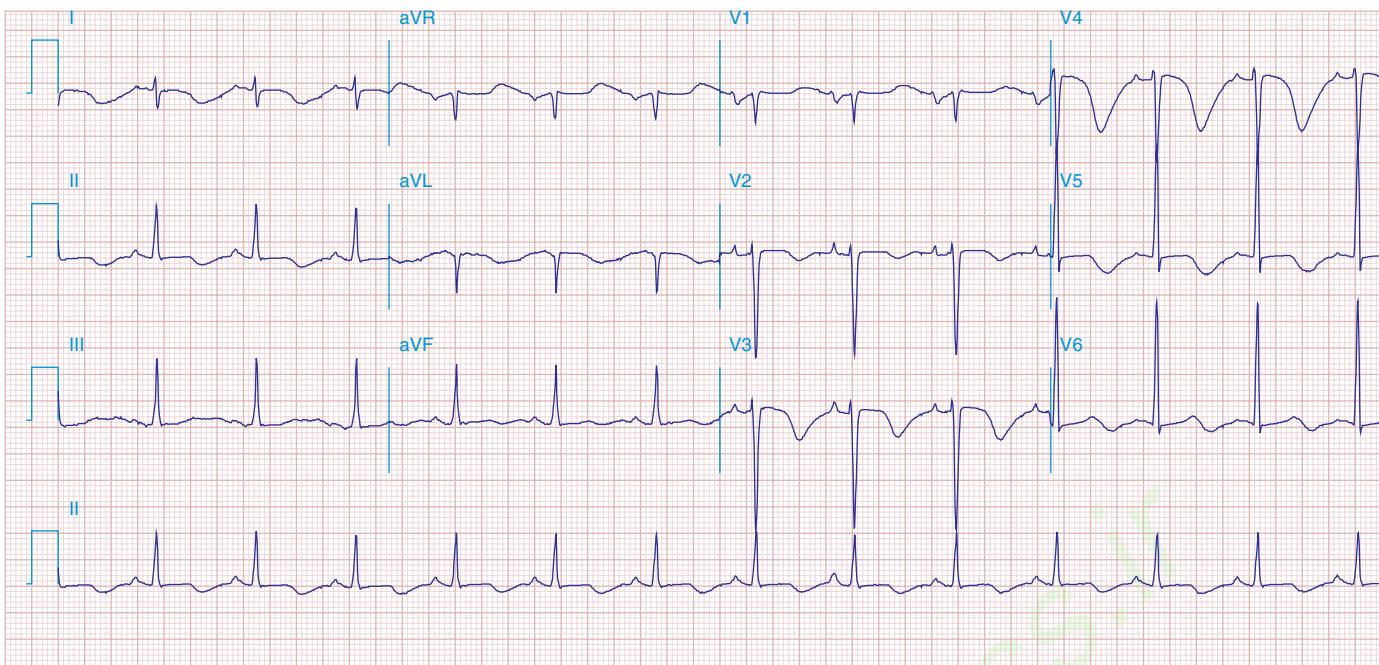


FIGURE 269e-16 SR, left atrial abnormality, and LVH by voltage criteria with borderline right-axis deviation in a patient with mixed mitral stenosis (left atrial abnormality and right-axis deviation) and mitral regurgitation (LVH). Prominent precordial T-wave inversions and QT prolongation also present.

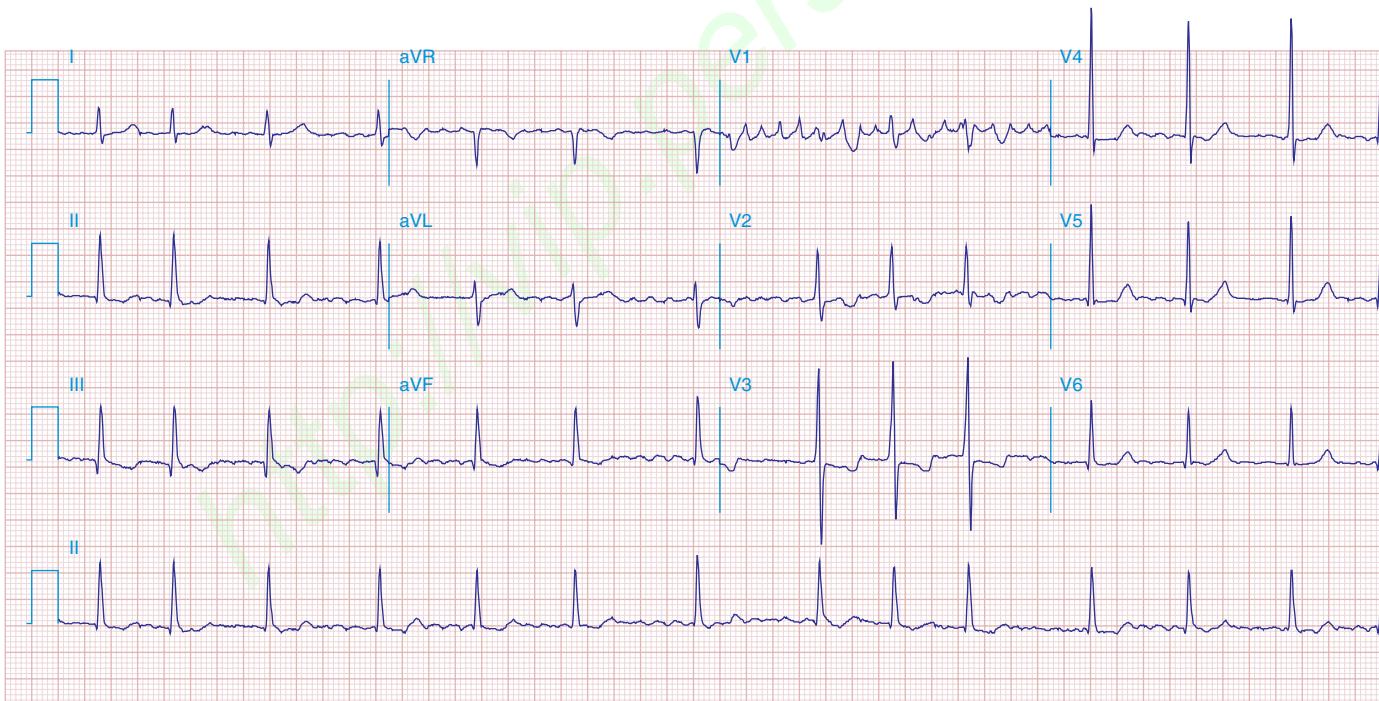


FIGURE 269e-17 Coarse AF, tall R in V_2 with vertical QRS axis (positive R in aVF) indicating RVH. Tall R in V_4 may be due to concomitant LVH. Patient had severe mitral stenosis with moderate mitral regurgitation.

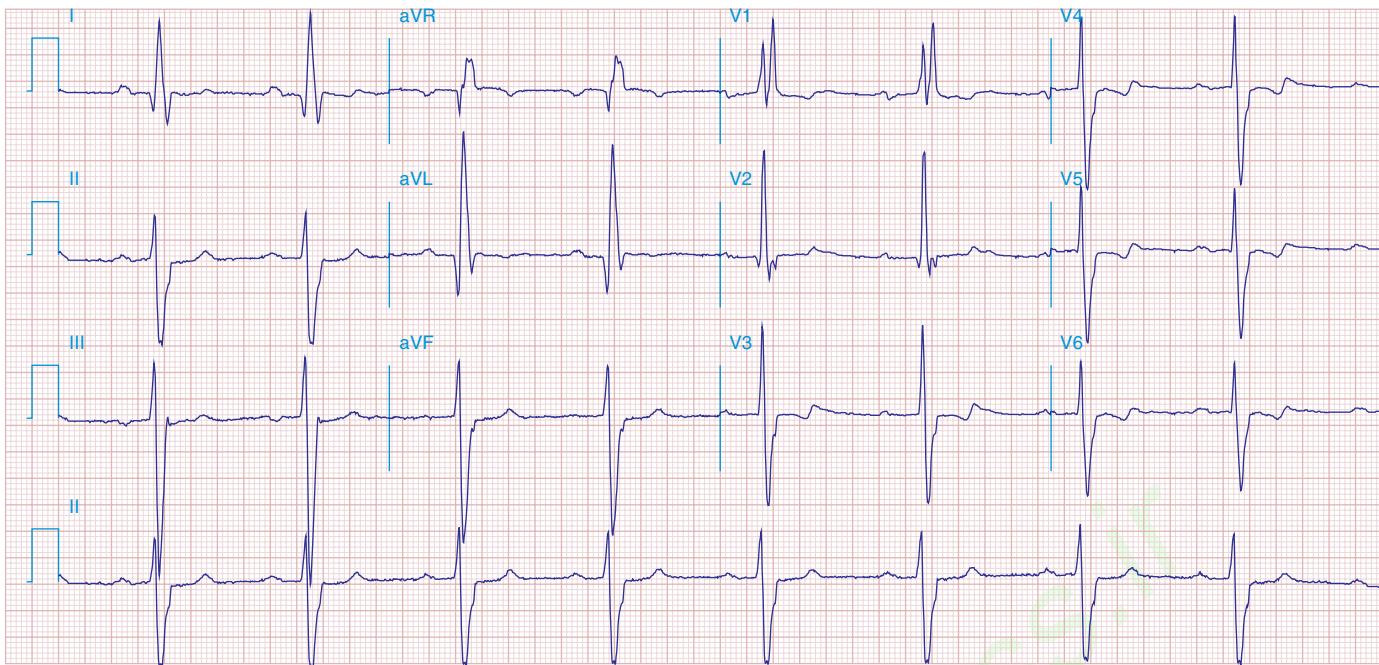


FIGURE 269e-18 SR; first-degree AV “block” (PR prolongation); LVH (tall R in aVL); RBBB (wide multiphasic R wave in V1) and left anterior fascicular block in a patient with HCM. Deep Q waves in I and aVL are consistent with septal hypertrophy.

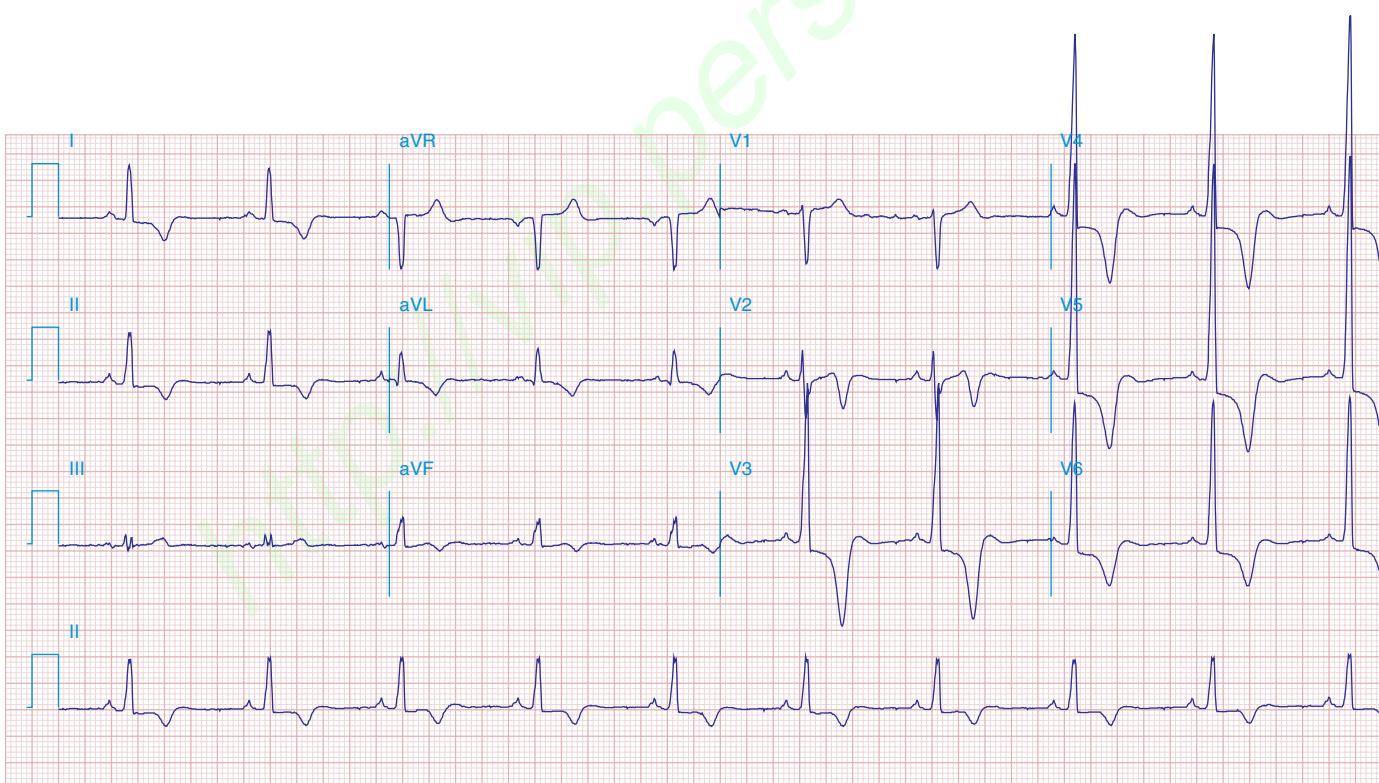


FIGURE 269e-19 LVH with deep T-wave inversions in limb leads and precordial leads. Striking T-wave inversions in mid-precordial leads suggest apical HCM (Yamaguchi's syndrome).

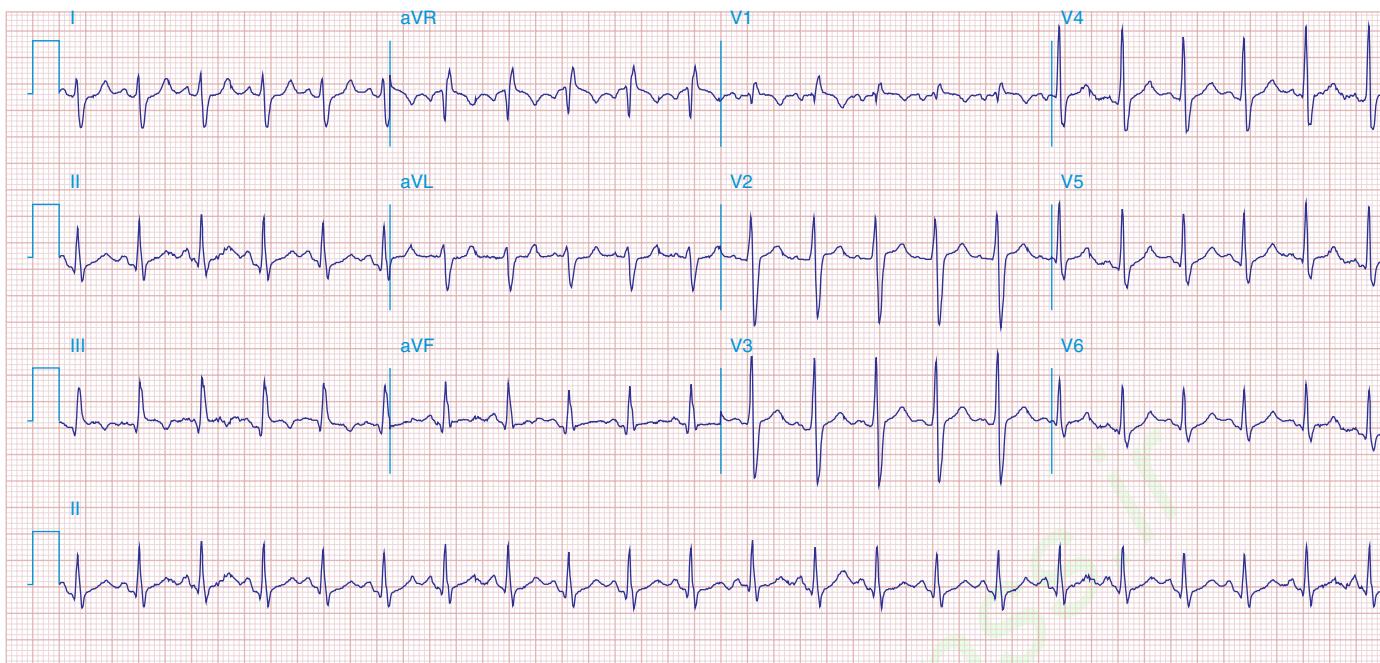


FIGURE 269e-20 Sinus tachycardia with S1Q3T3 pattern (T-wave inversion in III), incomplete RBBB, and right precordial T-wave inversions consistent with acute RV overload in a patient with pulmonary emboli.

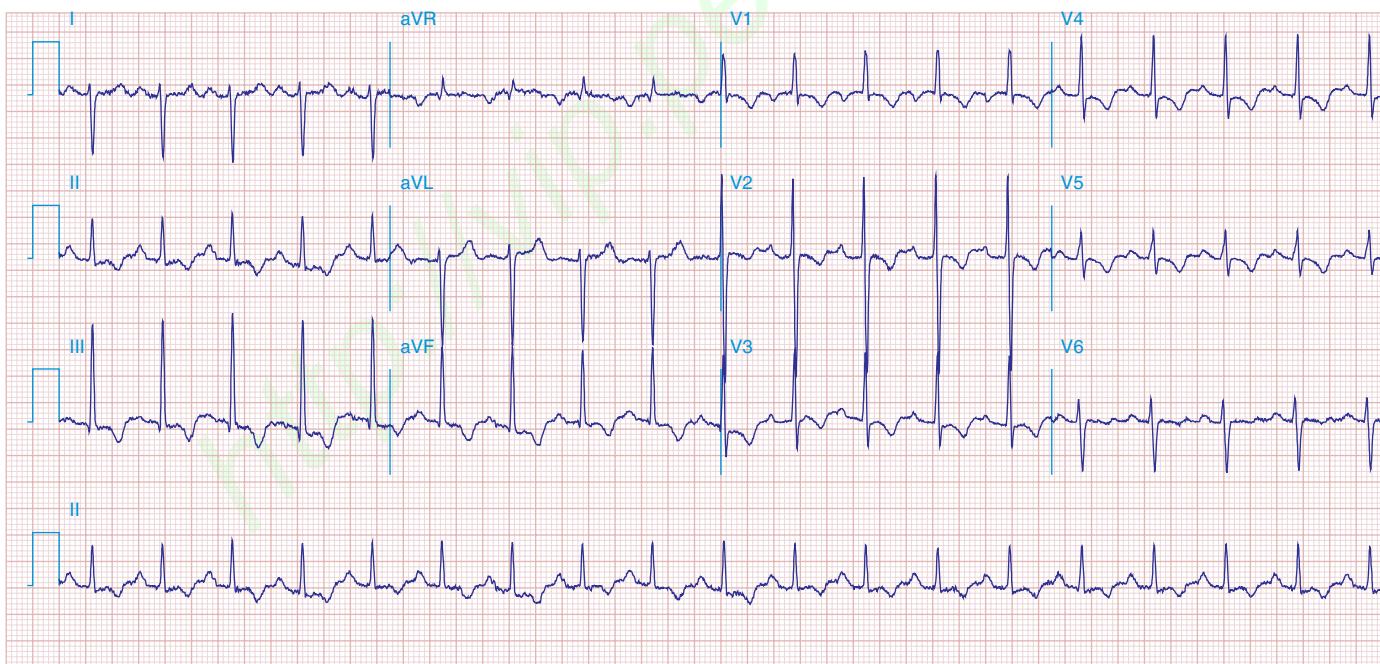


FIGURE 269e-21 Sinus tachycardia, right-axis deviation, RVH with tall R in V₁ and deep S in V₆, and inverted T waves in II, III, aVF, and V₁-V₅ in a patient with atrial septal defect and severe pulmonary hypertension.

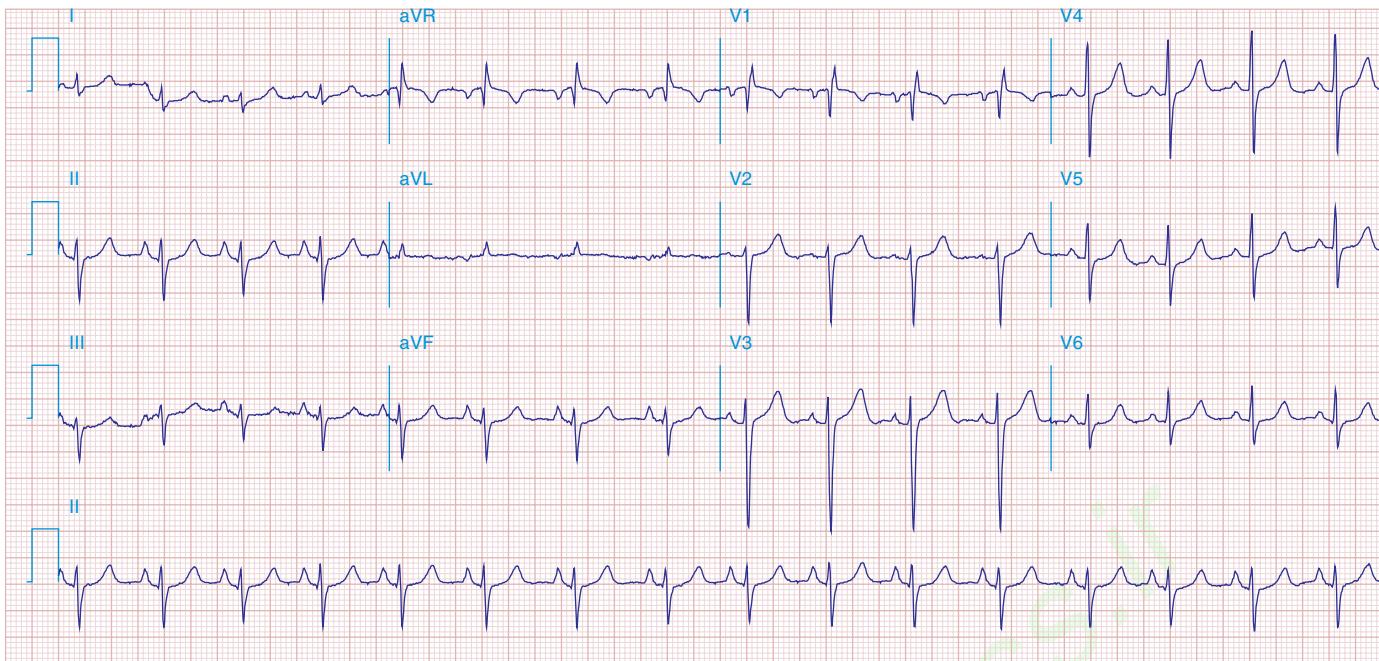


FIGURE 269e-22 Signs of right atrial/RV overload in a patient with chronic obstructive lung disease: (1) peaked P waves in II; (2) QR in V₁ with narrow QRS; (3) delayed precordial transition, with terminal S waves in V₅/V₆; (4) superior axis deviation with an S₁-S₂-S₃ pattern.

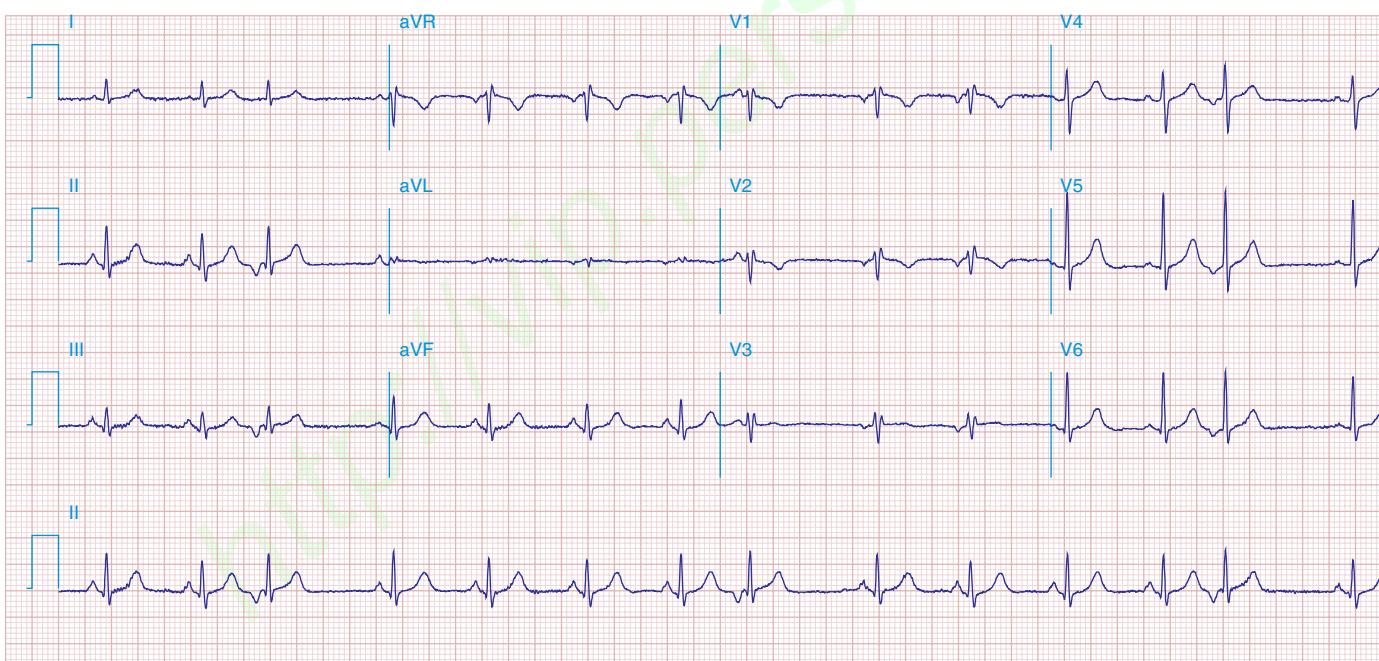


FIGURE 269e-23 (1) Low voltage; (2) incomplete RBBB (rsr' in V₁-V₃); (3) borderline peaked P waves in lead II with vertical P-wave axis (probable right atrial overload); (4) slow R-wave progression in V₁-V₃; (5) prominent S waves in V₆; and (6) atrial premature beats. This combination is seen typically in severe chronic obstructive lung disease.

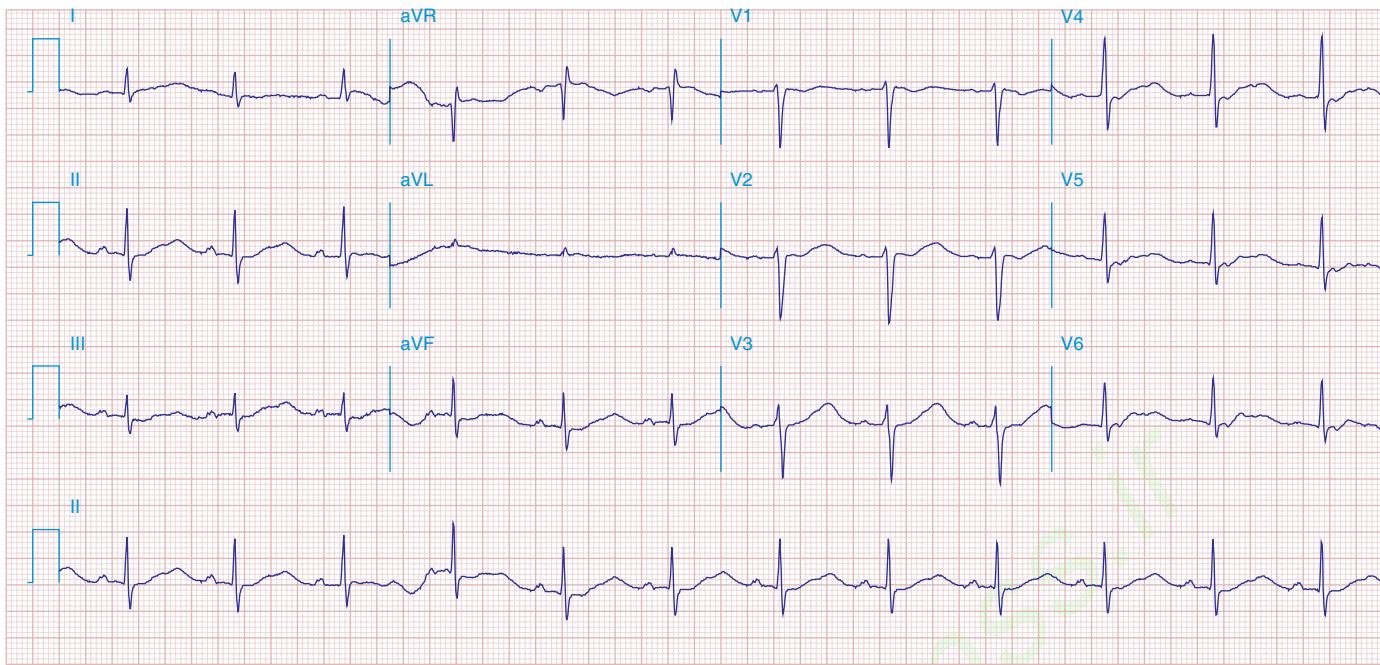


FIGURE 269e-24 Prominent U waves (II, III, and V₄–V₆) with ventricular repolarization prolongation in a patient with severe hypokalemia.

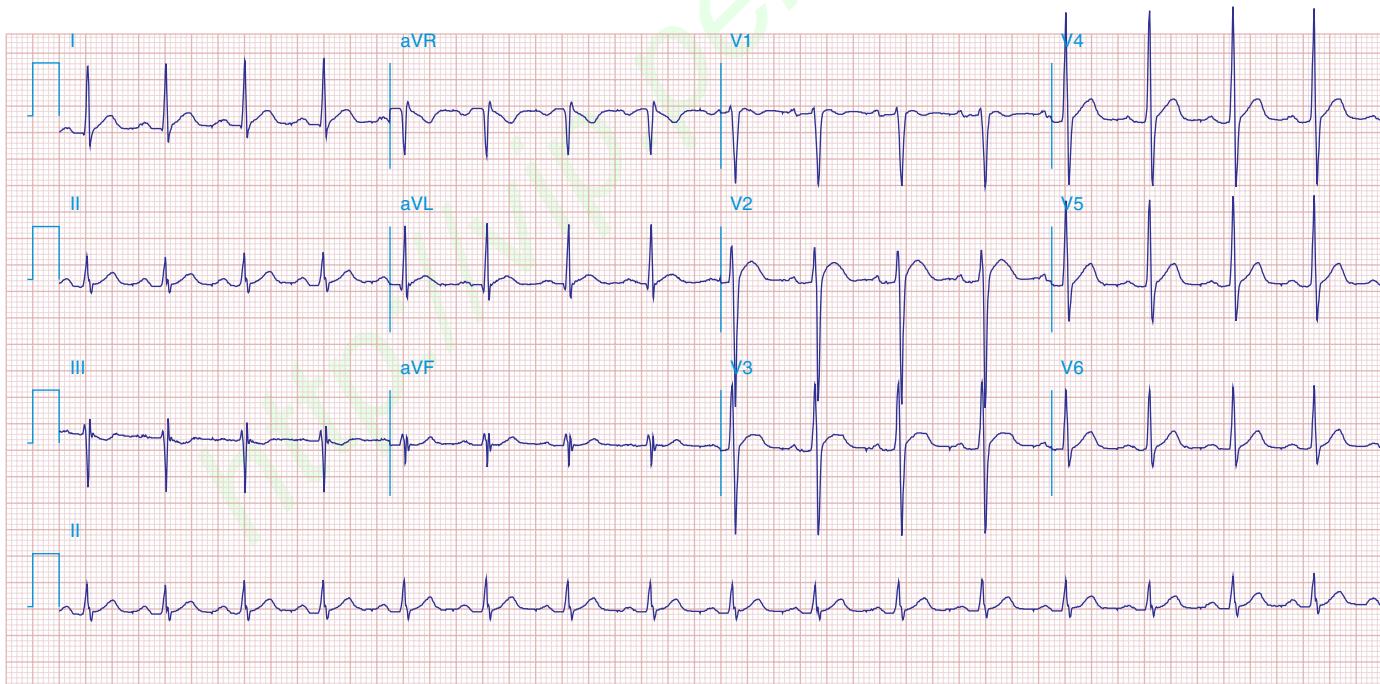


FIGURE 269e-25 Abbreviated ST segment such that the T wave looks like it takes off directly from QRS in some leads (I, V₄, aVL, and V₅) in a patient with severe hypercalcemia. Note also high takeoff of ST segment in V₂/V₃ simulating acute ischemia.

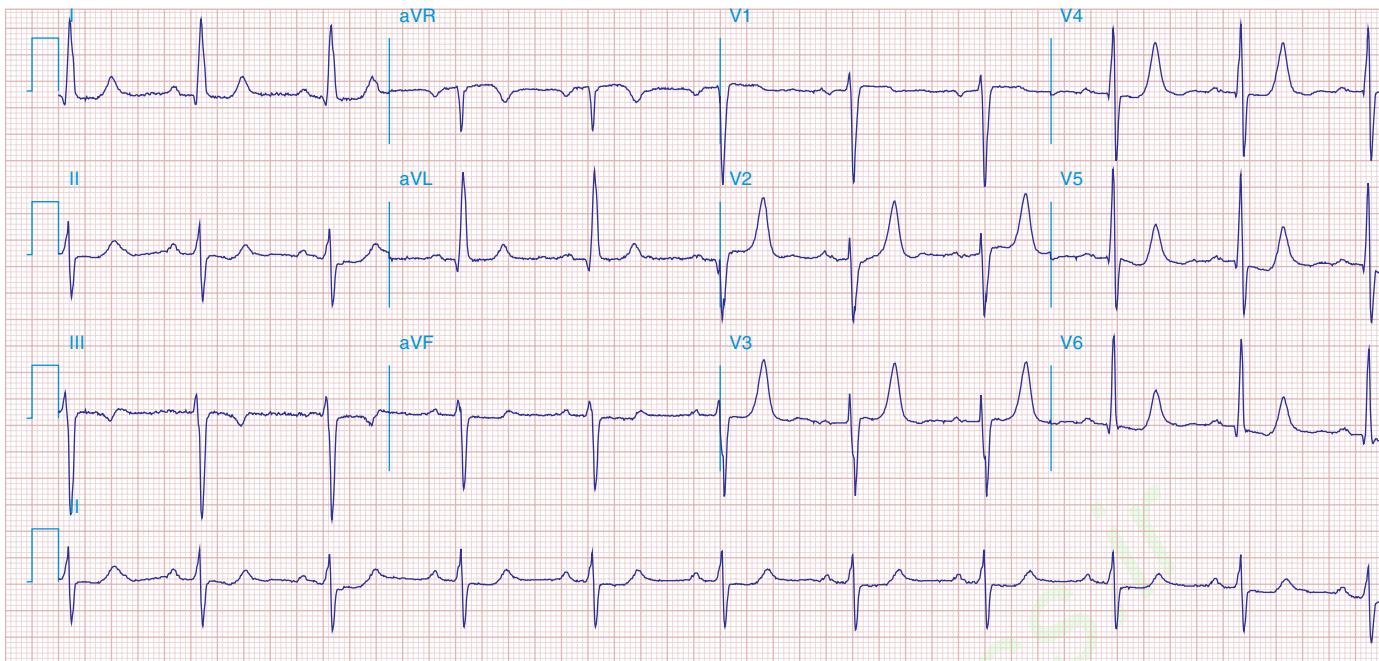


FIGURE 269e-26 SR with LVH, left atrial abnormality, and tall peaked T waves in the precordial leads with inferolateral ST depressions (II, III, aVF, and V_6); left anterior fascicular block and borderline prolonged QT interval in a patient with renal failure, hypertension, and hyperkalemia; prolonged QT is secondary to associated hypocalcemia.

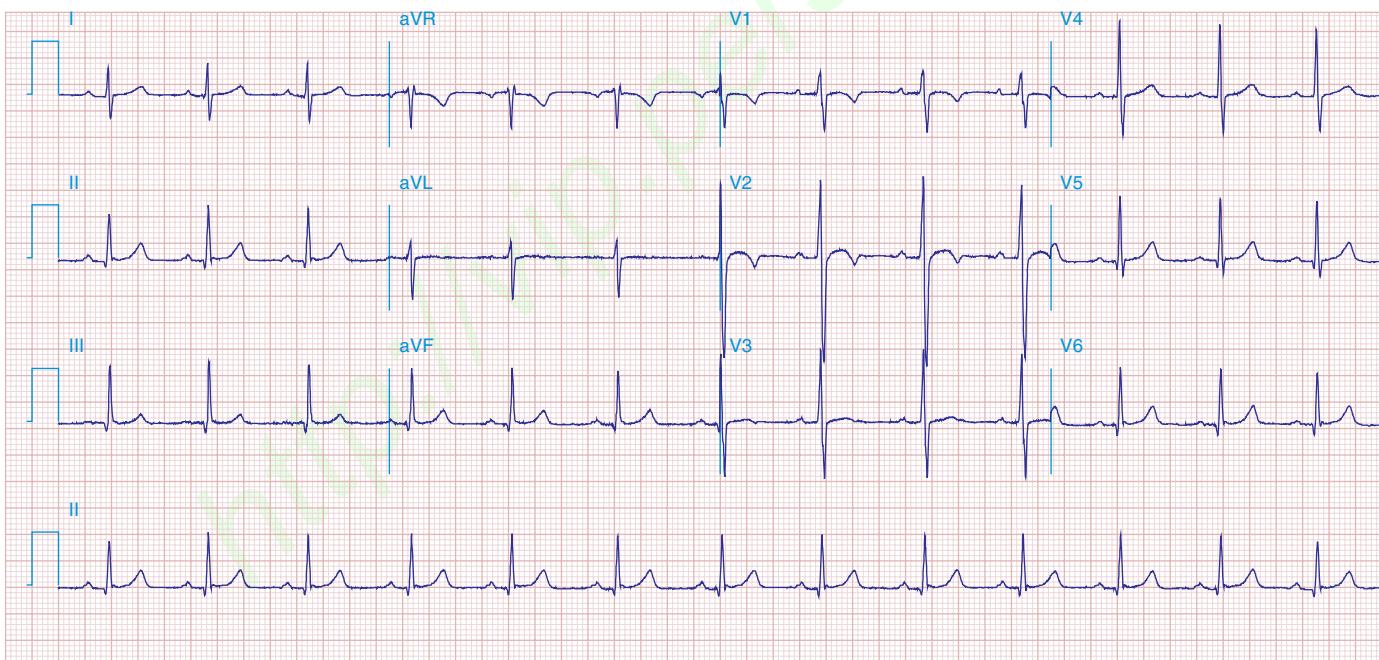


FIGURE 269e-27 Normal ECG in an 11-year-old male. T-wave inversions in V_1 - V_2 . Vertical QRS axis ($+90^\circ$) and early precordial transition between V_2 and V_3 are normal findings in children.

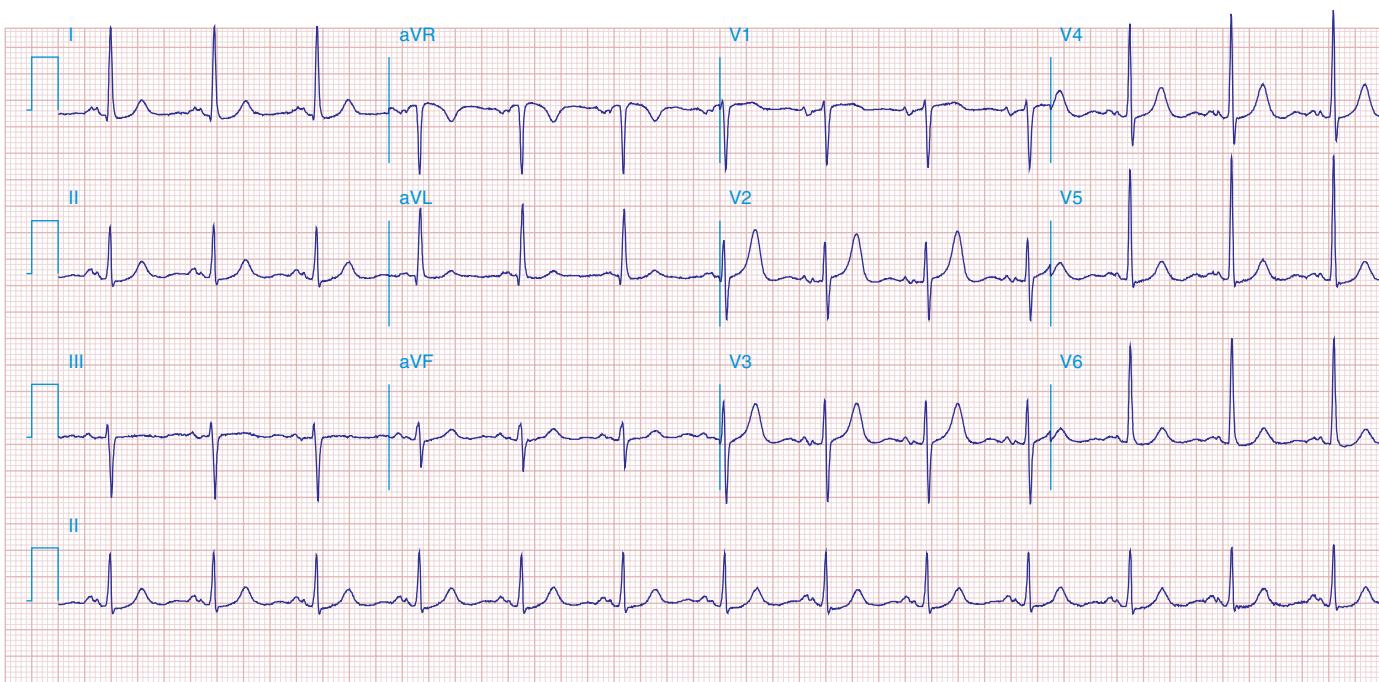


FIGURE 269e-28 Left atrial abnormality and LVH in a patient with long-standing hypertension.

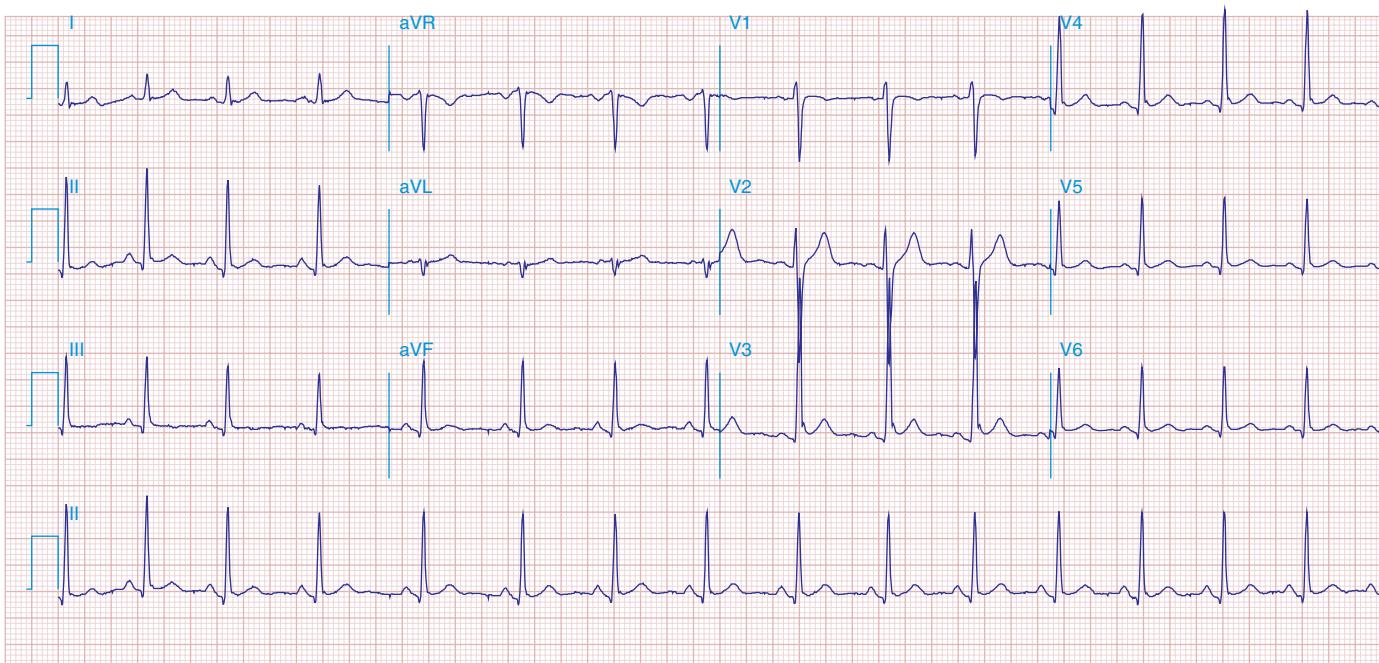


FIGURE 269e-29 Normal variant ST-segment elevations in a healthy 21-year-old male (commonly referred to as *benign early repolarization pattern*). ST elevations exhibit upward concavity and are most apparent in V_3 and V_4 , and less than 1 mm in the limb leads. Precordial QRS voltages are prominent, but within normal limits for a young adult. No evidence of left atrial abnormality or ST depression/T-wave inversions to go along with LVH.

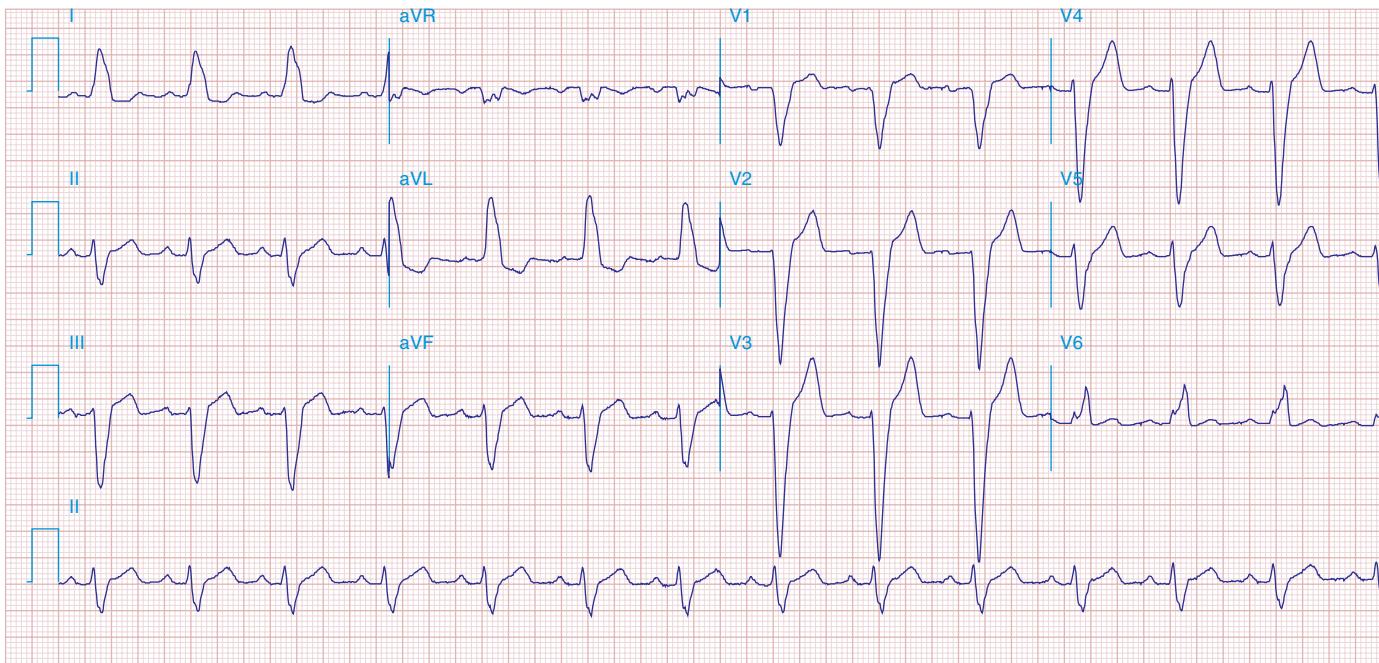


FIGURE 269e-30 SR with first-degree AV “block” (PR interval = 0.24 s) and complete LBBB.

MISCELLANEOUS



FIGURE 269e-31 Dextrocardia with: (1) inverted P waves in I and aVL; (2) negative QRS complex and T wave in I; and (3) progressively decreasing voltage across the precordium.

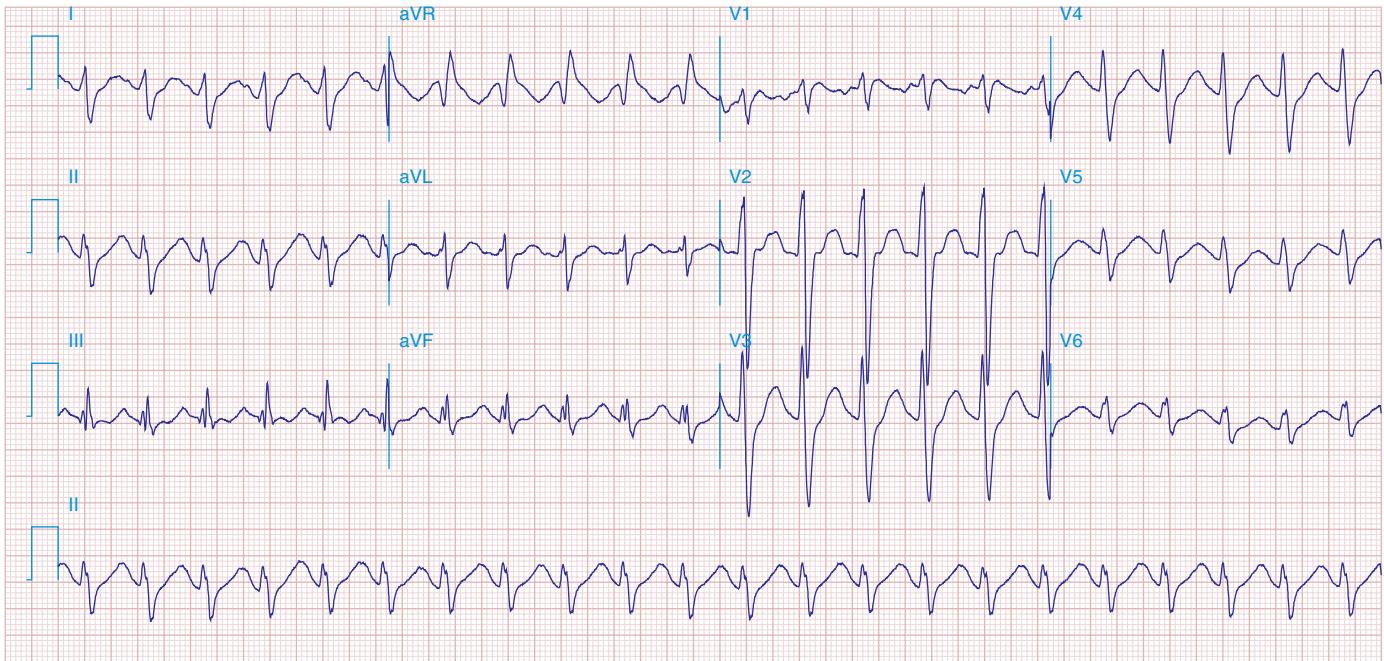


FIGURE 269e-32 Sinus tachycardia; intraventricular conduction delay (IVCD) with a rightward QRS axis. QT interval is prolonged for the rate. The triad of sinus tachycardia, a wide QRS complex, and a long QT in appropriate clinical context suggests tricyclic antidepressant overdose. Terminal S wave (rS) in I and terminal R wave (qR) in aVR are also noted as part of this IVCD variant.

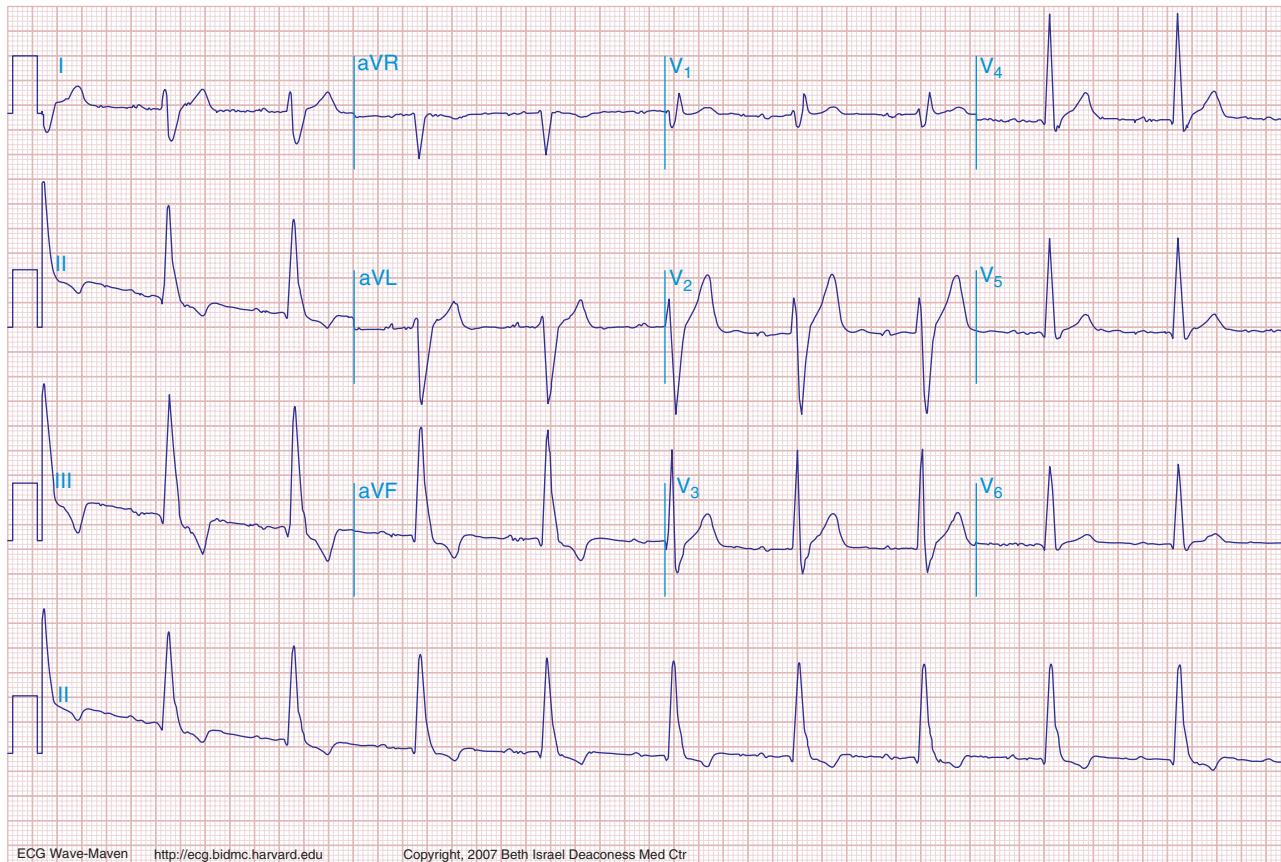


FIGURE 269e-33 Borderline sinus bradycardia (59 beats/min), prolonged PR interval (250 ms), and RBBB are present with marked right-axis deviation (RAD), the latter consistent with left posterior fascicular block (LPFB). LPFB is a diagnosis of exclusion, which requires ruling out lead reversal, normal variant, RV overload syndromes, or lateral MI, in particular, as causes of the RAD. This ECG also shows nondiagnostic Q waves in the inferior leads. In concert with RBBB, the LPFB indicates bifascicular block. (From LA Nathanson et al: ECG Wave-Maven. <http://ecg.bidmc.harvard.edu>.)

270e

Noninvasive Cardiac Imaging: Echocardiography, Nuclear Cardiology, and Magnetic Resonance/Computed Tomography Imaging

Marcelo F. Di Carli, Raymond Y. Kwong,
Scott D. Solomon

The ability to image the heart and blood vessels noninvasively has been one of the greatest advances in cardiovascular medicine since the development of the electrocardiogram. Cardiac imaging complements history taking and physical examination, blood and laboratory testing, and exercise testing in the diagnosis and management of most diseases of the cardiovascular system. Modern cardiovascular imaging consists of echocardiography (cardiac ultrasound), nuclear scintigraphy including positron emission tomography (PET) imaging, magnetic resonance imaging (MRI), and computed tomography (CT). These studies, often used in conjunction with exercise testing, can be used independently or in concert depending on the specific diagnostic needs. In this chapter, we review the principles of each of these modalities and the utility and relative benefits of each for the most common cardiovascular diseases.

PRINCIPLES OF MULTIMODALITY CARDIAC IMAGING

ECHOCARDIOGRAPHY

Echocardiography uses high-frequency sound waves (ultrasound) to penetrate the body, reflect from relevant structures, and generate an image. The basic physical principles of echocardiography are identical to other types of ultrasound imaging, although the hardware and software are optimized for evaluation of cardiac structure and function. Early echocardiography machines displayed “M-mode” echocardiograms in which a single ultrasound beam was displayed over time on a moving sheet of paper (Fig. 270e-1, left panel). Modern

echocardiographic machinery uses phased array transducers that contain up to 512 elements and emit ultrasound in sequence. The reflected ultrasound is then sensed by the receiving elements. A “scan converter” uses information about the timing and magnitude of the reflected ultrasound to generate an image (Fig. 270e-1, right panel). This sequence happens repeatedly in “real time” to generate moving images with frame rates that are typically greater than 30 frames per second, but can exceed 100 frames per second. The gray scale of the image features indicates the intensity of the reflected ultrasound; fluid or blood appears black, and highly reflective structures, such as calcifications on cardiac valves or the pericardium, appear white. Tissues such as myocardium appear more gray, and tissues such as muscle display a unique speckle pattern. Although M-mode echocardiography has largely been supplanted by two-dimensional echocardiography, it is still used because of its high temporal resolution and accuracy for making linear measurements.

The spatial resolution of ultrasound is dependent on the wavelength: the smaller the wavelength and the higher the frequency of the ultrasound beam, the greater are the spatial resolution and ability to discern small structures. Increasing the frequency of ultrasound will increase resolution but at the expense of reduced penetration. Higher frequencies can be used in pediatric imaging or transesophageal echocardiography where the transducer can be much closer to the structures being interrogated, and this is a rationale for using transesophageal echocardiography to obtain higher quality images.

Three-dimensional ultrasound transducers use a waffle-like matrix array transducer and receive a pyramidal data sector. Three-dimensional echocardiography is being increasingly used for assessment of congenital heart disease and valves, although current image quality lags behind two-dimensional ultrasound (Fig. 270e-2).

In addition to the generation of two-dimensional images that provide information about cardiac structure and function, echocardiography can be used to interrogate blood flow within the heart and blood vessels by using the Doppler principle to ascertain the velocity of blood flow. When ultrasound emitted from a transducer reflects off red blood cells that are moving toward the transducer, the reflected ultrasound will return at a slightly higher frequency than emitted; the opposite is true when flow is away from the transducer. That frequency difference, termed the Doppler shift, is directly related to the velocity

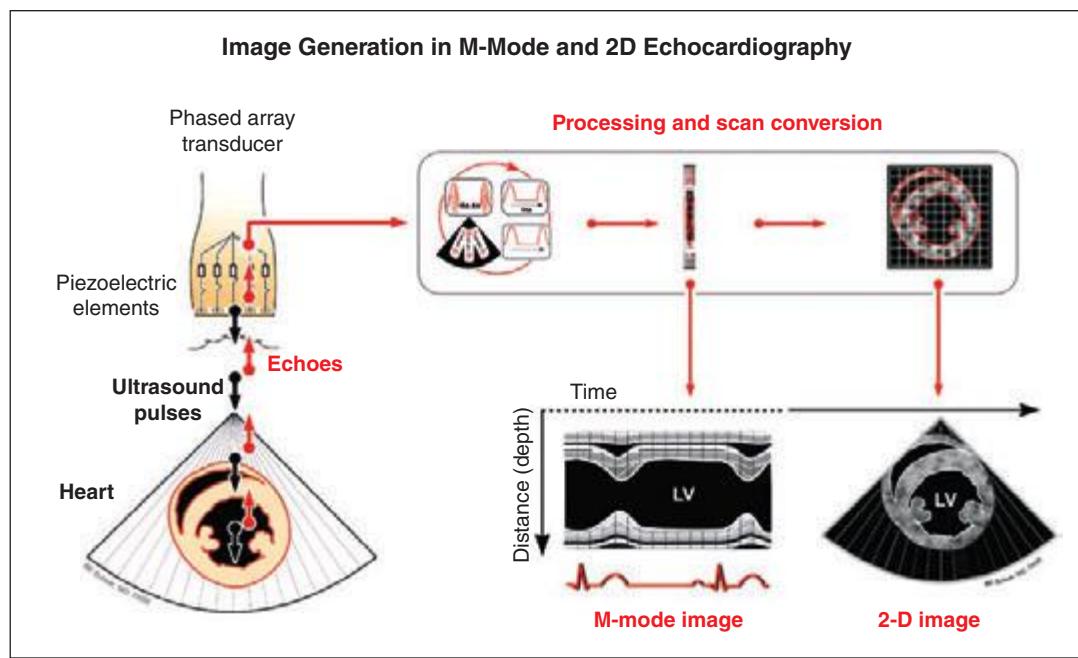


FIGURE 270e-1 Principle of image generation in two-dimensional (2D) echocardiography. An electronically steerable phased-array transducer emits ultrasound from piezoelectric elements, and returning echoes are used to generate a 2D image (right) using a scan converter. Early echocardiography machines used a single ultrasound beam to generate an “M-mode” echocardiogram (see text), although modern equipment generates M-mode echocardiograms digitally from the 2D data. LV, left ventricle.

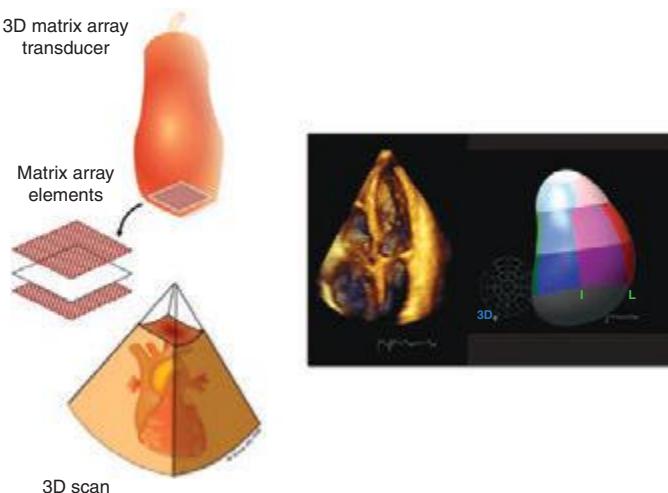


FIGURE 270e-2 Three-dimensional (3D) probe and 3D image.

of the flow of the red blood cells. The velocity of blood flow between two chambers will be directly related to the pressure gradient between those chambers. A modified form of the Bernoulli equation,

$$p = 4v^2$$

where p = the pressure gradient and v = the velocity of blood flow in meters per second, can be used to calculate this pressure gradient in the majority of clinical circumstances. This principle can be used to determine the pressure gradient between chambers and across valves and has become central to the quantitative assessment of valvular heart disease.

There are three types of Doppler ultrasound that are typically used in standard echocardiographic examinations: spectral Doppler, which consists of both pulsed wave Doppler and continuous wave Doppler, and color flow Doppler. Both types of spectral Doppler will display a waveform representing the velocity of blood flow, with time on the horizontal axis and velocity on the vertical axis. Pulsed wave Doppler is used to interrogate relatively low velocity flow and has the ability to determine blood flow velocity at a particular location within the heart. Continuous wave Doppler is used to assess high-velocity flow but can only identify the highest velocity in a particular direction and cannot interrogate the velocity at a specific depth location. Both of these techniques can only accurately assess velocities that are in the direction of the ultrasound scan lines, and velocities that are at an angle to the direction of the ultrasound beam will be underestimated. Color flow Doppler is a form of pulsed wave Doppler in which the velocity of blood flow is color encoded according to a scale and superimposed on a two-dimensional grayscale image in real time, giving the appearance of real-time flow within the heart. The Doppler principle

can also be used to assess the velocity of myocardial motion, which is a sensitive way to assess myocardial function (Fig. 270e-3). A standard full transthoracic echocardiographic examination consists of a series of two-dimensional views made up of different imaging planes from various scanning locations and spectral and color flow Doppler assessment.

Transesophageal echocardiography is a form of echocardiography in which the transducer is located on the tip of an endoscope that can be inserted into the esophagus. This procedure allows closer, less obstructed views of cardiac structures, without having to penetrate through chest wall, muscle, and ribs. Because less penetration is needed, a higher frequency probe can be used, and image quality and spatial resolution are generally higher than with standard transthoracic imaging, particularly for structures that are more posterior. Transesophageal echocardiography has become the test of choice for assessment of small lesions in the heart such as valvular vegetations, especially in the setting of a prosthetic valve disease, and intracardiac thrombi, including assessment of the left atrial appendage, which is difficult to visualize with standard transthoracic imaging, and for assessment of congenital abnormalities. Transesophageal echocardiography requires both topical and systemic anesthesia, generally conscious sedation, and carries additional risks such as potential damage to the esophagus, including the rare possibility of perforation, aspiration, and anesthesia-related complications. Patients generally need to give consent for transesophageal echocardiography and be monitored during and subsequent to the procedure. Transesophageal echocardiography can be carried out in intubated patients and is routinely used for intraoperative monitoring during cardiac surgery.

Stress echocardiography is routinely used to assess cardiac function during exercise and can be used to identify myocardial ischemia or to assess valvular function under exercise conditions. Stress echocardiography is typically performed in conjunction with treadmill or bicycle exercise testing, but can also be performed using pharmacologic stress most typically with an intravenous infusion of dobutamine (see section on stress imaging below).

Whereas typical echocardiographic equipment is large, bulky, and expensive, small hand-held ultrasound equipment developed over the last decade now offers diagnostic quality imaging in a package small enough to be carried on rounds (Fig. 270e-4). These relatively inexpensive point-of-care devices currently lack full diagnostic capabilities but represent an excellent screening tool if used by an experienced operator. As these units become even smaller and less expensive, they are being increasingly used not just by cardiologists, but also by emergency medicine physicians, intensivists, anesthesiologists, and internists.

RADIOPHARMACEUTICAL IMAGING

Radiopharmaceutical imaging techniques are commonly used for the evaluation of patients with known or suspected coronary artery disease (CAD),

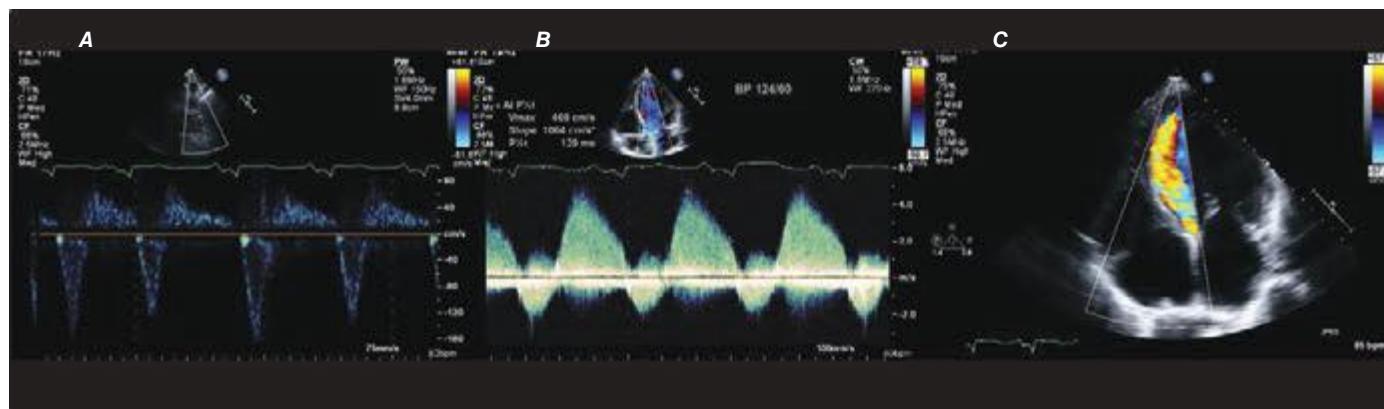


FIGURE 270e-3 Three types of Doppler ultrasound. **A** and **B**, Pulsed and continuous wave Doppler waveforms with time on horizontal axis and velocity of blood flow on vertical axis. **C**, Color flow Doppler, where velocities are encoded by colors according to scale on right side of screen and superimposed on a two-dimensional grayscale image.



FIGURE 270e-4 Two examples of hand-held ultrasound equipment: V-Scan (General Electric, left) and Sonosite (right).

including for initial diagnosis and risk stratification as well as the assessment of myocardial viability. These techniques use small amounts of radiopharmaceuticals (**Table 270e-1**), which are injected intravenously and trapped in the heart and/or vascular cells. Radioactivity within the heart and vasculature decays by emitting gamma rays. The interaction between these gamma rays and the detectors in specialized scanners (single-photon emission computed tomography [SPECT] and PET) creates a scintillation event or light output, which can be captured by digital recording equipment to form an image of the heart and vasculature. Like CT and MRI, radionuclide images also generate tomographic (three-dimensional) views of the heart and vasculature.

Radiopharmaceuticals Used in Clinical Imaging Table 270e-1 summarizes the most commonly used radiopharmaceuticals in clinical SPECT and PET imaging.

Protocols for Stress Myocardial Perfusion Imaging Both exercise and pharmacologic stress can be used for myocardial perfusion imaging. Exercise stress is generally preferred because it is physiologic and provides additional clinically important information (i.e., clinical and hemodynamic responses, ST-segment changes, exercise duration, and functional status). However, submaximal effort will lower the sensitivity of the test and should be avoided, especially if the test is requested for initial diagnosis of CAD. In patients who are unable to exercise or who exercise submaximally, pharmacologic stress offers an adequate alternative to exercise stress testing. Pharmacologic stress can be accomplished either with coronary vasodilators, such as adenosine, dipyridamole, or regadenoson, or β_1 -receptor agonists, such as dobutamine. For patients unable to exercise, vasodilators are the most commonly used stressors in combination with myocardial perfusion imaging. Dobutamine is a potent β_1 -receptor agonist that increases myocardial oxygen demand by augmenting contractility, heart rate, and blood pressure similar to exercise. It is generally used as an alternative to vasodilator stress in patients with chronic pulmonary disease, in whom vasodilators may be contraindicated. Dobutamine is also

commonly used as a pharmacologic alternative to stress testing in stress echocardiography.

Myocardial Perfusion and Viability Imaging Protocols

Imaging protocols are tailored to the individual patient based on the clinical question, patient's risk, ability to exercise, body mass index, and other factors.

For SPECT imaging, technetium-99m (^{99m}Tc)-labeled tracers are the most commonly used imaging agents because they are associated with the best image quality and the lowest radiation dose to the patient (**Fig. 270e-5**). Selection of the protocol (stress-only, single-day, or 2-day) depends on the patient and clinical question. After intravenous injection, myocardial uptake of ^{99m}Tc -labeled tracers is rapid (1–2 min). After uptake, these tracers become trapped intracellularly in mitochondria and show minimal change over time. This is why ^{99m}Tc tracers can be helpful in patients with chest pain of unclear etiology occurring at rest, because patients can be injected while having chest pain and imaged some time later after symptoms subside. Because the radiotracer is trapped at the time of injection, the images provide a snapshot of myocardial perfusion at the time of injection, even if the acquisition is delayed. Indeed, a normal myocardial perfusion study following a rest injection in a patient with active chest pain effectively excludes myocardial ischemia as the cause of chest pain (high negative predictive value). While used commonly in the past for perfusion imaging, thallium-201 protocols are now rarely used because they are typically associated with a higher radiation dose to the patient.

PET myocardial perfusion imaging is an alternative to SPECT and is associated with improved diagnostic accuracy and lower radiation dose to patients due to the fact that radiotracers are typically short lived (Table 270e-1). The ultra-short half-life of some PET radiopharmaceuticals in clinical use (e.g., rubidium-82) is the primary reason why imaging is generally combined with pharmacologic stress, as opposed to exercise, because this allows for faster imaging of these rapidly decaying radiopharmaceuticals. However, exercise is possible for relatively longer lived radiotracers (e.g., ^{13}N -ammonia). PET imaging protocols are typically faster than SPECT, but more expensive. For myocardial perfusion imaging, rubidium-82 does not require an on-site medical cyclotron (it is available from a strontium-82/rubidium-82 generator) and, thus, is the most commonly used radiopharmaceutical. ^{13}N -ammonia has better flow characteristics (higher myocardial extraction) and imaging properties than rubidium-82, but it does require an on-site medical cyclotron. In comparison to SPECT, PET has improved spatial and contrast resolution and provides absolute measures of myocardial perfusion (in mL/min per gram of tissue), thereby providing the patients' regional and global coronary flow reserve. The latter helps improve diagnostic accuracy and risk stratification, especially in obese patients, women, and higher risk individuals (e.g., diabetes mellitus) (**Fig. 270e-6**). Contemporary PET and SPECT scanners are combined with a CT scanner (so-called *hybrid PET/CT* and *SPECT/CT*). CT is used primarily to guide patient positioning in the field of view and for correcting inhomogeneities in radiotracer distribution due to attenuation by soft tissues (so-called *attenuation*

TABLE 270e-1 RADIOPHARMACEUTICALS FOR CLINICAL NUCLEAR CARDIOLOGY

Radiopharmaceutical	Imaging Technique	Physical Half-Life	Application
Technetium-99m sestamibi	SPECT	6 h	Myocardial perfusion imaging
Technetium-99m tetrofosmin	SPECT	6 h	Myocardial perfusion imaging
Thallium-201	SPECT	72 h	Myocardial perfusion imaging
Iodine-123 metaiodobenzylguanidine (MIBG)	SPECT	13 h	Cardiac sympathetic innervation
Rubidium-82	PET	76 s	Myocardial perfusion imaging
^{13}N -ammonia	PET	10 min	Myocardial perfusion imaging
^{18}F -fluorodeoxyglucose	PET	110 min	Myocardial viability and inflammation imaging

Abbreviations: PET, positron emission tomography; SPECT, single-photon emission computed tomography.

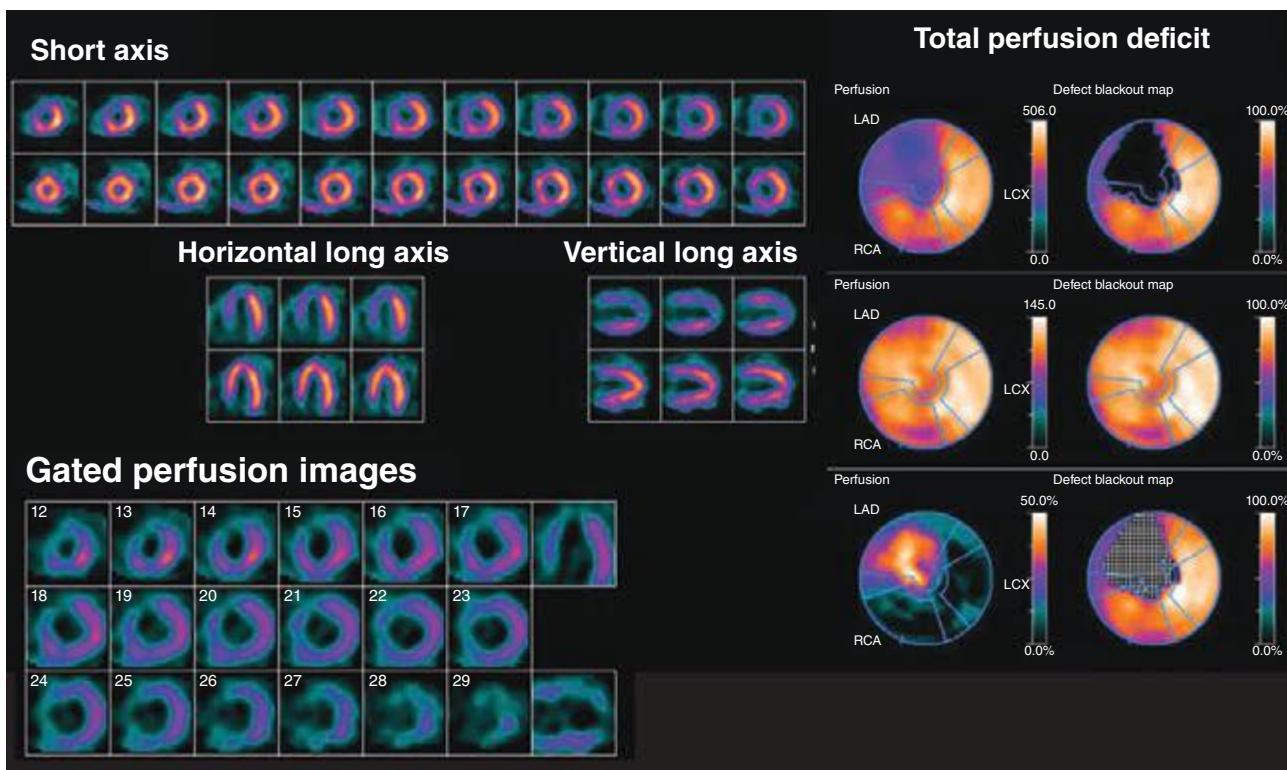


FIGURE 270e-5 Tomographic stress (top of each pair) and rest myocardial perfusion images with technetium-99m sestamibi single-photon emission computed tomography imaging demonstrating a large perfusion defect throughout the anterior and anteroseptal walls. The right panel demonstrates the quantitative extent of the perfusion abnormality at stress (top bull's-eye), at rest (middle bull's-eye), and the extent of defect reversibility (lower bull's-eye). The lower left panel demonstrates electrocardiogram-gated myocardial perfusion images from which one can determine the presence of regional wall motion abnormalities and calculate left ventricular volumes and ejection fraction.

correction). However, it can also be used to obtain diagnostic data including coronary artery calcium score and/or CT coronary angiography (discussed below).

For the evaluation of myocardial viability in patients with ischemic cardiomyopathy, myocardial perfusion imaging (with SPECT or PET) is usually combined with metabolic imaging (i.e., fluorodeoxyglucose [FDG] PET). In hospital settings lacking access to PET scanning, thallium-201 SPECT imaging is an excellent alternative.

CARDIAC COMPUTED TOMOGRAPHY

CT acquires images by passing a thin x-ray beam through the body at many angles to generate cross-sectional images. The x-ray transmission measurements are collected by a detector array and digitized into pixels that form an image. The grayscale information in individual pixels is determined by the attenuation of the x-ray beam along its path by tissues of different densities, referenced to the value for water in units known as Hounsfield units. In the resulting CT images, bone appears bright white, air is black, and blood and muscle show varying shades of gray. However, due to the limited contrast between cardiac chambers and vascular structures, iodinated contrast agents are necessary for most cardiovascular indications. Cardiac CT produces tomographic images of the heart and surrounding structures. With modern CT scanners, a three-dimensional dataset of the heart can be acquired in 5–15 s with submillimeter spatial resolution.

CT Calcium Scoring CT calcium scoring is the simplest application of cardiac CT and does not require administration of iodinated contrast. The presence of coronary artery calcification has been associated with increased burden of atherosclerosis and cardiovascular mortality. Coronary calcium is then quantified (e.g., Agatston score) and categorized as minimal (0–10), mild (10–100), moderate (100–400), or severe (>400) (Fig. 270e-7). Coronary artery calcium (CAC) scores are then normalized by age and gender and reported as percentile scores. Population-based studies in asymptomatic cohorts have reported high cardiac prognostic

value of CT calcium score. With appropriate techniques, the radiation dose associated with CAC scanning is very low (~1–2 mSv).

CT Coronary Angiography Coronary CT angiography (CTA) is emerging as a viable alternative to coronary angiography in selected patients. Imaging of the coronary arteries by CT is challenging because of their small luminal size and because of cardiac and respiratory motion. Respiratory motion can be reduced by breath-holding, and cardiac motion is best reduced by slowing the patient's heart rate, ideally to under 60 beats/min, using intravenous or oral beta blockade or other rate-lowering drugs. When performing a coronary CTA, image quality is further enhanced using sublingual nitroglycerin to enlarge the coronary lumen just prior to contrast injection. Imaging the whole-heart volume is synchronized to the administration of weight-based and appropriately timed intravenous iodinated contrast. Image acquisition is linked to the timing of the cardiac cycle through electrocardiogram (ECG) triggering. Prospective ECG triggering, whereby the x-ray beam is turned on during a specific part of the cardiac cycle (e.g., end systole, combined end-systolic and end-diastolic timing, or mid-diastole), is generally used to limit the radiation exposure to the patient by acquiring data only through that portion of the cardiac cycle with least motion. Dose modulation is another method that should be routinely used to reduce radiation when performing CTA. It delivers a maximal amount of x-ray during the portion of the cardiac cycle of interest, but reduces x-ray delivery throughout the remaining portion of the cardiac cycle. The resulting images are then postprocessed using a three-dimensional workstation, which facilitates interpretation of the coronary anatomy and estimation of the severity of atherosclerosis (Fig. 270e-7).

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) imaging is based on imaging of protons in hydrogen. Hydrogen is abundant because 80% of the human body consists of water. When put inside the MRI scanner,

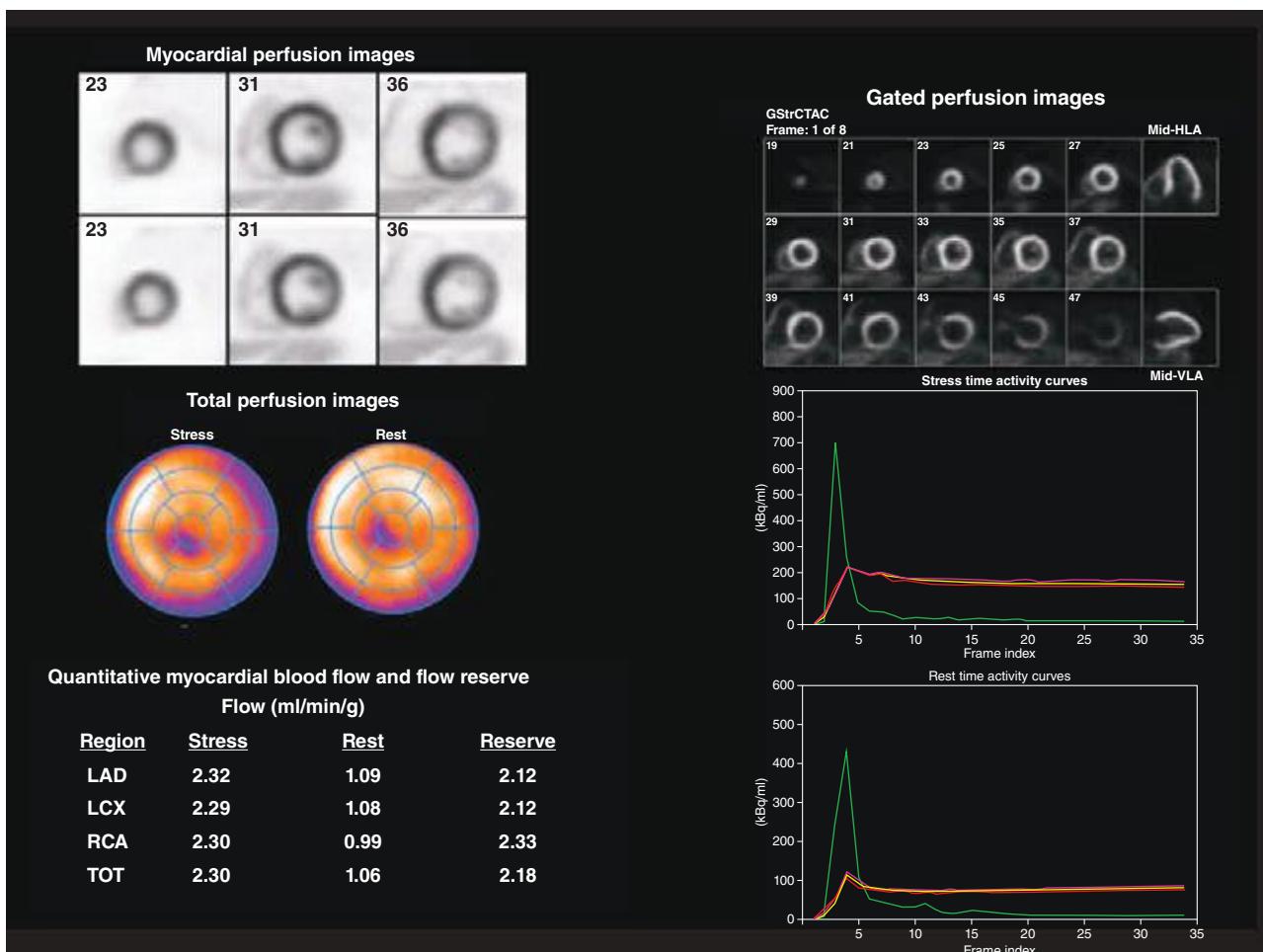


FIGURE 270e-6 Multidimensional cardiac imaging protocol with positron emission tomography. The left upper panel demonstrates stress and rest short-axis images of the left and right ventricles demonstrating normal regional myocardial perfusion. The middle panel demonstrates the quantitative bull's-eye display to evaluate the extent and severity of perfusion defects. The lower right panel illustrates the time-activity curves for quantification of myocardial blood flow. The right upper panel demonstrates electrocardiogram-gated myocardial perfusion images from which one can determine the presence of regional wall motion abnormalities and calculate left ventricular volumes and ejection fraction. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TOT, total left ventricle.

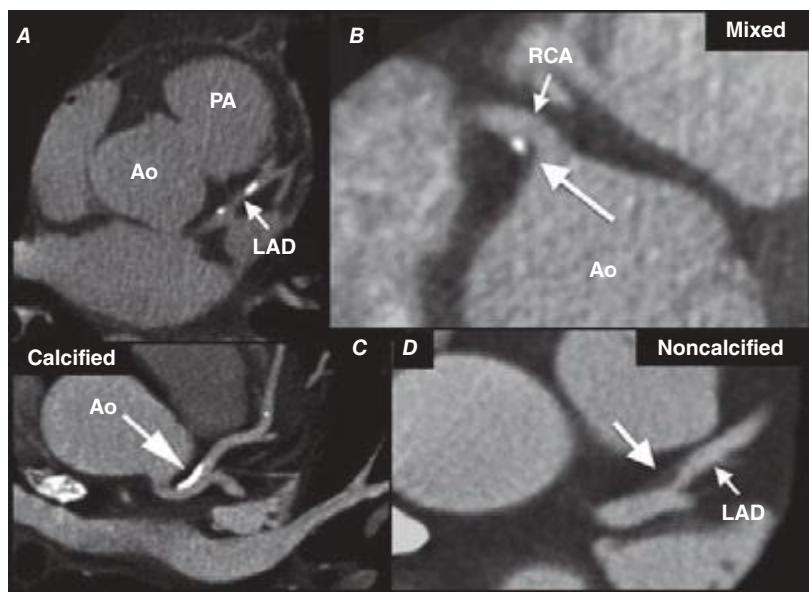


FIGURE 270e-7 Examples of non-contrast- and contrast-enhanced coronary imaging with computed tomography (CT). **A.** Calcified coronary plaques in the distal left main and proximal left anterior descending coronary artery (LAD) in a noncontrast cardiac CT scan. Calcium deposits are dense and present as bright white structures on CT, even without contrast enhancement. **B, C, and D.** Different types of atherosclerotic plaques on contrast-enhanced CT scans. Importantly, noncalcified plaques are evident only on contrast-enhanced CT scans. AO, aorta; PA, pulmonary artery; RCA, right coronary artery.

TABLE 270e-2 CLINICAL CARDIAC MAGNETIC RESONANCE PULSE SEQUENCES AND THEIR APPLICATION

Pulse Sequence	Key Imaging Interests
Cardiac Morphology	
Still frame imaging (black or bright blood)	Cardiac structures
Cardiac Function	
Cine imaging	Left ventricular volume and function
Cine myocardial tagging	Left ventricular deformation (strain)
Blood Flow Imaging	
Velocity-encoded phase contrast	Cardiac and great vessel flow
Stress Testing	
Myocardial perfusion imaging	Regional myocardial blood flow
Cine imaging	Regional wall motion
Myocardial Tissue Characterization	
Late gadolinium enhancement	Myocardial infarction and infiltrative disease
T2-weighted imaging	Myocardial edema
Iron content imaging	Myocardial iron infiltration
Magnetic Resonance Angiography	
Aorta, peripheral and coronary arteries	Luminal stenosis and vessel wall remodeling

the magnetic field causes the protons (spins) to spin around their axis (a process known as precession) at specific frequencies. Spins within water have a different frequency than spins within more complex macromolecules such as fat or protein. Inside the MRI, a set of gradient coils slightly modifies the magnetic field in each of the three orthogonal directions. As a result, this additional process alters the frequencies of spins, and now the spins can be spatially located inside the MRI bore. This system allows the MRI to selectively deposit radiofrequency energy (in the form of radiofrequency pulse) into specific locations of the body for the purpose of imaging those locations. Once the radiofrequency pulses stop, the energy absorbed by the body will quickly be released back. Using the proper arrangement of surface phased-array coils, this released energy can be read, and important information such as spin locations and frequencies can be digitally recorded in a data matrix known as the K-space, before reconstructed into a magnetic resonance image. Radiofrequency energy deposition into the patient's body can be arranged in many complex ways, known as pulse sequences, that allow extraction of different types of information from the body regions of interests. In CMR, these types of information in general are categorized under T1, T2, or T2* weighting, each of them containing a different combination of diagnostic information regarding cardiac structure, tissue characteristics, blood flow, or other physiologic properties of the heart.

In clinical CMR, most pulse sequences are T1-weighted sequences, which characterize cardiac structure and function, blood flow, and myocardial perfusion, whereas T2-weighted and T2*-weighted pulse sequences characterize myocardial edema and myocardial iron infiltration, respectively. A combination of more than one weighting is possible in some pulse sequences. ECG-triggered cine CMR is the modality that serves as a reference standard for quantifying ventricular volumes and function. Respiratory motion during CMR imaging is suppressed most commonly using repetitive patient breath-holding, but more advanced algorithms such as motion averaging or gating diaphragmatic motion (known as navigator guidance) are also used in clinical CMR. A list of common pulse sequence used in CMR is shown in [Table 270e-2](#).

ASSESSMENT OF CARDIAC STRUCTURE AND FUNCTION

Echocardiography, CMR, and cardiac CT are all capable of assessing cardiac structure and function, although echocardiography is generally considered the primary imaging method for these assessments. Radionuclide imaging can also be used to assess left ventricular

regional and global systolic function. Echocardiography is most often used to assess the size of all four chambers and thickness of ventricular walls, which are affected by both cardiac and systemic diseases.

The structure of the left ventricle is generally assessed by determining its volume and mass. Left ventricular volumes can be easily estimated from two-dimensional echocardiography by using one of several validated methods. The accuracy of these methods by echocardiography is limited by the fact that, as a nontomographic technique, foreshortening of the imaging plane can lead to underestimation of volumes. Moreover, virtually all of these methods require accurate identification of the endocardial border, which is dependent on image quality. In this regard, high-resolution tomographic techniques such as CMR or cardiac CT are considered generally more accurate for volumetric assessment. Three-dimensional echocardiography has several advantages over two-dimensional echocardiography by not requiring any geometric assumptions about the left ventricle for quantification of volumes and ejection fraction. However, acquisition of three-dimensional echocardiographic images requires substantial expertise, and these techniques are not widely used in practice.

Left ventricular dilatation is common to a number of cardiac diseases. For example, regional dysfunction secondary to myocardial infarction can ultimately lead to progressive ventricular dilatation or remodeling. Although dilatation often begins in the region affected by the infarction, subsequent compensatory dilatation can occur in remote myocardial regions as well. The presence of regional wall motion abnormalities associated with ventricular thinning (reflecting scar) in a coronary distribution is strongly suggestive of an ischemic etiology. Direct assessment of infarcted myocardium is possible with both CMR (evident as areas of late gadolinium enhancement [LGE]) and radionuclide imaging (as assessed by regional perfusion or metabolic defects at rest). CMR can be particularly useful in determining etiology of ventricular dilatation and dysfunction, with LGE in coronary distributions being nearly pathognomonic for infarction ([Video 270e-1](#)).

More global ventricular dilatation is seen in cardiomyopathy and dilatation due to valvular heart disease. Idiopathic, nonischemic cardiomyopathies will typically result in global ventricular dilatation and dysfunction, with thinning of the walls. Patients with substantial ventricular dyssynchrony due to conduction abnormalities will have a typical pattern of contraction (e.g., delay of contraction of the lateral wall with left bundle branch block). Although various methods for determining ventricular dyssynchrony have been proposed as ways to identify patients who would benefit from cardiac resynchronization therapy, it is not yet clear that they are superior to ECG assessment of QRS duration and morphology. As discussed later in this chapter, regurgitant lesions of either the mitral or aortic valves can lead to substantial ventricular dilatation, and assessment of ventricular size is integral in the evaluation and timing of surgical correction. Because changes in ventricular size are used clinically to determine which patients should undergo valve surgery, accurate assessment of changes in ventricular size is essential. Although serial echocardiography can provide these data, serial assessment by CMR may be more accurate when appreciation of subtle changes over time is important.

Left ventricular wall thickness and mass are also important measures of cardiac and systemic disease. The left ventricle will hypertrophy under any condition in which its afterload is increased, including conditions that obstruct outflow, such as aortic stenosis, hypertrophic cardiomyopathy, and subaortic membranes; in postcardiac aortic obstruction seen in coarctation; or in systemic conditions characterized by increased afterload, such as hypertension. The pattern of ventricular hypertrophy can change depending on the etiology. Aortic stenosis and hypertension are typically characterized by concentric hypertrophy, in which the ventricular walls thicken "concentrically" and cavity size is usually small. In volume overload conditions such as mitral or aortic regurgitation, there may be minimal increase in ventricular wall thickness, but substantial ventricular dilatation leads to marked increases in left ventricular mass.

Ventricular wall thickness can be measured and ventricular mass can be calculated by either echocardiography or CMR. Although radionuclide imaging and cardiac CT can also provide measures of

left ventricular mass, they are not generally used for this purpose. Although measurement of wall thickness with echocardiography is relatively straightforward and accurate, determining left ventricular mass by echocardiography requires using one of several formulas that takes into account both wall thickness and ventricular cavity dimensions. Assessment of left ventricular mass by CMR has the advantage of not requiring geometric assumptions and is thus more accurate than echocardiography.

ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC FUNCTION

Assessment of ejection fraction, or the percentage of blood ejected with each beat, has been the primary method to assess systolic function and is generally calculated by subtracting end-systolic volume from end-diastolic volume and dividing by end-diastolic volume. All cardiac imaging modalities can provide direct measurements of left ventricular ejection fraction (LVEF). As discussed above, tomographic techniques (e.g., CMR, CT, and radionuclide imaging [SPECT and PET]) are generally more accurate and reproducible than echocardiography because there are no geometric assumptions. A LVEF of 55% or greater is generally considered normal, and an LVEF of 50–55% is considered in the low-normal range.

Newer methods to assess systolic function, such as myocardial strain or deformation imaging using speckle-tracking methods on echocardiography or myocardial tagging on CMR, can provide a more sensitive approach to detection of systolic dysfunction. Additional assessments based on these novel methods include assessment of myocardial twist and torsion. Although these techniques are not used routinely, they may be especially useful in certain conditions such as valvular heart disease and early detection of cardiotoxicity following chemotherapy and/or radiation therapy. In addition to estimation or calculation of ejection fraction, stroke volume can be assessed by virtually all cardiac imaging methods, generally by subtracting the end-systolic volume from the end-diastolic volume, or by Doppler methods (only on echocardiography), and offers another measure of systolic function that provides independent information from ejection fraction.

ASSESSMENT OF LEFT VENTRICULAR DIASTOLIC FUNCTION

Echocardiography remains the primary method for clinical assessment of diastolic function. Recent advances in Doppler tissue imaging allow for accurate assessment of the velocity of myocardial wall motion by assessing the excursion of the mitral annulus in diastole. Mitral annular relaxation velocity, or E' , is inversely related to the time constant of relaxation, tau, and has been shown to have prognostic significance. Dividing the standard mitral inflow maximal velocity, E , by the mitral annular relaxation velocity yields E/E' , which has been shown to correlate with left ventricular filling pressures. The utility of standard E and A wave ratios for assessment of diastolic function has been questioned. Mitral deceleration time can be a useful measure if very short (<150 ms), suggesting restrictive physiology and severe diastolic dysfunction. Several grading methods for diastolic function have been proposed that take into account a number of diastolic parameters, including Doppler tissue-based relaxation velocities, pulmonary venous Doppler, and left atrial size (Fig. 270e-8). Diastolic function worsens with aging, and most diastolic parameters need to be adjusted for age.

ASSESSMENT OF RIGHT VENTRICULAR FUNCTION

Right ventricular size and function have been shown to be prognostically important in a variety of conditions. Right ventricular size and function can be assessed by echocardiography, CMR, CT, or radionuclide imaging methods. CMR is considered the most accurate noninvasive technique to evaluate the structure and right ventricular ejection fraction of the right ventricle (Video 270e-2). Although first-pass imaging by radionuclide angiography can provide accurate and reproducible measurements of right ventricular volumes and ejection fraction, it is not commonly used. Assessment of the right ventricle by echocardiography has generally been qualitative, owing in part to the unusual geometry of the right ventricle. However, several quantitative methods are available for assessment of right ventricular function,

including fractional area change ($FAC = [\text{diastolic area} - \text{systolic area}] / \text{diastolic area}$), which has been shown to correlate with outcomes in heart failure and after myocardial infarction. Excursion of the tricuspid annulus (tricuspid annular plane systolic excursion) is another widely used method to assess right ventricular function, although it is mostly used in research settings.

Abnormalities of right ventricular size and function are generally secondary to either diseases that affect the right ventricle intrinsically or disease in which the right ventricle responds to abnormalities elsewhere in the heart or pulmonary vasculature. Intrinsic diseases that affect the RV include congenital abnormalities, including hypoplastic right ventricle and arrhythmogenic right ventricular dysplasia, and acquired diseases, such as right ventricular infarction and infiltrative diseases that affect the right ventricle. Long-standing pulmonary hypertension or pulmonary outflow tract obstruction leads to right ventricular hypertrophy and ultimately dilatation. Although right ventricular dilatation can occur due to both chronic and acute processes, chronic right ventricular dilatation is usually secondary to long-standing increases in pulmonary pressures and can thus be distinguished from the acute processes that cause right ventricular dilatation. One such acute process that can cause profound right ventricular dilatation and dysfunction is acute pulmonary embolism. In the setting of acute occlusion of a pulmonary artery or branch, an acute rise in pulmonary vascular resistance causes a previously normal right ventricle to dilate and fail due to the increased afterload. In acute pulmonary embolism, right ventricular dilatation and dysfunction are signs of substantial hemodynamic compromise and are associated with a marked increase risk in likelihood of death. In addition to right ventricular dilatation, acute pulmonary embolism is often associated with a specific pattern of regional right ventricular dysfunction, commonly referred to as the McConnell sign, characterized by preservation of right ventricular wall motion in the basal and apical regions and dyskinesis in the region of the mid right ventricular free wall. This abnormality is highly specific for acute pulmonary embolism and is likely secondary to acute increases in right ventricular load.

Any disease that causes increased pulmonary vascular resistance can lead to right ventricular dilatation and dysfunction. Long-standing chronic obstructive pulmonary disease results in cor pulmonale in which right ventricular pressures become elevated as the right ventricle hypertrophies in response to the increased pulmonary vascular resistance. Acute pneumonia can cause findings that are similar to acute pulmonary embolism. In patients with right ventricular dilatation without obvious pulmonary disease, intracardiac shunts should be considered. The increased flow through the pulmonary vasculature as a result of an atrial septal or ventricular septal defect can, over time, result in elevation in pulmonary resistance with subsequent dilatation and hypertrophy of the right ventricle. Right ventricular dilatation and dysfunction also have prognostic significance in left-sided heart disease and have been shown to be important predictors of outcome in patients with heart failure or acute myocardial infarction.

In addition to assessment of left ventricular structure, assessment of the other cardiac chambers also provides important clues to intracardiac and systemic diseases. Enlargement of the left atrium is common in patients with hypertension and is also suggestive of increased left ventricular filling pressures; indeed, left atrial size is often termed the “hemoglobin A_{1c} ” of diastolic function, because left atrial enlargement reflects long-standing increase in left-sided filling pressures. Right atrial dilatation and dilatation of the inferior vena cava are common in conditions in which central venous pressure is elevated.

PATIENT SAFETY CONSIDERATIONS

RADIATION EXPOSURE

Both cardiac CT and radionuclide imaging expose patients to ionizing radiation. Several recent publications have raised concern regarding the potential harmful effects of ionizing radiation associated with cardiac imaging. The *effective dose* is a measure used to estimate the biologic effects of radiation and is expressed in millisieverts (mSv). However, measuring the radiation effective dose associated with diagnostic imaging is complex and imprecise and often results in varying estimates,

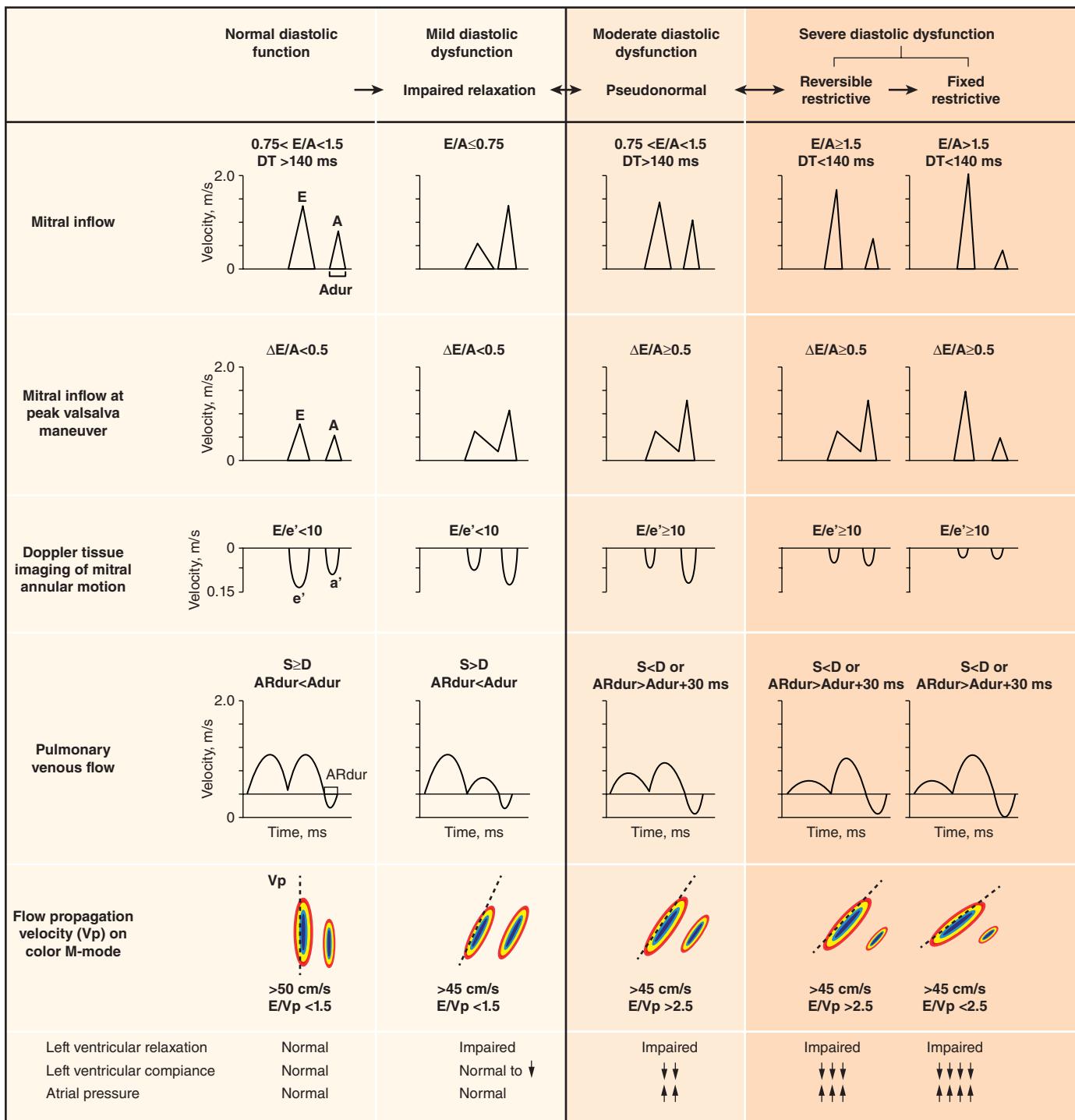


FIGURE 270e-8 Stages of diastolic function based on various parameters, including mitral inflow (with and without Valsalva maneuver), Doppler tissue imaging, pulmonary venous flow, and flow propagation. (Adapted with permission from MM Redfield *et al*: JAMA 289:194, 2003.)

even among experts. The effective dose from a typical myocardial perfusion SPECT scan ranges between ~4 and 11 mSv, depending on the protocol and type of scanner used. The effective dose from a typical myocardial perfusion PET scan is lower, ~2.5–4 mSv. Radiation exposure associated with cardiac CT is variable and, as with radioactive imaging, also depends on the imaging protocol and scanner used. Although historic radiation doses with cardiac CT have been quite high, the introduction of newer technologies described above (e.g., x-ray tube modulation, prospective ECG gating) has resulted in a significant dose reduction. The current average radiation dose for a coronary CTA ranges from 5–15 mSv and, in selected cases, can be as low as 1 mSv. Imaging laboratories follow the ALARA (as low as reasonably achievable) principle when balancing the clinical need

and imaging approach. By comparison, the average dose for invasive coronary angiography is ~7 mSv, whereas exposure to radiation from natural sources in the United States amounts to ~3 mSv annually.

The risk of a fatal malignancy from medical imaging-related radiation is difficult to estimate precisely but is likely small and difficult to discern from the background risk of natural malignancies. The small but potential radiation risks from imaging mandate an assessment of the risk-versus-benefit ratio in the individual patient. In this context, one must not fail to take into account the risks of missing important diagnostic information by not performing a test (which could potentially influence near-term management and outcomes) for a theoretical concern of a small long-term risk of malignancy. Before ordering any test, especially one associated with ionizing radiation, we must

ensure the appropriateness of the study and that the potential benefits outweigh the risks. The likelihood that the study being considered will affect clinical management of the patient should be addressed before testing is performed. It is also important that “routine” follow-up scans in asymptomatic individuals be avoided.

CONTRAST AGENTS

Contrast agents are commonly used in cardiac CT, CMR, and echocardiography. Although their use significantly enhances the diagnostic information of each of these tests, there are also potential risks from the administration of contrast agents that should be considered.

The risk of adverse reactions from iodinated contrast agents used in cardiac CT is well established. The precise pathogenesis of contrast reactions following intravascular administration of iodinated contrast media is not known. The overall incidence of contrast reactions is 0.4–3% with nonionic formulations and higher for ionic formulations. Most contrast adverse reactions are mild and self-limiting. The risk of contrast-induced nephropathy (CIN) in patients with relatively normal renal function (glomerular filtration rate [GFR] >60 mL/min) is low. In most patients, CIN is self-limited, and renal function usually returns to baseline within 7–10 days, without progressing to chronic renal failure. However, this risk increases in patients with GFR <60 mL/min, especially older diabetic subjects. In such patients, appropriate screening and pre- and postscan hydration are necessary.

The use of gadolinium-based contrast agents (GBCAs) in CMR imaging enhances the versatility of this technique. Although there are several commercially available GBCAs in the United States, their use in cardiac imaging is considered off-label. Mild reactions from GBCAs occur in ~1% of patients, but severe or anaphylactic reactions are very rare. All GBCAs are chelated to make the compounds nontoxic and to allow renal excretion. Exposure to the nonchelated component of GBCA (Gd³⁺) has been associated with a rare condition known as nephrogenic systemic fibrosis (NSF), which is an interstitial inflammatory reaction that leads to severe skin induration, contracture of the extremities, fibrosis of internal organs, and even death. Risk factors to developing NSF include high-dose (>0.1 mmol/kg) GBCA use in presence of severe renal dysfunction (estimated GFR [eGFR] <30 mL/min per 1.73 m²), need for hemodialysis, an eGFR <15 mL/min per 1.73 m², use of gadodiamine contrast agent, acute renal failure, acute systemic illness, and presence of concurrent pro-inflammatory events. With the use of weight-based dosing and pretest screening, recent data suggest that NSF is extremely rare. Previously, an incidence of 0.02% in 83,121 patients exposed to GBCA over 10 years was noted; however, with current eGFR screening guidelines that have been widely practiced since 2006, a near-zero incidence of NSF has been reported.

Contrast agents can also be used in echocardiography. Injected agitated saline is used routinely to assess cardiac shunts, because these “bubbles” are too large to traverse the pulmonary circulation. After saline injection, the presence of bubbles in the left side of the heart is indicative of shunt, although the location can sometimes be difficult to determine. Dedicated echocardiographic contrast agents have been developed for opacification of left-sided structures and perfusion, although these are only currently U.S. Food and Drug Administration (FDA) approved for

perfusion. These agents are either albumin- or lipid-based microspheres filled with inert gases, typically perfluorocarbons. They are considered extremely safe, although they have, in extremely rare instances, been associated with allergic reactions and neurologic events.

SAFETY CONSIDERATIONS OF CMR IN PATIENTS WITH PACEMAKERS AND DEFIBRILLATORS

The risks of performing CMR in the presence of a pacemaker include generation of electrical current from the metallic hardware (especially if wire loops exist), device movement induced by the magnetic field, inappropriate pacing and sensing, and heating as a result of the “antenna’s effect.” While the presence of a permanent pacemaker remains a contraindication to CMR, highly experienced centers had reported success in performing MRI in these patients in a carefully monitored clinical setting. In general, patients need to be not pacemaker-dependent, the setting of the pacemaker needs to be modified to asynchronous mode, and the pulse sequence needs to be modified to reduce the amount of radiofrequency energy deposition. Pacemakers implanted for less than 6 weeks and the presence of epicardial, abandoned, or nonfixation leads are considered unsafe. Collectively, evidence from combined reports of >250 patients with pacemaker models manufactured after year 2000 suggests that CMR at 1.5 T or less can be performed without significant risk for the patient and with minor nonpermanent alteration of pacemaker settings and function. Similar safety data exists for automatic implantable cardioverter-defibrillators (AICDs), but they are based only on small numbers of patients. In 2011, the first CMR-compatible FDA-approved permanent pacemaker became available commercially. Currently, no AICD has achieved FDA clearance for MRI compatibility.

PATIENT-CENTERED APPLICATIONS OF CARDIAC IMAGING

CORONARY ARTERY DISEASE

The basis for the diagnostic application of imaging tests in patients with known or suspected CAD should be viewed in light of the pretest probability of disease as well as the specific characteristics of imaging tests (i.e., sensitivity and specificity). In symptomatic patients, the prevalence or pretest probability of CAD differs based on the type of symptom (typical angina, atypical angina, noncardiac chest pain), as well as on age, gender, and coronary risk factors. In an individual patient, the results of the initial test informs the posttest likelihood of CAD. In patients undergoing sequential testing (e.g., ECG treadmill testing followed by stress imaging), the posttest probability of disease after the first test becomes the pretest likelihood of disease for the second test. Regardless of the sequence, the expectation is that a test will provide sufficient information to confirm or exclude the diagnosis of CAD and that such information will allow accurate risk stratification to be able to guide management decisions.

Table 270e-3 summarizes the relative diagnostic accuracies of cardiac imaging modalities for the diagnosis of CAD.

It is important to highlight that the vast majority of studies included in meta-analyses of the diagnostic accuracy of cardiac imaging modalities for the diagnosis of CAD were retrospective, small, single-center studies, comprising predominantly male patients with a high prevalence

TABLE 270e-3 COMPARATIVE DIAGNOSTIC ACCURACY OF CARDIAC IMAGING APPROACHES TO CORONARY ARTERY DISEASE

Imaging Modality	Published Data	Sensitivity	Specificity
Exercise echocardiography	15 studies (n = 1849 patients)	84%	82%
Dobutamine echocardiography	28 studies (n = 2246 patients)	80%	84%
SPECT MPI	113 studies (n = 11,212 patients)	88%	76%
Myocardial perfusion PET	9 studies (n = 650 patients)	93%	81%
CMR perfusion	37 studies (n = 2841 patients)	91%	81%
CMR wall motion	14 studies (n = 754 patients)	83%	86%
Coronary CTA	18 studies (n = 1286 patients)	99%	89%

Note: In these studies, the diagnosis of coronary artery disease was based on the presence of a >50% or >70% stenosis on invasive coronary angiography.

Abbreviations: CMR, cardiac magnetic resonance; CTA, computed tomography angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

of CAD (>50–60%). Multicenter studies assessing the performance of individual modalities or comparing different modalities have consistently resulted in more modest diagnostic accuracies, tracking more closely with how these tests perform in practice.

Stress Echocardiography The hallmark of myocardial ischemia during stress echocardiography is the development of new regional wall motion abnormalities and reduced systolic wall thickening (Video 270e-3). Stress echocardiography can be performed in conjunction with exercise or dobutamine stress. Stress echocardiography is best at identifying inducible wall motion abnormalities in previously normally contracting segments. In a patient with wall motion abnormalities at rest, the specificity of stress echocardiography is reduced, and worsening regional function of a previously abnormal segment might reflect worsening contractile function in the setting of increased wall stress rather than new evidence of inducible ischemia.

The advantages of stress echocardiography over other stress imaging techniques include its relatively good diagnostic accuracy, widespread availability, no use of ionizing radiation, and relatively low cost. Limitations of stress echocardiography include (1) the technical challenges associated with image acquisition at peak exercise because of exertional hyperpnoea and cardiac excursion, (2) the fact that rapid recovery of wall motion abnormalities can be seen with mild ischemia (especially with one-vessel disease, which limits sensitivity), (3) difficulty detecting residual ischemia within an infarcted territory because of resting wall motion abnormality, (4) high operator dependence for acquisition of echocardiographic data and analysis of images, and (5) the fact that good-quality complete images viewing all myocardial segments occurs in only 85% of patients. Newer techniques including second harmonic imaging and the use of intravenous contrast agents improve image quality, but their effect on diagnostic accuracy has not been well documented. The use of IV contrast agents may also allow assessment of myocardial perfusion, although this is not approved or generally reimbursed, and data concerning the utility of contrast perfusion echocardiography are limited.

As with nuclear perfusion imaging, stress echocardiography is often used for risk stratification in patients with suspected or known CAD. A negative stress echocardiogram is associated with an excellent prognosis, allowing identification of patients at low risk. Conversely, the risk of adverse events increases with the extent and severity of wall motion abnormalities on stress echocardiography.

Stress Radionuclide Imaging SPECT myocardial perfusion imaging is the most common form of stress imaging tests for CAD evaluation. The presence of a reversible myocardial perfusion defect is indicative of ischemia (Fig. 270e-9, left panel), whereas a fixed perfusion defect generally reflects prior myocardial infarction (Fig. 270e-9, right panel). As discussed above, PET has advantages compared to SPECT, but it is not widely available and is more expensive and, thus, considered an emerging technology in clinical practice.

Nuclear perfusion imaging is another robust approach to diagnose obstructive CAD, quantify the magnitude of inducible myocardial ischemia, assess the extent of tissue viability, and guide therapeutic management (i.e., selection of patients for revascularization). One of the most valuable clinical applications of radionuclide perfusion imaging is for risk stratification. It is well established that patients with a normal SPECT or PET study exhibit a median rate of major adverse cardiac events of <1% annually. Importantly, the risks of death and myocardial infarction increase linearly with increasing magnitude of perfusion abnormalities, reflecting the extent and severity of CAD.

Despite the widespread use and clinical acceptance of radionuclide imaging in CAD evaluation, a recognized limitation of this approach is that it often uncovers only coronary territories supplied by the most severe stenoses. Consequently, it is relatively insensitive to accurately

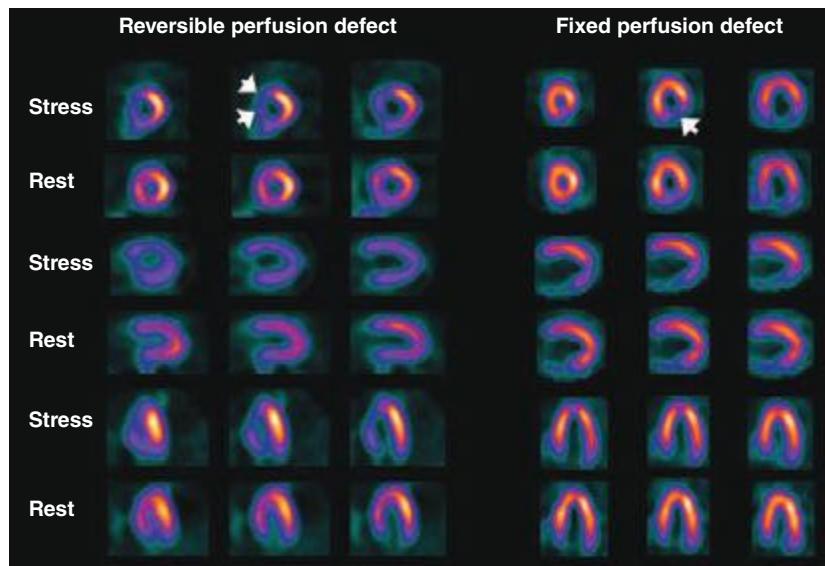


FIGURE 270e-9 Selected technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography images of two different patients demonstrating a reversible perfusion defect involving the anterior and septal left ventricular wall, reflecting ischemia in the left anterior descending coronary territory (arrows in left panel), and a fixed perfusion defect involving the inferior and inferolateral walls consistent with myocardial scar in the right coronary territory (arrow in right panel).

delineate the extent of obstructive angiographic CAD, especially in the setting of multivessel disease. The use of quantitative myocardial blood flow and coronary flow reserve with PET can help mitigate this limitation. In patients with so-called “balanced” ischemia or diffuse CAD, measurements of coronary flow reserve uncover areas of myocardium at risk that would generally be missed by performing only relative assessments of myocardial perfusion (Fig. 270e-10). Conversely, a normal coronary flow reserve is associated with a very high negative predictive value for excluding high-risk angiographic CAD. These measurements of coronary flow reserve also contribute to risk stratification across the spectrum of ischemic changes, including patients with visually normal myocardial perfusion.

HYBRID CT AND NUCLEAR PERFUSION IMAGING Because many of the newer generation nuclear medicine scanners integrate CT and a gamma camera in the same acquisition gantry, it is now possible to acquire and quantify myocardial scar and ischemia and CAC scoring from a single dual-modality study (SPECT/CT or PET/CT) (Fig. 270e-11). The rationale for this integrated approach is predicated on the fact that the perfusion imaging approach is designed to uncover only obstructive atherosclerosis. Conversely, CAC scoring (or CT coronary angiography) provides a quantitative measure of the anatomic extent of atherosclerosis. This provides an opportunity to improve the conventional models for risk assessment using nuclear imaging alone, especially in patients without known CAD.

Cardiac CT Voluminous plaques are more prone to calcification, and stenotic lesions frequently contain large amounts of calcium. Indeed, there is evidence that high CAC scores are generally predictive of a higher likelihood of obstructive CAD, and the available data support the concept of a threshold phenomenon governing this relationship (i.e., Agatston score >400). However, given the fact that CAC scores are not specific markers of obstructive CAD, one should be cautious in using this information as the basis for referral of patients to coronary angiography, especially in symptomatic patients with low-risk stress tests. Conversely, CAC scores <400, especially in symptomatic patients with intermediate-high likelihood of CAD, as in those with typical angina, may be less effective in excluding CAD, especially in young symptomatic men and women who may have primarily noncalcified atherosclerosis (Fig. 270e-12).

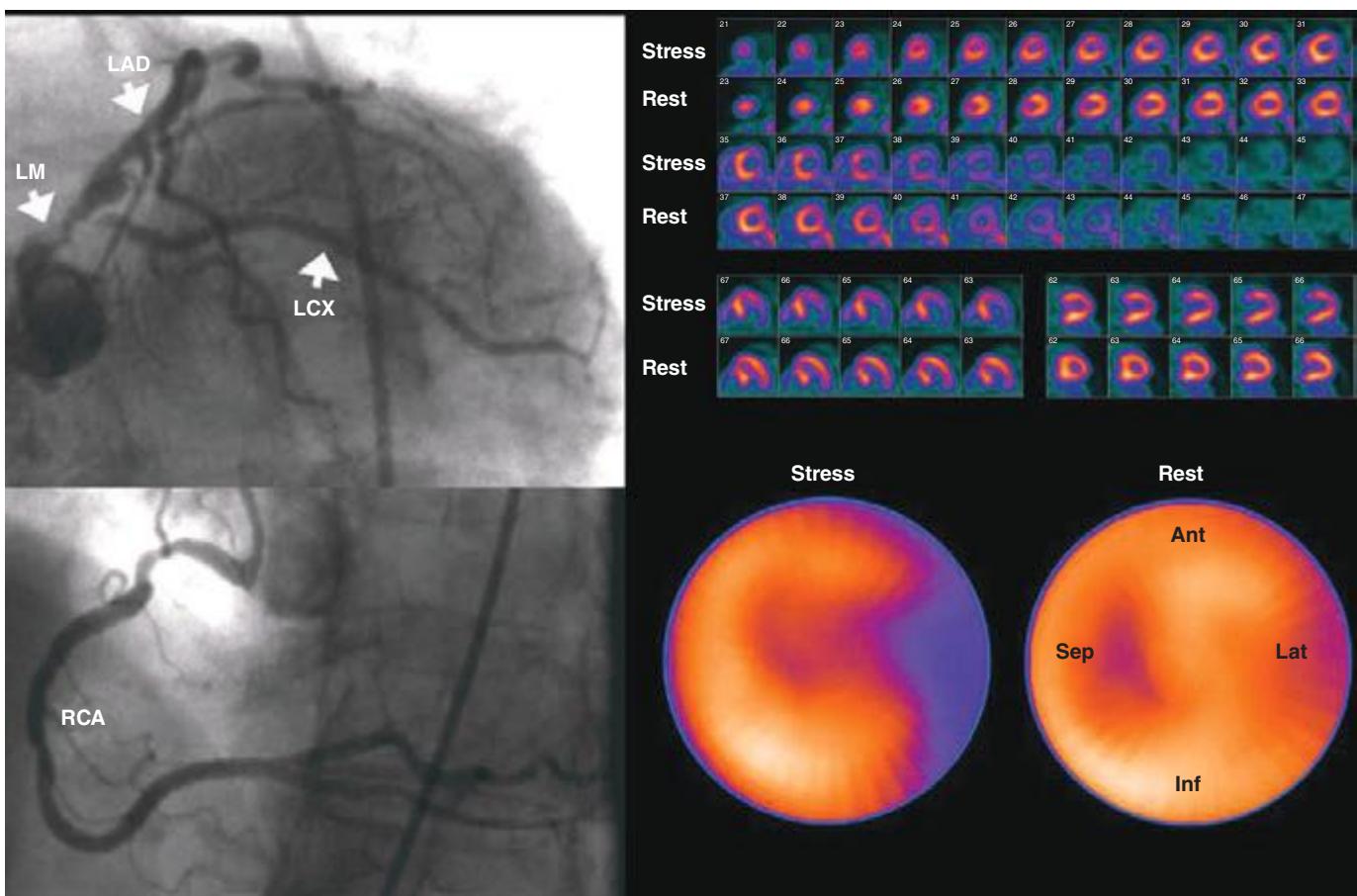


FIGURE 270e-10 Coronary angiographic (left panel) and rubidium-82 myocardial perfusion positron emission tomograph images (right panel) in an 85-year-old female with diabetes presenting with chest pain. The coronary angiogram demonstrates significant stenoses of the left main and circumflex coronary arteries. However, the perfusion images demonstrate only a reversible lateral wall defect. Quantification of stress and rest myocardial blood flow demonstrated a significant, global reduction on coronary flow reserve (estimated at 1.2, normal value >2.0), reflecting extensive myocardium risk that was underestimated by the semiquantitative estimates of myocardial perfusion. LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; RCA, right coronary artery.

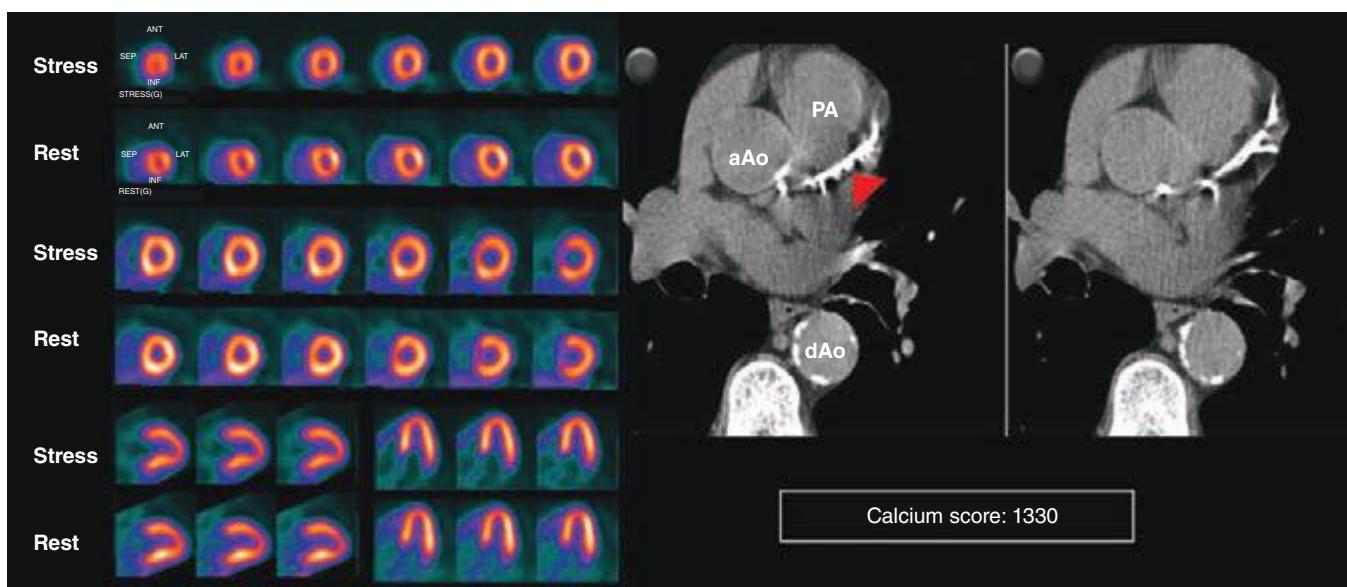


FIGURE 270e-11 Stress and rest rubidium-82 myocardial perfusion positron emission tomography (PET) images (left) and noncontrast gated computed tomography (CT) images (right) delineating the extent and severity of coronary artery calcifications obtained with integrated PET/CT imaging. The images demonstrate extensive atherosclerosis (Agatston coronary calcium score = 1330) without flow-limiting disease based on the normal perfusion study. aAo, ascending aorta; dAo, descending aorta; PA, pulmonary artery.

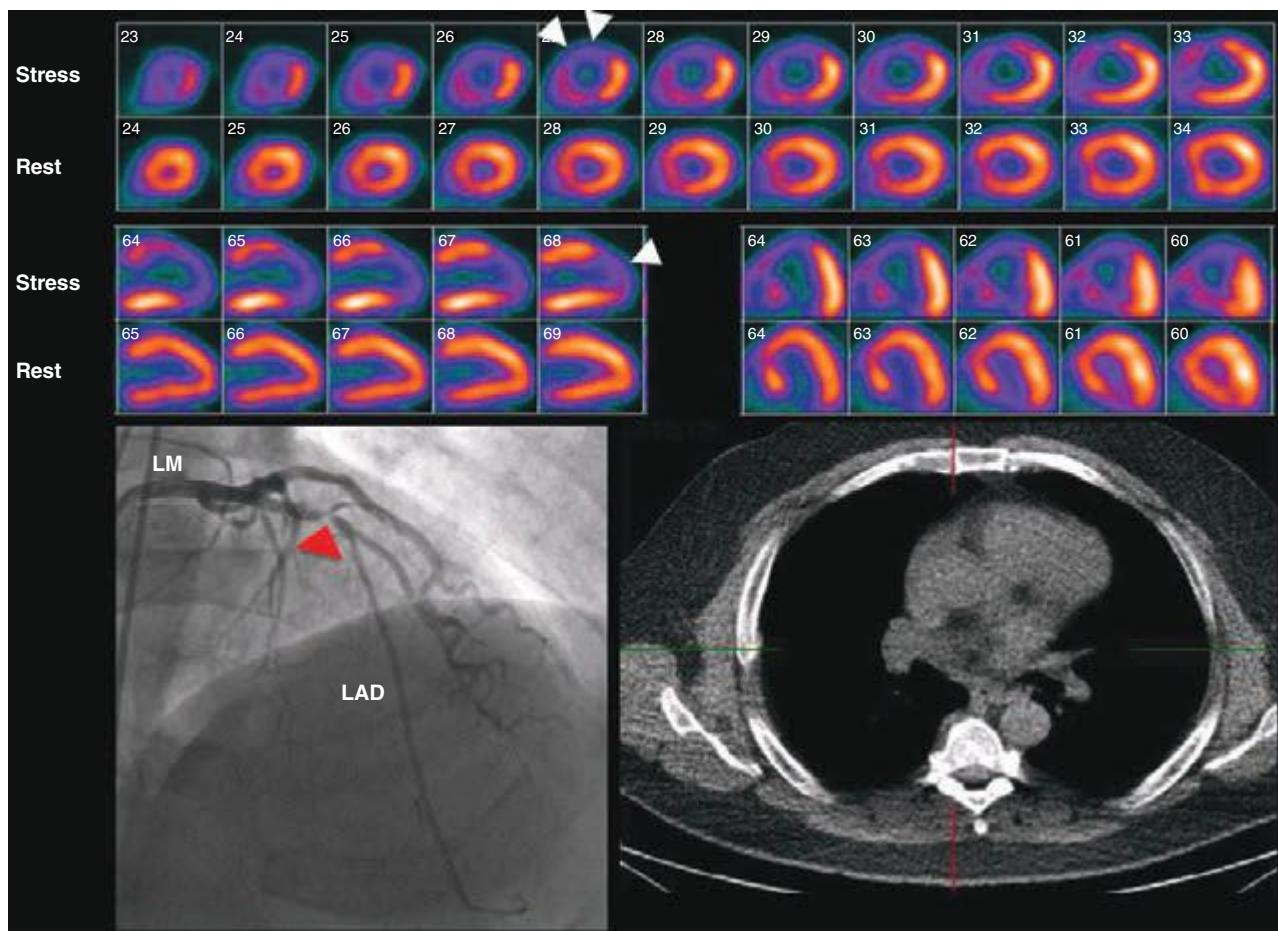


FIGURE 270e-12 Stress and rest rubidium-82 myocardial perfusion positron emission tomography images (top), noncontrast gated computed tomography images (lower right), and selected coronary angiographic images obtained on a 59-year-old male patient with atypical angina. Despite the absence of significant coronary calcifications (Agatston calcium score = 0), the perfusion images demonstrated a dense and reversible perfusion defect involving the anterior and anteroseptal walls (arrows), reflecting significant obstructive disease in the left anterior descending coronary artery (LAD), confirmed on angiography. LM, left main artery.

As discussed above, the improved temporal and spatial resolution of modern multidetector CT scanners offer a unique noninvasive approach to delineate the extent and severity of coronary atherosclerosis. The extremely high sensitivity of this approach offers a very effective means for excluding the presence of CAD (high negative predictive value) (Table 270e-3). In the setting of high coronary calcium scores (e.g., >400), however, specificity is reduced because the blooming artifact of calcium does not allow one to evaluate the vessel lumen accurately. Given the high negative predictive value of CTA, a normal scan result effectively excludes obstructive CAD and abolishes the need for further investigation. As discussed below, this may be quite useful in patients with low-intermediate clinical risk presenting to the emergency room for chest pain. However, the limited capability of this technique to determine the severity of stenosis and to predict which obstructions are flow limiting can make abnormal scan results more difficult to interpret, especially in terms of the possible need of coronary revascularization. There are emerging data suggesting that by adding a stress myocardial perfusion CT evaluation (similar to stress perfusion CMR) (Fig. 270e-13, top panel) or an estimated fractional flow reserve (so-called FFR_{CT}) (Fig. 270e-13, lower panel), one can define the hemodynamic significance of anatomic stenosis. However, these are not in routine clinical use and remain emerging technologies.

As with invasive coronary angiography, assessments of the extent of CAD by CTA can also provide useful prognostic information. A low 1-year cardiac event rate has been reported for patients without obstructive CAD on CTA. For patients with obstructive CAD, the risk of adverse cardiac events increases proportionally with the extent of angiographically obstructive CAD.

Although CTA can be helpful in assessing patency of bypass grafts, the assessment of stents is somewhat more challenging because the limited spatial resolution of CT and stent diameter (<3 mm being associated with the highest number of partial lumen visualization and nondiagnostic scans) both contribute to limited clinical results.

CMR Imaging The two approaches used with CMR to evaluate known or suspected CAD include the assessment of regional myocardial perfusion or wall motion at rest and during stress, the latter being analogous to dobutamine echocardiography. Although treadmill or bicycle exercise stress CMR is practiced in a small number of specialized centers, the logistics for stress MRI studies currently require the use of pharmacologic stress agents including vasodilators or dobutamine. Myocardial perfusion is evaluated by injecting a bolus of a GBCA followed by continuous data acquisition as the contrast passes through the cardiac chambers and into the myocardium. Relative perfusion deficits are recognized as regions of low signal intensity (black) within the myocardium (Video 270e-4). In addition, LGE imaging allows detection of bright areas of myocardial scar (white), which further enhances the utility of this approach for diagnosis of CAD (Fig. 270e-14).

The major advantage of dobutamine CMR over dobutamine echocardiography is better image quality and sharper definition of endocardial borders from the blood pool. Consequently, dobutamine CMR appears to have better diagnostic accuracy than dobutamine echocardiography for detection of CAD, especially in patients with poor acoustic window (Table 270e-3). A limitation of high-dose dobutamine stress CMR is that it bears the potential risk of severe side effects, such as hypotension and severe ventricular arrhythmias in the inhospitable

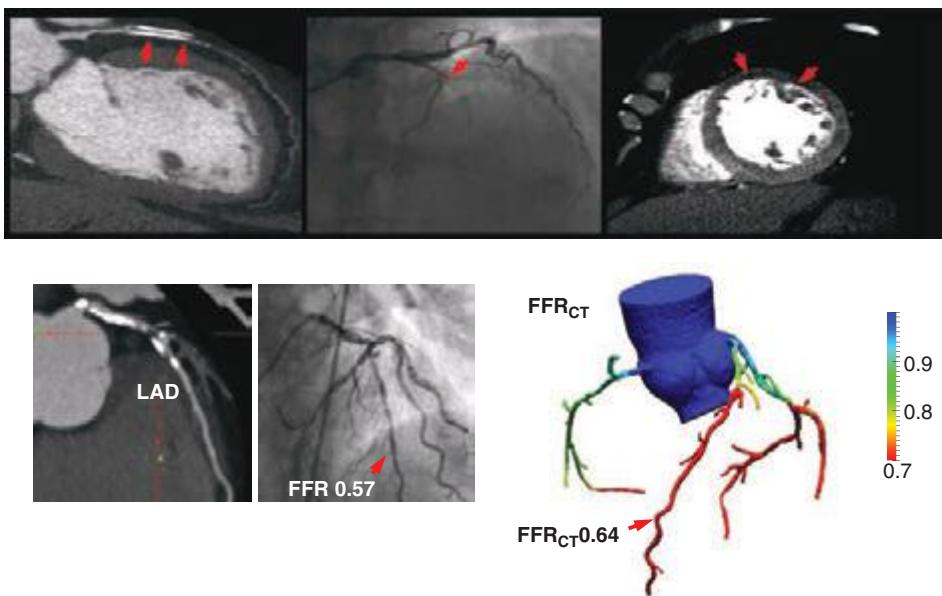


FIGURE 270e-13 Examples of novel approaches to the assessment of flow-limiting coronary artery disease (CAD) with cardiac computed tomography (CT). In the top panel, representative views of a coronary CT angiogram (CTA; left), coronary angiogram (middle), and stress myocardial perfusion CT (right) images in a patient with CAD and prior stenting of the left anterior descending coronary artery (LAD) are presented. On the CTA, the stent (arrows) is totally occluded as evidenced by the loss of contrast enhancement distal to the stent. The coronary angiogram demonstrates a concordant total occlusion of the LAD. On the perfusion CT images, there is a black rim (arrows) involving the anterior and anterolateral walls, indicating the lack of contrast opacification during stress consistent with myocardial ischemia. (Images courtesy of CORE 320 investigators.) The lower panel illustrates an example of fractional flow reserve (FFR) estimates with coronary CTA (left) compared to the reference standard of invasive FFR. The FFR reflects the pressure differential between a coronary segment distal to a stenosis and the aorta. In normal coronary arteries, there is no gradient, and FFR is 1. An FFR <0.80 is consistent with a hemodynamically significant stenosis. (Images courtesy of Dr. James Min, Cornell University, New York.)

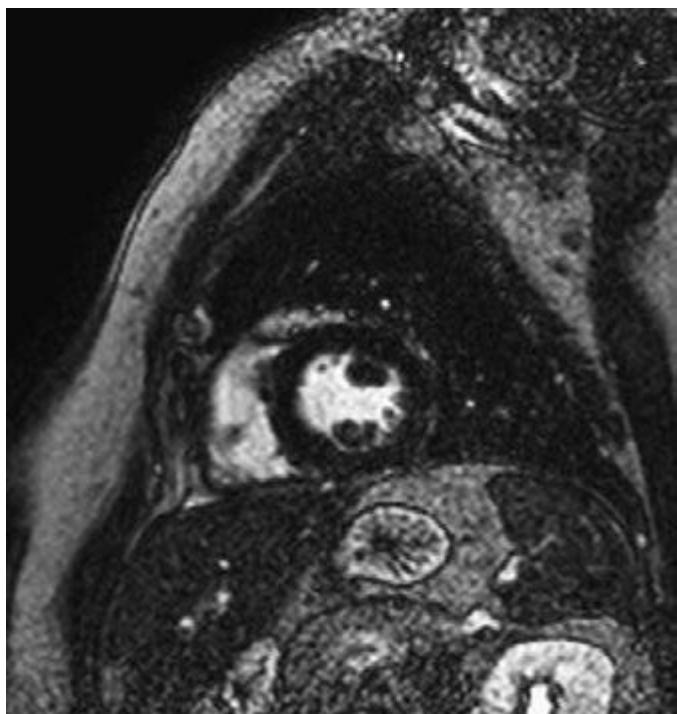


FIGURE 270e-14 The image shows the late gadolinium enhancement image of a mid short-axis view. There is no evidence of infarction in the anterior wall, which would be seen as bright white areas, indicating that the stress perfusion defect primarily represents myocardial ischemia. This patient had a significant stenosis of the left anterior descending coronary artery.

environment of the magnetic resonance scanner. It occurs rarely (~5%), and most cases can be prevented with proper monitoring of vital signs and regional cine function. The advantage of stress perfusion CMR over SPECT is its clearly higher spatial resolution, allowing detection of subendocardial defects that may be missed by SPECT. The addition of the information from LGE imaging allows differentiation of hypoperfused (potentially ischemic) from infarcted myocardium and characterizes the extent of myocardial ischemia.

As with other imaging modalities, there is evidence that ischemia measurements derived from stress CMR studies also have prognostic value. In line with the nuclear and echocardiography literature, a normal CMR study is associated with a good prognosis. Conversely, the presence of new wall motion abnormalities, regional perfusion defects, the combination of wall motion abnormalities and perfusion defects, and the presence of LGE are all predictors of adverse events.

Selecting a Testing Strategy in Patients without Known CAD As discussed above, there are many options for the evaluation of a patient with suspected CAD presenting with chest pain symptoms. The critical questions to be answered by a testing strategy include the following: (1) Does the chest pain reflect obstructive CAD? (2) What are the short- and long-term risks? (3) Does the patient need to be considered for revascularization?

For symptomatic patients without a prior history of CAD and a normal or nearly normal resting ECG who are able to exercise, the American College of Cardiology/American Heart Association guidelines recommend standard exercise treadmill testing (ETT) as the initial testing strategy. The guidelines further suggest that patients who are categorized as low risk by ETT (e.g., those achieving >10 metabolic equivalents [METS] without chest pain or ECG changes) be treated initially with medical therapy, and those with high-risk ETT findings (i.e., typical angina with >2 mm ST-segment depression in multiple leads, ST elevation during exercise, drop in blood pressure, or sustained ventricular arrhythmias) be referred for coronary angiography.

The use of exercise testing in women presents difficulties that are not seen in men, reflecting the differences in the lower prevalence of obstructive CAD in women and the different accuracy of exercise testing in men and women. Compared with men, the lower pretest probability of disease in women means that more test results are false positive. In some of these patients, a positive ETT may reflect true myocardial ischemia caused by microvascular coronary artery dysfunction (so-called *microvascular disease*). In addition, the inability of many women to exercise to maximum aerobic capacity, the greater prevalence of mitral valve prolapse and microvascular disease in women, and possibly other reasons may contribute to the differences with men as well. The difficulties of using exercise testing for diagnosing obstructive CAD in women have led to speculation that stress imaging may be preferred over standard stress testing. However, recent data from the WOMEN study suggests that in symptomatic, low-risk women who are able to exercise, standard ETT is a very effective initial diagnostic strategy as compared to stress radionuclide imaging. Women included in the study were randomized to standard ETT or exercise radionuclide perfusion imaging. The primary endpoint was the 2-year incidence of major adverse cardiac

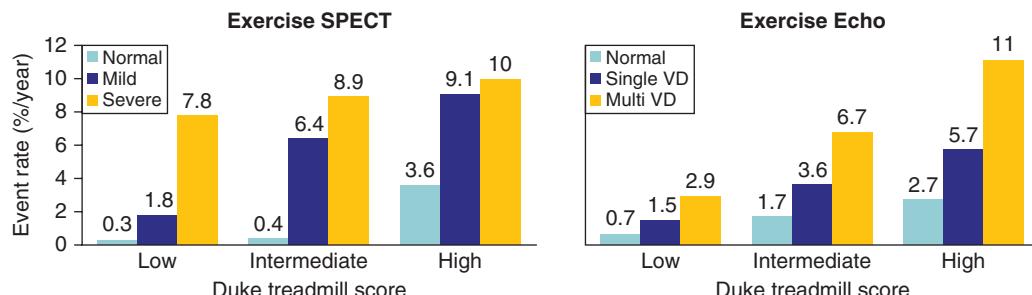


FIGURE 270e-15 Incremental risk stratification of stress imaging over Duke treadmill score in patients with suspected coronary artery disease. Stress imaging is most valuable in the intermediate-risk group. SPECT, single-photon emission computed tomography; VD, vessel disease. (Reproduced with permission from R Hachamovitch *et al*: *Circulation* 93:905, 1996; and TH Marwick *et al*: *Circulation* 103:2566, 2001.)

events, defined as CAD death or hospitalization for an acute coronary syndrome or heart failure. At 2 years, there was no difference in major adverse cardiac events. As expected, ETT resulted in 48% lower costs compared to exercise radionuclide imaging.

Patients with intermediate-high risk after ETT (e.g., low exercise duration, chest pain, and/or ST-segment depression without high-risk features) will often require additional testing, either stress imaging or noninvasive CT coronary angiography, to more accurately characterize clinical risk. Most common stress imaging strategies in intermediate-risk patients include stress echocardiography and radionuclide imaging. In such patients, stress imaging with either SPECT or echocardiography has been shown to accurately reclassify patients who are initially classified as intermediate risk by ETT as low or high risk (Fig. 270e-15). Following this staged strategy of applying the low-cost ETT first and reserving more expensive imaging to refine risk stratification to patients initially classified as intermediate risk by ETT is more cost effective than applying stress or anatomic imaging as the initial test routinely.

A stress imaging strategy is the recommended first step for patients who are unable to exercise to an adequate workload and/or those with abnormal resting ECGs (e.g., left ventricular hypertrophy with strain, left bundle branch block). Importantly, the most recent documents regarding appropriate use of radionuclide and echocardiography imaging also considered that an imaging strategy may be an appropriate first step in patients with intermediate-high likelihood of CAD (e.g., diabetics, renal impairment) due to increased overall sensitivity for diagnosis of CAD and improved risk stratification.

In considering the potential clinical application of imaging modalities, the evidence supporting the role of assessment of ischemia versus anatomy must be considered. From the discussion above, a normal CTA is helpful because it effectively excludes the presence of obstructive CAD and the need for further testing, defines a low clinical risk, and makes management decisions regarding referral to coronary angiography straightforward. Because of its limited accuracy to define stenosis severity and predict ischemia, however, abnormal CTA results are more problematic to interpret and to use as the basis for defining the potential need of invasive coronary angiography and revascularization. In such patients, a follow-up stress test is usually required to determine the possible need of revascularization (Fig. 270e-16).

The justification of stress imaging in testing strategies has hinged on the identification of which patients may benefit from a revascularization strategy by means of noninvasive estimates of jeopardized myocardium rather than angiography-derived anatomic stenoses. Indeed, there is evidence that only the presence of moderate-severe ischemia identifies patients with apparent improved survival with revascularization. Patients with mild or no ischemia are better candidates for optimal medical therapy. The advantages of this approach include

avoidance of excess catheterizations with their associated cost and risk and the potential for intervening unnecessarily. The acceptable diagnostic accuracy of stress imaging approaches, along with their robust risk stratification, and the ability of ischemia information to identify patients who would benefit from revascularization suggest a potential role as a first imaging strategy in patients with intermediate-high likelihood of CAD. Although the available data suggest similar diagnostic accuracy for SPECT, PET, echocardiography, and CMR, the choice of strategy depends on availability and local expertise.

Selecting a Testing Strategy in Patients with Known CAD Use and selection of testing strategies in symptomatic patients with established CAD (i.e., prior angiography, prior myocardial infarction, prior revascularization) differ from those in patients without prior CAD. Although standard

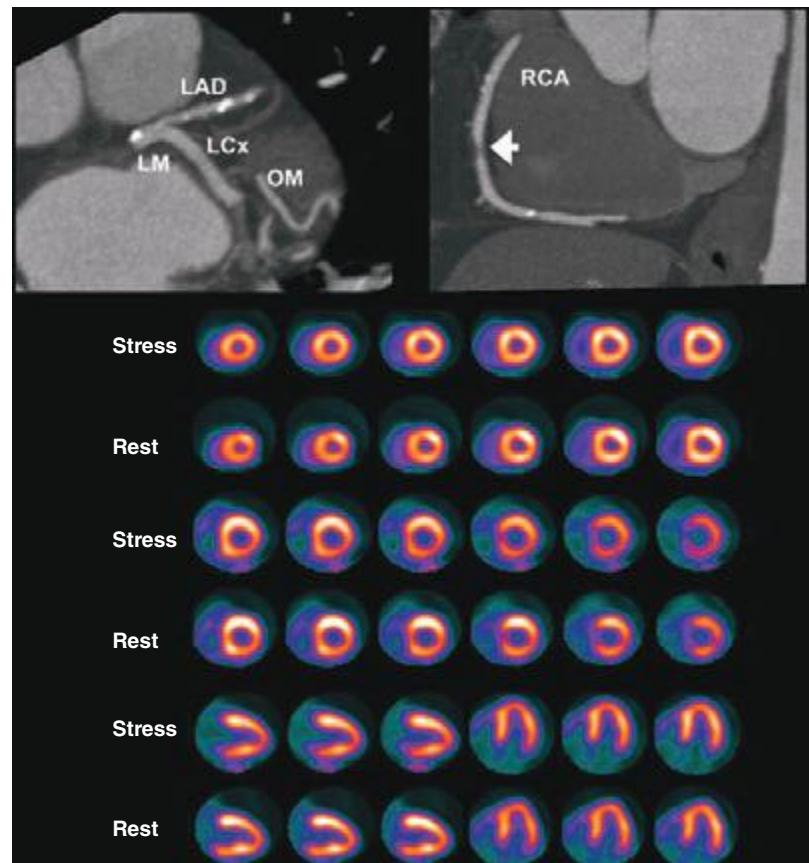


FIGURE 270e-16 Selected views from coronary computed tomography angiographic (CTA) images (top panel) and stress and rest rubidium-82 myocardial perfusion positron emission tomography images (lower panel) obtained on a 64-year-old male patient with atypical angina. The CTA images demonstrate dense focal calcifications in the left main (LM) and left anterior descending (LAD) coronary arteries and a significant noncalcified plaque in the mid right coronary artery (RCA; arrow). The myocardial perfusion images demonstrated no evidence of flow-limiting stenosis. LCx, left circumflex artery; OM, obtuse marginal branch.

ETT may help distinguish cardiac from noncardiac chest pain, exercise ECG has a number of limitations following myocardial infarction and revascularization (especially coronary artery bypass grafting). These patients frequently have rest ECG abnormalities. In addition, there is a clinical need to document both the magnitude and localization of ischemia to be able to direct therapy, especially the potential need for targeted revascularization. Consequently, imaging tests are preferred for evaluating patients with known CAD.

There are also important differences in the effectiveness of imaging tests in these patients. As discussed above, coronary CTA is limited in patients with prior revascularization. Patients with prior coronary artery bypass grafting are a particularly heterogeneous group with respect to the anatomic basis of ischemia and its implications for subsequent morbidity and mortality. In addition to graft attrition, progression of disease in the native coronary arteries is not uncommon in symptomatic patients. While CTA provides excellent visualization of the bypass grafts, the native circulation tends to get heavily calcified and is generally not a good target for imaging with CTA. Likewise, blooming artifacts from metallic stents also limit the application of coronary CTA in patients with prior percutaneous coronary intervention. Although newer stent material may change the potential role of CTA in the future, it is probably not the first line of testing in these patients. If an anatomic strategy is indicated, direct referral to invasive angiography is preferred.

Stress imaging approaches are especially useful and preferred in symptomatic patients with established CAD. As in patients without prior CAD, normal imaging studies in symptomatic patients with established CAD also identify a low-risk cohort. In those with abnormal stress imaging studies, the degree of abnormality relates to posttest risk. In addition, stress imaging approaches can localize and quantify the magnitude of ischemia (especially with perfusion imaging), thereby assisting in planning targeted revascularization procedures. As in patients without prior CAD, the choice of stress imaging strategy depends on availability and local expertise.

Testing Strategy Considerations in Patients Presenting with Chest Pain to the Emergency Department Although acute chest pain is a frequent reason for patient visits to the emergency department (ED), only a small minority of those presentations represent an acute coronary syndrome (ACS). Strategies used in the evaluation of these patients include novel cardiac biomarkers (e.g., serum troponins), conventional stress testing (ETT), and noninvasive cardiac imaging. It is generally accepted that the primary goal of this evaluation is exclusion of ACS and other serious conditions rather than detection of CAD.

The routine evaluation of acute chest pain in most centers in the United States includes admission to a chest pain unit to rule out ACS with the use of serial ECGs and cardiac biomarkers. In selected patients, stress testing with or without imaging may be used for further risk stratification. Stress echocardiography and radionuclide imaging are among the most frequently used imaging approaches in these patients. The relative strengths and weaknesses of these testing options have been discussed above. Both approaches have been shown to be effective for identifying low-risk patients who can be safely discharged from the ED. Multiparametric CMR imaging has also been used successfully in patients with acute chest pain. In addition to the combined assessment of regional and global left ventricular function, myocardial perfusion, and tissue viability, it is also possible to evaluate the presence of myocardial edema to characterize the myocardium at risk secondary to reduced coronary flow (Video 270e-5). Due to its ability to probe multiple aspects of myocardial physiology, cardiac anatomy, and tissue characterization with LGE imaging, CMR is also useful in diagnosing conditions that mimic ACS (e.g., acute myocarditis, takotsubo cardiomyopathy, pericarditis) (Fig. 270e-17). Thus, CMR imaging offers unique information of myocardial pathophysiology in the spectrum of ACS and is, perhaps, the most versatile of all noninvasive imaging techniques. Unfortunately, it is not widely available even at specialized centers and is not a first-line testing strategy. The main disadvantages of the “functional” testing strategy are that it is time consuming and is generally associated with a prolonged length of stay and, thus, is more costly.

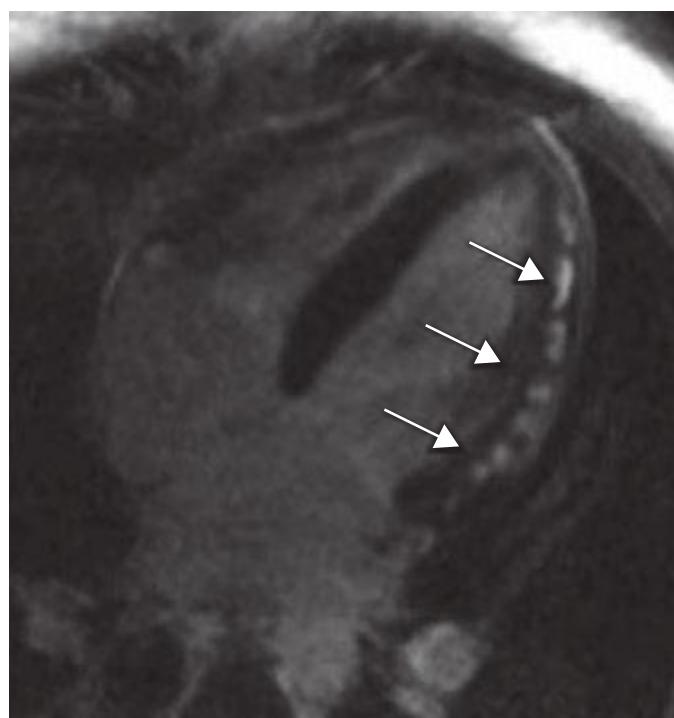


FIGURE 270e-17 A four-chamber long-axis late gadolinium enhancement (LGE) image of a patient with acute myocarditis.

Note that the LGE primarily involved the epicardial aspect of the myocardium (arrows), sparing the endocardium, which is a feature that distinguishes myocarditis from myocardial infarction, which affects the endocardium. Also note the multiple foci of LGE in this case affecting the lateral wall of the left ventricle. Viral myocarditis often presents with this pattern.

As discussed above, coronary CTA is a rapid and accurate imaging technique to exclude the presence of CAD and is well suited for the evaluation of patients with acute chest pain (Fig. 270e-18). Several single-center and, more recently, multicenter studies have demonstrated the feasibility, safety, and accuracy of coronary CTA in the ED. There have been four randomized controlled trials evaluating the efficacy of coronary CTA as the initial testing strategy as compared to usual care (which typically includes stress imaging). Patients in these trials had a very low clinical risk. Overall, there were no deaths and very few myocardial infarctions without differences between the groups. Likewise, there were no differences in postdischarge ED visits or rehospitalizations. These studies showed decreased length of stay with coronary CTA, and most but not all reported cost savings. An observation from a recent meta-analysis was that, compared to usual care, more patients assigned to coronary CTA underwent cardiac catheterization (6.3% vs 8.4%, respectively) and revascularization (2.6% vs 4.6%, respectively). The relative increased frequency in the referral to cardiac catheterization and revascularization after coronary CTA compared to stress imaging testing strategies has also been observed in patients with stable chest pain syndromes.

Taken together, the available data clearly suggest that not all patients presenting with acute chest pain require specialized imaging testing. Patients with very low clinical risk and negative biomarkers (especially high-sensitivity troponin assays) can be safely triaged. The use of imaging tests in patients with low-intermediate risk should be carefully considered, especially given the trade-offs discussed above.

VALVULAR HEART DISEASE

Abnormalities of any of the four valvular structures in the heart can lead to significant cardiac dysfunction, heart failure, or even death. Echocardiography, CMR, and cardiac CT can be used for the evaluation of valvular heart disease, although echocardiography has generally been considered the first imaging test of choice for the assessment of valvular heart disease. In addition, echocardiography is the most cost-effective screening method for valvular heart disease. In some cases,

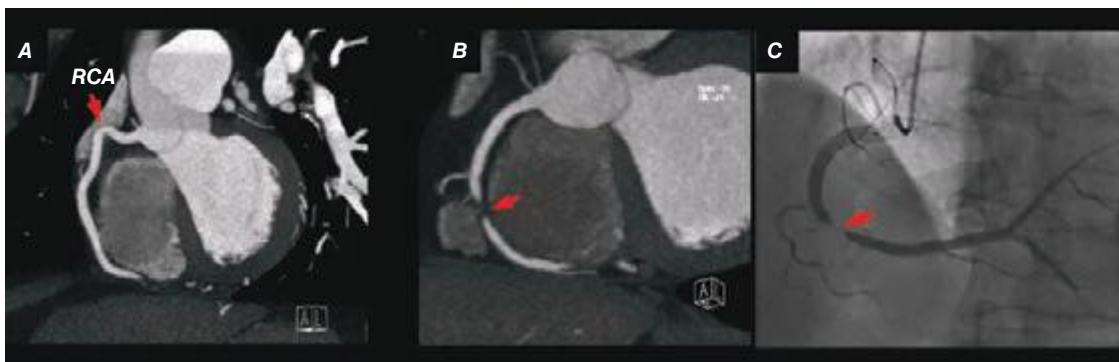


FIGURE 270e-18 Representative coronary computed tomography angiographic (CTA) images of two patients presenting to the emergency department with chest pain and negative biomarkers. The patient in **A** had angiographically normal coronary arteries; the panel shows a representative view of the right coronary artery (RCA). **B** and **C** show a corresponding significant stenosis in the mid portion of the RCA on both the CTA (**B**) and invasive angiographic view (**C**). (Images courtesy of Dr. Quynh Truong, Massachusetts General Hospital, Boston, MA.)

CMR can complement echocardiography when echocardiographic acoustic window is inadequate, quantifying blood flow data more precisely, or providing complimentary assessment of adjacent vascular structures relevant to the valvular condition.

Echocardiography can be used to assess both regurgitant and stenotic lesions of any of the cardiac valves. Typical indications for echocardiography to assess valvular heart disease include cardiac murmurs identified on physical examination, symptoms of breathlessness that may represent valvular heart disease, syncope or presyncope, and preoperative exams in patients undergoing bypass surgery. A standard echocardiographic examination should include qualitative and quantitative assessment of all valves regardless of indication and should serve as an adequate screening test for significant valvular disease.

General Principles of Valvular Assessment • DIRECT VISUALIZATION OF VALVULAR STRUCTURES Direct visualization of valve structures by two-dimensional echocardiography represents the first step in valvular evaluation. The morphology of valvular structures provides useful information regarding the etiology and severity of valvular disease. For example, two-dimensional imaging assessment of the aortic valve can identify the number of leaflets, determine whether the valve is bicuspid or tricuspid, and determine the severity of calcification and degree of leaflet excursion. Similarly, the classic appearance of a rheumatic mitral valve is extremely useful in determining the etiology of mitral stenosis, and mitral valve prolapse can be instantly identified without even the need for Doppler-based quantification.

EVALUATION OF STENOTIC VALVES As described earlier in the chapter, evaluation of stenotic valves generally includes estimation of the pressure gradient across the stenosis and determination of the valve area. Both of these measures have diagnostic and prognostic value. For example, when Doppler echocardiography is used to assess the maximal velocity across a stenotic aortic valve, this calculation will provide an accurate measure of the instantaneous gradient across the valve. This gradient will be higher than the mean gradient, as well as higher than that peak-to-peak gradient obtained at cardiac catheterization. This gradient is dependent on both the degree of stenosis and the contractile function of the left ventricle. Patients with significant left ventricular dysfunction may have severe aortic stenosis but will be unable to generate a high gradient across the valve because generated pressure within the left ventricle will be diminished.

Assessment of stenotic valves generally requires estimation of both the pressure gradient across the valve and the valve area. Pressure gradient is estimated through direct application of the Bernoulli principle, and the formula $p = 4v^2$ is usually sufficient to estimate the gradient across the valve. Several methods can be used to estimate valve areas, including the continuity principle based on the principle of conservation of mass. By this method, flow is estimated in two places. For example, for assessment of the aortic valve area, we measure the flow in the region of the left ventricular outflow tract and the cross-sectional area in this region, the product of which should be equal to the flow

across the stenotic aortic valve and its cross-sectional area. Estimation of the mitral valve area in patients with suspected mitral stenosis can also be performed in a number of ways, including planimetry of the valve directly, estimation with continuity methods, or the most commonly used pressure half-time method, in which the stenosis severity is estimated by the time it takes for the pressure—estimated from velocity by the Bernoulli equation—to reach half of its original value during mitral inflow.

EVALUATION OF REGURGITANT LESIONS Regurgitant lesions are generally assessed by both visual assessment of the valve morphology and a variety of Doppler-based methods to assess the severity of regurgitation. The etiology of regurgitation can often be inferred from visual inspection. For example, prolapse of the mitral valve leaflets—and to a lesser extent, the aortic valve leaflets—can be easily visualized with two-dimensional echocardiography. In general, valvular regurgitation can be caused by abnormalities of the valve leaflets themselves or abnormalities of the annulus and supporting structures, and these can usually be distinguished visually on transthoracic echocardiography (see discussion below).

Quantification of valvular regurgitation is more difficult with echocardiography than quantification of valvular stenoses. Doppler-based methods are best suited to assess blood velocities rather than volumetric flow. The most widely used technique for assessing the severity of valvular regurgitation is color flow Doppler estimation, which is qualitative. More quantitative methods such as the proximal isovelocity surface area (PISA) method (see below) allow for more accurate assessment of regurgitation and provide estimation of the regurgitant fraction and effective regurgitant orifice area but are less widely used. Assessment of regurgitant lesions with CMR also has a number of advantages (see below).

Assessment of Aortic Stenosis Aortic stenosis, one of the most common forms of valvular heart disease, most often occurs because of gradual progression of valvular calcification in both normal and congenitally abnormal valves. Assessment of aortic stenosis is most commonly performed with echocardiography, although techniques for quantitative assessment of aortic stenosis with CMR have been developed and increasingly used over the past decade. Echocardiographic assessment generally begins with visual inspection of the valve, usually in the parasternal long-axis and short-axis views. This allows for assessment of valvular morphology, whether it is tricuspid, bicuspid, or some variant; degree of leaflet calcification; and leaflet excursion.

The normal aortic valve consists of three leaflets or cusps: the right coronary, the left coronary, and the noncoronary cusps. Abnormalities of cusp development are some of the most common congenital heart anomalies, the most common of which is bicuspid aortic valve, with two opening leaflets rather than three (Fig. 270e-19). The aortic valve can be visualized on echocardiography, although sometimes it can be difficult to distinguish true bicuspid aortic valve from variants, including the presence of a vestigial commissure (raphe). Bicuspid aortic

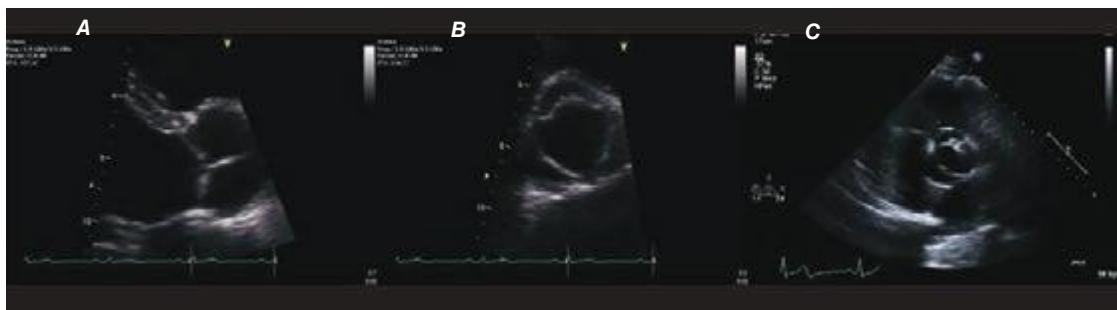


FIGURE 270e-19 Normal aortic valve in the parasternal long-axis view (**A**) and short-axis view (**B**), and bicuspid aortic valve showing typical 10 o'clock to 4 o'clock leaflet orientation (**C**).

valve, one of the most common congenital anomalies, predisposes to both aortic stenosis and aortic insufficiency.

As discussed above, the degree of aortic stenosis is assessed by estimating both the pressure gradient across the valve and the valve area. Patients with moderate aortic stenosis or higher generally have peak instantaneous velocities of 3.0 m/s and higher, and often higher than 4.0 m/s, corresponding to pressure gradients of 36 and 64 mmHg, respectively. Because pressure gradients across the aortic valve can be underestimated in patients with severe left ventricular dysfunction, estimation of valve area by the continuity principle is the most accurate technique for assessing the severity of the stenosis. However, evaluation of the patient with so-called low-flow or low-gradient aortic stenosis can be challenging and can sometimes require provocative testing such as dobutamine echocardiography. In these cases, it is important to distinguish whether the valve is indeed capable of opening further or simply behaving like a stenotic valve because of the low-pressure gradient.

Aortic valve areas less than 1.0 cm^2 are generally considered severe, and valve areas less than 0.6 cm^2 are considered critical. Because patients with good left ventricular function can often tolerate severe aortic stenosis for a considerable period of time, valve areas or gradients alone should not be used to determine whether an individual patient should undergo aortic valve surgery, as this remains a clinical decision.

Some patients with apparent aortic stenosis actually have subvalvular or even supravalvular obstruction. Hypertrophic cardiomyopathy represents the classic form of subvalvular aortic stenosis, but this is usually easily distinguished from aortic stenosis on echocardiography as the valve leaflets can be seen opening during systole. Subaortic membranes can behave very similarly to leaflet aortic stenosis, and the membranes themselves can be very thin and difficult to visualize, although the presence of a murmur, a gradient across the valve with aortic leaflets that appear to open normally, is highly suggestive of a membrane. Supravalvular aortic stenosis, although exceedingly rare, also occurs.

The emergence of transcatheter aortic valve intervention as a therapeutic option for patients with severe aortic stenosis who are not optimal candidates for surgical replacement has resulted in a very important clinical role for multimodality imaging. Imaging plays a critical role in preprocedural planning, intraprocedural implantation optimization, and follow-up of these patients. CT plays an important role in defining the eligibility of the proposed access site (CTA of the aorta and iliac arteries) and in defining the anatomic relationships between the aortic valve and aortic root, left ventricle, and coronary ostia. Cardiac CT and transesophageal echocardiography are also used to define the device size. Transesophageal echocardiography is used during the device implantation to ensure the best prosthesis-patient match, to assess prosthesis position and function after deployment, and to identify immediate complications (e.g.,

aortic insufficiency, paravalvular leak resulting from patient-prosthesis mismatch). Echocardiography is the imaging modality of choice for long-term surveillance.

Assessment of Aortic Regurgitation Assessment of aortic regurgitation requires qualitative assessment of the aortic valve structure. Aortic regurgitation is common with congenital abnormalities of the aortic valve, the most common of which is bicuspid aortic valve. Aortic regurgitation often coexists with aortic stenosis, and it is not uncommon for patients to have both severe aortic stenosis and regurgitation. Congenital abnormalities of the aortic leaflets, such as bicuspid aortic valve, are common causes of aortic insufficiency. Dilatation of the aortic root, as occurs in patients with hypertension and other disorders in which aortic dilatation can occur, can also lead to aortic regurgitation even when the valve leaflets are intrinsically normal due to malcoaptation of the leaflets. Aortic root dilatation is common in patients with aortic regurgitation, both as a cause or coexisting lesion, and the aortic root and ascending aorta should be measured and followed in these patients (Fig. 270e-20).

Because aortic regurgitation can result in dilatation of the left ventricle over time with ultimate reduction in ventricular function, caring for the patient with aortic regurgitation requires serial assessment of ventricular size and function. Patients whose ventricles dilate beyond an end-systolic diameter of 5.5 cm or whose LVEF declines below normal are at significantly higher risk of death or heart failure, and these measures are often used to decide the need for valve surgery. Quantitation of regurgitation itself can be performed using a number of methods. Semiquantitative visual assessment of aortic regurgitant jet width and depth by color flow Doppler remains the most used. The jet diameter as a ratio of the left ventricular outflow tract diameter proximal to the valve represents one of the most reliable indices of severity and correlates well with angiographic assessment. Similarly, the vena contracta, which represents the smallest diameter of the regurgitant flow at the level of the valve, can be used to assess the severity of aortic regurgitation. Other Doppler-based methods include assessing the pressure half-time, or rate of decline of the pressure gradient between the aorta and left ventricle, a measure of acuity of aortic regurgitation, and assessing aortic flow reversal in the descending aorta. The regurgitant volume can be calculated by comparing the

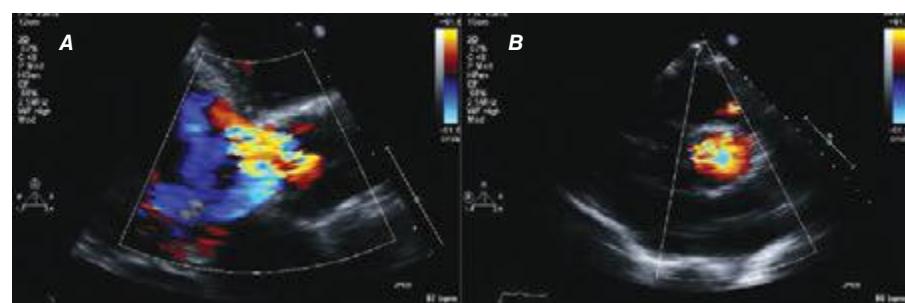


FIGURE 270e-20 Aortic regurgitation visualized by color flow Doppler in the parasternal long-axis view (**A**) and the parasternal short-axis view (**B**).

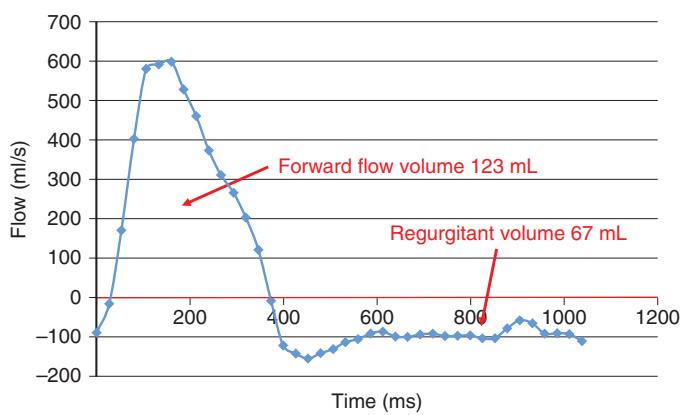


FIGURE 270e-21 The resultant flow curve generated from phase contrast imaging demonstrates a forward flow of 123 mL and a regurgitant volume of 67 mL, yielding a regurgitant fraction of 54% indicating severe aortic regurgitation.

flow across the aortic and pulmonic valves, assuming the pulmonic valve is competent.

CMR offers a number of advantages over echocardiography in the assessment of aortic regurgitation. CMR can be more accurate than echocardiography for assessing small changes in cardiac size or function that can occur over time in patients with aortic insufficiency. In addition, CMR techniques can very accurately quantify regurgitant volume in patients with aortic insufficiency, a known limitation of echocardiography. CMR can also capture three-dimensional imaging

of the aortic size that in some cases can be helpful in determining the etiology of the aortic regurgitation or in monitoring the patient (Fig. 270e-21 and Video 270e-6).

Assessment of Mitral Regurgitation The normal mitral valve consists of an anterior and posterior leaflet in a saddle shape configuration (Fig. 270e-22). The leaflets are attached to the papillary muscles via chordae tendineae that insert on the ventricular side of the leaflets. Mitral regurgitation can occur due to abnormalities of the leaflets, the chordal structures, or the ventricle, or any combination of these (Fig. 270e-23).

Mitral valve prolapse, in which one leaflet moves behind the plane of the other leaflet, can be due to myxomatous degeneration of the valves and leaflet redundancy, disruption of chordal structures secondary to degenerative disease, or papillary muscle rupture or dysfunction following myocardial infarction. Regurgitant jets can be visualized using color flow Doppler. The velocity of regurgitant jets is driven by the pressure gradient between the two chambers. This velocity tends to be quite high for left-sided regurgitant lesions, including mitral regurgitation and aortic regurgitation, resulting in turbulent jets on color flow Doppler (Fig. 270e-23). Visual estimation of color flow Doppler is generally sufficient for qualitative assessment of regurgitant severity but can dramatically under- or overestimate regurgitation severity, particularly when regurgitant jets are quite eccentric. For this reason, quantitative assessment is generally recommended, especially when making clinical decisions about surgical intervention. The PISA method is generally used for quantitative assessment of severity of mitral regurgitation. This method relies on estimation of the velocity of flow acceleration at a specific distance proximal to the valve with the assumption that the flow accelerates in concentric hemispheres.

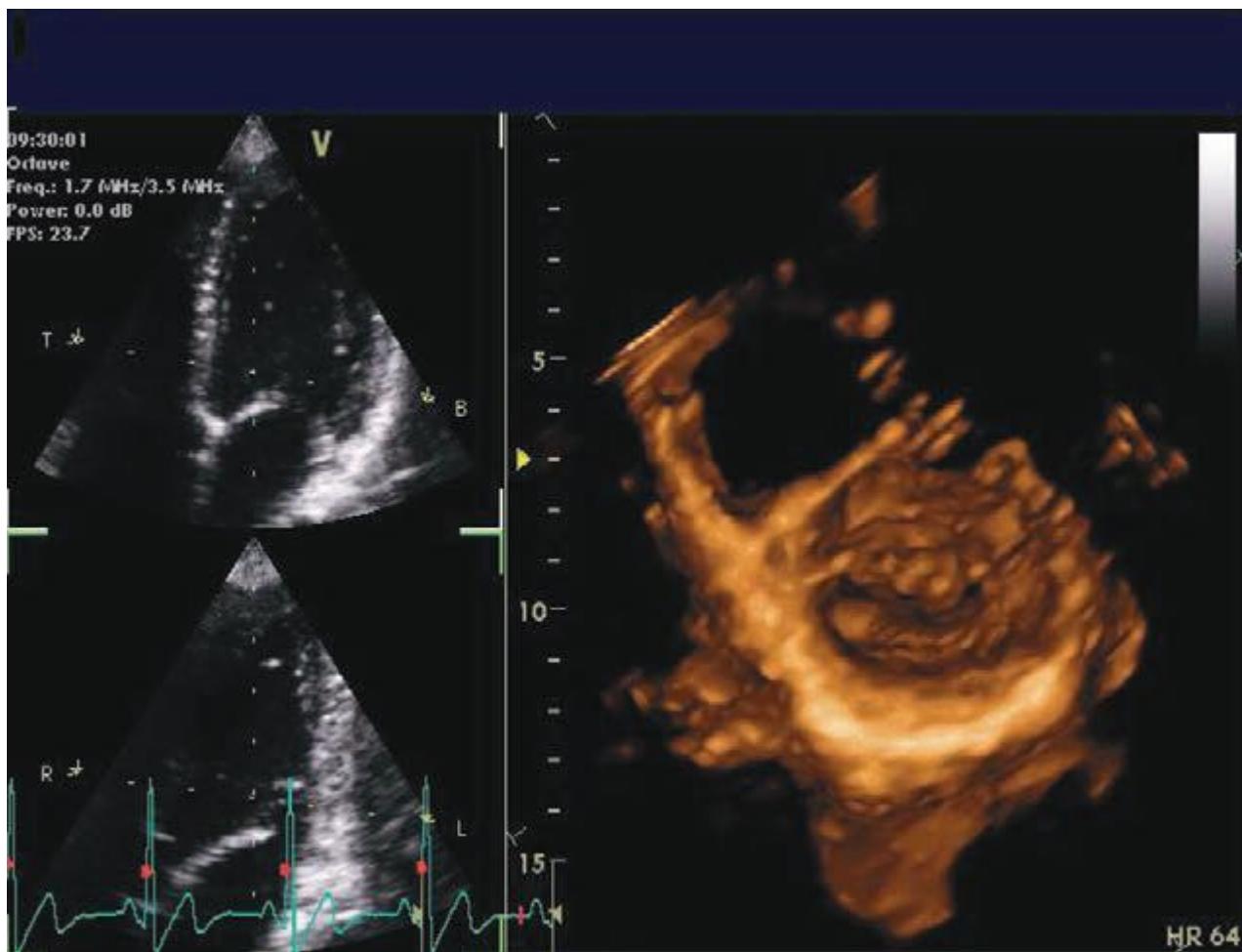


FIGURE 270e-22 Normal mitral valve in two-dimensional views (left) and with three-dimensional imaging (right).

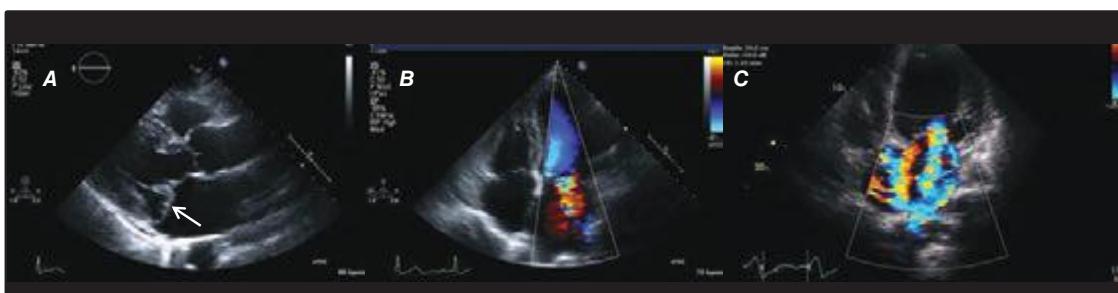


FIGURE 270e-23 **A.** Mitral valve prolapse with posterior leaflet visualized prolapsing behind the plane of the anterior leaflet (arrow). **B.** Color flow Doppler showing mitral regurgitation in a patient with mitral valve prolapse. **C.** Severe functional mitral regurgitation in a patient with a dilated left ventricle.

As with aortic insufficiency, assessment of ventricular structure and function is also integral in the evaluation of mitral regurgitation. Although some patients have mitral regurgitation due to intrinsic abnormalities of the valve itself, in others, the valve can be relatively normal but the mitral regurgitation can be secondary to dilatation and remodeling of the left ventricle. So-called functional mitral regurgitation is generally secondary to apical displacement of the papillary muscles in a dilated ventricle, resulting in the leaflets of the mitral valve being pulled toward the apex of the heart, resulting in poor coaptation during systole and resultant relatively central mitral regurgitation. This type of mitral regurgitation can generally be distinguished from intrinsic mitral valve disease, and the surgical or procedural treatment of these conditions can be different. Knowledge of the etiology of mitral regurgitation can be important for a surgeon planning mitral valve surgery. Moreover, new procedural approaches to mitral valve disease may be different depending on the etiology.

Ventricular dilatation is an important predictor of outcome in patients with mitral regurgitation of any cause. It is important to realize that in a patient with significant mitral regurgitation, a large portion of the blood being ejected from the left ventricle with every beat is regurgitant, thus artificially increasing the ejection fraction. Thus, an ejection fraction of 55% in a patient with severe mitral regurgitation may actually represent substantial reduction in myocardial systolic function.

CMR can be helpful in evaluating mitral regurgitation in a subset of patients when echocardiographic assessment is inadequate. CMR can directly quantify regurgitant volume of the mitral regurgitant jet or indirectly quantify regurgitant volume by measuring the difference of left ventricular stroke volume and aortic forward flow.

Assessment of Mitral Stenosis Rheumatic mitral disease remains the most common cause of mitral stenosis, although mitral stenosis can also result from severe calcification of the mitral leaflets. Rheumatic mitral stenosis has a distinct appearance characterized by tethering at the leaflet tips and relative pliability of the leaflets themselves, resulting in a hockey stick-type deformation particularly of the anterior leaflet (Fig. 270e-24). Narrowing of the mitral orifice impedes flow from the left atrium to the left ventricle, resulting in increased pressures in the left atrium, which are then transmitted backward into the pulmonary vasculature and the right side of the heart. When mitral stenosis is suspected, echocardiography can be useful for determining etiology (specifically whether it is rheumatic or not), estimating the valve areas and gradients across the valve, assessing the left atrium, and assessing right ventricular size and function. Assessment of left atrial size and right ventricular size and function is particularly useful in helping determine the severity of the mitral stenosis.

MYOCARDIAL INFARCTION AND HEART FAILURE

Role of Imaging after Myocardial Infarction Imaging can be particularly useful in the immediate and long-term follow-up of patients with myocardial infarction. As discussed earlier in the chapter, CMR is the best technique for direct assessment of infarcted myocardium. LGE imaging by CMR provides accurate delineation of infarct size and morphology. In a recent multicenter study, LGE imaging by CMR identified infarct location accurately and detected acute and chronic infarcts with a sensitivity of 99% and 94%, respectively. With an in-plane spatial resolution of 1.5–2 mm and a high contrast-to-noise ratio, LGE by CMR has excellent sensitivity in detecting small areas of myocardial scar. In addition, regions of microvascular obstruction (no-reflow) can be seen as dense hypoenhanced areas within the core of a bright region of infarction. Both the presence of LGE and microvascular obstruction are markers of increased clinical risk.

While echocardiography is often used to assess myocardial function immediately after myocardial infarction, myocardial stunning is common in the early post-myocardial infarction period, especially in patients who undergo reperfusion therapy. In these patients, either partial or complete recovery of ventricular function is common within several days, so that early estimation of ejection fraction may be misleading. In patients with uncomplicated myocardial infarction, imaging can generally be deferred for several days so that a more accurate assessment of cardiac function, including regional wall motion, can be assessed (Fig. 270e-25).

Echocardiography is the best method for assessment of patients with suspected mechanical complications after myocardial infarction. These include mitral regurgitation secondary to either papillary muscle dysfunction or rupture of papillary muscle head, ventricular septal defect, or even cardiac rupture. A new severe systolic murmur should raise suspicions for either severe mitral regurgitation or ventricular septal defect. While cardiac rupture is often catastrophic, contained ruptures, also known as pseudoaneurysms, can occur, and early diagnosis and surgical treatment are the best way to maximize survival. The presence of thrombus within the pericardial space following myocardial infarction should immediately raise suspicion of myocardial rupture and represents a surgical emergency.

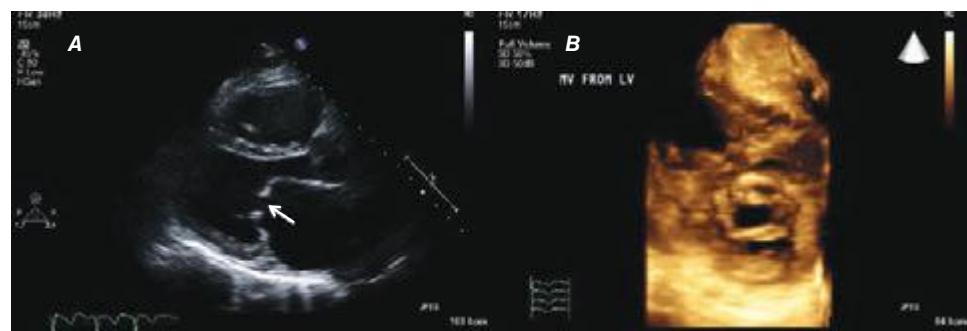


FIGURE 270e-24 **A.** Rheumatic mitral stenosis showing pliable leaflets tethered at the tips (arrow). Note the characteristically enlarged left atrium. **B.** Mitral stenosis visualized from a three-dimensional echocardiogram.



FIGURE 270e-25 Acute left anterior descending artery distribution myocardial infarction at end systole showing akinetic region (arrows).

Some patients demonstrate progressive left ventricular dilatation and dysfunction, known as cardiac remodeling, after myocardial infarction. Assessment of cardiac function and regional wall motion is useful in the follow-up period, generally between 1 and 6 months following infarction. The persistence of left ventricular systolic dysfunction following infarction is used to determine the type of therapy (e.g., angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are typically used in patients with systolic dysfunction following myocardial infarction).

In patients with acute or subacute myocardial infarction, investigation of residual ischemia and/or viability is occasionally an important

clinical question, especially among those with recurrent symptoms after myocardial infarction (**Fig. 270e-26**). All cardiac imaging techniques can provide information regarding myocardial viability and ischemia. In the absence of definitive trials offering head-to-head comparisons between techniques in large series of patients, uncertainty persists concerning the relative accuracies of each method for predicting functional and prognostic benefit after revascularization. Thus, one should exercise caution in the interpretation of the relative diagnostic accuracy of each imaging technology. Nevertheless, the available data suggest that radionuclide imaging, especially PET, is highly sensitive, with higher negative predictive value than dobutamine echocardiography. In contrast, dobutamine echocardiography tends to be associated with higher specificity and positive predictive accuracy than the radionuclide imaging methods. The experience with CMR suggests that it offers similar predictive accuracies as those seen with dobutamine echocardiography.

Role of Imaging in New-Onset Heart Failure Echocardiography is usually a first-line test in patients presenting with new-onset heart failure. As discussed above, this test provides a direct assessment of ventricular function and can help distinguish patients with reduced ejection fraction from those with preserved ejection fraction. In addition, it provides additional structural information including an assessment of valves, myocardium, and pericardium.

Although coronary angiography is commonly performed in patients with reduced ejection fraction, the determination of heart failure etiology in an individual patient may be difficult even if angiographically obstructive CAD is present. Indeed, patients with heart failure and no angiographic CAD may have typical angina or regional wall motion abnormalities on noninvasive imaging, whereas patients with angiographically obstructive CAD may have no symptoms of angina

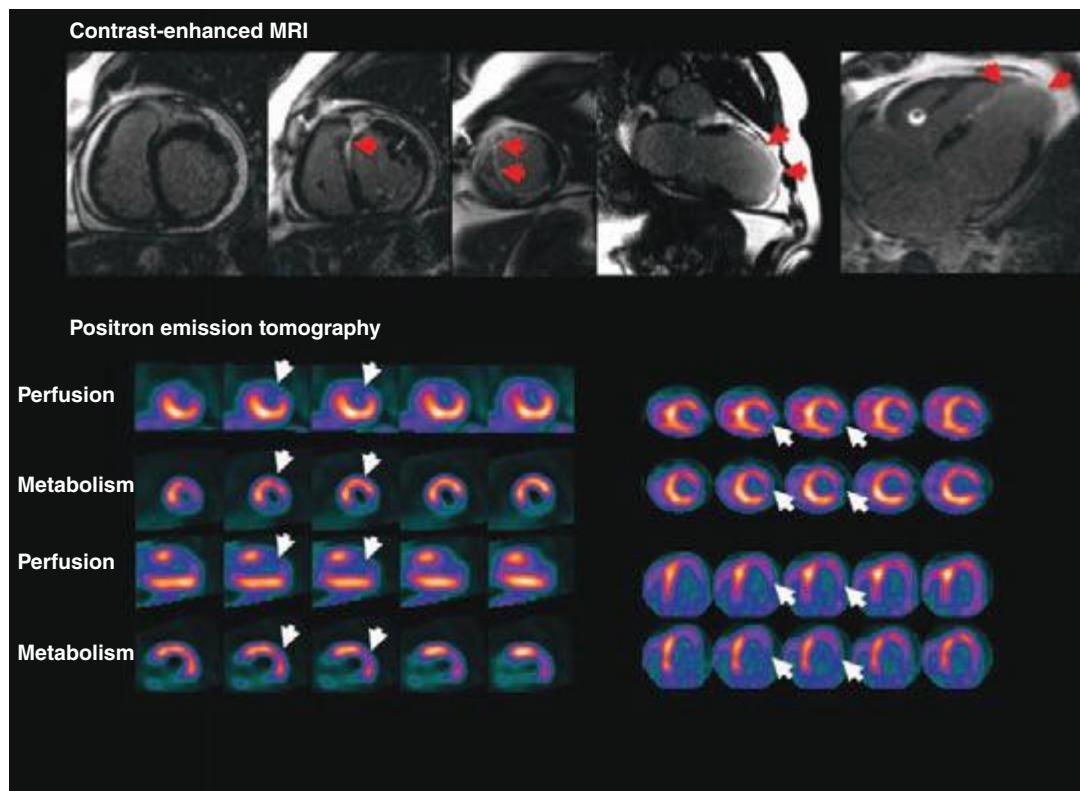


FIGURE 270e-26 Examples of myocardial viability patterns obtained with cardiac magnetic resonance imaging (MRI) and positron emission tomography (PET) in three different patients with coronary artery disease. The top panel demonstrates extensive late gadolinium enhancement (bright white areas) involving the anterior, anteroseptal, and apical left ventricular walls (arrows), consistent with myocardial scar and nonviable myocardium. The lower left panel demonstrates rubidium-82 myocardial perfusion and ^{18}F -fluorodeoxyglucose (FDG) images showing a large and severe perfusion defect in the anterior, anterolateral, and apical walls, indicating preserved glucose metabolism (so-called perfusion-metabolic mismatch) consistent with viable myocardium. The right lower panel shows similar PET images demonstrating concordant reduction in perfusion and metabolism (so called perfusion-metabolic match) in the lateral wall, consistent with nonviable myocardium.

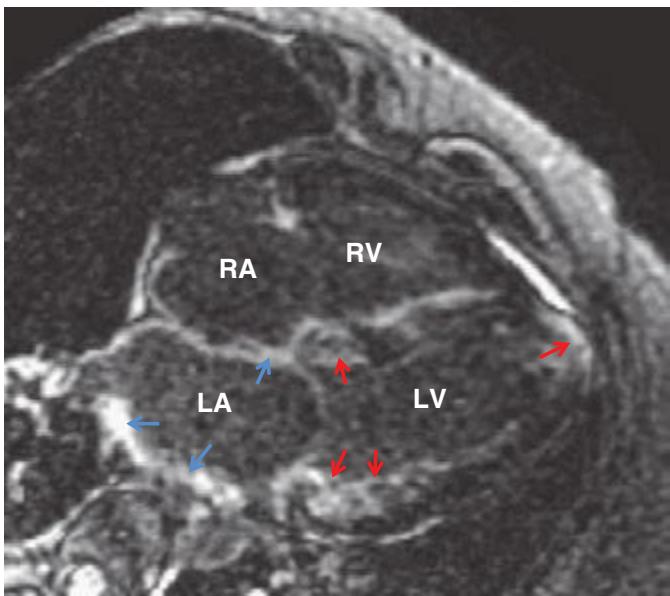


FIGURE 270e-27 A case of cardiac amyloidosis. Note on this late gadolinium enhancement image that there were multiple foci of gadolinium accumulation in the left ventricle (LV) myocardium (red arrows), as well as the left atrial (LA) walls (blue arrows). The LV walls were markedly increased in thickness, and both atria were dilated, consistent with a restrictive cardiac morphology. The blood pool signal was diminished after contrast injection, which was consistent with high burden of amyloid disease in other organs that causes gadolinium concentration in the blood to rapidly go down. RA, right atrium; RV, right ventricle.

or history of myocardial infarction. Thus, the appropriate classification for any given patient is not always clear, and it often requires the complementary information of coronary angiography and noninvasive imaging. Stress radionuclide imaging and echocardiography can be helpful in delineating the extent and severity of inducible myocardial ischemia and viability. Multiparametric CMR can be quite helpful in the differential diagnosis of heart failure etiologies. Apart from quantifying left and right ventricular volumes and function, CMR can provide information about myocardial ischemia and scar. The pattern of LGE helps differentiate infarction (typically starting in the subendocardium and involving a coronary territory) from other forms of infiltrative or inflammatory cardiomyopathies (typically involving the mid- or subepicardial layers without following a coronary distribution) (Fig. 270e-27). In addition, it can assess the presence of myocardial edema (e.g., myocarditis) and quantify myocardial iron deposition that can potentially lead to cardiac toxicity. Infiltrative cardiomyopathy such as amyloidosis typically has a restrictive cardiomyopathy pattern (bilateral atrial enlargement and biventricular increased wall thickness). CMR of patients with cardiac amyloidosis often also demonstrates a characteristic pattern of diffuse endocardial infiltration of the left ventricle and the atria (Fig. 270e-27). Hypertrophic

cardiomyopathy has variable degree of increased ventricular thickness, and often is seen to have outflow obstruction and intense LGE in regions with marked hypertrophy (Fig. 270e-28). CMR also can quantify myocardial iron content in patients at risk of iron-overload cardiomyopathy (Video 270e-7).

PET metabolic imaging has a complementary role in the evaluation of infiltrative cardiomyopathies, especially sarcoidosis. In patients with suspected cardiac sarcoidosis, the presence of focal and/or diffuse glucose uptake can help identify areas of active sarcoidosis. In addition, for patients undergoing immunosuppressive therapy, PET is frequently used to monitor therapeutic response (Fig. 270e-29). In patients with ischemic cardiomyopathy, radionuclide imaging in general and PET in particular are frequently used to quantify the presence and extent of myocardial ischemia and viability to assist with clinical decision making related to myocardial revascularization (Fig. 270e-26).

ASSESSING CARDIAC FUNCTION IN PATIENTS UNDERGOING CANCER TREATMENT

Therapies used to treat cancer can adversely affect the cardiovascular system. As the efficacy of cancer treatment and survival improve, many patients are presenting with late adverse consequences from chemotherapy and/or radiation therapy on cardiovascular function. Thus, the morbidity and mortality from late cardiovascular complications threaten to offset the early gains in cancer survival, especially among children and young adults. Early recognition and treatment of cardiomyocyte injury are critical for successful application of preventative therapies, but difficult because the adverse effects on cardiac function are a relatively late manifestation after exposure to anticancer therapy.

The accepted standard for clinical diagnosis of cardiototoxicity is defined as a >5% reduction in LVEF to <55% with symptoms of heart failure, or a >10% drop in LVEF to <55% in patients who are asymptomatic. Thus, noninvasive imaging plays a major role in diagnosing and monitoring for cardiac toxicity in patients undergoing cancer treatment. Radionuclide angiography has been the technique of choice

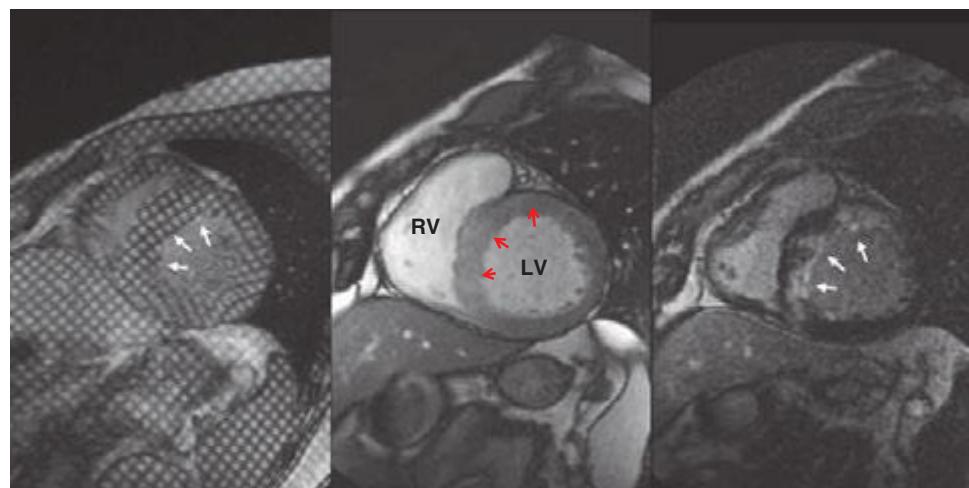


FIGURE 270e-28 This figure demonstrates three pulse sequence techniques by cardiac magnetic resonance that are often used to assess patients with hypertrophic cardiomyopathy, all displayed in the mid short-axis scan plane. The center panel demonstrates that the left ventricle (LV) was markedly thickened in its wall thickness especially in the LV septum (red arrows). This finding was matched by marked regions of late gadolinium enhancement (LGE), which was consistent with fibrosis in these segments (right panel, white arrows). The left panel was cine myocardial tagging in the same slice plane. Myocardial tagging is used to assess the normal intramyocardial strain by assessing distortion of the myocardial grids during systole. In this case, despite normal-appearing systolic radial wall thickening, the myocardial strain as assessed by the distortion of grids was markedly reduced (left panel, white arrows). This finding is consistent with substantial myofibril disarray in the anterior and anteroseptal segments in this patient. RV, right ventricle.

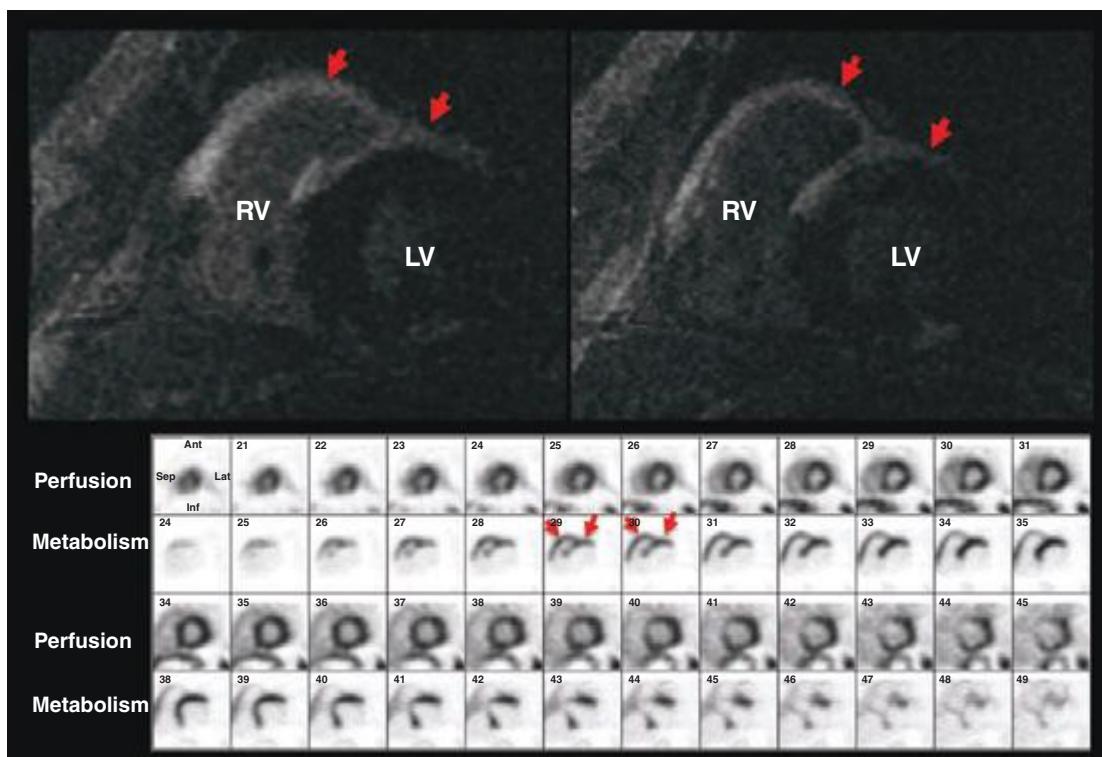


FIGURE 270e-29 Representative cardiac magnetic resonance (CMR; top panel) and positron emission tomography (PET; lower panel) images from a 45-year-old male presenting with complete heart block. The CMR images demonstrate extensive late gadolinium enhancement in the subepicardial left ventricular (LV) anterior and anteroseptal walls and also in the right ventricular (RV) free wall (arrows). The PET images demonstrate extensive fluorodeoxyglucose uptake in the same areas, most consistent with active inflammation due to sarcoidosis.

for quite some time. However, this is rapidly changing, and echocardiography now plays a major role in this application.

Recently, more novel imaging approaches have been advocated, including deformation imaging with echocardiography and fibrosis imaging with CMR. These techniques have shown promising results in experimental animal models and in humans. In addition, there are also proof-of-concept studies in animal models using molecular imaging approaches targeting the mechanisms of cardiac toxicity (e.g., apoptosis and oxidant stress), which can presumably provide the earliest signs of the off-target effects of these therapies. However, all of these techniques are currently considered experimental.

PERICARDIAL DISEASE

The fibroelastic pericardial sac surrounding the heart consists of a visceral, or epicardial, layer and a parietal layer, with a generally small amount of pericardial fluid in between layers. The pericardium is generally quite pliable and moves easily with the heart during contraction and relaxation. Abnormalities of the pericardium can affect cardiac function primarily by impairing the heart's ability to fill. Inflammation of the pericardium can lead to an accumulation of fluid between the two layers, or *pericardial effusion*, which can be visualized by echocardiography, CMR, or CT. Other reasons for accumulation of pericardial fluid include infection, malignancy, and bleeding into the pericardium. The latter can be the result of catastrophic processes such as trauma, cardiac rupture, perforation in the setting of a cardiac procedure, cardiac surgery, or dissection of the aorta with extension in the pericardium.

Echocardiography remains the initial test of choice for assessing pericardial disease, especially effusions (Fig. 270e-30). Moreover, echocardiography can be useful in evaluating for pericardial constrictive physiology, in which a thick noncompliant pericardium impairs cardiac filling. The location, size, and physiologic consequences of accumulated pericardial effusion can generally easily be determined by echocardiography. Pericardial tamponade occurs when enough pericardial fluid accumulates so that the intrapericardial pressure exceeds filling pressures of the heart, generally the right ventricle. The balance between intrapericardial pressure and ventricular pressure is

more important than the extent of fluid accumulation. Conditions in which pericardial effusions accumulate over a long period of time, as can be the case in the setting of malignant effusions, can lead to large pericardial fluid accumulations without the classic hemodynamic findings associated with pericardial tamponade. In contrast, rapid accumulations of pericardial fluid, such as those that occur due to cardiac rupture or perforation, can lead to tamponade physiology without very large effusions. In patients with suspected pericardial effusion or tamponade, echocardiography can usually be performed rapidly, at the bedside, and even by operators with limited skill. The distance from the parietal to the visceral pericardial layer can be measured, and when this exceeds approximately 1 cm, an effusion is considered significant. Echocardiographic features suggestive of tamponade include diastolic collapse of the right ventricular free wall, suggestive of pericardial pressures that exceed right ventricular filling pressures, and Doppler evidence of respiratory flow variation, which is the Doppler equivalent



FIGURE 270e-30 Pericardial effusion with tamponade physiology. The right ventricle (arrow) is small and collapsing in end diastole due to increased pericardial pressure.

of pulsus paradoxus. Despite the benefits of echocardiography in suspected pericardial tamponade, the diagnosis of tamponade remains a clinical diagnosis, and other important features, such as patient's blood pressure in the presence of pulsus paradoxus, needs to be taken into account when considering therapeutic options.

Chronic inflammation of the pericardium can lead to thickening and potentially calcification of the parietal pericardium, resulting in pericardial constriction in which diastolic filling can be severely impaired. In these cases, filling of the ventricles comes to an abrupt halt when the volume of ventricular filling is impaired by the constricting pericardium. Assessment of pericardial thickness in these patients is important, but it is just as important to note that approximately one in five patients with severe pericardial constriction have no significant pericardial thickening by imaging or at surgery. Thus, a lack of thickened pericardium does not rule out pericardial constriction, and patients' signs and symptomatology and physiologic evidence of constriction should be assessed independently. Pericardial constriction typically demonstrates marked respiratory changes in diastolic flow on Doppler echocardiography, in contrast to restrictive cardiomyopathy, but substantial overlap exists. CT and CMR offer tomographic, whole-heart assessment of pericardial thickening and other anatomy abnormalities in pericardial constriction (enlarged atria, vena cavas, pleural and pericardial effusions) (Fig. 270e-31 and Video 270e-8). CMR offers the additional information of pericardial fibrosis and inflammation by LGE imaging, as well as evidence of constrictive physiology (e.g., regional relaxation concordance due to myocardial adhesions, paradoxical septal motion at rest or during Valsalva maneuver).

CARDIAC THROMBUS AND MASS

Echocardiography is usually the modality that first detects the presence of a cardiac mass. Differential diagnoses of an intracardiac mass most often include thrombus, tumor, or vegetation. Given their unrestricted tomographic views and multiplanar three-dimensional imaging, CMR and CT can complement echocardiography by further characterizing the physical features of the cardiac mass. Compared to CT, CMR has the advantage of higher tissue contrast differentiation, more robust cine imaging, and the use of multifaceted techniques within the same imaging session to determine the physiologic characteristics of the mass. Gadolinium contrast enhancement patterns of increased capillary perfusion can help to determine the presence and extent of



FIGURE 270e-32 Cardiac thrombus (arrow) in an apical aneurysmal region following acute myocardial infarction.

vascularity within the mass, relevant for differentiating tumor from thrombus. Structures that are known to mimic a cardiac mass include (1) anatomic variants, such as the Eustachian valve, Chiari network, crista sagittalis or terminalis, and the right ventricular moderator band, and (2) "pseudotumors," such as interatrial septal aneurysm, coronary or aortic aneurysm, lipomatous hypertrophy of interatrial septum, hiatal hernia, or a catheter/pacemaker lead. A number of coexisting conditions should raise the likelihood of a cardiac thrombus (Fig. 270e-32), including regional wall motion abnormality from infarction or ventricular aneurysm, atrial fibrillation leading to slow flow in the left atrial appendage, or presence of venous catheters or recent endovascular injury. CMR has the advantage of being able to assess regional wall motion and infarction or ventricular aneurysm in matching scan planes, adjacent to the cardiac thrombus, using cine and LGE imaging, respectively. For ventricular thrombus, gadolinium-enhanced LGE imaging can detect thrombus at a higher sensitivity than echocardiography by depicting high-contrast difference between the dark thrombus and its adjacent structures and by imaging in three dimensions. In addition, mural thrombus does not enhance on first-pass perfusion and often has a characteristic "etched" appearance (black border surrounding a bright center) on LGE imaging, thus providing higher diagnostic specificity than anatomic information alone (Fig. 270e-33). Comparing the signal intensities of a mass before and after contrast injection may confirm the lack of tissue vascularity (i.e., thrombus)

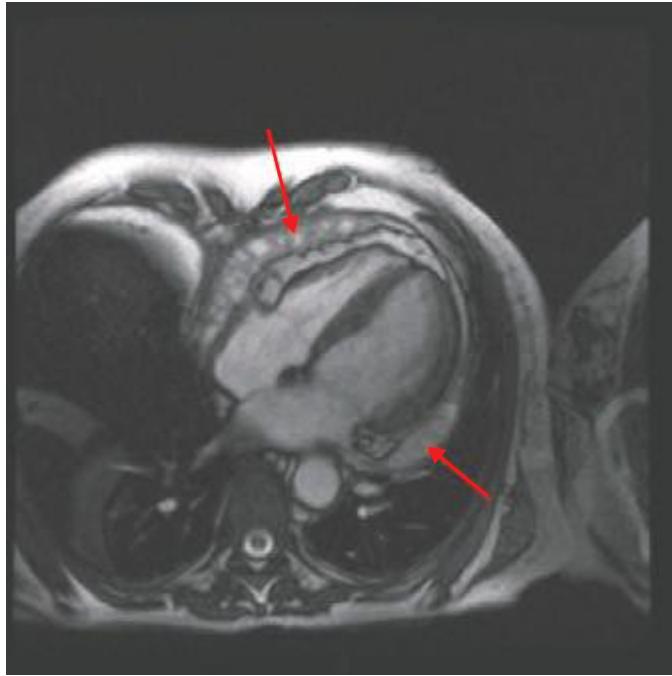


FIGURE 270e-31 A female patient developed pericardial constriction and right heart failure, secondary to radiation therapy for breast cancer. Note the multiple pericardial adhesions (red arrows).

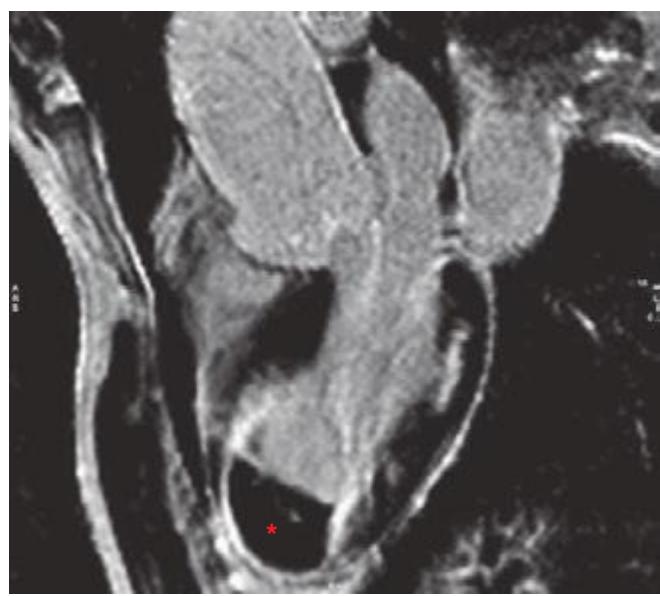


FIGURE 270e-33 Late gadolinium enhancement image of a massive anterior infarction complicated by a dyskinetic left ventricular LV aneurysm and intracavitory thrombus (red asterisk).

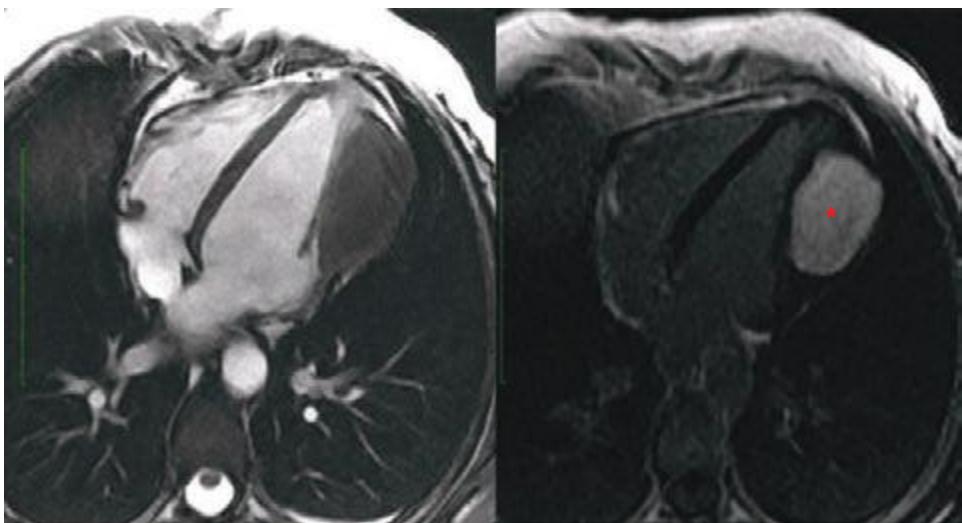


FIGURE 270e-34 A case of a cardiac fibroma. A patient presented with shortness of breath and was found to have a large myocardial mass on echocardiography. Cine cardiac magnetic resonance imaging confirmed the large myocardial mass involving the anterolateral wall. Shortly after gadolinium contrast was injected, the myocardial mass demonstrated intense accumulation of contrast on LGE imaging (right panel, asterisk). This is a case of cardiac fibroma. The patient also has gingival hyperplasia and bifid thoracic ribs, a part of the rare Gorlin's syndrome.

by the lack of signal enhancement after contrast administration. Like intracardiac thrombus, regions of microvascular obstruction also appear dark, but microvascular obstruction is confined within the myocardium and surrounded by infarction and thus can be differentiated from intracardiac thrombus. CMR imaging for small thrombus in the left atrial appendage is difficult due to slow flow in the atrium and rhythm irregularity from atrial fibrillation, but it may be helpful in cases where transesophageal echocardiography is suboptimal or not feasible.

The majority of cardiac malignancy is metastatic, and metastatic cardiac malignancy is far more common than primary cardiac malignancies; these metastatic involvements of the heart are the result of direct invasion (e.g., lung and breast), lymphatic spread (e.g., lymphomas and melanomas), or hematogenous spread (e.g., renal cell carcinoma). Primary benign cardiac tumors are seen mostly in children and young adults and include atrial myxoma, rhabdomyoma, fibroma, and endocardial fibroelastoma (Fig. 270e-34). Atrial myxomas are often seen as a round or multilobed mass in the left atrium (75%), right atrium (20%), or ventricles or mixed chambers (5%). They typically have inhomogeneous brightness in the center on cine steady-state free precession imaging due to their gelatinous contents and may have a pedunculated attachment to the fossa ovalis. Primary malignant cardiac tumors are extremely rare and include angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma.

ROLE OF IMAGING IN INFECTIOUS AND INFLAMMATORY DISEASE

Patients with suspected endocarditis often undergo echocardiography for the purpose of identifying vegetations or intramyocardial abscesses. Vegetations are generally highly mobile structures that most typically are attached to valves or present in areas of the heart with turbulent flow. The absence of a vegetation on echocardiography does not rule out endocarditis, because small vegetations

below the resolution of the imaging techniques can be present. Echocardiography remains the best technique for assessment of vegetations because its high temporal resolution allows visualization of the typical oscillating motion, although large vegetations can be visualized with other techniques (Fig. 270e-35). The size and location of a vegetation do not necessarily provide any specific information about the type of infection. Abscesses, particularly around the aortic and mitral annuli, are particularly concerning in patients with endocarditis and should be suspected in patients with prolongation of cardiac intervals in the setting of endocarditis. Visualization of both vegetations and possible abscesses is best done with transesophageal echocardiography, particularly in patients with prosthetic valves. Indeed, transesophageal echocardiography is the first test of choice in a patient with a mechanical mitral or aortic valve and suspected endocarditis (Fig. 270e-35). Vegetations should be measured because their size has prognostic importance and can be used to decide whether a patient should be taken to surgery.

PET metabolic imaging is emerging as a potentially useful imaging technique to identify the source of infection in patients with prosthetic valves, vascular grafts, and implantable pacemakers/defibrillators, especially in patients in whom echocardiography and/or blood cultures are negative. There is an emerging literature documenting the potential value of macrophage-targeted metabolic imaging with ¹⁸F-FDG and PET (Fig. 270e-36). Likewise, FDG PET is also useful to identify vascular inflammation and monitor the response to immunosuppressive therapy (Fig. 270e-37).

EVALUATION OF COMMON CONGENITAL ABNORMALITIES IN THE ADULT

While a discussion of complex congenital heart disease is beyond the scope of this chapter, a number of common congenital abnormalities are present in adults, and cardiac imaging is essential to diagnosing and managing these conditions. Abnormalities of the interatrial

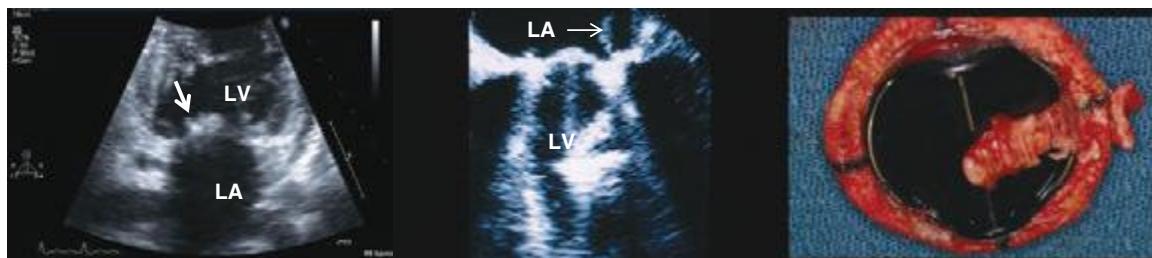


FIGURE 270e-35 Vegetation on native mitral valve (left panel, arrow). Left atrium (LA) and left ventricle (LV) are indicated. Middle panel shows a vegetation on a mechanical prosthesis (St. Jude) indicated by an arrow; right panel shows vegetation on prosthesis after excision.

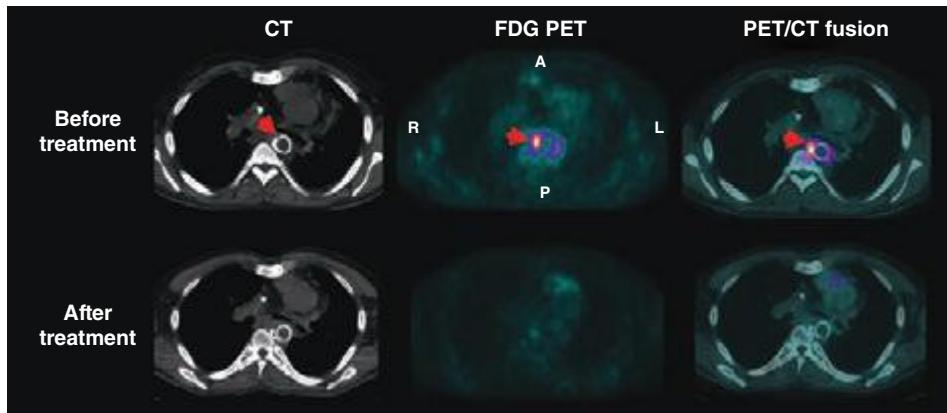


FIGURE 270e-36 Representative cross-sectional computed tomography (CT; *left*), fluorodeoxyglucose (FDG) positron emission tomography (PET; *middle*), and fused CT and PET (*right*) images before and after antibiotic treatment in a patient with fever and suspected infection of the stent placed in the descending portion of the aortic arch (arrow) for treatment of aortic coarctation. The FDG images before treatment demonstrate intense glucose uptake within the stent, consistent with inflammation/infection. The *lower panel* demonstrates significant attenuation of the FDG signal after treatment. (*Images courtesy of Dr. Sharmila Durbala, Brigham and Women's Hospital.*)

septum probably represent the most common adult congenital cardiac abnormalities. Patent foramen ovale (PFO) can be identified in almost 25% of patients. In patients with PFO, a one-way flap in the region of the fossa ovalis is normally kept close by the left atrial pressure, which is generally higher than right atrial pressure for the majority of the cardiac cycle. However, right-to-left flow through a PFO can occur any time the right atrial pressure exceeds the left atrial pressure, including with maneuvers or conditions in which intrathoracic pressure is increased. The presence of a PFO can increase the likelihood of the paradoxical embolus, and thus the presence of a PFO should be determined in patients with stroke or systemic embolus of unknown etiology. Because the one-way flap of the PFO will be closed during much of the cardiac cycle, color flow Doppler will usually not reveal a PFO. Instead, agitated saline (bubble study) is the best way to assess for PFO or atrial septal defect. Saline is agitated and injected peripherally and then enters the right atrium. If no shunt is present, only the right side of the heart will be pacified because the air bubbles will be too small to traverse the lungs. Because PFO is a one-way flap, maneuvers should be used to temporarily increase right atrial pressure. Either a Valsalva maneuver or sniff maneuver can be effective.

Atrial septal defects occur most commonly in the region of the fossa ovalis, referred to as secundum-type defects (Fig. 270e-38). Additional atrial septal defects include defects of the sinus venosus and atrium primum. Color flow Doppler echocardiography is usually sufficient for diagnosis of a secundum-type atrial septal defect, but agitated saline is generally needed for the diagnosis of other types of atrial septal defects.

Ventricular septal defects can generally be visualized by color flow Doppler as turbulent high-velocity jets from the left to the right ventricle. In cases where the jet origin is unclear, continuous wave Doppler can estimate the velocities. These would be expected to be

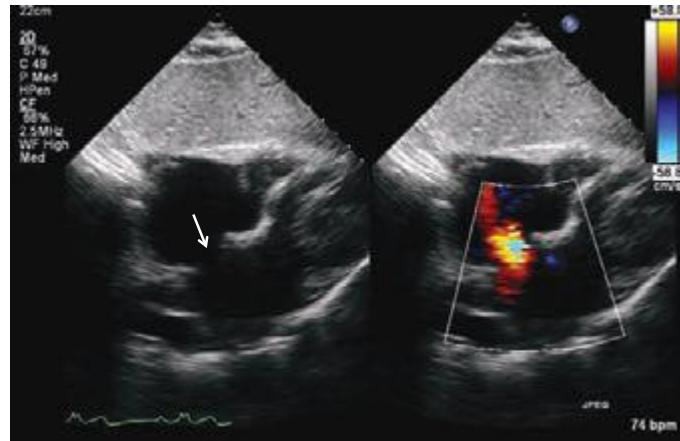


FIGURE 270e-38 Large secundum-type atrial septal defect (arrow) noted in the subcostal view with color flow Doppler showing flow through the defect (right).

extremely high to reflect the pressure gradient between the left and right ventricles. Defects can occur in both the muscular and membranous portions of the ventricular septum.

In patients with either atrial or ventricular septal defects, estimation of the severity of the left-to-right shunt is essential and can be an important determinant in management decisions. Shunts are generally assessed by echocardiography by assessing the relationship between pulmonary flow and aortic flow, the Qp/Qs ratio. Shunts and cardiac anatomy of most congenital heart diseases can also be accurately evaluated by CMR (Fig. 270e-39).

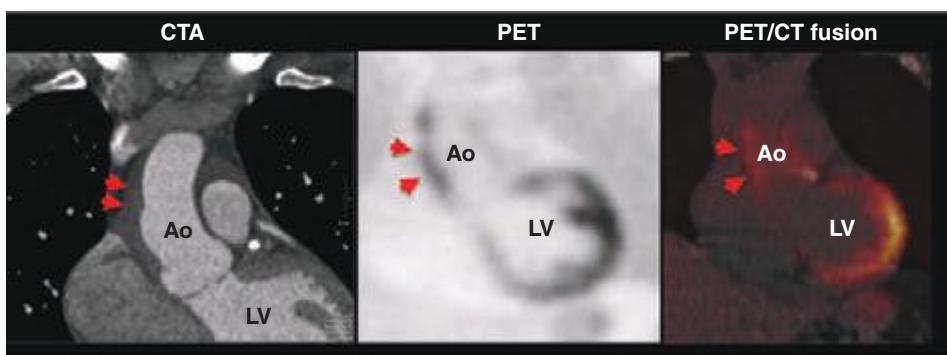


FIGURE 270e-37 Representative coronal computed tomography (CT) angiographic (CTA; *left panel*), fluorodeoxyglucose (FDG) positron emission tomography (PET; *middle panel*), and fused CT and PET (*right panel*) images in a patient with suspected aortitis. The CTA images demonstrate thickening of the ascending aorta (Ao), which correlates with intense, focal FDG uptake consistent with active inflammation. LV, left ventricle.

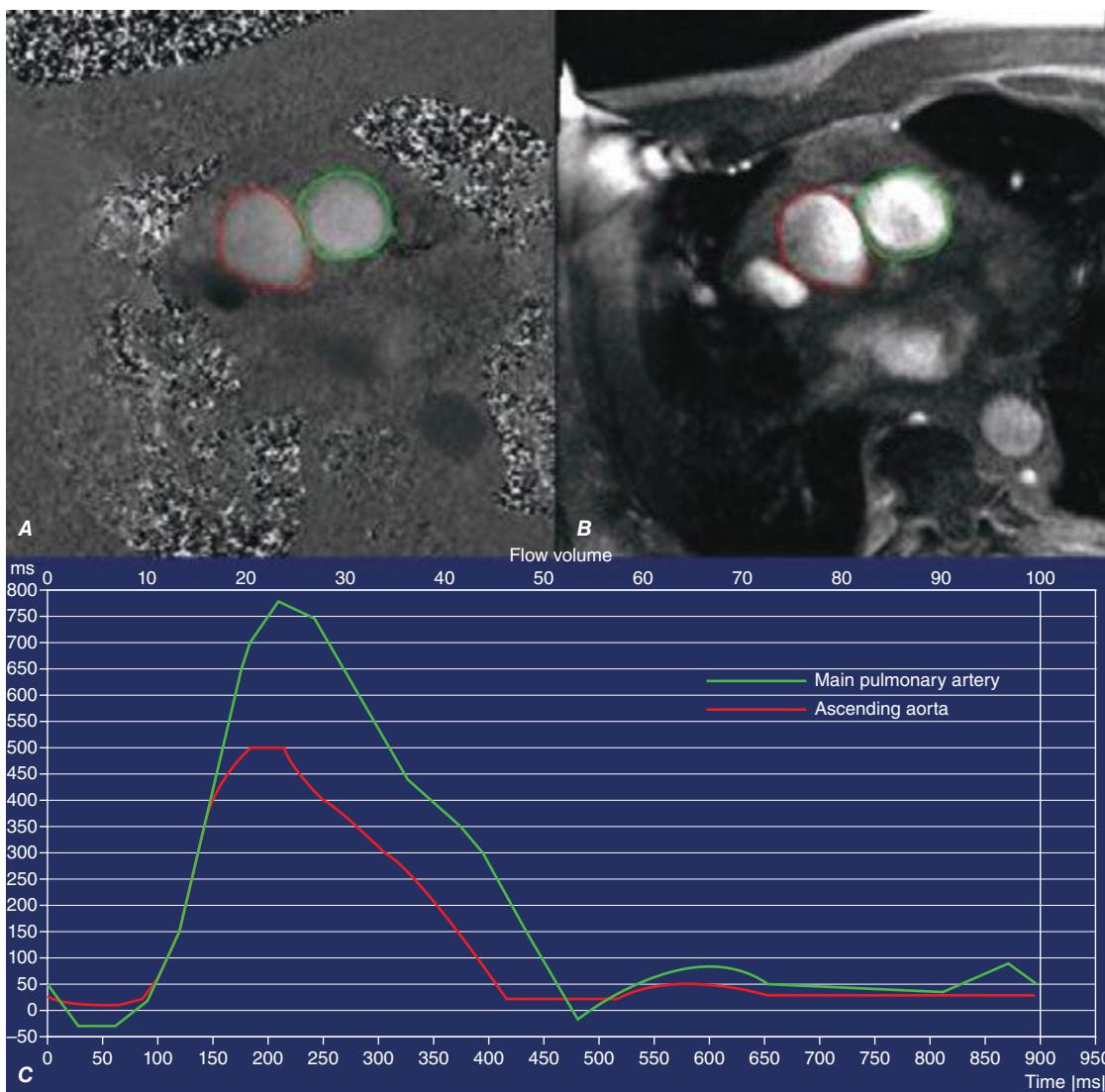


FIGURE 270e-39 **A** and **B** are phase contrast images that display blood flow (phase images on **A**) and anatomy (structural images on **B**) of the aorta (red) and pulmonary artery (green). **C** demonstrates the flow curves of the aorta (red) and the pulmonary artery (green). Note that the total flow (area under the curve) was substantially higher in the pulmonary artery than the aorta, indicative of a marked elevated pulmonary-to-systemic shunt ratio, as a result of the partial anomalous pulmonary venous return that drained into the superior vena cava.

VIDEO 270e-1 Cine steady-state free precession (SSFP) imaging (left) in short axis in a patient who had a large anterior myocardial infarction. Only one cut of a stack of short axis is shown. This method allows quantification of left ventricular (LV) and right ventricular (RV) volumes in diastole and systole and calculation of the LV ejection fraction, stroke volumes, and cardiac output (a product of LV stroke volume and heart rate). Note that in this case there is anterior and anteroseptal akinesia (lack of systolic wall thickening, as shown by the left cine movie, red arrows) matching by a near-transmural myocardial infarction as seen by the matching late gadolinium enhancement (LGE) image (right picture, white arrows).

VIDEO 270e-2 This is cine cardiac magnetic resonance (CMR) imaging of a patient in the long-axis four-chamber view. Note that the basal aspect of the right ventricular (RV) free wall is thickened, aneurysmal, and akinetic (red arrows). The global RV systolic function is mildly reduced, and the RV is dilated. CMR can image the RV using tomographic views and can quantify the RV volumes and ejection fraction volumetrically. This is a patient who presented with syncopal spells and inducible ventricular tachycardia on subsequent workup. He was diagnosed to have arrhythmogenic right ventricular dysplasia.

VIDEO 270e-3 Exercise echocardiogram showing rest images on left and poststress images on right, with parasternal long-axis, upper panel, and apical four-chamber, lower panel, end-systolic

frames. Following exercise, the distal septal/apical region becomes akinetic. A = upper left (UL); B = upper right (UR); C = lower left (LL); D = lower right (LR).

VIDEO 270e-4 The video shows cardiac magnetic resonance (CMR) myocardial perfusion imaging during vasodilating stress, in three parallel-short-axis views. An bolus of gadolinium contrast was injected intravenously while rapid imaging acquisition occurred. The contrast enhances the right ventricle first, then travels through the pulmonary circulation, enters the left ventricle (LV), and then perfuses the LV myocardium. Myocardial perfusion defects with this technique show as black subendocardial rims, reflecting lack of contrast accumulation due to ischemia and/or scar. In this case, the anterior wall has a severe perfusion defect (red arrow). Figure 270-14 shows the late gadolinium enhancement (LGE) image of a mid short-axis view. There is no evidence of infarction in the anterior wall, which would be seen as bright white areas, indicating that the stress perfusion defect primarily represents myocardial ischemia. This patient had a significant stenosis of the left anterior descending coronary artery.

VIDEO 270e-5 A 60-year-old female presented with intermittent chest pain of 3 days in duration but was pain free at the time of assessment in the emergency room. Admission electrocardiogram (ECG) demonstrated T-wave inversion in the anterior precordial lead, but cardiac enzymes were normal. A resting cardiac magnetic

resonance (CMR) study reviewed a large area of anteroseptal hypokinesia (*left picture*, region of hypokinesia shown by the *red arrows*), matching with a large resting perfusion defect (*middle picture*, perfusion defect shown by the *blue arrows*). Late gadolinium enhancement (LGE) imaging (*right picture*), however, did not show any enhancement to indicate any infarction in the anteroseptal wall, suggesting that the hypocontractile and hypoperfused anteroseptal wall was viable. Urgent coronary angiography demonstrated an acute thrombus in the mid left anterior descending coronary artery, which required coronary stenting. This case represents an example of acute coronary syndrome with hibernating but viable myocardium in the anteroseptal wall. The anteroseptal wall recovered contractile function when reassessed 6 months later.

VIDEO 270e-6 A patient with severe aortic regurgitation quantified by cardiac magnetic resonance (CMR). Notice the dark flow jet during diastolic across the aortic valve. For quantitation of the aortic regurgitation severity, a cross-sectional cut was made just below the aortic valve, perpendicular to the aortic regurgitation jet, using phase

contrast flow imaging. Apart from aortic regurgitation fraction and volume, CMR also can volumetrically quantify ventricular sizes and dimensions of the aorta, which are useful in monitoring patients with aortic valve diseases.

VIDEO 270e-7 These are T2* images of the heart (*left panel*) and the liver (*right panel*) of a patient who has hemochromatosis.

Note that iron and the liver are markedly darkened in these movies, indicating high load of iron in the heart muscle and liver. The rate of signal reduction (decay) in the myocardium and liver can be calculated as T2* value expressed in milliseconds. In this case, the T2* was at 10 ms. T2* <20 ms in patients with cardiomyopathy has been shown to indicate iron toxicity as the etiology of the cardiomyopathy, and it carries prognostic value for such patients at risk of cardiac iron toxicity.

VIDEO 270e-8 This video shows the heart in long and short axis.

Note the large atria, thickened pericardium, and extensive pericardial adhesions. Given the extensive pericardial adhesions, there is little shearing motion of the ventricles against the parietal pericardium.

271e Atlas of Noninvasive Imaging

Marcelo F. Di Carli, Raymond Y. Kwong, Scott D. Solomon

This chapter provides “movie” image clips as they are viewed in clinical practice, as well as additional static images. Noninvasive cardiac imaging is essential to the diagnosis and management of patients with known or suspected cardiovascular disease. This atlas supplements [Chap. 270e](#), which describes the principles and clinical applications of these important techniques.

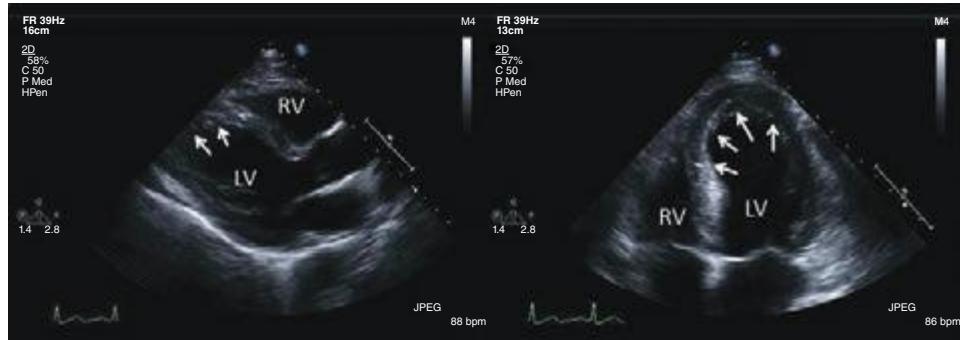


FIGURE 271e-1 A 48-year-old man with new-onset substernal chest pain. Echocardiography shows evidence of acute anterior myocardial infarction involving the interventricular septum and apex secondary to an occlusion of the left anterior descending coronary artery seen from the parasternal long axis view (left) and the apical four-chamber view (right). LV, left ventricle; RV, right ventricle. ([See Videos 271e-1 and 271e-2.](#))

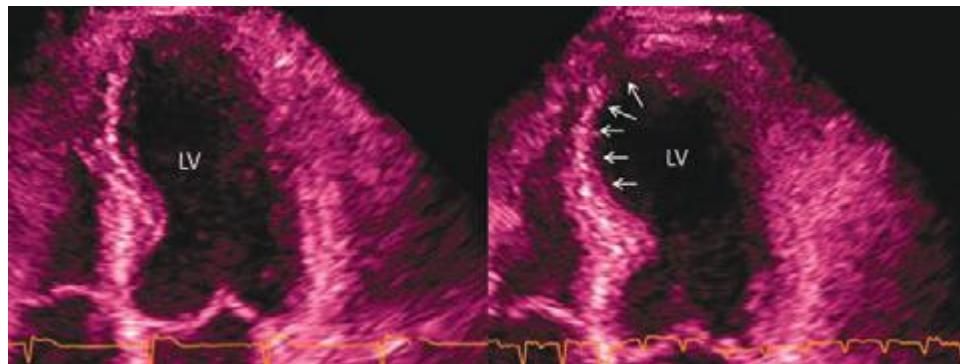


FIGURE 271e-2 A 55-year-old man with exertional chest discomfort and dyspnea. He exercised for 12 min on a standard Bruce protocol, experiencing typical chest pain and ST-segment depression in V_2-V_5 . End-systolic frame of a stress echocardiogram shows apical four-chamber view at rest (left) and after exercise (right). After exercise, there is a clear regional wall motion abnormality in the distal septum through the apex, consistent with a stenosis in the left anterior descending artery distribution (arrows). LV, left ventricle. ([See Videos 271e-3 and 271e-4.](#))

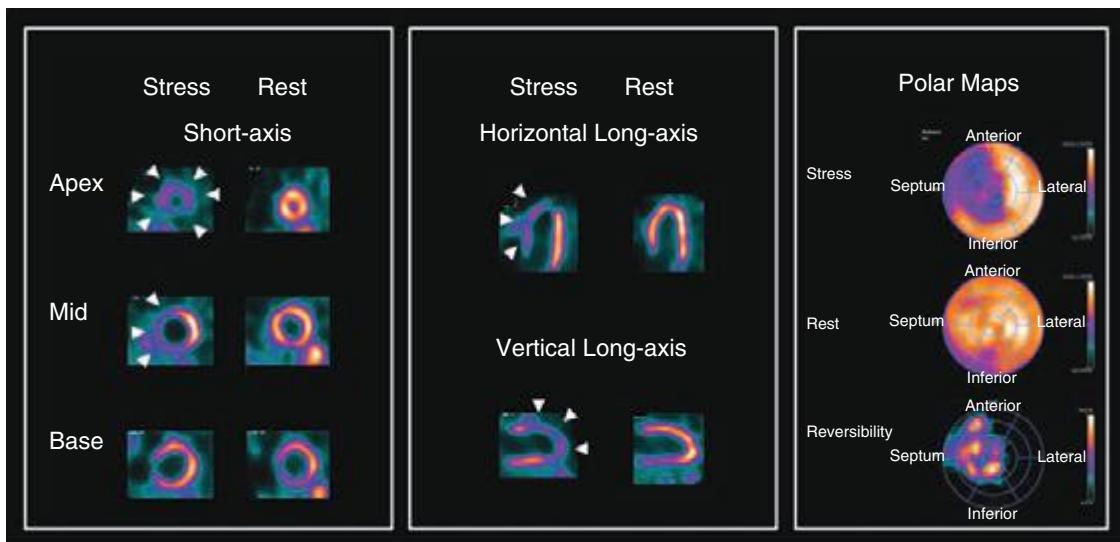


FIGURE 271e-3 Exercise single-photon emission computed tomography (SPECT) myocardial perfusion technetium-99m (^{99m}Tc) sestamibi scan in a 54-year-old male with a history of coronary artery disease and a prior coronary stent. The stress images (left and middle) show a large defect involving the apex, all apical segments, mid-inferior, mid-inferoseptum, and mid-anteroseptum (arrowheads), which is completely reversible at rest (right), reflecting a large area of exercise-induced myocardial ischemia throughout the left anterior descending coronary territory. The bull's eye displays on the right panel depict the semiquantitative extent of ischemia (light yellow and blue areas represent the extent and severity of ischemia).

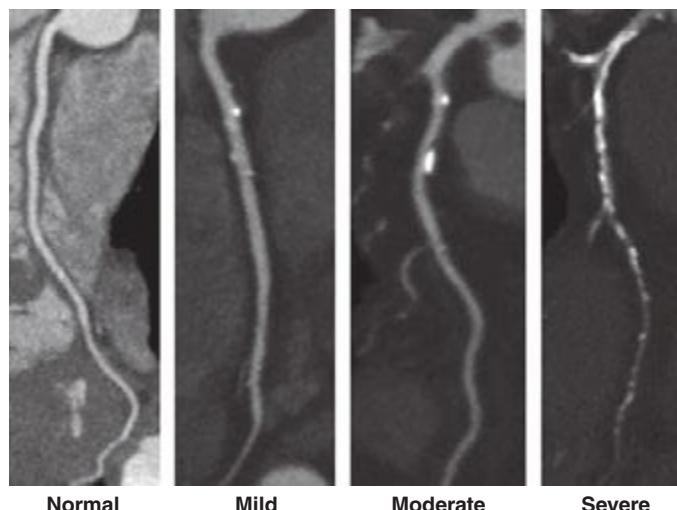
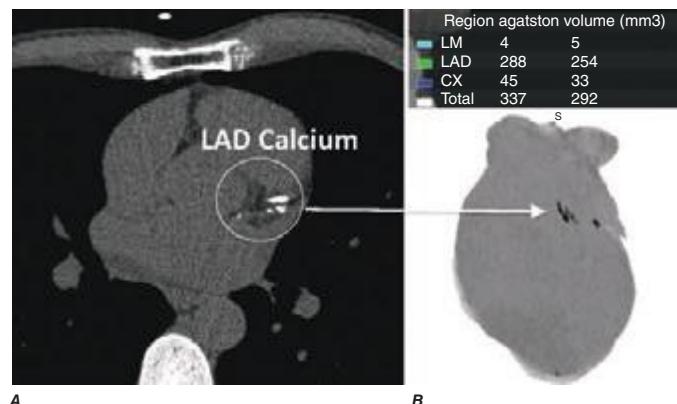


FIGURE 271e-4 Coronary computed tomography angiography (CTA). Curved multiplanar reformations demonstrating coronary artery disease severity, defined as normal (no plaque or stenosis), mild (<40%), moderate (40–69%), and severe (>70%) luminal narrowing. By guidelines for CTA reporting, alternative classification provides for stenosis grading as normal, minimal (1–24%), mild (25–49%), moderate (50–69%), severe (70–99%), and occluded (100%). (From GL Raff et al: SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr* 3:122, 2009; with permission.)



- CAC score 271e = 96th percentile for age, race and ethnicity¹
- 10-year hard CHD risk is 6% (observed age) vs 30% (arterial age)^{2#}

FIGURE 271e-5 Coronary artery calcium (CAC) scan on a 51-year-old white male without clinical cardiovascular disease or treated diabetes, referred for CAC for risk stratification to guide preventive therapies. **A.** Gated, noncontrast cardiac computed tomography (CT; 3-mm slice thickness), axial view, demonstrating calcified left anterior descending (LAD) artery atherosclerosis. **B.** Whole-heart three-dimensional image reconstruction, inverted maximum-intensity projection, demonstrating overall burden of CAC with predominant LAD distribution (arrow). **Top right.** CAC scores for each coronary artery with calcified plaque involvement, scored by Agatston method and total volume. ¹For white male with observed age 51 years, total cholesterol 220 mg/dL, high-density lipoprotein 45 mg/dL, nonsmoker, no hypertension, and systolic blood pressure 120 mmHg. Calculated arterial age is 81 years. CHD, coronary heart disease; CX, left circumflex artery; LM, left main artery. ²Data from RL McClelland et al: *Circulation* 113:30–37, 2006. [#]Data from RL McClelland et al: *Am J Cardiol* 103: 59–63, 2009.

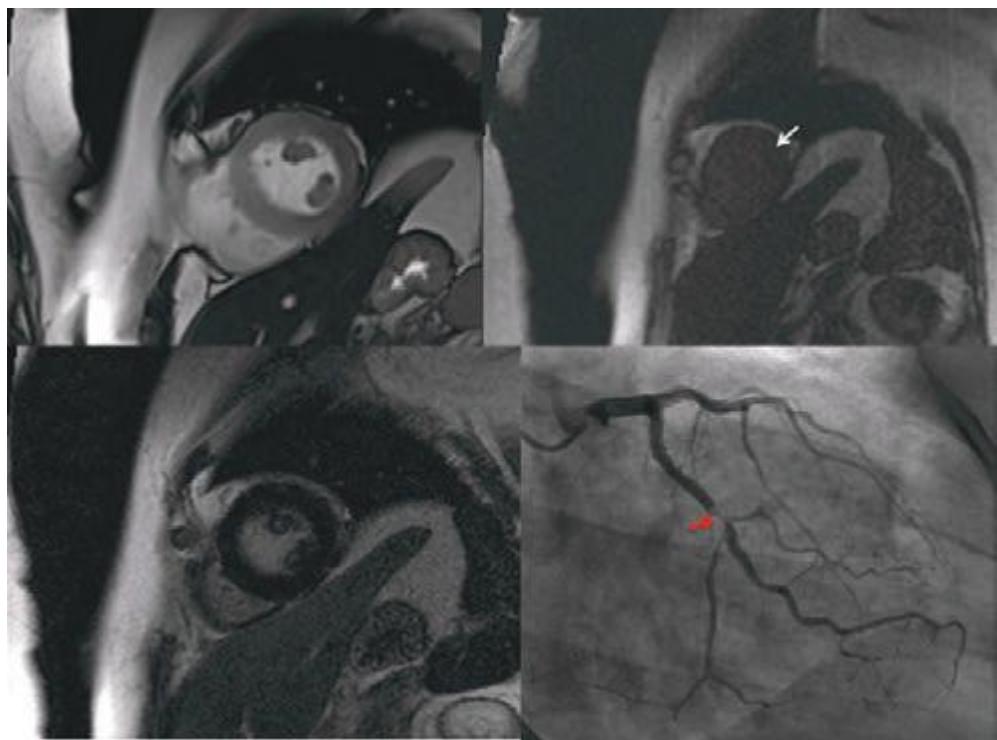


FIGURE 271e-6 Cardiac magnetic resonance (CMR) stress myocardial perfusion images in a 60-year-old patient with atypical chest pain. Cine movie short-axis image (left upper panel) shows normal left ventricle size and global and regional function at rest. During vasodilator stress, there is marked reduction of lateral wall perfusion (white arrow, right upper panel) as well as a mild defect in the septal wall. This region is confirmed to be viable by matching late gadolinium enhancement imaging (left lower panel), which demonstrated no evidence of infarction in the lateral wall. These findings are consistent with a severe coronary stenosis in the left circumflex artery. On angiography performed subsequently, there is a tight lesion in the left circumflex artery (red arrow, right lower panel). (See Videos 271e-5 and 271e-6.)

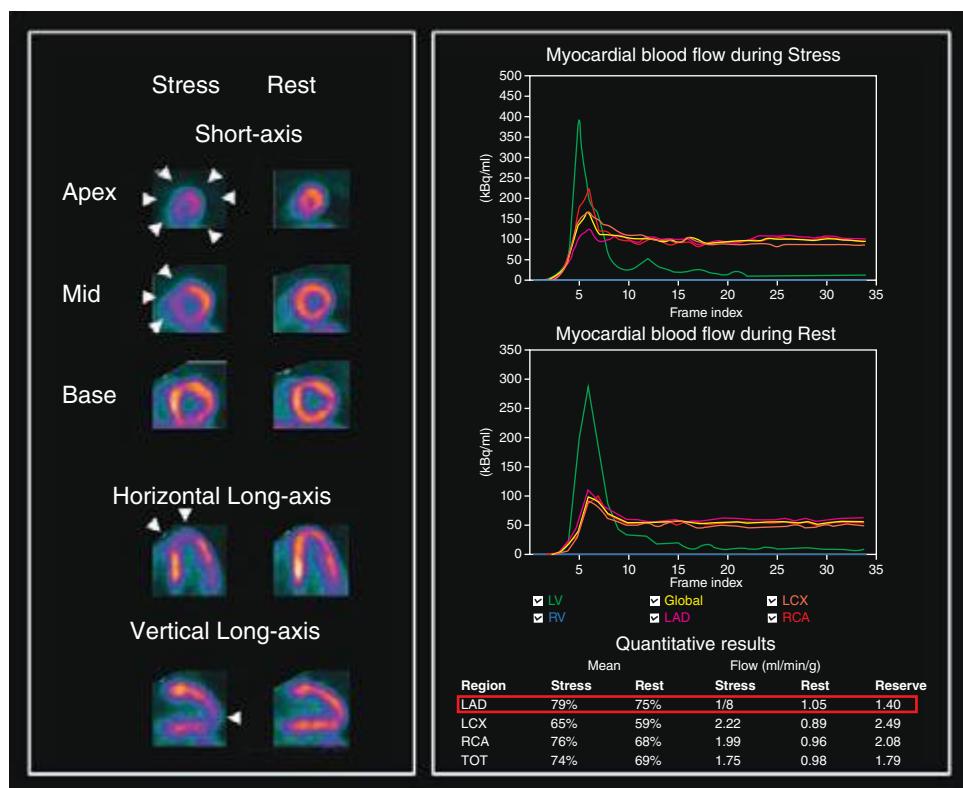


FIGURE 271e-7 Adenosine positron emission tomography (PET) myocardial perfusion ^{13}N -ammonia scan in a 60-year-old female with atypical chest pain. The stress images (left) show a large defect involving the apex, all apical segments, mid-inferior, mid-inferoseptum, and mid-anteroseptum (arrowheads), which is completely reversible at rest (right). This is consistent with a medium-sized area of stress-induced ischemia in the mid portion of the left anterior descending (LAD) coronary artery. The right panel illustrates the time-activity curves used for quantification of myocardial blood flow (in mL/min per g of tissue) at peak stress (upper panel) and at rest (lower panel). Coronary flow reserve is then calculated as the ratio of stress/rest myocardial blood flow. The coronary flow reserve is abnormal in the LAD territory, and normal in the left circumflex (LCX) and right coronary artery (RCA) territories (i.e., >2.0). TOT, total left ventricle.

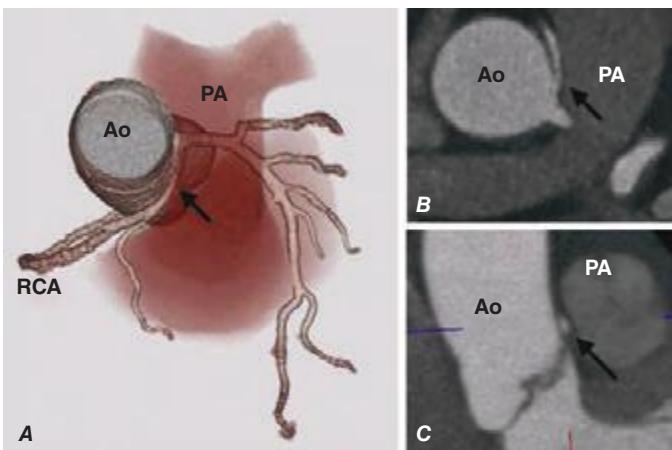


FIGURE 271e-8 Coronary computed tomography angiography (CTA) obtained on a 35-year-old female presenting to an outpatient clinic with a history of unexplained syncope and a 6-month complaint of intermittent, atypical chest pain occurring primarily during rest. Physical examination is normal. An exercise treadmill test is performed demonstrating good exercise capacity with no exertional chest pain or ischemic ECG changes. For persistent, unexplained symptoms, coronary CTA is obtained. **A.** Three-dimensional cardiac CT image reconstruction demonstrating anomalous right coronary artery (RCA) origin from the left coronary cusp with an acute angle takeoff (arrow) and an intraarterial course between the aorta (Ao) and main pulmonary artery (PA). **B, C.** Contrast-enhanced CTA in two-dimensional axial (**B**) and coronal oblique views (**C**) demonstrating proximal RCA intraarterial course between the Ao and main PA.

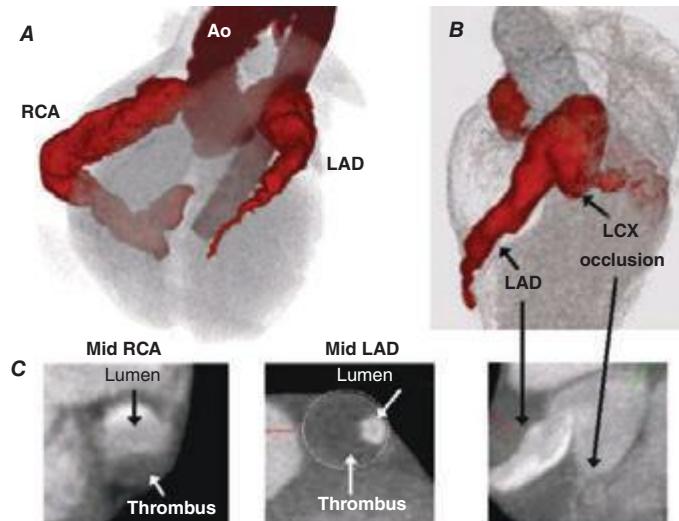


FIGURE 271e-9 Coronary computed tomography angiography (CTA) obtained from a 13-year-old boy with a history of Kawasaki disease who presented with limited exercise capacity and occasional, atypical chest pain. **A, B.** Three-dimensional cardiac CT image reconstruction demonstrating large three-vessel coronary artery diffuse aneurysms with proximal, nondominant left circumflex (LCX) artery occlusion. **C.** Two-dimensional contrast-enhanced coronary CTA demonstrating mid-RCA and mid-LAD thrombi that are nonocclusive layered and near circumferential thrombi, respectively, and proximal LCX occlusion. Ao, aorta; CT, computed tomography; LAD, left anterior descending; RCA, right coronary artery.

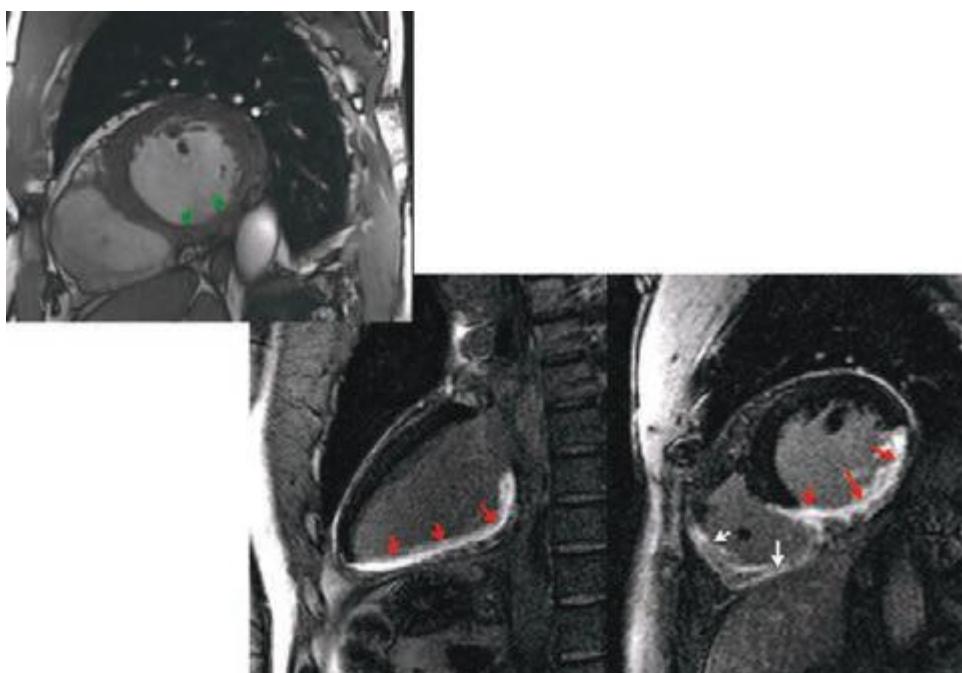


FIGURE 271e-10 A case of viability assessment in a patient with inferior myocardial infarction. The cine movie in the upper panel shows an area of inferior akinesis (green arrows). Magnetic resonance image demonstrates transmural contrast enhancement of the inferior wall (red arrows) and the right ventricle (white arrows), which is consistent with infarction. Imaging the heart 10–15 min after injection of gadolinium allows for the accumulation of gadolinium in infarcted tissue (red arrows), which identifies nonviable infarcted myocardium as bright. Viability assessment, as in this case, can provide guidance for any benefits of invasive coronary intervention. In this case, the inferior wall is nonviable. Apart from the inferior wall infarction (red arrows), there is extensive right ventricular infarction (white arrows). (See Video 271e-7.)

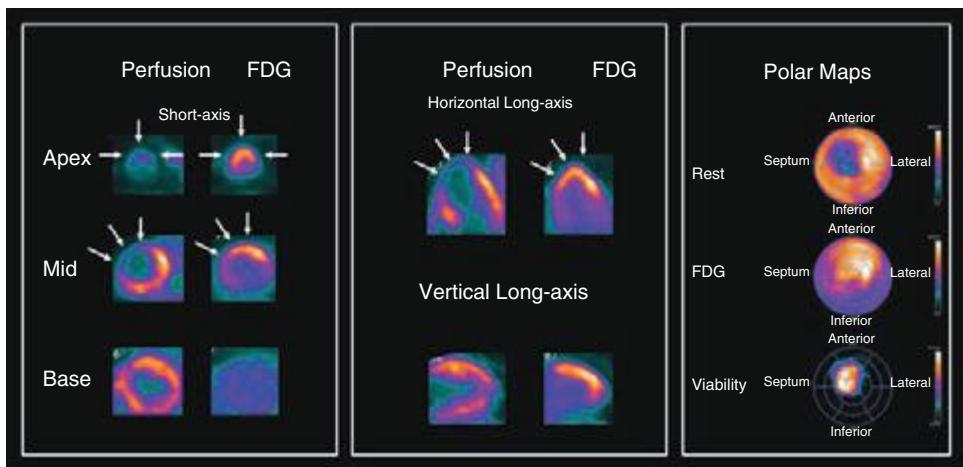


FIGURE 271e-11 Rest myocardial perfusion and metabolism positron emission tomography (PET) scan obtained with ^{13}N -ammonia (perfusion) and ^{18}F -fluorodeoxyglucose (FDG; glucose metabolism) in a 48-year-old male with a prior myocardial infarction. The rest perfusion images show a large defect involving the apex, apical segments, and mid-anteroseptal and anterior segments (arrowheads), which has associated increase in glucose uptake (perfusion-metabolic mismatch), reflecting viable but hibernating myocardium throughout the left anterior descending coronary territory.

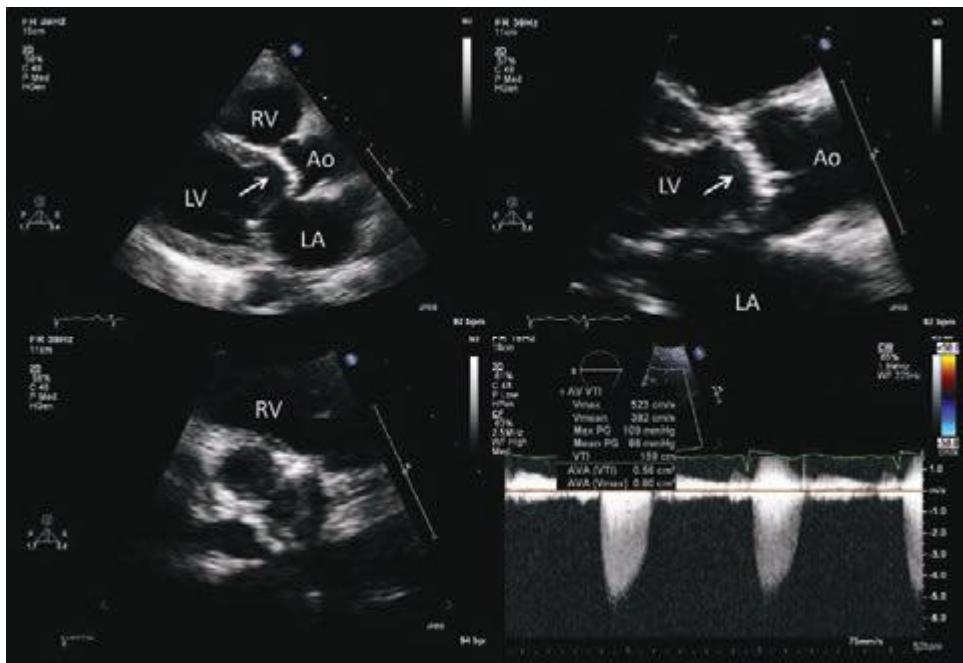


FIGURE 271e-12 A 70-year-old patient with known cardiac murmur and progressive shortness of breath and a recent episode of syncope. Echocardiography shows severe calcific aortic stenosis. A heavily calcified aortic valve (arrow) is shown in the parasternal long-axis views (top panels) and short-axis view (bottom left). Doppler interrogation shows a peak transaortic velocity of 5.2 m/s consistent with a peak instantaneous gradient of 109 mmHg and a mean gradient of 66 mmHg, and a corresponding aortic valve area of $<0.6\text{ cm}^2$ (lower right). Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. (See Videos 271e-8, 271e-9, and 271e-10.)



FIGURE 271e-13 A 66-year-old patient with multiple myeloma and progressive shortness of breath. Echocardiography shows features typical of cardiac amyloidosis, including thickened myocardium with a “sparkly” appearance and left atrial enlargement. Systolic function is mildly reduced, and diastolic function is severely reduced. LA, left atrium; LV, left ventricle; RV, right ventricle. (See Videos 271e-11 and 271e-12.)

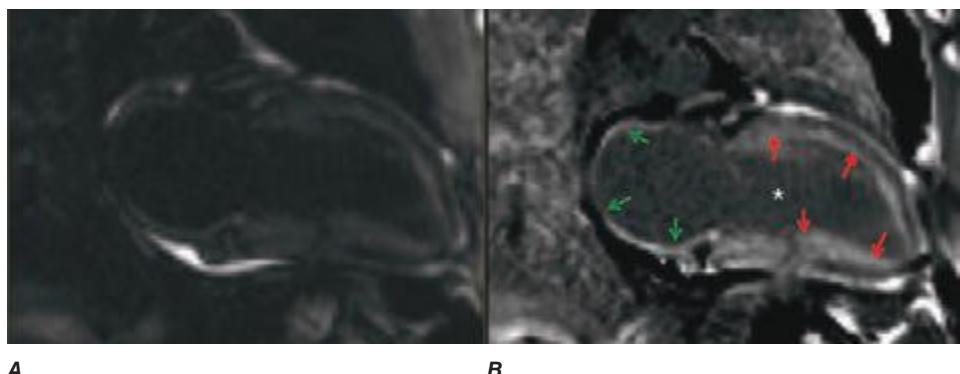


FIGURE 271e-14 Magnetic resonance image with contrast enhancement in magnitude (**A**), and phase-sensitive reconstructed images (**B**) 5–10 min after injection of gadolinium in a patient with transthyretin (TTR)-mediated amyloidosis. The phase-sensitive reconstruction (**B**) enhances the region of abnormal collection of gadolinium, making gadolinium enhancement in the ventricle (red arrows) and the atrium (green arrows) more prominent. Amyloidosis causes accumulation of abnormal interstitial proteins, which results in late gadolinium enhancement in a diffuse subendocardial pattern (red arrows). Blood pool signal is characteristically dark (asterisk) owing to sequestration of gadolinium into other organs.

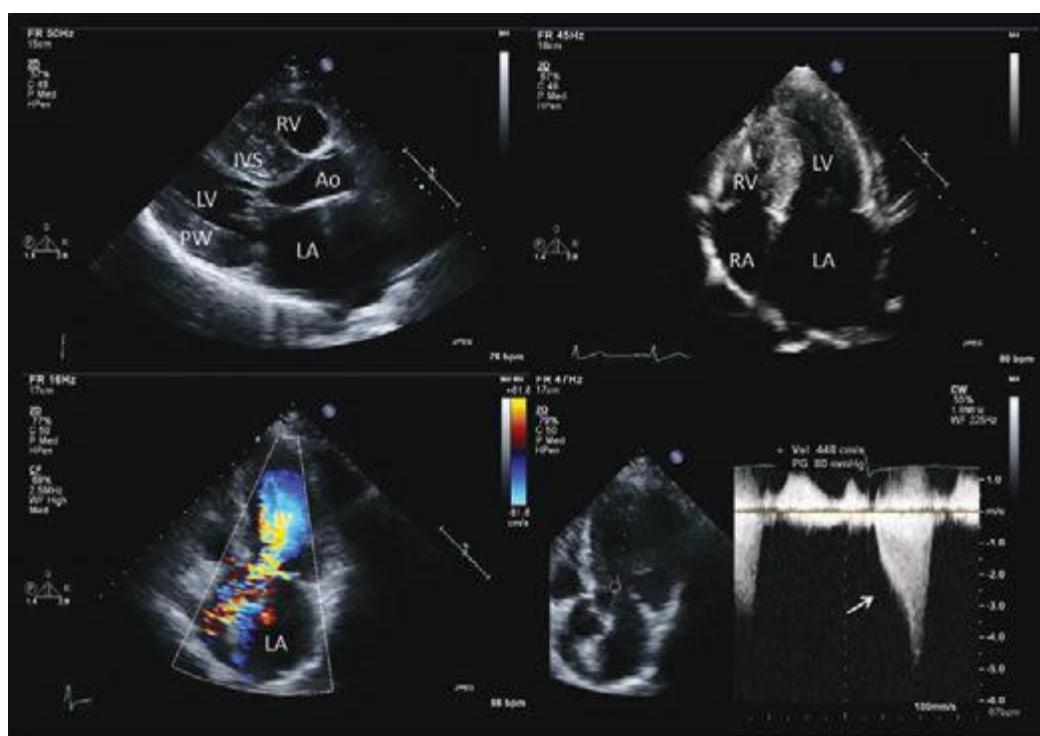


FIGURE 271e-15 A 34-year-old woman with known cardiac murmur and syncope with a family history of sudden cardiac death. Echocardiogram shows classic findings of hypertrophic cardiomyopathy, including marked left ventricular wall thickness, particularly in the interventricular septum, notable in the parasternal long-axis view (upper left) and apical view (upper right). Note reverse septal curvature in the apical view (upper left). There is substantial flow acceleration through the left ventricular outflow tract (lower left) with evidence of a late peaking systolic gradient (arrow, lower right) caused by outflow tract obstruction. Ao, aorta; IVS, interventricular septum; LA, left atrium; LV, left ventricle; PW, posterior wall; RV, right ventricle. (See Videos 271e-13, 271e-14, and 271e-15.)

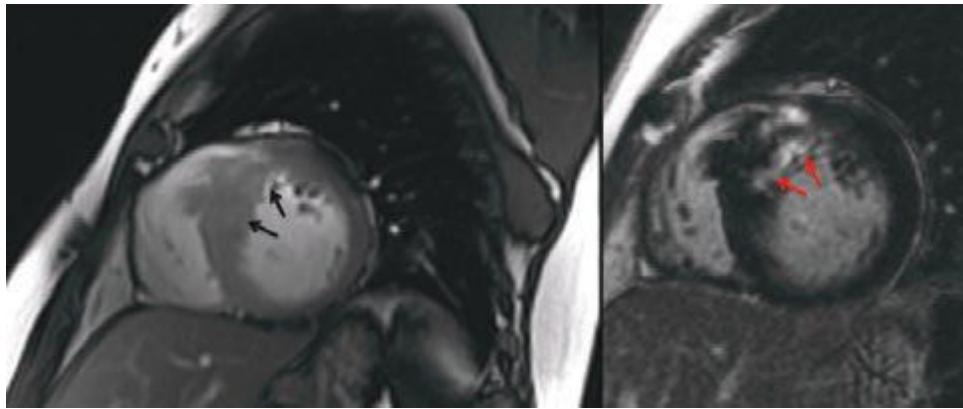


FIGURE 271e-16 Magnetic resonance image with contrast enhancement in a patient with hypertrophic cardiomyopathy. Note the marked thickened anteroseptal wall (black arrows, left panel) consistent with asymmetric septal hypertrophy. After contrast is injected, this region demonstrated heterogeneous foci of contrast enhancement (right panel, red arrows) consistent with myocardial fibrosis due to myofibril disarray in this condition. This typical enhancement pattern of hypertrophic cardiomyopathy is found in the areas of maximum wall thickness, typically at the anteroseptum as in this case. (See Video 271e-16.)

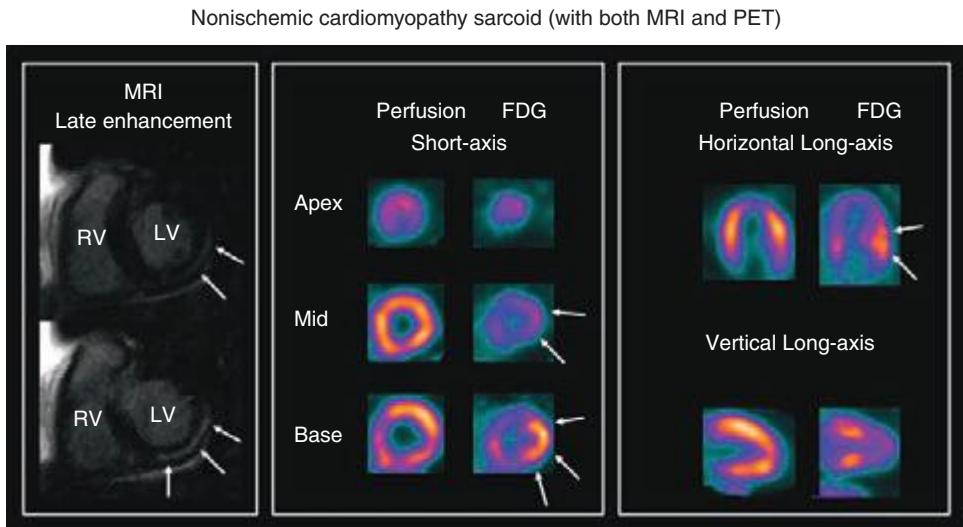


FIGURE 271e-17 Late gadolinium enhancement cardiac magnetic resonance imaging (MRI) (left panel) and rest myocardial perfusion and fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) studies (middle and right panels) in a 48-year-old male with a complete heart block. The MRI images demonstrate a linear area of mid-wall late gadolinium enhancement involving the inferior and inferolateral walls (arrows). The myocardial perfusion images were normal. However, the FDG images demonstrated a focal area of intense glucose uptake in the inferolateral wall, corresponding to the area of late enhancement on MRI. This is consistent with focal active sarcoidosis. LV, left ventricle; RV, right ventricle.

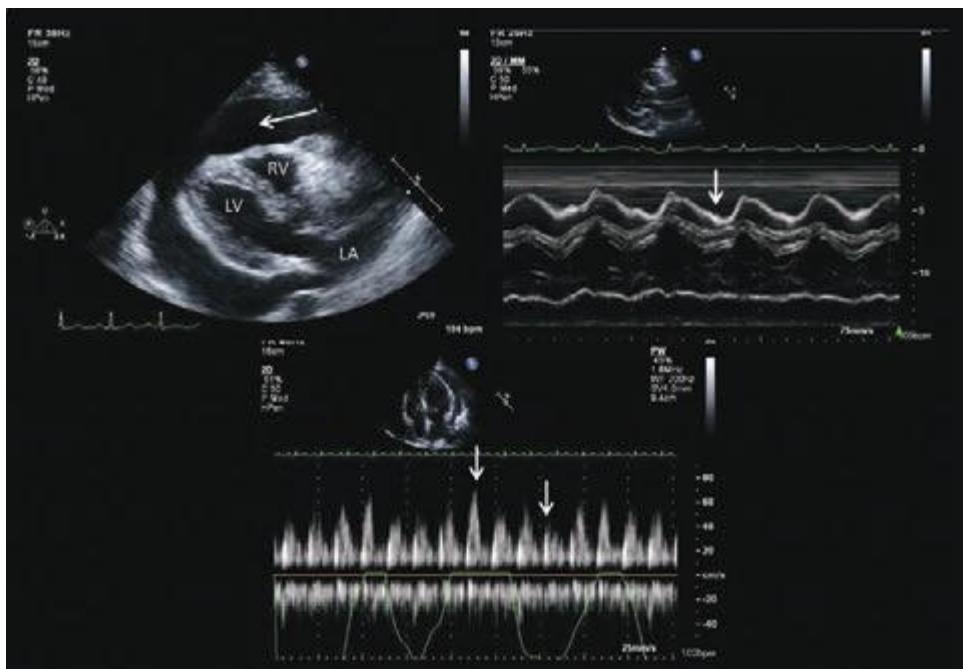


FIGURE 271e-18 A 46-year-old patient with malignant melanoma who presents with acute shortness of breath. Echocardiogram reveals a large pericardial effusion (arrow, upper left) with evidence of cardiac tamponade. M-mode echocardiography (upper right) shows evidence of collapse of the right ventricular free wall during diastole (arrow). Doppler echocardiography (lower panel) shows evidence of respiratory flow variation, consistent with a pulsus paradoxus. LA, left atrium; LV, left ventricle; RV, right ventricle. (See Video 271e-17.)

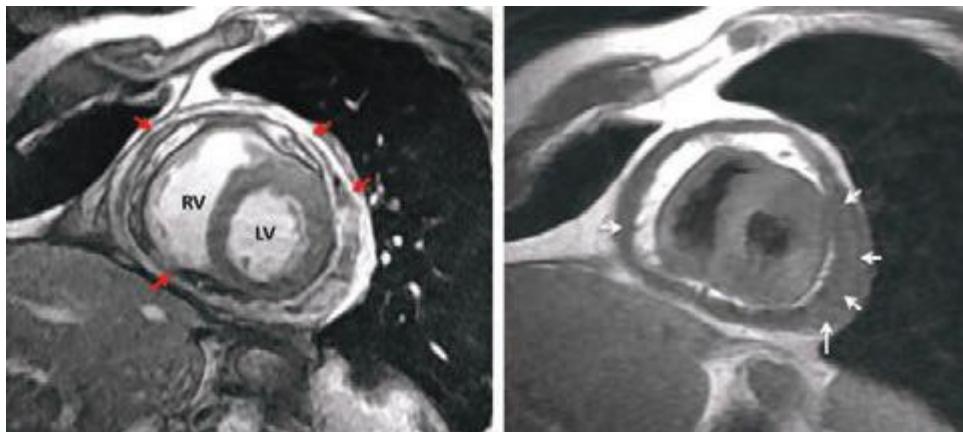


FIGURE 271e-19 Diffuse pericardial thickening (left; red arrows) and circumferential effusion (right; white arrows) associated with effusive-constrictive pericarditis. Effusive-constrictive pericarditis is a progressive condition that has varying degrees of hemodynamic consequences due initially to the collection of pericardial fluid and ultimately to pericardial constriction. It is typically suspected in cases where pericardiocentesis fails to normalize intracardiac pressures. In this example, pericardial fluid analysis resulted in a sterile exudate of leukocytes and erythrocytes. LV, left ventricle; RV, right ventricle.

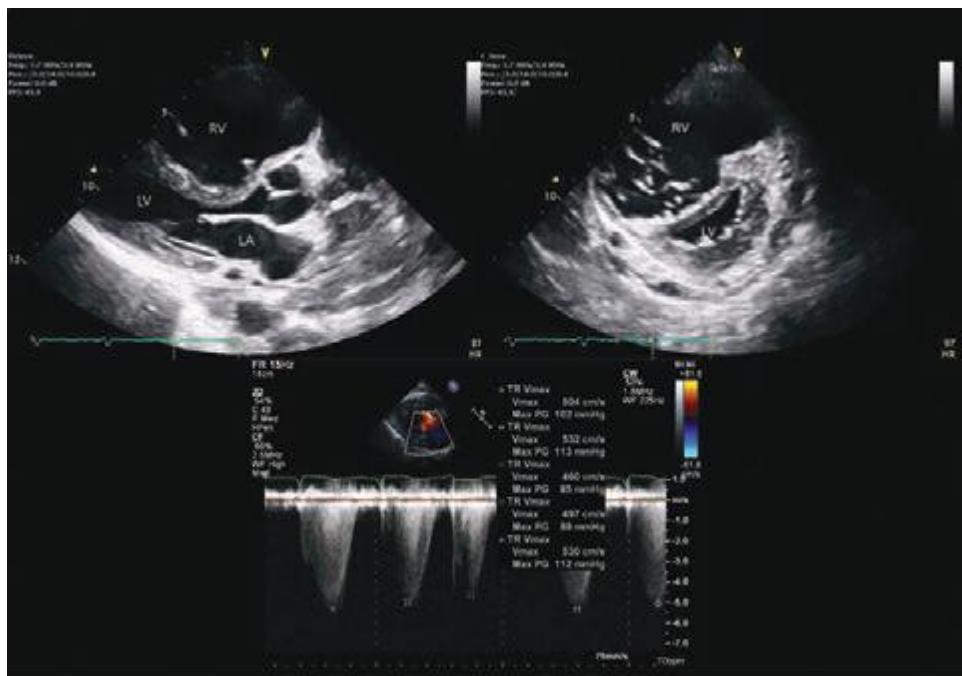


FIGURE 271e-20 A 48-year-old woman with severe idiopathic pulmonary hypertension. Echocardiography reveals evidence of marked right ventricular volume and pressure overload as evidenced by enlarged right ventricle (upper left and right), small left ventricle (upper left and upper right), and flattening of the interventricular septum (D-shaped septum) in systole and diastole (upper right). Tricuspid regurgitation velocity, which reflects the pressure gradient between the right ventricle and the left ventricle, is markedly elevated at 5 m/s, consistent with a right ventricle to right atrial pressure gradient of 100 mmHg, which is consistent with systemic right-sided pressures. LA, left atrium; LV, left ventricle; RV, right ventricle. (See Videos 271e-18 and 271e-19.)

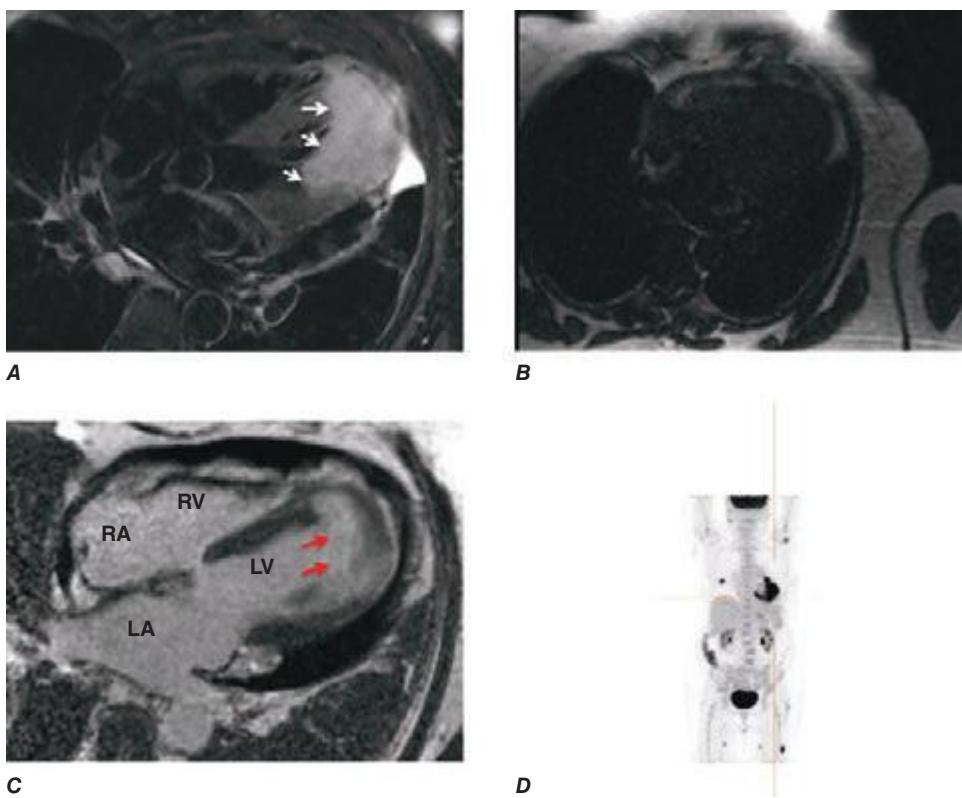


FIGURE 271e-21 Metastatic cardiac tumor diagnosed by cardiac magnetic resonance (MR) in a patient who presented with chest pain and inferior ST elevation. Left heart catheterization was normal. Cardiac MR demonstrates extensive myocardial edema (**A**, white arrows) with marked reduction in first perfusion (**B**) and accumulation of gadolinium within the cardiac mass 10–15 min after injection of gadolinium (**C**, red arrows). **D**. Positron emission tomography scan showed increased fluorodeoxyglucose uptake in a lung mass as well as in the cardiac mass, consistent with cardiac metastasis. Biopsy of the lung mass revealed adenosquamous carcinoma of the lung. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (See Videos 271e-20 and 271e-21.)

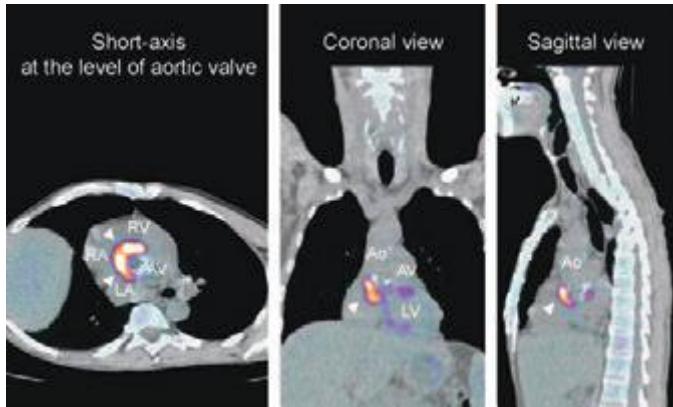


FIGURE 271e-22 Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in a 52-year-old male with a prior aortic valve replacement who presented with fever and was found to have *Haemophilus parainfluenzae* bacteremia. The multiplanar reformatted fused PET/CT images demonstrate intense FDG uptake surrounding the aortic valve prosthesis (arrowheads), compatible with a paravalvular abscess. The patient was found to have purulent fluid around the valve during surgery, and he underwent an aortic valve replacement. Ao, aorta; AV, aortic valve; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

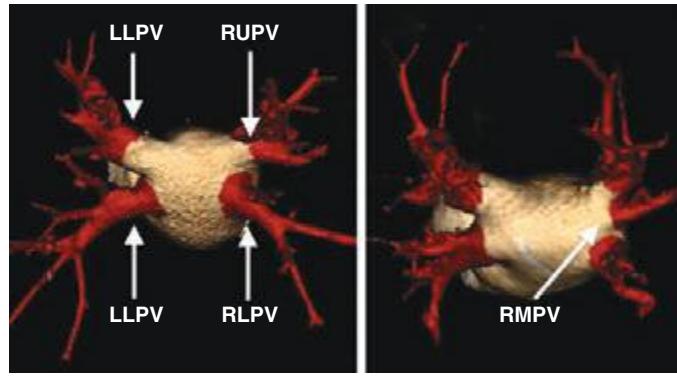


FIGURE 271e-23 Cardiac computed tomography (CT) pulmonary vein mapping in a 62-year-old male with symptomatic, paroxysmal atrial fibrillation referred for cardiac CT for pulmonary vein mapping prior to planned pulmonary vein isolation. Three-dimensional image reconstruction, demonstrating (A) normal pulmonary vein anatomy and (B) common variant with presence of separate right middle pulmonary vein (RMPV) ostium. LLPV, left lower pulmonary vein; LUPV, left upper pulmonary vein; RLPV, right lower pulmonary vein; RUPV, right upper pulmonary vein.

272 Diagnostic Cardiac Catheterization and Coronary Angiography

Jane A. Leopold, David P. Faxon

Diagnostic cardiac catheterization and coronary angiography are considered the gold standard in the assessment of the anatomy and physiology of the heart and its associated vasculature. In 1929, Forssmann demonstrated the feasibility of cardiac catheterization in humans when he passed a urological catheter from a vein in his arm to his right atrium and documented the catheter's position in the heart by x-ray. In the 1940s, Cournand and Richards applied this technique to patients with cardiovascular disease to evaluate cardiac function. These three physicians were awarded the Nobel Prize in 1956. In 1958, Sones inadvertently performed the first selective coronary angiography when a catheter in the left ventricle slipped back across the aortic valve, engaged the right coronary artery, and power-injected 40 mL of contrast down the vessel. The resulting angiogram provided superb anatomic detail of the artery, and the patient suffered no adverse effects. Sones went on to develop selective coronary catheters, which were modified further by Judkins, who developed preformed catheters and allowed coronary artery angiography to gain widespread use as a diagnostic tool. In the United States, cardiac catheterization is the second most common operative procedure, with more than one million procedures performed annually.

CARDIAC CATHETERIZATION

INDICATIONS, RISKS, AND PREPROCEDURE MANAGEMENT

Cardiac catheterization and coronary angiography are indicated to evaluate the extent and severity of cardiac disease in symptomatic patients and to determine if medical, surgical, or catheter-based interventions are warranted (**Table 272-1**). They are also used to exclude severe disease in symptomatic patients with equivocal findings on noninvasive studies and in patients with chest-pain syndromes of unclear etiology for whom a definitive diagnosis is necessary for management. Cardiac catheterization is not mandatory prior to cardiac surgery in some younger patients who have congenital or valvular heart disease that is well defined by noninvasive imaging and who do not have symptoms or risk factors that suggest concomitant coronary artery disease.

The risks associated with elective cardiac catheterization are relatively low, with a reported risk of 0.05% for myocardial infarction, 0.07% for stroke, and 0.08–0.14% for death. These risks increase substantially if the catheterization is performed emergently, during acute myocardial infarction or in hemodynamically unstable patients.

TABLE 272-1 INDICATIONS FOR CARDIAC CATHETERIZATION AND CORONARY ANGIOGRAPHY

Coronary Artery Disease
Asymptomatic or Symptomatic
High risk for adverse outcome based on noninvasive testing
Sudden cardiac death
Sustained (>30 s) monomorphic ventricular tachycardia
Nonsustained (<30 s) polymorphic ventricular tachycardia
Symptomatic
Canadian Cardiology Society Class II, III, or IV stable angina on medical therapy
Acute coronary syndrome (unstable angina and non-ST-segment elevation myocardial infarction)
Chest-pain syndrome of unclear etiology and equivocal findings on noninvasive tests
ST-Segment Elevation Acute Myocardial Infarction
Reperfusion with primary percutaneous coronary intervention
Persistent or recurrent ischemia
Pulmonary edema and/or reduced ejection fraction
Cardiogenic shock or hemodynamic instability
Risk stratification or positive stress test after acute myocardial infarction
Mechanical complications—mitral regurgitation, ventricular septal defect
Valvular Heart Disease
Suspected severe valve disease in symptomatic patients—dyspnea, angina, heart failure, syncope
Infective endocarditis with need for cardiac surgery
Asymptomatic patients with aortic regurgitation and cardiac enlargement or ↓ ejection fraction
Prior to cardiac surgery in patients with suspected coronary artery disease
Congestive Heart Failure
New onset with angina or suspected undiagnosed coronary artery disease
New-onset cardiomyopathy of uncertain cause or suspected to be due to coronary artery disease
Congenital Heart Disease
Prior to surgical correction, when symptoms or noninvasive testing suggests coronary disease
Suspicion for congenital coronary anomalies
Pericardial Disease
Symptomatic patients with suspected cardiac tamponade or constrictive pericarditis
Cardiac Transplantation
Preoperative and postsurgical evaluation
Other Conditions
Hypertrophic cardiomyopathy with angina
Diseases of the aorta when knowledge of coronary artery involvement is necessary for management

Additional risks of the procedure include tachy- or bradyarrhythmias that require countershock or pharmacologic therapy, acute renal failure leading to transient or permanent dialysis, vascular complications that necessitate surgical repair, and significant access-site bleeding. Of these risks, vascular access-site bleeding is the most common complication, occurring in 1.5–2.0% of patients, with major bleeding events associated with a worse short- and long-term outcome.

In patients who understand and accept the risks associated with cardiac catheterization, there are no absolute contraindications when the procedure is performed in anticipation of a life-saving intervention. Relative contraindications do, however, exist; these include decompensated congestive heart failure; acute renal failure; severe chronic renal insufficiency, unless dialysis is planned; bacteremia; acute stroke; active gastrointestinal bleeding; severe, uncorrected electrolyte abnormalities; a history of an anaphylactic/anaphylactoid reaction to iodinated contrast agents; and a history of allergy/bronchospasm to aspirin in patients for whom progression to a percutaneous coronary intervention is likely and aspirin desensitization has not been performed.

Contrast allergy and contrast-induced acute kidney injury merit further consideration, because these adverse events may occur in otherwise healthy individuals and prophylactic measures exist to reduce risk. Allergic reactions to contrast agents occur in <5% of cases, with severe anaphylactoid (clinically indistinguishable from anaphylaxis, but not mediated by an IgE mechanism) reactions occurring in 0.1%–0.2% of patients. Mild reactions manifest as nausea, vomiting, and urticaria, while severe anaphylactoid reactions lead to hypotensive shock, pulmonary edema, and cardiorespiratory arrest. Patients with a history of significant contrast allergy should be premedicated with corticosteroids and antihistamines (H_1 - and H_2 -blockers) and studies performed with nonionic, low-osmolar contrast agents that have a lower reported rate of allergic reactions.

Contrast-induced acute kidney injury, defined as an increase in creatinine >0.5 mg/dL or 25% above baseline that occurs 48–72 hours after contrast administration, occurs in ~2–7% of patients with rates of 20–30% reported in high-risk patients, including those with diabetes mellitus, congestive heart failure, chronic kidney disease, anemia, and older age. Dialysis is required in 0.3–0.7% of patients and is associated with a fivefold increase in in-hospital mortality. For all patients, adequate intravascular volume expansion with intravenous 0.9% saline (1.0–1.5 mL/kg per hour) for 3–12 hours before and continued 6–24 hours after the procedure limits the risk of contrast-induced acute kidney injury. Pretreatment with *N*-acetylcysteine (Mucomyst) has not reduced the risk of contrast-induced acute kidney injury consistently and, therefore, is no longer recommended routinely. Diabetic patients treated with metformin should stop the drug 48 hours prior to the procedure to limit the associated risk of lactic acidosis. Other strategies to decrease risk include the administration of sodium bicarbonate (3 mL/kg per hour) 1 hour before and 6 hours after the procedure; use of low- or iso-osmolar contrast agents; and limiting the volume of contrast to <100 mL per procedure.

Cardiac catheterization is performed after the patient has fasted for 6 hours and has received intravenous conscious sedation to remain awake but sedated during the procedure. All patients with suspected coronary artery disease are pretreated with 325 mg aspirin. In patients in whom the procedure is likely to progress to a percutaneous coronary intervention, an additional antiplatelet agent should be started: clopidogrel (600-mg loading dose and 75 mg daily) or prasugrel (60-mg loading dose and 10 mg daily), or ticagrelor (180-mg loading and 90 mg twice daily). Prasugrel should not be selected for individuals with prior stroke or transient ischemic attack. Warfarin is held starting 2–3 days prior to the catheterization to allow the international normalized ratio (INR) to fall to <1.7 and limit access-site bleeding complications. Cardiac catheterization is a sterile procedure, so antibiotic prophylaxis is not required.

TECHNIQUE

Cardiac catheterization and coronary angiography provide a detailed hemodynamic and anatomic assessment of the heart and coronary arteries. The selection of procedures is dependent on the patient's symptoms and clinical condition, with some direction provided by noninvasive studies.

Vascular Access Cardiac catheterization procedures are performed using a percutaneous technique to enter the femoral artery and vein as the preferred access sites for left and right heart catheterization, respectively. A flexible sheath is inserted into the vessel over a guidewire, allowing diagnostic catheters to be introduced into the vessel and advanced toward the heart using fluoroscopic guidance. The radial artery (or brachial artery) may also be used as an arterial access site in patients, particularly those with peripheral arterial disease that involves the abdominal aorta, iliac, or femoral vessels; severe iliac artery tortuosity; morbid obesity; or preference for early postprocedure ambulation. Use of radial-artery access is gaining popularity due to a lower rate of access-site bleeding complications. A normal Allen's test confirming dual blood supply to the hand from the radial and ulnar arteries is recommended prior to access at this site. The internal jugular or antecubital veins serve as alternate access sites to the

right heart when the patient has an inferior vena cava filter in place or requires prolonged hemodynamic monitoring.

Right Heart Catheterization This procedure measures pressures in the right heart. Right heart catheterization is no longer a routine part of diagnostic cardiac catheterization, but it is reasonable in patients with unexplained dyspnea, valvular heart disease, pericardial disease, right and/or left ventricular dysfunction, congenital heart disease, and suspected intracardiac shunts. Right heart catheterization uses a balloon-tipped flotation catheter that is advanced sequentially to the right atrium, right ventricle, pulmonary artery, and pulmonary wedge position (as a surrogate for left atrial pressure) using fluoroscopic guidance; in each cardiac chamber, pressure is measured and blood samples are obtained for oxygen saturation analysis to screen for intracardiac shunts.

Left Heart Catheterization This procedure measures pressures in the left heart as a determinant of left ventricular performance. With the aid of fluoroscopy, a catheter is guided to the ascending aorta and across the aortic valve into the left ventricle to provide a direct measure of left ventricular pressure. In patients with a tilting-disc prosthetic aortic valve, crossing the valve with a catheter is contraindicated, and the left heart may be accessed via a transseptal technique from the right atrium using a needle-tipped catheter to puncture the atrial septum at the fossa ovalis. Once the catheter crosses from the right to the left atrium, it can be advanced across the mitral valve to the left ventricle. This technique is also used for mitral valvuloplasty. Heparin is given for prolonged procedures to limit the risk of stroke from embolism of clots that may form on the catheter. For patients with heparin-induced thrombocytopenia, the direct thrombin inhibitors bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg per hour for the duration of the procedure) or argatroban (350 µg/kg bolus, 15 µg/kg per minute for the duration of the procedure) may be used.

HEMODYNAMICS

A comprehensive hemodynamic assessment involves obtaining pressure measurements in the right and left heart and peripheral arterial system and determining the cardiac output (Table 272-2). The shape

TABLE 272-2 NORMAL VALUES FOR HEMODYNAMIC MEASUREMENTS

Pressures (mmHg)	
Right atrium	
Mean	0–5
a wave	1–7
v wave	1–7
Right ventricle	
Peak systolic/end diastolic	17–32/1–7
Pulmonary artery	
Peak systolic/end diastolic	17–32/1–7
Mean	9–19
Pulmonary capillary wedge (mean)	4–12
Left atrium	
Mean	4–12
a wave	4–15
v wave	4–15
Left ventricle	
Peak systolic/end diastolic	90–130/5–12
Aorta	
Peak systolic/end diastolic	90–130/60–85
Mean	70–100
(Resistances [dyn·s]/cm⁵)	
Systemic vascular resistance	900–1400
Pulmonary vascular resistance	40–120
Oxygen Consumption Index ([L-min]/m²)	
Arteriovenous oxygen difference (vol %)	3.5–4.8
Cardiac index ([L-min]/m ²)	2.8–4.2

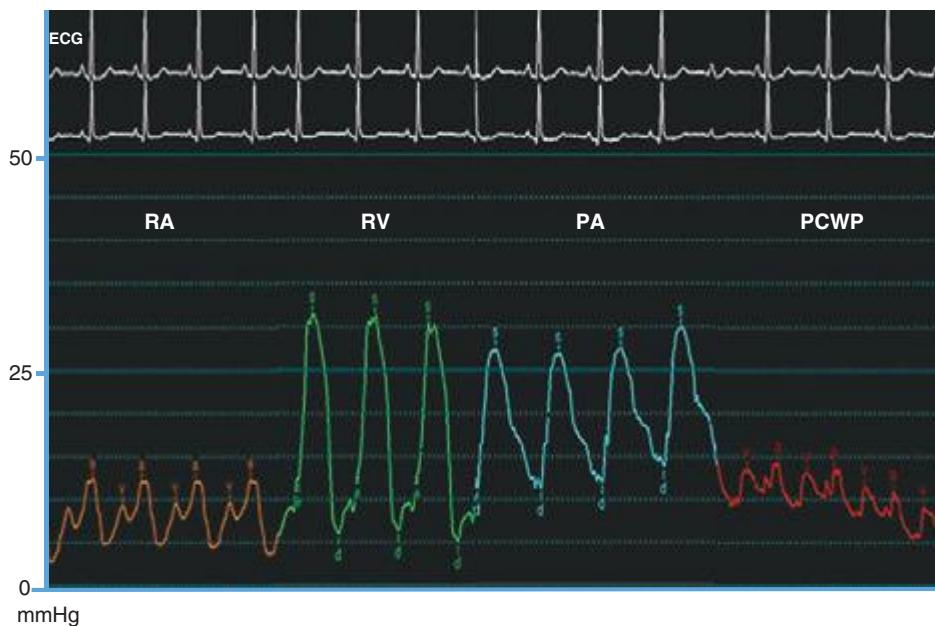


FIGURE 272-1 Normal hemodynamic waveforms recorded during right heart catheterization. Atrial pressure tracings have a characteristic “a” wave that reflects atrial contraction and a “v” wave that reflects pressure changes in the atrium during ventricular systole. Ventricular pressure tracings have a low-pressure diastolic filling period and a sharp rise in pressure that occurs during ventricular systole. d, diastole; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrium; RV, right ventricle; s, systole.

and magnitude of the pressure waveforms provide important diagnostic information; an example of normal pressure tracings is shown in Fig. 272-1. In the absence of valvular heart disease, the atria and ventricles are “one chamber” during diastole when the tricuspid and mitral valves are open while in systole, when the pulmonary and aortic valves are open, the ventricles and their respective outflow tracts are considered “one chamber.” These concepts form the basis by which hemodynamic measurements are used to assess valvular stenosis. When aortic stenosis is present, there is a systolic pressure gradient between the left ventricle and the aorta; when mitral stenosis is present, there is a diastolic pressure gradient between the pulmonary capillary wedge (left atrial) pressure and the left ventricle (Fig. 272-2). Hemodynamic measurements also discriminate between aortic stenosis and hypertrophic obstructive cardiomyopathy where the asymmetrically hypertrophied septum creates a dynamic intraventricular pressure gradient during ventricular systole. The magnitude of this obstruction is measured using an end-hole catheter positioned at the left ventricular apex that is pulled back while recording pressure; once the catheter has passed the septal obstruction and is positioned in the apex of the left ventricle, a gradient can be measured between the left ventricular apex and the aorta. Hypertrophic obstructive cardiomyopathy is confirmed by the Brockenbrough-Braunwald sign: following a premature ventricular contraction, there is an increase in the left ventricular–aorta pressure gradient with a simultaneous decrease in the aortic pulse pressure. These findings are absent in aortic stenosis.

Regurgitant valvular lesions increase volume (and pressure) in the “receiving” cardiac chamber. In severe mitral and tricuspid regurgitation, the increase in blood flow to the atria takes place during ventricular systole, leading to an increase in the v wave (two times greater than the mean pressure). Severe aortic regurgitation leads to a decrease in aortic diastolic pressure with a concomitant rise in left ventricular end-diastolic pressure, resulting in equalization of pressures between the two chambers at end-diastole.

Hemodynamic measurements are also used to differentiate between cardiac tamponade, constrictive pericarditis, and restrictive cardiomyopathy (Table 272-3). In cardiac tamponade, right atrial pressure is increased with a decreased or absent “y” descent, indicative of impaired right atrial emptying in diastole, and there is diastolic equalization of pressures in all cardiac chambers. In constrictive pericarditis, right atrial pressure is elevated with a prominent “y” descent, indicating rapid filling of the right ventricle during early diastole. A diastolic dip and plateau or “square root sign,” in the ventricular waveforms due to an abrupt halt in ventricular filling during diastole; right ventricular and pulmonary artery pressures are elevated; and discordant pressure changes in the right and left ventricles with inspiration (right ventricular systolic pressure increases while left ventricular systolic pressure decreases) are observed. The latter hemodynamic phenomenon is the most specific for constriction. Restrictive cardiomyopathy may be distinguished from constrictive pericarditis by a marked increase in right ventricular and pulmonary artery systolic pressures (usually >60 mmHg), a separation of the left and right ventricular diastolic pressures by

>5 mmHg (at baseline or with acute volume loading), and concordant changes in left and right ventricular diastolic filling pressures with inspiration (both increase).

Cardiac Output Cardiac output is measured by the Fick method or the thermodilution technique. Typically, the Fick method and thermodilution technique are both performed during cardiac catheterization, although the Fick method is considered more reliable in the presence of tricuspid regurgitation and in low-output states. The Fick method

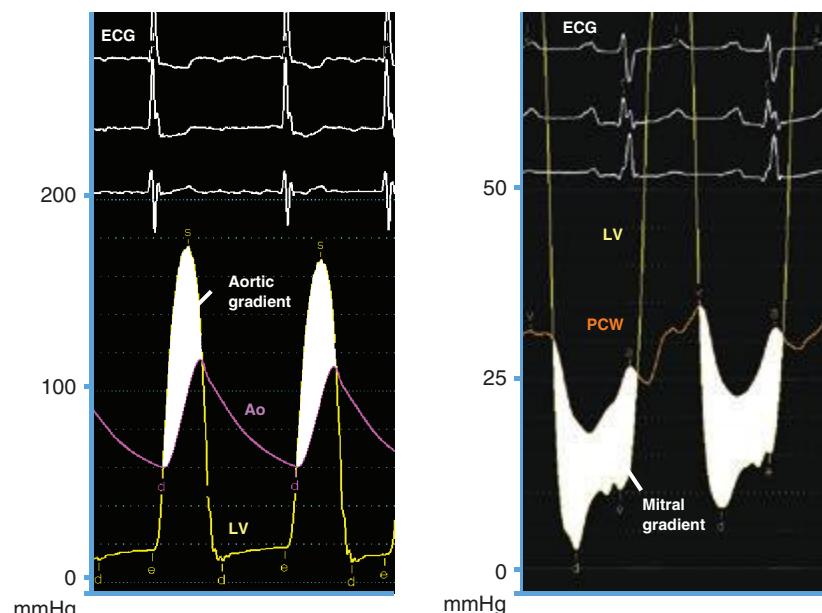


FIGURE 272-2 Severe aortic and mitral stenosis. Simultaneous recording of left ventricular (LV) and aortic (Ao) pressure tracings demonstrates a 62-mmHg mean systolic gradient (shaded area) that corresponds to an aortic valve area of 0.6 cm^2 (left). Simultaneous recording of LV and pulmonary capillary wedge (PCW) pressure tracings reveals a 14-mmHg mean diastolic gradient (shaded area) that is consistent with critical mitral stenosis (mitral valve area = 0.5 cm^2). d, diastole; e, end diastole; s, systole.

TABLE 272-3 HEMODYNAMIC FINDINGS IN TAMPOONADE, CONSTRICITIVE PERICARDITIS, AND RESTRICTIVE CARDIOMYOPATHY

	Cardiac Tamponade	Constrictive Pericarditis	Effusive-Constrictive Pericarditis	Restrictive Cardiomyopathy
Pericardial pressure	↑	↑	↑	Normal
Right atrium pressure	↑	↑	↑ (Fails to decrease by 50% or to <10 mmHg after pericardiocentesis)	↑
Right atrium pressure waveform	Prominent "x" descent Diminished or absent "y" descent	Prominent "x" descent Prominent "y" descent	Prominent "x" descent "y" descent less prominent than expected	Prominent "y" descent
Right ventricle systolic pressure	<50 mmHg	<50 mmHg	<50 mmHg	>60 mmHg
Right ventricle end-diastolic pressure		>1/3 right ventricular systolic pressure Equals left ventricular end-diastolic pressure within 5 mmHg	>1/3 right ventricular systolic pressure Equals left ventricular end-diastolic pressure within 5 mmHg	<1/3 right ventricular systolic pressure Less than left ventricular end-diastolic pressure by ≥5 mmHg
Right ventricle pressure waveform		Dip and plateau or "square root" sign	Dip and plateau or "square root" sign	Dip and plateau or "square root" sign
Right ventricle-left ventricle systolic pressure relationship with inspiration	Discordant	Discordant	Discordant	Concordant

uses oxygen as the indicator substance and is based on the principle that the amount of a substance taken up or released by an organ (oxygen consumption) is equal to the product of its blood flow (cardiac output) and the difference in the concentration of the substance in the arterial and venous circulation (arterial-venous oxygen difference). Thus, the formula for calculating the Fick cardiac output is:

$$\text{Cardiac output (L/min)} = (\text{oxygen consumption [mL/min]}) / (\text{arterial-venous oxygen difference [mL/L]})$$

Oxygen consumption is estimated as 125 mL oxygen/minute × body surface area, and the arterial-venous oxygen difference is determined by first calculating the oxygen carrying capacity of blood (hemoglobin [g/100 mL] × 1.36 [mL oxygen/g hemoglobin] × 10) and multiplying this product by the fractional oxygen saturation. The thermodilution method measures a substance that is injected into and adequately mixes with blood. In contemporary practice, thermodilution cardiac outputs are measured using temperature as the indicator. Measurements are made with a thermistor-tipped catheter that detects temperature deviations in the pulmonary artery after the injection of 10 mL of room-temperature normal saline into the right atrium.

Vascular Resistance Resistance across the systemic and pulmonary circulations is calculated by extrapolating from Ohm's law of electrical resistance and is equal to the mean pressure gradient divided by the mean flow (cardiac output). Therefore, systemic vascular resistance is ($(\text{mean aortic pressure} - \text{mean right atrial pressure}) / \text{cardiac output}$) multiplied by 80 to convert the resistance from Wood units to $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$. Similarly, the pulmonary vascular resistance is ($(\text{mean pulmonary artery} - \text{mean pulmonary capillary wedge pressure}) / \text{cardiac output}$) × 80. Pulmonary vascular resistance is lowered by oxygen, nitroprusside, calcium channel blockers, prostacyclin infusions, and inhaled nitric oxide; these therapies may be administered during catheterization to determine if increased pulmonary vascular resistance is fixed or reversible.

Valve Area Hemodynamic data may also be used to calculate the valve area using the Gorlin formula that equates the area to the flow across the valve divided by the pressure gradient between the cardiac chambers surrounding the valve. The formula for the assessment of valve area is: $\text{Area} = (\text{cardiac output [cm}^3/\text{min]}/[\text{systolic ejection period or diastolic filling period}][\text{heart rate}]) / 44.3 \times \text{square root of the pressure gradient}$, where $C = 1$ for aortic valve and 0.85 for the mitral valve. A valve area of <1.0 cm^2 and a mean gradient of greater than 40 mmHg indicate severe aortic stenosis, while a valve area of <1.5 cm^2 and a mean gradient >5–10 mmHg is consistent with

moderate-to-severe mitral stenosis; in symptomatic patients with a mitral valve area >1.5 cm^2 , a mean gradient >15 mmHg, pulmonary artery pressure >60 mmHg, or a pulmonary artery wedge pressure >25 mmHg after exercise is also considered significant and may warrant intervention. The modified Hakki formula has also been used to estimate aortic valve area. This formula calculates the valve area as the cardiac output (L/min) divided by the square root of the pressure gradient. Aortic valve area calculations based on the Gorlin formula are flow-dependent and, therefore, for patients with low cardiac outputs, it is imperative to determine if a decreased valve area actually reflects a fixed stenosis or is overestimated by a low cardiac output and stroke volume that is insufficient to open the valve leaflets fully. In these instances, cautious hemodynamic manipulation using dobutamine to increase the cardiac output and recalculation of the aortic valve area may be necessary.

Intracardiac Shunts In patients with congenital heart disease, detection, localization, and quantification of the intracardiac shunt should be evaluated. A shunt should be suspected when there is unexplained arterial desaturation or increased oxygen saturation of venous blood. A "step up" or increase in oxygen content indicates the presence of a left-to-right shunt while a "step down" indicates a right-to-left shunt. The shunt is localized by detecting a difference in oxygen saturation levels of 5–7% between adjacent cardiac chambers. The severity of the shunt is determined by the ratio of pulmonary blood flow (Q_p) to the systemic blood flow (Q_s), or $Q_p/Q_s = ([\text{systemic arterial oxygen content} - \text{mixed venous oxygen content}] / [\text{pulmonary vein oxygen content} - \text{pulmonary artery oxygen content}])$. For an atrial septal defect, a shunt ratio of 1.5 is considered significant and factored with other clinical variables to determine the need for intervention. When a congenital ventricular septal defect is present, a shunt ratio of ≥2.0 with evidence of left ventricular volume overload is a strong indication for surgical correction.

VENTRICULOGRAPHY AND AORTOGRAPHY

Ventriculography to assess left ventricular function may be performed during cardiac catheterization. A pigtail catheter is advanced retrograde across the aortic valve into the left ventricle and 30–45 mL of contrast is power-injected to visualize the left ventricular chamber during the cardiac cycle. The ventriculogram is usually performed in the right anterior oblique projection to examine wall motion and mitral valve function. Normal wall motion is observed as symmetric contraction of all segments; hypokinetic segments have decreased contraction, akinetic segments do not contract, and dyskinetic segments appear to bulge paradoxically during systole (Fig. 272-3). Ventriculography may also reveal a left ventricular aneurysm, pseudoaneurysm, or diverticulum and can be used to assess mitral valve prolapse and the severity of mitral regurgitation. The degree of mitral regurgitation is estimated

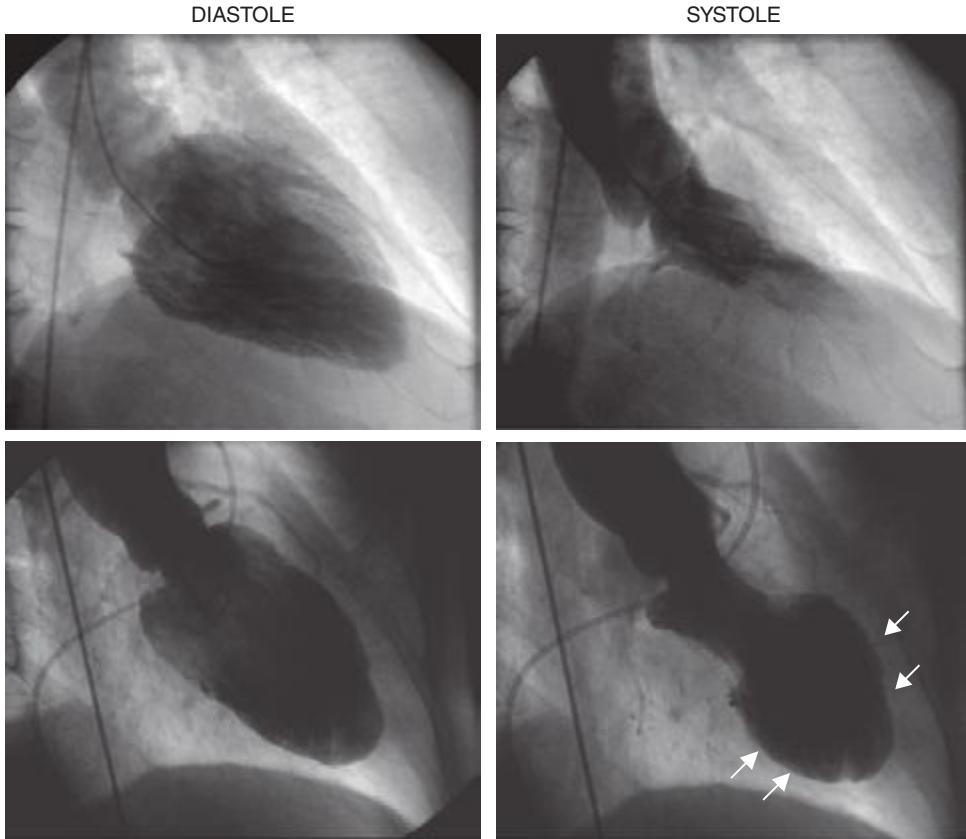


FIGURE 272-3 Left ventriculogram at end diastole (left) and end systole (right). In patients with normal left ventricular function, the ventriculogram reveals symmetric contraction of all walls (top). Patients with coronary artery disease may have wall motion abnormalities on ventriculography as seen in this 60-year-old male following a large anterior myocardial infarction. In systole, the anterior, apical, and inferior walls are akinetic (white arrows) (bottom).

by comparing the density of contrast opacification of the left atrium with that of the left ventricle. Minimal contrast reflux into the left atrium is considered 1+ mitral regurgitation, while contrast density in the left atrium that is greater than that in the left ventricle with reflux of contrast into the pulmonary veins within three beats defines 4+ mitral regurgitation. Ventriculography performed in the left anterior oblique projection can be used to identify a ventricular septal defect. Calculation of the ventricular volumes in systole and diastole allows calculation of stroke volume and cardiac output.

Aortography in the cardiac catheterization laboratory visualizes abnormalities of the ascending aorta, including aneurysmal dilation and involvement of the great vessels, as well as dissection with compression of the true lumen by an intimal flap that separates the true and false

lumina. Aortography can also be used to identify patent saphenous vein grafts that elude selective cannulation, identify shunts that involve the aorta such as a patent ductus arteriosus, and provide a qualitative assessment of aortic regurgitation using a 1+4+ scale similar to that used for mitral regurgitation.

CORONARY ANGIOGRAPHY

Selective coronary angiography is almost always performed during cardiac catheterization and is used to define the coronary anatomy and determine the extent of epicardial coronary artery and coronary artery bypass graft disease. Specially shaped coronary catheters are used to engage the left and right coronary ostia. Hand injection of radiopaque contrast agents creates a coronary “luminogram” that is recorded as radiographic images (cine angiography). Because the coronary arteries are three-dimensional objects that are in motion with the cardiac cycle, angiograms of the vessels using several different orthogonal projections are taken to best visualize the vessels without overlap or foreshortening.

The normal coronary anatomy is highly variable between individuals, but, in general, there are two coronary ostia and three major coronary vessels—the left anterior descending, the left circumflex, and the right coronary arteries with the left anterior descending and left circumflex

arteries arising from the left main coronary artery (Fig. 272-4). When the right coronary artery is the origin of the atrioventricular nodal branch, the posterior descending artery, and the posterior lateral vessels, the circulation is defined as right dominant; this is found in ~85% of individuals. When these branches arise from the left circumflex artery as occurs in ~5% of individuals, the circulation is defined as left dominant. The remaining ~10% of patients have a codominant circulation with vessels arising from both the right and left coronary circulation. In some patients, a ramus intermedius branch arises directly from the left main coronary artery; this finding is a normal variant. Coronary artery anomalies occur in 1–2% of patients, with separate ostia for the left anterior descending and left circumflex arteries being the most common (0.41%).

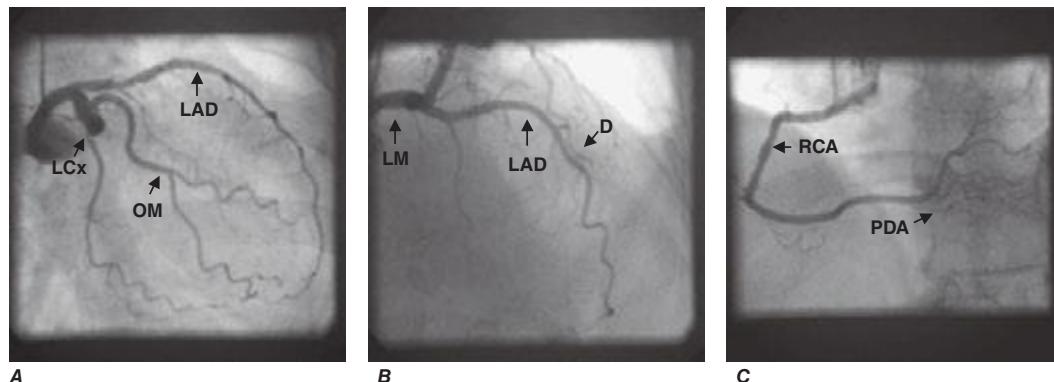


FIGURE 272-4 Normal coronary artery anatomy. **A.** Coronary angiogram showing the left circumflex (LCx) artery and its obtuse marginal (OM) branches. The left anterior descending artery (LAD) is also seen but may be foreshortened in this view. **B.** The LAD and its diagonal (D) branches are best seen in cranial views. In this angiogram, the left main (LM) coronary artery is also seen. **C.** The right coronary artery (RCA) gives off the posterior descending artery (PDA), so this is a right dominant circulation.

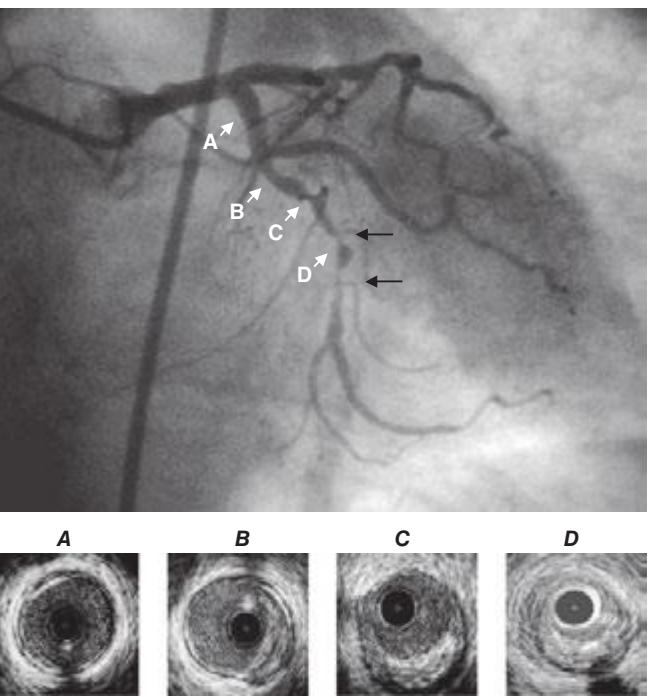


FIGURE 272-5 Coronary stenoses on cine angiogram and intravascular ultrasound. Significant stenoses in the coronary artery are seen as narrowings (black arrows) of the vessel. Intravascular ultrasound shows a normal segment of artery (**A**), areas with eccentric plaque (**B, C**), and near total obliteration of the lumen at the site of the significant stenosis (**D**). Note that the intravascular ultrasound catheter is present in the images as a black circle.

Coronary angiography visualizes coronary artery stenoses as luminal narrowings on the cine angiogram. The degree of narrowing is referred to as the percent stenosis and is determined visually by comparing the most severely diseased segment with a proximal or distal “normal segment”; a stenosis >50% is considered significant (Fig. 272-5). Online quantitative coronary angiography can provide a more accurate assessment of the percent stenosis and lessen the tendency to overestimate lesion severity visually. The presence of a myocardial bridge, which most commonly involves the left anterior descending artery, may be mistaken for a significant stenosis; this occurs when a portion of the vessel dips below the epicardial surface into the myocardium and is subject to compressive forces during ventricular systole. The key to differentiating a myocardial bridge from a fixed stenosis is that the “stenosed” part of the vessel returns to normal during diastole. Coronary calcification is also seen during angiography prior to the injection of contrast agents. Collateral blood vessels may be seen traversing from one vessel to the distal vasculature of a severely stenosed or totally occluded vessel. Thrombolysis in myocardial infarction (TIMI) flow grade, a measure of the relative duration of time that it takes for contrast to opacify the coronary artery fully, may provide an additional clue to the degree of lesion severity, and the presence of TIMI grade 1 (minimal filling) or 2 (delayed filling) suggests that a significant coronary artery stenosis is present.

INTRAVASCULAR ULTRASOUND, OPTICAL COHERENCE TOMOGRAPHY, AND FRACTIONAL FLOW RESERVE

During coronary angiography, intermediate stenoses (40–70%), indeterminate findings, or anatomic findings that are incongruous with the patient’s symptoms may require further interrogation. In these cases, intravascular ultrasound provides a more accurate anatomic assessment of the coronary artery and the degree of coronary atherosclerosis

(Fig. 272-5). Intravascular ultrasound (IVUS) is performed using a small flexible catheter with a 40-mHz transducer at its tip that is advanced into the coronary artery over a guidewire. Data from intravascular ultrasound studies may be used to image atherosclerotic plaque precisely, determine luminal cross-sectional area, and measure vessel size; it is also used during or following percutaneous coronary intervention to assess the stenosis and determine the adequacy of stent placement. Optical coherence tomography (OCT) is a catheter-based imaging technique that uses near-infrared light to generate images with better spatial resolution than IVUS; however, the depth of field is smaller. The advantage of OCT imaging over IVUS lies in its ability to image characteristics of the atherosclerotic plaque (lipid, fibrous cap) with high definition and to assess coronary stent placement, apposition, and patency (Fig. 272-6).

Measurement of the fractional flow reserve provides a functional assessment of the stenosis and is more accurate in predicting long-term clinical outcome than imaging techniques. The fractional flow reserve is the ratio of the pressure in the coronary artery distal to the stenosis divided by the pressure in the artery proximal to the stenosis at maximal vasodilation. Fractional flow reserve is measured using a coronary pressure-sensor guidewire at rest and at maximal hyperemia following the injection of adenosine. A fractional flow reserve of <0.80 indicates a hemodynamically significant stenosis that would benefit from intervention.

POSTPROCEDURE CARE

Once the procedure is completed, vascular access sheaths are removed. If the femoral approach is used, direct manual compression or vascular closure devices that immediately close the arteriotomy site with a staple/clip, collagen plug, or sutures are used to achieve hemostasis. These devices decrease the length of supine bed rest (from 6 hours to 2–4 hours) and improve patient satisfaction but have not been shown definitively to be superior to manual compression with respect to access-site complications. With radial-artery access, bed rest is needed for only 2 hours. When cardiac catheterization is performed as an elective outpatient procedure, the patient completes postprocedure bed rest in a monitored setting and is discharged home with instructions to liberalize fluids because contrast agents promote an osmotic diuresis, to avoid strenuous activity, and to observe the vascular access site for signs of complications. Overnight hospitalization may be required for high-risk patients with significant comorbidities, patients with complications occurring during the catheterization, or patients who have undergone a percutaneous coronary intervention. Hypotension early after the procedure may be due to inadequate fluid replacement or retroperitoneal bleeding from the access site. Patients who received >2 Gy of radiation during the procedure should be examined for signs of erythema. For patients who received higher doses (>5 Gy), clinical follow-up within 1 month to assess for skin injury is recommended.

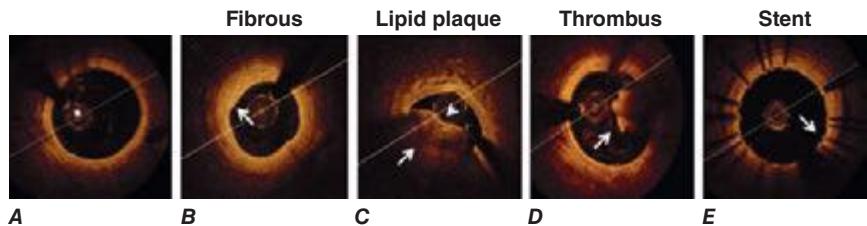


FIGURE 272-6 Optical coherence tomography imaging. **A.** The optical coherence tomography (OCT) catheter (*) in the lumen of a coronary artery with limited neointima formation. The intima is seen with high definition, but unlike intravascular ultrasound imaging, the vessel media and adventitia are not well visualized. **B.** A fibrous plaque (arrow) is characterized by a bright signal. **C.** A large, eccentric, lipid-rich plaque obscures part of the vessel lumen. Because lipid in the plaque absorbs light, the lipid-rich plaque appears as a dark area with irregular borders (arrow). The plaque is covered by a thin fibrous cap (arrowhead) typical of a vulnerable plaque. **D.** A thrombus (arrow) adherent to a ruptured plaque that is protruding into the vessel lumen. **E.** A coronary stent is well opposed to the vessel wall. The stent struts appear as short bright lines with dropout behind the struts (arrow).

SECTION 3 DISORDERS OF RHYTHM

273e Principles of Electrophysiology

David D. Spragg, Gordon F. Tomaselli

HISTORY AND INTRODUCTION

The field of cardiac electrophysiology was ushered in with the development of the electrocardiogram (ECG) by Einthoven at the turn of the twentieth century. Subsequent recording of cellular membrane currents demonstrated that the body surface ECG is the timed sum of the cellular action potentials in the atria and ventricles. In the late 1960s, the development of intracavitory recording, in particular, His bundle electrograms, marked the beginning of contemporary clinical electrophysiology. Adoption of radiofrequency technology to ablate cardiac tissue in the early 1990s heralded the birth of interventional cardiac electrophysiology.

The clinical problem of sudden death caused by ventricular arrhythmias, most commonly in the setting of coronary artery obstruction, was recognized as early as the late nineteenth century. The problem was vexing and led to the development of pharmacologic and non-pharmacologic therapies, including transthoracic defibrillators, cardiac massage, and, most recently, implantable defibrillators. Over time the limitations of antiarrhythmic drug therapy have been highlighted repeatedly in clinical trials, and now ablation and devices are first-line therapy for a number of cardiac arrhythmias.

In the last two decades, the genetic basis of a number of heritable arrhythmias has been elucidated, revealing important insights into the mechanisms not only of these rare arrhythmias but also of similar rhythm disturbances observed in more common forms of heart disease.

DESCRIPTIVE PHYSIOLOGY

The normal cardiac impulse is generated by pacemaker cells in the sinoatrial node situated at the junction of the right atrium and the superior vena cava (see Fig. 268-1). This impulse is transmitted slowly through nodal tissue to the anatomically complex atria, where it is conducted more rapidly to the atrioventricular node (AVN), inscribing the P wave of the ECG (see Fig. 268-2). There is a perceptible delay in conduction through the anatomically and functionally heterogeneous AVN. The time needed for activation of the atria and the AVN delay is represented as the PR interval of the ECG. The AVN is the only electrical connection between the atria and the ventricles in the normal heart. The electrical impulse emerges from the AVN and is transmitted to the His-Purkinje system, specifically the common bundle of His, then the left and right bundle branches, and then to the Purkinje network, facilitating activation of ventricular muscle. In normal circumstances, the ventricles are activated rapidly in a well-defined fashion that is determined by the course of the Purkinje network, and this inscribes the QRS complex (see Fig. 268-2). Recovery of electrical excitability occurs more slowly and is governed by the time of activation and duration of regional action potentials. The relative brevity of epicardial action potentials in the ventricle results in repolarization that occurs first on the epicardial surface and then proceeds to the endocardium, which inscribes a T wave normally of the same polarity as the QRS complex. The duration of ventricular activation and recovery is determined by the action potential duration and is represented on the body surface ECG by the QT interval (see Fig. 268-2).

Cardiac myocytes exhibit a characteristically long action potential (200–400 ms) compared with neurons and skeletal muscle cells (1–5 ms). The action potential profile is sculpted by the orchestrated activity of multiple distinctive time- and voltage-dependent ionic currents (Fig. 273e-1A). The currents are carried by transmembrane

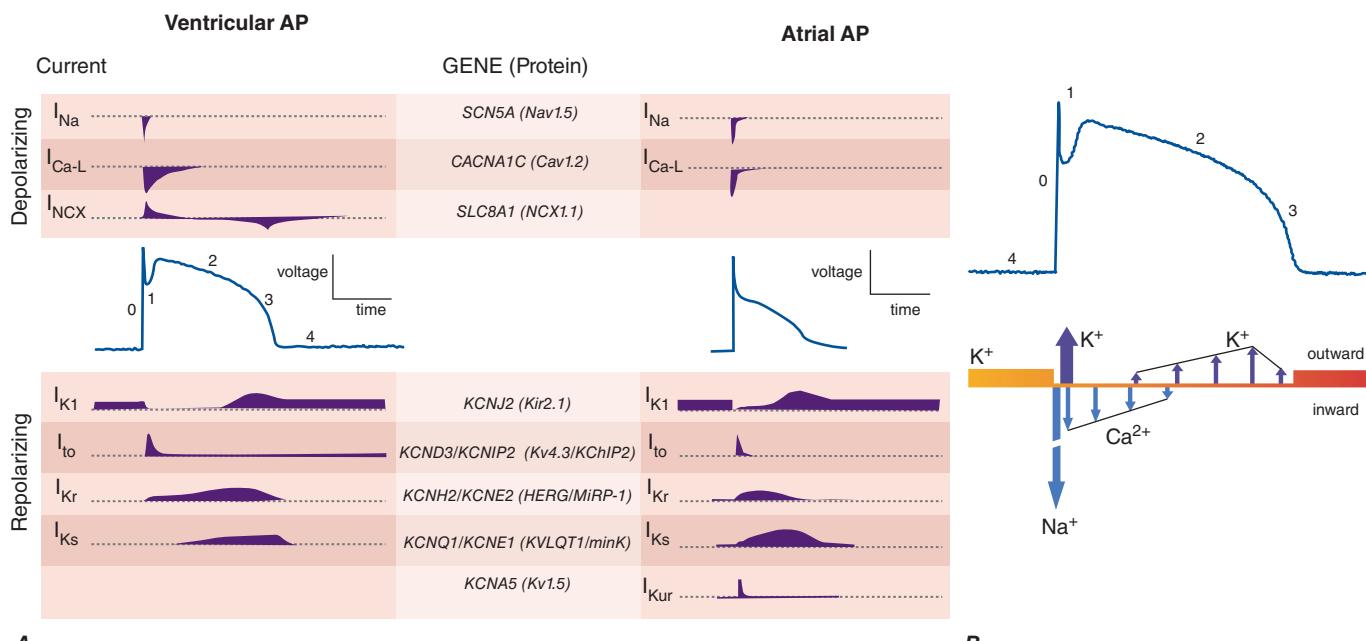


FIGURE 273e-1 **A.** Cellular atrial and ventricular action potentials. Phases 0–4 are the rapid upstroke, early repolarization, plateau, late repolarization, and diastole, respectively. The ionic currents and their respective genes are shown above and below the action potentials. The currents that underlie the action potentials vary in atrial and ventricular myocytes. **B.** A ventricular action potential with a schematic of the ionic currents flowing during the phases of the action potential. Potassium current (I_{K1}) is the principal current during phase 4 and determines the resting membrane potential of the myocyte. Sodium current generates the upstroke of the action potential (phase 0); activation of I_{Na} with inactivation of the Na current inscribes early repolarization (phase 1). The plateau (phase 2) is generated by a balance of repolarizing potassium currents and depolarizing calcium current. Inactivation of the calcium current with persistent activation of potassium currents (predominantly I_{Kr} and I_{Ks}) causes phase 3 repolarization.

proteins that passively conduct ions down their electrochemical gradients through selective pores (ion channels), actively transport ions against their electrochemical gradient (pumps, transporters), or electrogenically exchange ionic species (exchangers).

Action potentials in the heart are regionally distinct. The regional variability in cardiac action potentials is a result of differences in the number and types of ion channel proteins expressed by different cell types in the heart. Further, unique sets of ionic currents are active in pacemaking and muscle cells, and the relative contributions of these currents may vary in the same cell type in different regions of the heart (Fig. 273e-1A).

Ion channels are complex, multisubunit transmembrane glycoproteins that open and close in response to a number of biologic stimuli, including a change in membrane voltage, ligand binding (directly to the channel or to a G protein-coupled receptor), and mechanical deformation (Fig. 273e-2). Other ion motive exchangers and transporters contribute importantly to cellular excitability in the heart. Ion pumps establish and maintain the ionic gradients across the cell membrane that serve as the driving force for current flow through ion channels. Transporters or exchangers that do not move ions in an electrically neutral manner (e.g., the sodium-calcium exchanger transports three Na^+ for one Ca^{2+}) are termed *electrogenic* and contribute directly to the action potential profile.

The most abundant superfamily of ion channels expressed in the heart is voltage gated. Several structural themes are common to all voltage-dependent ion channels. First, the architecture is modular, consisting either of four homologous subunits (e.g., K channels) or of four internally homologous domains (e.g., Na and Ca channels). Second, the proteins fold around a central pore lined by amino acids that exhibit exquisite conservation within a given channel family of like selectivity (e.g., all Na channels have very similar P segments). Third, the general strategy for activation gating (opening and closing in response to changes in membrane voltage) is highly conserved: the fourth transmembrane segment (S4), studded with positively charged residues, lies within the membrane field and moves in response to depolarization, opening the channel. Fourth, most ion channel complexes include not only the pore-forming proteins (α subunits) but also auxiliary subunits (e.g., β subunits) that modify channel function (Fig. 273e-2).

Na and Ca channels are the primary carriers of depolarizing current in both the atria and the ventricles; inactivation of these currents and activation of repolarizing K currents hyperpolarize the heart cells, reestablishing the negative resting membrane potential (Fig. 273e-1B). The *plateau phase* is a time when little current is flowing, and relatively minor changes in depolarizing or repolarizing currents can have profound effects on the shape and duration of the action profile. Mutations in subunits of these channel proteins produce arrhythmic alterations in the action potentials that cause long and short QT syndrome, Brugada syndrome, idiopathic ventricular fibrillation, familial atrial fibrillation, and some forms of conduction system disease.

MECHANISMS OF CARDIAC ARRHYTHMIAS

Cardiac arrhythmias result from abnormalities of electrical impulse generation, conduction, or both. Bradyarrhythmias typically arise from disturbances in impulse formation at the level of the sinoatrial node or from disturbances in impulse propagation at any level, including exit block from the sinus node, conduction block in the AVN, and impaired conduction in the His-Purkinje system. Tachyarrhythmias can be classified according to mechanism, including enhanced automaticity (spontaneous depolarization of atrial, junctional, or ventricular pacemakers), triggered arrhythmias (initiated by afterdepolarizations occurring during or immediately after cardiac repolarization, during phase 3 or 4 of the action potential), or reentry (circus propagation of a depolarizing wavefront). A variety of mapping and pacing maneuvers typically performed during invasive electrophysiologic testing can often determine the underlying mechanism of a tachyarrhythmia (Table 273e-1).

Alterations in Impulse Initiation: Automaticity Spontaneous (phase 4) diastolic depolarization underlies the property of automaticity characteristic of pacemaking cells in the sinoatrial (SA) and atrioventricular

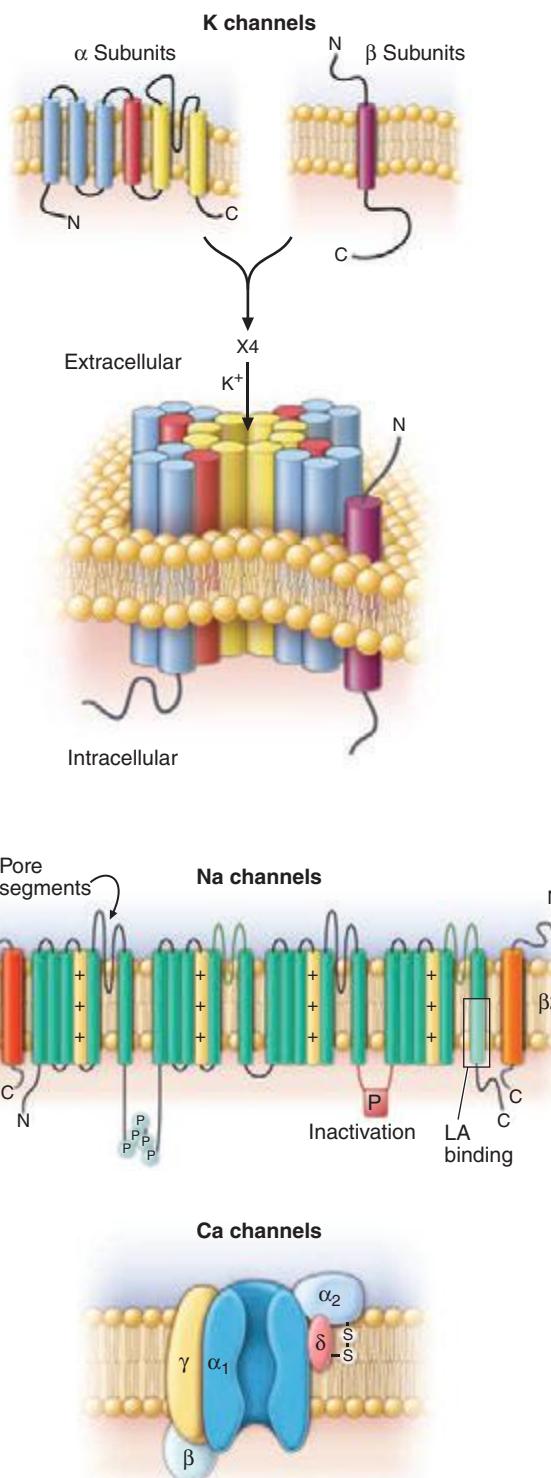


FIGURE 273e-2 Topology and subunit composition of the voltage-dependent ion channels. Potassium channels are formed by the tetramerization of α or pore-forming subunits and one or more β subunits; only single β subunits are shown for clarity. Sodium and calcium channels are composed of α subunits with four homologous domains and one or more ancillary subunits. In all channel types, the loop of protein between the fifth and sixth membrane-spanning repeat in each subunit or domain forms the ion-selective pore. In the case of the sodium channel, the channel is a target for phosphorylation, the linker between the third and fourth homologous domain is critical to inactivation, and the sixth membrane-spanning repeat in the fourth domain is important in local anesthetic antiarrhythmic drug binding. The Ca channel is a multisubunit protein complex with the α_1 subunit containing the pore and major drug binding domain.

TABLE 273e-1 ARRHYTHMIA MECHANISMS

Electrophysiologic Property	Molecular Components	Mechanism	Prototypic Arrhythmias
Cellular			
Impulse Initiation			
Automaticity	I_p , I_{Ca-L} , I_{Ca-T} , I_K , I_{K1}	Suppression/acceleration of phase 4	Sinus bradycardia, sinus tachycardia
Triggered automaticity	Calcium over-load, I_{Ti} I_{Ca-L} , I_K , I_{Na}	DADs EADs	Digitalis toxicity, reperfusion VT Torsades des pointes, congenital and acquired
Excitation			
	I_{Na}	Suppression of phase 0	Ischemic VF
	I_{K-ATP}	AP shortening, inexcitability	
Repolarization			
	I_{Ca-L}	Suppression	AV block
	I_{Na} , I_{Ca-L} , I_K , I_{K1} , Ca^{2+} homeostasis	AP prolongation, EADs, DADs	Polymorphic VT (HF, LVH)
	I_{Ca-L} , K channels, Ca^{2+} homeostasis	AP shortening	Atrial fibrillation
Multicellular			
Cellular Coupling	Connexins (Cx43), I_{Na} , I_{K-ATP}	Decreased coupling	Ischemic VT/VF
Tissue Structure	Extracellular matrix, collagen	Excitable gap and functional reentry	Monomorphic VT, atrial fibrillation

Abbreviations: AP, action potential; AV, atrioventricular; DADs, delayed afterdepolarizations; EADs, early afterdepolarizations; HF, heart failure; LVH, left ventricular hypertrophy; VF, ventricular fibrillation; VT, ventricular tachyarrhythmia.

(AV) nodes, His-Purkinje system, coronary sinus, and pulmonary veins. Phase 4 depolarization results from the concerted action of a number of ionic currents, including K^+ currents, Ca^{2+} currents, electrogenic Na, K-ATPase, the Na-Ca exchanger, and the so-called funny, or pacemaker, current (I_p); however, the relative importance of these currents remains controversial.

The rate of phase 4 depolarization and, therefore, the firing rates of pacemaker cells are dynamically regulated. Prominent among the factors that modulate phase 4 is autonomic nervous system tone. The negative chronotropic effect of activation of the parasympathetic nervous system is a result of the release of acetylcholine that binds to muscarinic receptors, releasing G protein $\beta\gamma$ subunits that activate a potassium current (I_{KACH}) in nodal and atrial cells. The resulting increase in K^+ conductance opposes membrane depolarization, slowing the rate of rise of phase 4 of the action potential. Conversely, augmentation of sympathetic nervous system tone increases myocardial catecholamine concentrations, which activate both α - and β -adrenergic receptors. The effect of β_1 -adrenergic stimulation predominates in pacemaking cells, augmenting both L-type Ca current (I_{Ca-L}) and I_p , thus increasing the slope of phase 4. Enhanced sympathetic nervous system activity can dramatically increase the rate of firing of SA nodal cells, producing sinus tachycardia with rates >200 beats/min. By contrast, the increased rate of firing of Purkinje cells is more limited, rarely producing ventricular tachyarrhythmias >120 beats/min.

Normal automaticity may be affected by a number of other factors associated with heart disease. Hypokalemia and ischemia may reduce the activity of Na, K-ATPase, thereby reducing the background repolarizing current and enhancing phase 4 diastolic depolarization. The end result would be an increase in the spontaneous firing rate of pacemaking cells. Modest increases in extracellular potassium may render the maximum diastolic potential more positive, thereby also increasing the firing rate of pacemaking cells. A more significant increase in $[K^+]_o$, however, renders the heart inexcitable by depolarizing the membrane potential.

Normal or enhanced automaticity of subsidiary latent pacemakers produces escape rhythms in the setting of failure of more dominant pacemakers. Suppression of a pacemaker cell by a faster rhythm leads to an increased intracellular Na^+ load ($[Na^+]_i$), and extrusion of Na^+ from the cell by Na, K-ATPase produces an increased background repolarizing current that slows phase 4 diastolic depolarization. At slower rates, $[Na^+]_i$ is decreased, as is the activity of the Na, K-ATPase, resulting in progressively more rapid diastolic depolarization and warm-up of the tachycardia rate. Overdrive suppression and warm-up are characteristic of, but may not be observed in, all automatic tachycardias. Abnormal conduction into tissue with enhanced automaticity (*entrance block*) may blunt or eliminate the phenomena of overdrive suppression and warm-up of automatic tissue.

Abnormal automaticity may produce atrial tachycardia, accelerated idioventricular rhythms, and ventricular tachycardia, particularly associated with ischemia and reperfusion. It has also been suggested that injury currents at the borders of ischemic myocardium may depolarize adjacent nonischemic tissue, predisposing to automatic ventricular tachycardia.

Afterdepolarizations and Triggered Automaticity Triggered automaticity or activity refers to impulse initiation that is dependent on afterdepolarizations (Fig. 273e-3). Afterdepolarizations are membrane voltage oscillations that occur during (early afterdepolarizations, EADs) or after (delayed afterdepolarizations, DADs) an action potential.

The cellular feature common to the induction of DADs is the presence of an increased Ca^{2+} load in the cytosol and sarcoplasmic reticulum. Digitalis glycoside toxicity, catecholamines, and ischemia all can enhance Ca^{2+} loading sufficiently to produce DADs. Accumulation of lysophospholipids in ischemic myocardium with consequent Na^+ and Ca^{2+} overload has been suggested as a mechanism for DADs and triggered automaticity. Cells from damaged areas or cells that survive a myocardial infarction may display spontaneous release of calcium from the sarcoplasmic reticulum, and this may generate “waves” of intracellular calcium elevation and arrhythmias.

EADs occur during the action potential and interrupt the orderly repolarization of the myocyte. Traditionally, EADs have been thought to arise from action potential prolongation and reactivation of depolarizing currents, but more recent experimental evidence suggests a previously unappreciated interrelationship between intracellular calcium loading and EADs. Cytosolic calcium may increase when action potentials are prolonged. This, in turn, appears to enhance L-type Ca current, further prolonging action potential duration as well as providing the inward current driving EADs. Intracellular calcium loading by action potential prolongation may also enhance the likelihood of DADs. The interrelationship among intracellular $[Ca^{2+}]$, EADs, and DADs may be one explanation for the susceptibility of hearts that are

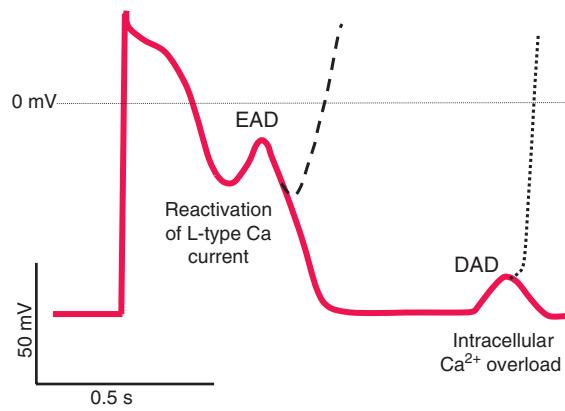


FIGURE 273e-3 Schematic action potentials with early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs). Afterdepolarizations are spontaneous depolarizations in cardiac myocytes. EADs occur before the end of the action potential (phases 2 and 3), interrupting repolarization. DADs occur during phase 4 of the action potential after completion of repolarization. The cellular mechanisms of EADs and DADs differ (see text).

calcium loaded (e.g., in ischemia or congestive heart failure) to develop arrhythmias, particularly on exposure to action potential–prolonging drugs.

EAD-triggered arrhythmias exhibit rate dependence. In general, the amplitude of an EAD is augmented at slow rates when action potentials are longer. Indeed, a fundamental condition that underlies the development of EADs is action potential and QT prolongation. Hypokalemia, hypomagnesemia, bradycardia, and, most commonly, drugs can predispose to the generation of EADs, invariably in the context of prolonging the action potential. Antiarrhythmics with class IA and III action (see below) produce action potential and QT prolongation intended to be therapeutic but frequently causing arrhythmias. Noncardiac drugs such as phenothiazines, nonsedating antihistamines, and some antibiotics can also prolong the action potential duration and predispose to EAD-mediated triggered arrhythmias. Decreased $[K^+]$ _o paradoxically may decrease membrane potassium currents (particularly the delayed rectifier current, I_{Kr}) in the ventricular myocyte, explaining why hypokalemia causes action potential prolongation and EADs. In fact, potassium infusions in patients with the congenital long QT syndrome (LQTS) and in those with drug-induced acquired QT prolongation shorten the QT interval.

EAD-mediated triggered activity probably underlies initiation of the characteristic polymorphic ventricular tachycardia, torsades des pointes, seen in patients with congenital and acquired forms of LQTS. Structural heart disease, such as cardiac hypertrophy and heart failure, may also delay ventricular repolarization (so-called electrical remodeling) and predispose to arrhythmias related to abnormalities of repolarization. The abnormalities of repolarization in hypertension and heart failure are often magnified by concomitant drug therapy or electrolyte disturbances.

Abnormal Impulse Conduction: Reentry The most common arrhythmia mechanism is reentry resulting from abnormal electrical impulse conduction and is defined as the circulation of an activation wave around an inexcitable obstacle. The requirements for reentry are two electrophysiologically dissimilar pathways for impulse propagation around an inexcitable region (Fig. 273e-4). Reentry can occur around a fixed anatomic structure (e.g., myocardial scar), with a stable pattern of cardiac depolarization moving in series over the anterograde and retrograde limbs of the circuit. This form of reentry, referred to as *anatomic reentry* or *excitable gap reentry* (see below), is initiated when a depolarizing wavefront encounters an area of unidirectional conduction block in the retrograde limb of the circuit. Conduction across the anterograde limb occurs with a delay that, if of sufficient duration, allows for recovery of conduction in the retrograde limb with reentry of the depolarization wave into the retrograde limb of

the circuit. Sustained reentry requires that the functional dimension of depolarized tissue or the tachycardia wavelength (λ = conduction velocity \times refractory period) fits within the total anatomic length of the circuit, referred to as the path length. When the path length of the circuit exceeds the λ of the tachycardia, the region between the head of the activation wave and the refractory tail is referred to as the excitable gap. Anatomically determined, excitable gap reentry can explain several clinically important tachycardias, such as AV reentry, atrial flutter, bundle branch reentry ventricular tachycardia, and ventricular tachycardia in scarred myocardium.

Reentrant arrhythmias may exist in the heart in the absence of an excitable gap and with a tachycardia wavelength nearly the same size as the path length. In this case, the wavefront propagates through partially refractory tissue without a fixed anatomic obstacle and no fully excitable gap; this is referred to as *leading circle reentry*, a form of functional reentry (reentry that depends on functional properties of the tissue). Unlike excitable gap reentry, there is no fixed anatomic circuit in leading circle reentry, and it may, therefore, not be possible to disrupt the tachycardia with pacing or destruction of a part of the circuit. Furthermore, the circuit in leading circle reentry tends to be less stable than that in excitable gap reentrant arrhythmias, with large variations in cycle length and a predilection to termination. There is strong evidence to suggest that less organized arrhythmias, such as atrial and ventricular fibrillation, are associated with more complex activation of the heart and are due to functional reentry.

Catheter-based and pharmacologic therapies for reentrant arrhythmias are designed to disrupt the anatomic circuit or alter the relationship between the wavelength and path length of the arrhythmia circuit, eliminating pathologic conduction. For example, antiarrhythmic drugs that prolong the action potential (Class III) are effective if they sufficiently prolong the λ such that it can no longer fit within the anatomic circuit. Catheter ablation is often undertaken with the goal of identifying and destroying a critical limb of the reentrant circuit (i.e., ablation of the cavoatrial isthmus in the treatment of typical, right atrial flutter). Due to the less defined pathways of myocardial activation seen in functional reentry, ablation of these rhythms tends to target initiating triggers (e.g., pulmonary vein potentials in catheter ablation of atrial fibrillation) rather than the anatomic circuit.

Structural heart disease is associated with changes in conduction and refractoriness that increase the risk of reentrant arrhythmias. Chronically ischemic myocardium exhibits a downregulation of the gap junction channel protein (connexin 43) that carries intercellular ionic current. The border zones of infarcted and failing ventricular myocardium exhibit not only functional alterations of ionic currents but also remodeling of tissue and altered distribution of gap junctions. The changes in gap junction channel expression and distribution, in combination with macroscopic tissue alterations, support a role for slowed conduction in reentrant arrhythmias that complicate chronic coronary artery disease (CAD). Aged human atrial myocardium exhibits altered conduction, manifest as highly fractionated atrial electrograms, producing an ideal substrate for the reentry that may underlie the very common development of atrial fibrillation in the elderly.

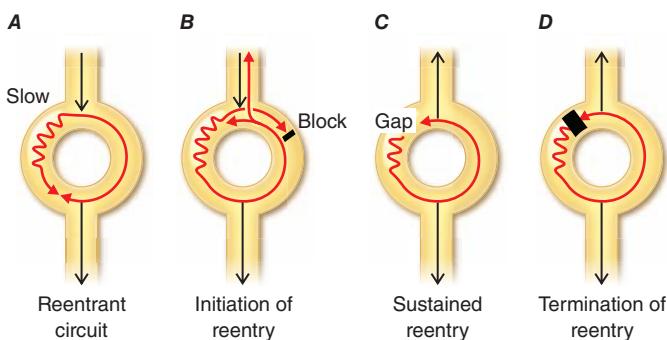


FIGURE 272-4 Schematic diagram of reentry. **A.** The circuit contains two limbs, one with slow conduction. **B.** A premature impulse blocks in the fast pathway and conducts over the slow pathway, allowing the fast pathway to recover so that the activation wave can reenter the fast pathway from the retrograde direction. **C.** During sustained reentry utilizing such a circuit, a gap (excitable gap) exists between the activating head of the wave and the recovering tail. **D.** One mechanism of termination of reentry occurs when the conduction and recovery characteristics of the circuit change and the activating head of the wave collides with the tail, extinguishing the tachycardia.

APPROACH TO THE PATIENT: Cardiac Arrhythmias

The evaluation of patients with suspected cardiac arrhythmias is highly individualized; however, two key features—the history and ECG—are pivotal in directing the diagnostic workup and therapy. Patients with cardiac arrhythmias exhibit a wide spectrum of clinical presentations that range from asymptomatic ECG abnormalities to survival from cardiac arrest. In general, the more severe the presenting symptoms are, the more aggressive the evaluation and treatment are. Loss of consciousness that is believed to be of cardiac origin typically mandates an exhaustive search for the etiology and often requires invasive, device-based therapy. The presence of structural heart disease and prior myocardial infarction dictates a change in the approach to the management of syncope or ventricular

arrhythmias. The presence of a family history of serious ventricular arrhythmias or premature sudden death will influence the evaluation of presumed heritable arrhythmias.

The physical examination is focused on determining whether there is cardiopulmonary disease that is associated with specific cardiac arrhythmias. The absence of significant cardiopulmonary disease often, but not always, suggests benignity of the rhythm disturbance. In contrast, palpitations, syncope, or near syncope in the setting of significant heart or lung disease have more ominous implications. In addition, the physical examination may reveal the presence of a persistent arrhythmia such as atrial fibrillation.

The judicious use of noninvasive diagnostic tests is an important element in the evaluation of patients with arrhythmias, and there is no test more important than the ECG, particularly if recorded at the time of symptoms. Uncommon but diagnostically important signatures of electrophysiologic disturbances may be unearthed on the resting ECG, such as delta waves in Wolff-Parkinson-White (WPW) syndrome, prolongation or shortening of the QT interval, right precordial ST-segment abnormalities in Brugada syndrome, and epsilon waves in arrhythmogenic right ventricular dysplasia. Variants of body surface ECG recording can provide important information about arrhythmia substrates and triggers. Holter monitoring and event recording, either continuous or intermittent, record the body surface ECG over longer periods, enhancing the possibility of observing the cardiac rhythm during symptoms. Holter monitoring is particularly useful in assessing daily symptoms thought to be attributable to arrhythmia or for quantifying a particular arrhythmia phenomenon (e.g., premature ventricular complex burden). Ambulatory event monitors are indicated when symptoms thought to be due to arrhythmia occur less frequently (i.e., several episodes per month), and, because the monitors are typically patient-activated, they are optimal for correlating symptoms with rhythm disturbances. Implantable long-term monitors permit prolonged telemetric monitoring both for diagnosis and to assess the efficacy of therapy. Implantable monitors are typically used for the evaluation of malignant symptoms that occur quite infrequently and that cannot be provoked at diagnostic electrophysiology study.

Exercise electrocardiography is important in determining the presence of myocardial demand ischemia; more recently, analysis of the morphology of the QT interval with exercise has been used to assess the risk of serious ventricular arrhythmias. The exercise ECG may be particularly useful in patients with symptoms that occur during activity. Cardiac imaging plays an important role in the detection and characterization of myocardial structural abnormalities that may render the heart more susceptible to arrhythmia. Ventricular tachyarrhythmias, for instance, occur more frequently in patients with ventricular systolic dysfunction and chamber dilation, in hypertrophic cardiomyopathy, and in the setting of infiltrative diseases such as sarcoidosis. Supraventricular arrhythmias may be associated with particular congenital conditions, including AV reentry in the setting of Ebstein's anomaly. Echocardiography is a frequently employed imaging technique to screen for disorders of cardiac structure and function. Increasingly, magnetic resonance imaging of the myocardium is being used to screen for scar burden, fibrofatty infiltration of the myocardium as seen in arrhythmogenic right ventricular cardiomyopathy, and other structural changes that affect arrhythmia susceptibility.

Head-up tilt (HUT) testing is useful in the evaluation of patients with syncope in whom there is a suspicion that exaggerated vagal tone or vasodepression may play a causal role. The physiologic response to HUT is incompletely understood; however, redistribution of blood volume and increased ventricular contractility occur consistently. Exaggerated activation of a central reflex in response to HUT produces a stereotypic response of an initial increase in heart rate, then a drop in blood pressure followed by a reduction in heart rate characteristic of neurally mediated hypotension. Other responses to HUT may be observed in patients with orthostatic

hypotension and autonomic insufficiency. HUT is used most often in patients with recurrent syncope, although it may be useful in patients with single syncopal episodes with associated injury, particularly in the absence of structural heart disease. In patients with structural heart disease, HUT may be indicated in those with syncope, in whom other causes (e.g., asystole, ventricular tachyarrhythmias) have been excluded. HUT has been suggested as a useful tool in the diagnosis of and therapy for recurrent idiopathic vertigo, chronic fatigue syndrome, recurrent transient ischemic attacks, and repeated falls of unknown etiology in the elderly. Importantly, HUT is relatively contraindicated in the presence of severe CAD with proximal coronary stenoses, known severe cerebrovascular disease, severe mitral stenosis, and obstruction to left ventricular outflow (e.g., aortic stenosis).

Electrophysiologic testing is central to the understanding and treatment of many cardiac arrhythmias. Indeed, most frequently, electrophysiologic testing is interventional, providing both diagnosis and therapy. The indications for electrophysiologic testing fall into several categories: to define the mechanism of an arrhythmia; to deliver catheter-based ablative treatment; and to determine the etiology of symptoms that may be caused by an arrhythmia (e.g., syncope, palpitations). The components of the electrophysiologic test are baseline measurements of conduction under resting and stressed (rate or pharmacologic) conditions and maneuvers, both pacing and pharmacologic, to induce arrhythmias. A number of sophisticated electrical mapping and catheter-guidance techniques have been developed to facilitate catheter-based therapeutics in the electrophysiology laboratory.

TREATMENT CARDIAC ARRHYTHMIAS

ANTIARRHYTHMIC DRUG THERAPY

The interaction of antiarrhythmic drugs with cardiac tissues and the resulting electrophysiologic changes are complex. An incomplete understanding of the effects of these drugs has produced serious missteps that have had adverse effects on patient outcomes and the development of newer pharmacologic agents. Currently, antiarrhythmic drugs have been relegated to an ancillary role in the treatment of most cardiac arrhythmias.

There are several explanations for the complexity of antiarrhythmic drug action: the structural similarity of target ion channels; regional differences in the levels of expression of channels and transporters, which change with disease; time and voltage dependence of drug action; and the effect of these drugs on targets other than ion channels. Because of the limitations of any scheme to classify antiarrhythmic agents, a shorthand that is useful in describing the major mechanisms of action is of some utility. Such a classification scheme was proposed in 1970 by Vaughan-Williams and later modified by Singh and Harrison. The classes of antiarrhythmic action are class I, local anesthetic effect due to blockade of Na^+ current; class II, interference with the action of catecholamines at the β -adrenergic receptor; class III, delay of repolarization due to inhibition of K^+ current or activation of depolarizing current; and class IV, interference with calcium conductance (Table 273e-2). Class I antiarrhythmics have been further subdivided based on the kinetics and potency of Na^+ channel binding; class Ia agents (quinidine, procainamide) are those with moderate potency and intermediate kinetics; class Ib agents (lidocaine, mexiletine) are those with low potency and rapid kinetics; and class Ic drugs (flecainide, propafenone) are those with high potency and the slowest kinetics. The limitations of the Vaughan-Williams classification scheme include multiple actions of most drugs, overwhelming consideration of antagonism as a mechanism of action, and the fact that several agents have none of the four classes of action in the scheme.

CATHETER ABLATION

The use of catheter ablation is based on the principle that there is a critical anatomic region of impulse generation or propagation that

TABLE 273e-2 ANTIARRHYTHMIC DRUG ACTIONS

Drug	Class Actions				Miscellaneous Action
	I	II	III	IV	
Quinidine	++		++		α -Adrenergic blockade
Procainamide	++		++		Ganglionic blockade
Flecainide	+++		+		
Propafenone	++	+			
Sotalol		++	+++		
Dofetilide			+++		
Amiodarone	++	++	+++	+	α -Adrenergic blockade
Ibutilide			+++		Na^+ channel activator

is required for the initiation and maintenance of cardiac arrhythmias. Destruction of such a critical region results in the elimination of the arrhythmia. The use of radiofrequency (RF) energy in clinical medicine is nearly a century old. The first catheter ablation using a

DC energy source was performed in the early 1980s by Scheinman and colleagues. By the early 1990s, RF had been adapted for use in catheter-based ablation in the heart (**Fig. 273e-5**).

The RF band (300–30,000 kHz) is used to generate energy for several biomedical applications, including coagulation and cauterization of tissues. Energy of this frequency will not stimulate skeletal muscle or the heart and heats tissue by a resistive mechanism, with the intensity of heating and tissue destruction being proportional to the delivered power. Alternative, less frequently used energy sources for catheter ablation of cardiac arrhythmias include microwaves (915 MHz or 2450 MHz), lasers, ultrasound, and freezing (cryoablation). Of these alternative ablation techniques, cryoablation is being used clinically with the most frequency, especially ablation in the region of the AVN. At temperatures just below 32°C, membrane ion transport is disrupted, producing depolarization of cells, decreased action potential amplitude and duration, and slowed conduction velocity (resulting in local conduction block)—all of which are reversible if the tissue is rewarmed in a timely fashion.

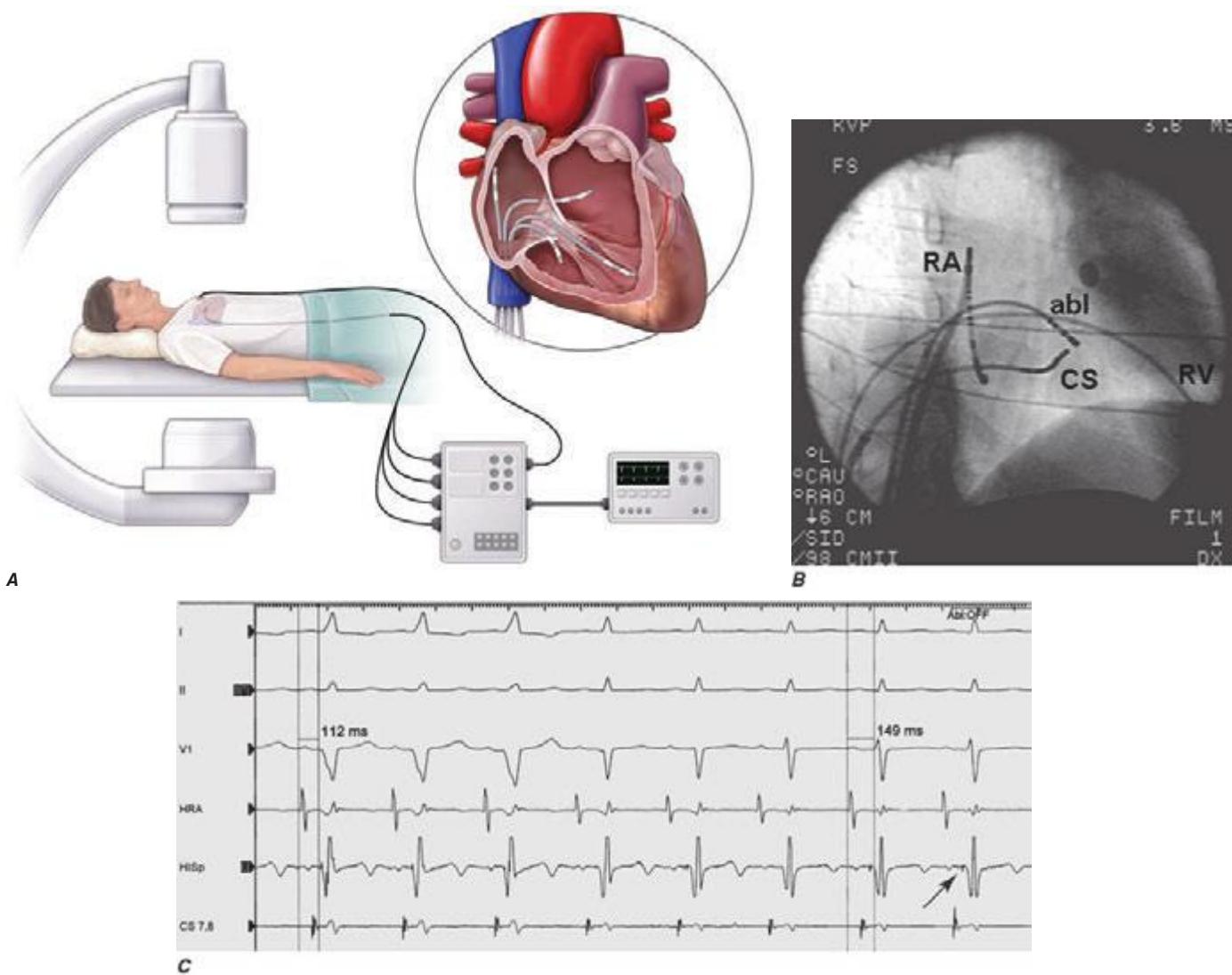


FIGURE 273e-5 Catheter ablation of cardiac arrhythmias. **A.** A schematic of the catheter system and generator in a patient undergoing radiofrequency catheter ablation (RFCA); the circuit involves the catheter in the heart and a dispersive patch placed on the body surface (usually the back). The inset shows a diagram of the heart with a catheter located at the AV valve ring for ablation of an accessory pathway. **B.** A right anterior oblique fluoroscopic image of the catheter position for ablation of a left-sided accessory pathway. A catheter is placed in the atrial side of the mitral valve ring (abl) via a transseptal puncture. Other catheters are placed in the coronary sinus (CS), in the right atrium (RA), and in the right ventricular (RV) apex to record local electrical activation. **C.** Body surface electrocardiogram recordings (I, II, V₁) and endocardial electrograms (HRA, high right atrium; HISp, proximal His bundle electrogram; CS 7, 8, recordings from poles 7 and 8 of a decapolar catheter placed in the coronary sinus) during RFCA of a left-sided accessory pathway in a patient with Wolff-Parkinson-White syndrome. The QRS narrows at the fourth complex; the arrow shows the His bundle electrogram, which becomes apparent with elimination of ventricular preexcitation over the accessory pathway.

Tissue cooling can be used for mapping and ablation. Cryomapping can be used to confirm the location of a desired ablation target, such as an accessory pathway in WPW syndrome, or can be used to determine the safety of ablation around the AVN by monitoring AV conduction during cooling. Another advantage of cryoablation is that once the catheter tip cools below freezing, it adheres to the tissue, increasing catheter stability independent of the rhythm or pacing.

DEVICE THERAPY

Bradyarrhythmias due either to primary sinus node dysfunction or to atrioventricular conduction defects are readily treated through implantation of a permanent pacemaker. Clinical indications for pacemaker implantation often depend on the presence either of symptomatic bradycardia or of an unreliable endogenous escape rhythm and are more fully reviewed in [Chaps. 274 and 275](#).

Ventricular tachyarrhythmias, particularly those occurring in the context of progressive structural heart diseases such as ischemic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, may recur despite therapy with antiarrhythmic drugs or catheter ablation. In appropriate candidates, implantation of an internal cardioverter-defibrillator (ICD) may reduce mortality rates from sudden cardiac death. In a subset of patients with congestive heart failure (CHF) and ventricular mechanical dyssynchrony, ICD or pacemaker platforms can be used to provide cardiac resynchronization therapy, typically through implantation of a left ventricular pacing lead. In patients with dyssynchronous CHF, such therapy has been shown to improve both morbidity and mortality rates.

SECTION 3 DISORDERS OF RHYTHM

PART 10

Disorders of the Cardiovascular System

274 The Bradyarrhythmias: Disorders of the Sinoatrial Node

David D. Spragg, Gordon F. Tomaselli

Electrical activation of the heart normally originates in the sinoatrial (SA) node, the predominant pacemaker. Other subsidiary pacemakers in the atrioventricular (AV) node, specialized conducting system, and muscle may initiate electrical activation if the SA node is dysfunctional or suppressed. Typically, subsidiary pacemakers discharge at a slower rate and, in the absence of an appropriate increase in stroke volume, may result in tissue hypoperfusion.

Spontaneous activation and contraction of the heart are a consequence of the specialized pacemaking tissue in these anatomic locales. As described in *Chap. 273e*, action potentials in the heart are regionally heterogeneous. The action potentials in cells isolated from nodal tissue are distinct from those recorded from atrial and ventricular myocytes (*Fig. 274-1*). The complement of ionic currents present in nodal cells results in a less

negative resting membrane potential compared with atrial or ventricular myocytes. Electrical diastole in nodal cells is characterized by slow diastolic depolarization (phase 4), which generates an action potential as the membrane voltage reaches threshold. The action potential upstrokes (phase 0) are slow compared with atrial or ventricular myocytes, being mediated by calcium rather than sodium current. Cells with properties of SA and AV nodal tissue are electrically connected to the remainder of the myocardium by cells with an electrophysiologic phenotype between that of nodal cells and that of atrial or ventricular myocytes. Cells in the SA node exhibit the most rapid phase 4 depolarization and thus are the dominant pacemakers in a normal heart.

Bradycardia results from a failure of either impulse initiation or impulse conduction. Failure of impulse initiation may be caused by depressed automaticity resulting from a slowing or failure of phase 4 diastolic depolarization (*Fig. 274-2*), which may result from disease or exposure to drugs. Prominently, the autonomic nervous system modulates the rate of phase 4 diastolic depolarization and thus the firing rate of both primary (SA node) and subsidiary pacemakers. Failure of conduction of an impulse from nodal tissue to atrial or ventricular myocardium may produce bradycardia as a result of exit block. Conditions that alter the activation and connectivity of cells (e.g., fibrosis) in the heart may result in failure of impulse conduction.

SA node dysfunction and AV conduction block are the most common causes of pathologic bradycardia. SA node dysfunction may be difficult to distinguish from physiologic sinus bradycardia, particularly in the young. SA node dysfunction increases in frequency between the fifth and sixth decades of life and should be considered in patients with fatigue, exercise intolerance, or syncope and sinus bradycardia.

Permanent pacemaking is the only reliable therapy for symptomatic bradycardia in the absence of extrinsic and reversible etiologies such as increased vagal tone, hypoxia, hypothermia, and drugs (*Table 274-1*). Approximately 50% of the 150,000 permanent pacemakers implanted in the United States and 20–30% of the 150,000 of those in Europe were implanted for SA node disease.

STRUCTURE AND PHYSIOLOGY OF THE SA NODE

The SA node is composed of a cluster of small fusiform cells in the sulcus terminalis on the epicardial surface of the heart at the right atrial–superior vena caval junction, where they envelop the SA nodal artery. The SA node is structurally heterogeneous, but the central prototypic nodal cells have fewer distinct myofibrils than does the surrounding atrial myocardium, no intercalated disks visible on light microscopy, a poorly developed sarcoplasmic reticulum, and no T-tubules. Cells in the peripheral regions of the SA node are transitional in both structure and function. The SA nodal artery arises from the right coronary artery in 55–60% and the left circumflex artery in 40–45% of persons. The SA node is richly innervated by sympathetic and parasympathetic nerves and ganglia.

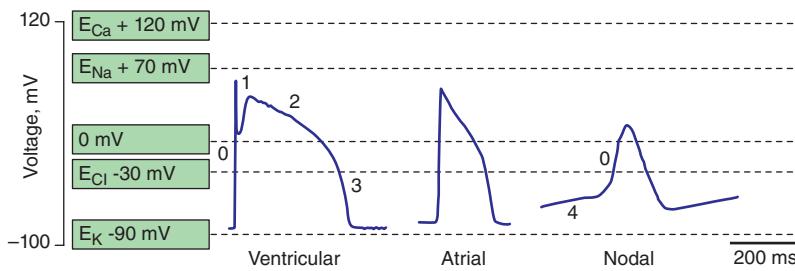


FIGURE 274-1 Action potential profiles recorded in cells isolated from sinoatrial or atrioventricular nodal tissue compared with those of cells from atrial or ventricular myocardium. Nodal cell action potentials exhibit more depolarized resting membrane potentials, slower phase 0 upstrokes, and phase 4 diastolic depolarization.

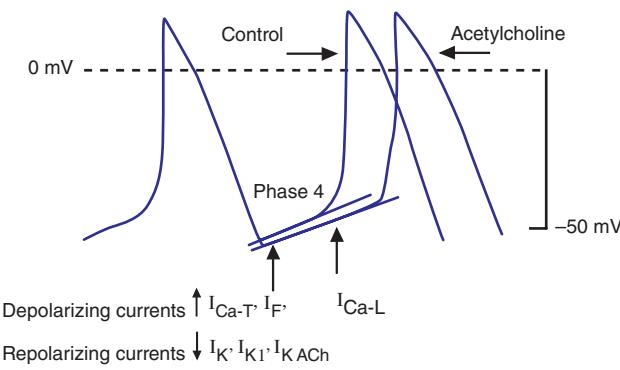


FIGURE 274-2 Schematics of nodal action potentials and the currents that contribute to phase 4 depolarization. Relative increases in depolarizing L- (I_{Ca-L}) and T- (I_{Ca-T}) type calcium and pacemaker currents (I_p) along with a reduction in repolarizing inward rectifier (I_{K1}) and delayed rectifier (I_K) potassium currents result in depolarization. Activation of ACh-gated (I_{KACH}) potassium current and beta blockade slow the rate of phase 4 and decrease the pacing rate. (Modified from J Jalife et al: Basic Cardiac Electrophysiology for the Clinician, Blackwell Publishing, 1999.)

Irregular and slow propagation of impulses from the SA node can be explained by the electrophysiology of nodal cells and the structure of the SA node itself. The action potentials of SA nodal cells are characterized by a relatively depolarized membrane potential (Fig. 274-1) of -40 to -60 mV, slow phase 0 upstroke, and relatively rapid phase 4 diastolic depolarization compared with the action potentials recorded in cardiac muscle cells. The relative absence of inward rectifier

potassium current (I_{K1}) accounts for the depolarized membrane potential; the slow upstroke of phase 0 results from the absence of available fast sodium current (I_{Na}) and is mediated by L-type calcium current (I_{Ca-L}); and phase 4 depolarization is a result of the aggregate activity of a number of ionic currents. Prominently, both L- and T-type (I_{Ca-T}) calcium currents, the pacemaker current (so-called funny current, or I_p) formed by hyperpolarization-activated cyclic nucleotide-gated channels, and the electrogenic sodium-calcium exchanger provide depolarizing current that is antagonized by delayed rectifier (I_K) and acetylcholine-gated (I_{KACH}) potassium currents. I_{Ca-L} , I_{Ca-T} , and I_p are modulated by β -adrenergic stimulation and I_{KACH} by vagal stimulation, explaining the exquisite sensitivity of diastolic depolarization to autonomic nervous system activity. The slow conduction within the SA node is explained by the absence of I_{Na} and poor electrical coupling of cells in the node, resulting from sizable amounts of interstitial tissue and a low abundance of gap junctions. The poor coupling allows for graded electrophysiologic properties within the node, with the peripheral transitional cells being silenced by electrotonic coupling to atrial myocardium.

Etiology of SA Nodal Disease

SA nodal dysfunction has been classified as intrinsic or extrinsic. The distinction is important because extrinsic dysfunction is often reversible and generally should be corrected before pacemaker therapy is considered (Table 274-1). The most common causes of extrinsic SA node dysfunction are drugs and autonomic nervous system influences that suppress automaticity and/or compromise conduction. Other extrinsic causes include hypothyroidism, sleep apnea, and conditions likely to occur in critically ill patients such as hypothermia, hypoxia, increased intracranial pressure (Cushing's response), and endotracheal suctioning via activation of the vagus nerve.

Intrinsic sinus node dysfunction is degenerative and often is characterized pathologically by fibrous replacement of the SA node or its connections to the atrium. Acute and chronic coronary artery disease (CAD) may be associated with SA node dysfunction, although in the setting of acute myocardial infarction (MI; typically inferior), the abnormalities are transient. Inflammatory processes may alter SA node function, ultimately producing replacement fibrosis. Pericarditis, myocarditis, and rheumatic heart disease have been associated with SA nodal disease with sinus bradycardia, sinus arrest, and exit block. Carditis associated with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and mixed connective tissue disorders (MCTDs) may also affect SA node structure and function. Senile amyloidosis is an infiltrative disorder in patients typically in the ninth decade of life; deposition of amyloid protein in the atrial myocardium can impair SA node function. Some SA node disease is iatrogenic and results from direct injury to the SA node during cardiothoracic surgery.

Rare heritable forms of sinus node disease have been described, and several have been characterized genetically. Autosomal dominant sinus node dysfunction in conjunction with supraventricular tachycardia (i.e., tachycardia-bradycardia variant of sick-sinus syndrome [SSS2]) has been linked to mutations in the pacemaker current (I_p) subunit gene *HCN4* on chromosome 15. An autosomal recessive form of SSS1 with the prominent feature of atrial inexcitability and absence of P waves on the electrocardiogram (ECG) is caused by mutations in the cardiac sodium channel gene, *SCN5A*, on chromosome 3. Variants in myosin heavy chain 6 (*MYH6*) increase the susceptibility to SSS (SSS3). SA node dysfunction associated with myopia has been described but not genetically characterized. There are several neuromuscular diseases, including Kearns-Sayre syndrome (ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy) and myotonic dystrophy, that have a predilection for the conducting system and SA node.

SSS in both the young and the elderly is associated with an increase in fibrous tissue in the SA node. The onset of SSS may be hastened by coexisting disease, such as CAD, diabetes mellitus, hypertension, and valvular diseases and cardiomyopathies.

Clinical Features of SA Node Disease

SA node dysfunction may be completely asymptomatic and manifest as an ECG anomaly such as sinus bradycardia; sinus arrest and

TABLE 274-1 ETIOLOGIES OF SA NODE DYSFUNCTION

Extrinsic	Intrinsic
Autonomic	Sick-sinus syndrome (SSS)
Carotid sinus hypersensitivity	Coronary artery disease (chronic and acute MI)
Vasovagal (cardioinhibitory) stimulation	Inflammatory
Drugs	Pericarditis
Beta blockers	Myocarditis (including viral)
Calcium channel blockers	Rheumatic heart disease
Digoxin	Collagen vascular diseases
Ivabradine	Lyme disease
Antiarrhythmics (class I and III)	Senile amyloidosis
Adenosine	Congenital heart disease
Clonidine (other sympatholytics)	TGA/Mustard and Fontan repairs
Lithium carbonate	Iatrogenic
Cimetidine	Radiation therapy
Amitriptyline	Postsurgical
Phenothiazines	Chest trauma
Narcotics (methadone)	Familial
Pentamidine	SSS2, AD, OMIM #163800 (15q24-25)
Hypothyroidism	SSS1, AR OMIM #608567 (3p21)
Sleep apnea	SSS3, AD, OMIM #614090 (14q11.2)
Hypoxia	SA node disease with myopia, OMIM #182190
Endotracheal suctioning (vagal maneuvers)	Kearns-Sayre syndrome, OMIM #530000
Hypothermia	Myotonic dystrophy
Increased intracranial pressure	Type 1, OMIM #160900 (19q13.2-13.3) Type 2, OMIM #602668 (3q13.3-q24) Friedreich's ataxia, OMIM #229300 (9q13, 9p23-p11)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MI, myocardial infarction; OMIM, Online Mendelian Inheritance in Man (database); TGA, transposition of the great arteries.

exit block; or alternating supraventricular tachycardia, usually atrial fibrillation, and bradycardia. Symptoms associated with SA node dysfunction, in particular tachycardia-bradycardia syndrome, may be related to both slow and fast heart rates. For example, tachycardia may be associated with palpitations, angina pectoris, and heart failure, and bradycardia may be associated with hypotension, syncope, presyncope, fatigue, and weakness. In the setting of SSS, overdrive suppression of the SA node may result in prolonged pauses and syncope upon termination of the tachycardia. In many cases, symptoms associated with SA node dysfunction result from concomitant cardiovascular disease. A significant minority of patients with SSS develop signs and symptoms of heart failure that may be related to slow or fast heart rates.

One-third to one-half of patients with SA node dysfunction develop supraventricular tachycardia, usually atrial fibrillation or atrial flutter. The incidence of persistent atrial fibrillation in patients with SA node dysfunction increases with advanced age, hypertension, diabetes mellitus, left ventricular dilation, valvular heart disease, and ventricular pacing. Remarkably, some symptomatic patients may experience an improvement in symptoms with the development of atrial fibrillation, presumably from an increase in their average heart rate. Patients with the tachycardia-bradycardia variant of SSS, similar to patients with atrial fibrillation, are at risk for thromboembolism, and *those at greatest risk*, including patients ≥ 65 years and patients with a prior history of stroke, valvular heart disease, left ventricular dysfunction, or atrial enlargement, should be treated with anticoagulants. Up to one-quarter of patients with SA node disease will have concurrent AV conduction disease, although only a minority will require specific therapy for high-grade AV block.

The natural history of SA node dysfunction is one of varying intensity of symptoms even in patients who present with syncope. Symptoms related to SA node dysfunction may be significant, but overall mortality usually is not compromised in the absence of other significant comorbid conditions. These features of the natural history need to be taken into account in considering therapy for these patients.

ELECTROCARDIOGRAPHY OF SA NODE DISEASE

The electrocardiographic manifestations of SA node dysfunction include sinus bradycardia, sinus pauses, sinus arrest, sinus exit block, tachycardia (in SSS), and chronotropic incompetence. It is often difficult to distinguish pathologic from physiologic sinus bradycardia. By definition, sinus bradycardia is a rhythm driven by the SA node with a rate of <60 beats/min; sinus bradycardia is very common and typically benign. Resting heart rates <60 beats/min are very common in young healthy individuals and physically conditioned subjects. A sinus rate of <40 beats/min in the awake state in the absence of physical conditioning generally is considered abnormal. Sinus pauses and sinus arrest result from failure of the SA node to discharge, producing a pause without P waves visible on the ECG (Fig. 274-3). Sinus pauses of up to 3 s are common in awake athletes, and pauses of this duration or longer may be observed in asymptomatic elderly subjects. Intermittent failure of conduction from the SA node produces sinus exit block. The severity of sinus exit block may vary in a manner similar to that of AV block (Chap. 275). Prolongation of conduction from the sinus node will not be apparent on the ECG; second-degree SA block will

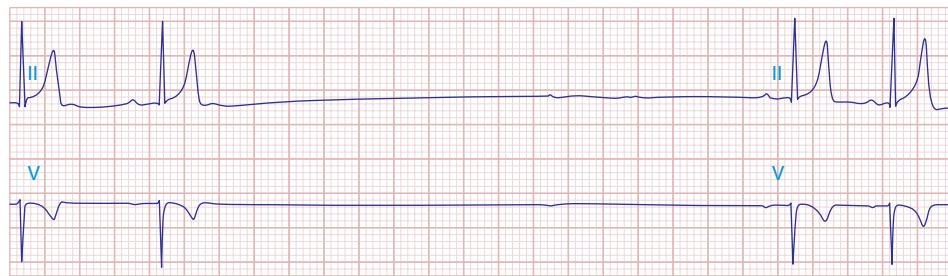


FIGURE 274-3 Sinus slowing and pauses on the electrocardiogram (ECG). The ECG is recorded during sleep in a young patient without heart disease. The heart rate before the pause is slow, and the PR interval is prolonged, consistent with an increase in vagal tone. The P waves have a morphology consistent with sinus rhythm. The recording is from a two-lead telemetry system in which the tracing labeled II mimics frontal lead II and V represents Modified Central Lead 1, which mimics lead V₁ of the standard 12-lead ECG.

produce intermittent conduction from the SA node and a regularly irregular atrial rhythm.

Type I second-degree SA block results from progressive prolongation of SA node conduction with intermittent failure of the impulses originating in the sinus node to conduct to the surrounding atrial tissue. Second-degree SA block appears on the ECG as an intermittent absence of P waves (Fig. 274-4). In type II second-degree SA block, there is no change in SA node conduction before the pause. Complete or third-degree SA block results in no P waves on the ECG. Tachycardia-bradycardia syndrome is manifest as alternating sinus bradycardia and atrial tachyarrhythmias. Although atrial tachycardia, atrial flutter, and atrial fibrillation may be observed, the latter is the most common tachycardia. Chronotropic incompetence is the inability to increase the heart rate in response to exercise or other stress appropriately and is defined in greater detail below.

DIAGNOSTIC TESTING

SA node dysfunction is most commonly a clinical or electrocardiographic diagnosis. Sinus bradycardia or pauses on the resting ECG are rarely sufficient to diagnose SA node disease, and longer-term recording and symptom correlation generally are required. Symptoms in the absence of sinus bradycardias may be sufficient to exclude a diagnosis of SA node dysfunction.

Electrocardiographic recording plays a central role in the diagnosis and management of SA node dysfunction. Despite the limitations of the resting ECG, longer-term recording employing Holter or event monitors may permit correlation of symptoms with the cardiac rhythm. Many contemporary event monitors may be automatically triggered to record the ECG when certain programmed heart rate criteria are met. Implantable ECG monitors permit long-term recording (12–18 months) in particularly challenging patients.

Failure to increase the heart rate with exercise is referred to as *chronotropic incompetence*. This is alternatively defined as failure to reach 85% of predicted maximal heart rate at peak exercise or failure to achieve a heart rate >100 beats/min with exercise or a maximal heart rate with exercise less than two standard deviations below that of an age-matched control population. Exercise testing may be useful in dis-



FIGURE 274-4 Mobitz type I SA nodal exit block. A theoretical SA node electrogram (SAN EG) is shown. Note that there is grouped beating producing a regularly irregular heart rhythm. The SA node EG rate is constant with progressive delay in exit from the node and activation of the atria, inscribing the P wave. This produces subtly decreasing P-P intervals before the pause, and the pause is less than twice the cycle length of the last sinus interval.

criminating chronotropic incompetence from resting bradycardia and may aid in the identification of the mechanism of exercise intolerance.

Autonomic nervous system testing is useful in diagnosing carotid sinus hypersensitivity; pauses >3 s are consistent with the diagnosis but may be present in asymptomatic elderly subjects. Determining the intrinsic heart rate (IHR) may distinguish SA node dysfunction from slow heart rates that result from high vagal tone. The normal IHR after administration of 0.2 mg/kg propranolol and 0.04 mg/kg atropine is $117.2 - (0.53 \times \text{age})$ in beats/min; a low IHR is indicative of SA disease.

Electrophysiologic testing may play a role in the assessment of patients with presumed SA node dysfunction and in the evaluation of syncope, particularly in the setting of structural heart disease. In this circumstance, electrophysiologic testing is used to rule out more malignant etiologies of syncope, such as ventricular tachyarrhythmias and AV conduction block. There are several ways to assess SA node function invasively. They include the sinus node recovery time (SNRT), defined as the longest pause after cessation of overdrive pacing of the right atrium near the SA node (normal: <1500 ms or, corrected for sinus cycle length, <550 ms), and the sinoatrial conduction time (SACT), defined as one-half the difference between the intrinsic sinus cycle length and a noncompensatory pause after a premature atrial stimulus (normal <125 ms). The combination of an abnormal SNRT, an abnormal SACT, and a low IHR is a sensitive and specific indicator of intrinsic SA node disease.

TREATMENT

SINOATRIAL NODE DYSFUNCTION

Since SA node dysfunction is not associated with increased mortality rates, the aim of therapy is alleviation of symptoms. Exclusion of extrinsic causes of SA node dysfunction and correlation of the cardiac rhythm with symptoms is an essential part of patient management. Pacemaker implantation is the primary therapeutic intervention in patients with symptomatic SA node dysfunction. Pharmacologic considerations are important in the evaluation and management of patients with SA nodal disease. A number of drugs modulate SA node function and are extrinsic causes of dysfunction (Table 274-1). Beta blockers and calcium channel blockers increase SNRT in patients with SA node dysfunction, and antiarrhythmic drugs with class I and III action may promote SA node exit block. In general, such agents should be discontinued before decisions regarding the need for permanent pacing in patients with SA node disease are made. Chronic pharmacologic therapy for sinus bradycardias is limited. Some pharmacologic agents may improve SA node function; digitalis, for example, has been shown to shorten SNRT in patients with SA node dysfunction. Isoproterenol or atropine administered IV may increase the sinus rate acutely. Theophylline has been used both acutely and chronically to increase heart rate but has liabilities when used in patients with tachycardia-bradycardia syndrome, increasing the frequency of supraventricular tachyarrhythmias, and in patients with structural heart disease, increasing the risk of potentially serious ventricular arrhythmias. Currently, there is only a single randomized study of therapy for SA node dysfunction. In patients with resting heart rates <50 and >30 beats/min on a Holter monitor, patients who received dual-chamber pacemakers experienced significantly fewer syncopal episodes and had symptomatic improvement compared with patients randomized to theophylline or no treatment.

In certain circumstances, sinus bradycardia requires no specific treatment or only temporary rate support. Sinus bradycardia is common in patients with acute inferior or posterior MI and can be exacerbated by vagal activation induced by pain or the use of drugs such as morphine. Ischemia of the SA nodal artery probably occurs in acute coronary syndromes more typically with involvement with the right coronary artery, and even with infarction, the effect on SA node function most often is transient.

Sinus bradycardia is a prominent feature of carotid sinus hypersensitivity and neurally mediated hypotension associated with vasovagal syncope that responds to pacemaker therapy. Carotid

hypersensitivity with recurrent syncope or presyncope associated with a predominant cardioinhibitory component responds to pacemaker implantation. Several randomized trials have investigated the efficacy of permanent pacing in patients with drug-refractory vasovagal syncope, with mixed results. Although initial trials suggested that patients undergoing pacemaker implantation have fewer recurrences and a longer time to recurrence of symptoms, at least one follow-up study did not confirm these results.

PERMANENT PACEMAKERS

Nomenclature and Complications The main therapeutic intervention in SA node dysfunction is permanent pacing. Since the first implementation of permanent pacing in the 1950s, many advances in technology have resulted in miniaturization, increased longevity of pulse generators, improvement in leads, and increased functionality. To better understand pacemaker therapy for bradycardias, it is important to be familiar with the fundamentals of pacemaking. Pacemaker modes and function are named using a five-letter code. The first letter indicates the chamber(s) that is paced (O, none; A, atrium; V, ventricle; D, dual; S, single), the second is the chamber(s) in which sensing occurs (O, none; A, atrium; V, ventricle; D, dual; S, single), the third is the response to a sensed event (O, none; I, inhibition; T, triggered; D, inhibition + triggered), the fourth refers to the programmability or rate response (R, rate responsive), and the fifth refers to the existence of antitachycardia functions if present (O, none; P, antitachycardia pacing; S, shock; D, pace + shock). Almost all modern pacemakers are multiprogrammable and have the capability for rate responsiveness using one of several rate sensors: activity or motion, minute ventilation, or QT interval. The most commonly programmed modes of implanted single- and dual-chamber pacemakers are VVIR and DDDR, respectively, although multiple modes can be programmed in modern pacemakers.

Although pacemakers are highly reliable, they are subject to a number of complications related to implantation and electronic function. In adults, permanent pacemakers are most commonly implanted with access to the heart by way of the subclavian-superior vena cava venous system. Rare, but possible, acute complications of transvenous pacemaker implantation include infection, hematoma, pneumothorax, cardiac perforation, diaphragmatic/phrenic nerve stimulation, and lead dislodgment. Limitations of chronic pacemaker therapy include infection, erosion, lead failure, and abnormalities resulting from inappropriate programming or interaction with the patient's native electrical cardiac function. Rotation of the pacemaker pulse generator in its subcutaneous pocket, either intentionally or inadvertently, often referred to as "twiddler's syndrome," can wrap the leads around the generator and produce dislodgment with failure to sense or pace the heart. The small size and light weight of contemporary pacemakers make this a rare complication.

Complications stemming from chronic cardiac pacing also result from disturbances in atrioventricular synchrony and/or left ventricular mechanical synchrony. Pacing modes that interrupt or fail to restore atrioventricular synchrony may lead to a constellation of signs and symptoms, collectively referred to as pacemaker syndrome, that include neck pulsation, fatigue, palpitations, cough, confusion, exertional dyspnea, dizziness, syncope, elevation in jugular venous pressure, canon A waves, and stigmata of congestive heart failure, including edema, rales, and a third heart sound. Right ventricular apical pacing can induce dyssynchronous activation of the left ventricle, leading to compromised left ventricular systolic function, mitral valve regurgitation, and the previously mentioned stigmata of congestive heart failure. Maintenance of AV synchrony can minimize the sequelae of pacemaker syndrome. Selection of pacing modes that minimize unnecessary ventricular pacing or implantation of a device capable of right and left ventricular pacing (biventricular pacing) can help minimize the deleterious consequences of pacing-induced mechanical dyssynchrony at the ventricular level.

1470 Pacemaker Therapy in SA Node Dysfunction Pacing in SA nodal disease is indicated to alleviate symptoms of bradycardia. Consensus guidelines published by the American Heart Association (AHA)/American College of Cardiology/Heart Rhythm Society (ACC/HRS) outline the indications for the use of pacemakers and categorize them by class based on levels of evidence. Class I conditions are those for which there is evidence or consensus of opinion that therapy is useful and effective. In class II conditions, there is conflicting evidence or a divergence of opinion about the efficacy of a procedure or treatment; in class IIa conditions, the weight of evidence or opinion favors treatment; and in class IIb conditions, efficacy is less well established by the evidence or opinion of experts. In class III conditions, the evidence or weight of opinion indicates that the therapy is not efficacious or useful and may be harmful.

Class I indications for pacing in SA node dysfunction include documented symptomatic bradycardia, sinus node dysfunction-associated long-term drug therapy for which there is no alternative, and symptomatic chronotropic incompetence. Class IIa indications include those outlined previously in which sinus node dysfunction is suspected but not documented and for syncope of unexplained origin in the presence of major abnormalities of SA node dysfunction. Mildly symptomatic individuals with heart rates consistently <40 beats/min constitute a class IIb indication for pacing. Pacing is not indicated in patients with SA node dysfunction who do not have symptoms and in those in whom bradycardia is associated with the use of nonessential drugs (**Table 274-2**).

There is some controversy about the mode of pacing that should be employed in SA node disease. A number of randomized, single-blind trials of pacing mode have been performed. There are no trials that demonstrate an improvement in mortality rate with AV synchronous pacing compared with single-chamber pacing in SA node disease. In some of these studies, the incidence of atrial fibrillation and thromboembolic events was reduced with AV synchronous pacing. In trials of patients with dual-chamber pacemakers designed to compare single-chamber with dual-chamber pacing by crossover design, the need for AV synchronous pacing due to pacemaker syndrome was common. Pacing modes that preserve AV synchrony appear to be associated with a reduction in the incidence of atrial fibrillation and improved quality of life. Because of the low but finite

incidence of AV conduction disease, patients with SA node dysfunction usually undergo dual-chamber pacemaker implantation.

Pacemaker Therapy in Carotid Sinus Hypersensitivity and Vasovagal Syncpe Carotid sinus hypersensitivity, if accompanied by a significant cardioinhibitory component, responds well to pacing. In this circumstance, pacing is required only intermittently and single-chamber ventricular pacing is often sufficient. The mechanism of vasovagal syncpe is incompletely understood but appears to involve activation of cardiac mechanoreceptors with consequent activation of neural centers that mediate vagal activation and withdrawal of sympathetic nervous system tone. Several randomized clinical trials have been performed in patients with drug-refractory vasovagal syncpe, with some studies suggesting reduction in the frequency and the time to recurrent syncpe in patients who were paced compared with those who were not. A recent follow-up study to one of those initial trials, however, found less convincing results, casting some doubt on the utility of pacing for vagally mediated syncpe.

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The Bradyarrhythmias: Disorders of the Atrioventricular Node

David D. Spragg, Gordon F. Tomaselli

Impulses generated in the sinoatrial (SA) node or in ectopic atrial loci are conducted to the ventricles through the electrically and anatomically complex atrioventricular (AV) node. As described in **Chap. 274**, the electrophysiologic properties of nodal tissue are distinct from atrial and ventricular myocardium. Cells located in the AV node sit at a relatively higher resting membrane potential than surrounding atrial and ventricular myocytes, exhibit spontaneous depolarization during phase 4 of the action potential, and have slower phase 0 depolarization (mediated by calcium influx in nodal tissue) than that seen in ventricular tissue (mediated by sodium influx).

Bradycardia may occur when conduction across the AV node is compromised, resulting in ineffective ventricular rates, with the possibility of attendant symptoms, including fatigue, syncope, and (if subsidiary pacemaker activity is insufficient) even death. It is important to recognize that in the setting of disturbed AV conduction, SA activation and atrial systole may occur at normal or even accelerated rates, while ventricular activation is either slowed or nonexistent. Transient AV conduction block is common in the young and is most likely the result of high vagal tone found in up to 10% of young adults. Acquired and persistent failure of AV conduction is decidedly rare in healthy adult populations, with an estimated incidence of 200 per million population per year. In the setting of myocardial ischemia, aging and fibrosis, or cardiac infiltrative diseases, however, persistent AV block is much more common.

As with symptomatic bradycardia arising from SA node dysfunction, permanent pacing is the only reliable therapy for symptoms arising from AV conduction block. Approximately 50% of the 150,000 permanent pacemakers implanted in the United States and 70–80% of those in Europe are implanted for disorders of AV conduction.

STRUCTURE AND PHYSIOLOGY OF THE AV NODE

The AV conduction axis is structurally complex, involving the atria and ventricles as well as the AV node. Unlike the SA node, the AV node is a subendocardial structure originating in the transitional zone, which is composed of aggregates of cells in the posterior-inferior right atrium. Superior, medial, and posterior transitional atrionodal bundles converge on the compact AV node. The compact AV node (~1 × 3 × 5 mm) is situated at the apex of the triangle of Koch, which is defined by the coronary sinus ostium posteriorly, the septal tricuspid valve annulus anteriorly, and the tendon of Todaro superiorly. The compact AV node continues as the penetrating AV bundle where it immediately traverses the central fibrous body and is in close proximity to the

TABLE 274-2 SUMMARY OF GUIDELINES FOR PACEMAKER IMPLANTATION IN SA NODE DYSFUNCTION

Class I

1. SA node dysfunction with symptomatic bradycardia or sinus pause
2. Symptomatic SA node dysfunction as a result of essential long-term drug therapy with no acceptable alternatives
3. Symptomatic chronotropic incompetence
4. Atrial fibrillation with bradycardia and pauses >5 s

Class IIa

1. SA node dysfunction with heart rates <40 beats/min without a clear and consistent relationship between bradycardia and symptoms
2. SA node dysfunction with heart rates <40 beats/min on an essential long-term drug therapy with no acceptable alternatives, without a clear and consistent relationship between bradycardia and symptoms
3. Syncope of unknown origin when major abnormalities of SA node dysfunction are discovered or provoked by electrophysiologic testing

Class IIb

1. Mildly symptomatic patients with waking chronic heart rates <40 beats/min

Class III

1. SA node dysfunction in asymptomatic patients, even those with heart rates <40 beats/min
2. SA node dysfunction in which symptoms suggestive of bradycardia are not associated with a slow heart rate
3. SA node dysfunction with symptomatic bradycardia due to nonessential drug therapy

Source: Modified from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008 and CM Tracy et al: J Am Coll Cardiol 61:e6, 2013.

aortic, mitral, and tricuspid valve annuli; thus, it is subject to injury in the setting of valvular heart disease or its surgical treatment. The penetrating AV bundle continues through the annulus fibrosis and emerges along the ventricular septum adjacent to the membranous septum as the bundle of His. The right bundle branch (RBB) emerges from the distal AV bundle in a band that traverses the right ventricle (moderator band). In contrast, the left bundle branch (LBB) is a broad subendocardial sheet of tissue on the septal left ventricle. The Purkinje fiber network emerges from the RBB and LBB and extensively ramifies on the endocardial surfaces of the right and left ventricles, respectively.

The blood supply to the penetrating AV bundle is from the AV nodal artery and first septal perforator of the left anterior descending coronary artery. The bundle branches also have a dual blood supply from the septal perforators of the left anterior descending coronary artery and branches of the posterior descending coronary artery. The AV node is highly innervated with postganglionic sympathetic and parasympathetic nerves. The bundle of His and distal conducting system are minimally influenced by autonomic tone.

The cells that constitute the AV node complex are heterogeneous with a range of action potential profiles. In the transitional zones, the cells have an electrical phenotype between those of atrial myocytes and cells of the compact node (see Fig. 274-1). Atrionodal transitional connections may exhibit *decremental conduction*, defined as slowing of conduction with increasingly rapid rates of stimulation. Fast and slow AV nodal pathways have been described, but it is controversial whether these two types of pathway are anatomically distinct or represent functional heterogeneities in different regions of the AV nodal complex. Myocytes that constitute the compact node are depolarized (resting membrane potential ~ -60 mV) and exhibit action potentials with low amplitudes, slow upstrokes of phase 0 (<10 V/s), and phase 4 diastolic depolarization; high-input resistance; and relative insensitivity to external $[K^+]$. The action potential phenotype is explained by the complement of ionic currents expressed. AV nodal cells lack a robust inward rectifier potassium current (I_{K1}) and fast sodium current (I_{Na}); L-type calcium current ($I_{Ca,L}$) is responsible for phase 0; and phase 4 depolarization reflects the composite activity of the depolarizing currents—funny current (I_f), $I_{Ca,L}$, T-type calcium current ($I_{Ca,T}$), and sodium calcium exchanger current (I_{NCX})—and the repolarizing currents—delayed rectifier (I_{Kr}) and acetylcholine-gated (I_{KACH}) potassium currents. Electrical coupling between cells in the AV node is tenuous due to the relatively sparse expression of gap junction channels (predominantly connexin-40) and increased extracellular volume.

The His bundle and the bundle branches are insulated from ventricular myocardium. The most rapid conduction in the heart is observed in these tissues. The action potentials exhibit very rapid upstrokes (phase 0), prolonged plateaus (phase 2), and modest automaticity (phase 4 depolarization). Gap junctions, composed largely of connexin-40, are abundant, but bundles are poorly connected transversely to ventricular myocardium.

ETIOLOGY OF AV CONDUCTION DISEASE

Conduction block from the atrium to the ventricle can occur for a variety of reasons in a number of clinical situations, and AV conduction block may be classified in a number of ways. The etiologies may be functional or structural, in part analogous to extrinsic and intrinsic causes of SA nodal dysfunction. The block may be classified by its severity from first to third degree or complete AV block or by the location of block within the AV conduction system. Table 275-1 summarizes the etiologies of AV conduction block. Those that are functional (autonomic, metabolic/endocrine, and drug-related) tend to be reversible. Most other etiologies produce structural changes, typically fibrosis, in segments of the AV conduction axis that are generally permanent. Heightened vagal tone during sleep or in well-conditioned individuals can be associated with all grades of AV block. Carotid sinus hypersensitivity, vasovagal syncope, and cough and micturition syncope may be associated with SA node slowing and AV conduction block. Transient metabolic and endocrinologic disturbances as well as a number of pharmacologic agents also may produce reversible AV conduction block.

TABLE 275-1 ETIOLOGIES OF ATRIOVENTRICULAR BLOCK

Autonomic	
Carotid sinus hypersensitivity	Vasovagal
Metabolic/Endocrine	
Hyperkalemia	Hypothyroidism
Hypermagnesemia	Adrenal insufficiency
Drug-Related	
Beta blockers	Adenosine
Calcium channel blockers	Antiarrhythmics (class I and III)
Digitalis	Lithium
Infectious	
Endocarditis	Tuberculosis
Lyme disease	Diphtheria
Chagas' disease	Toxoplasmosis
Syphilis	
Heritable/Congenital	
Congenital heart disease	Faciocapulohumeral MD, OMIM #158900 (4q35)
Maternal SLE	Emery-Dreifuss MD, OMIM #310300 (Xq28)
Kearns-Sayre syndrome, OMIM #530000	Progressive familial heart block, type IA OMIM #113900 (3p21)
Myotonic dystrophy	Progressive familial heart block, type IB, OMIM #604559 (19q13.32)
Type 1, OMIM #160900 (19q13.2-13.3)	Progressive familial heart block, type II, OMIM %140400
Type 2, OMIM #602668 (3q13.3-q24)	
Inflammatory	
SLE	MCTD
Rheumatoid arthritis	Scleroderma
Infiltrative	
Amyloidosis	Hemochromatosis
Sarcoidosis	
Neoplastic/Traumatic	
Lymphoma	Radiation
Mesothelioma	Catheter ablation
Melanoma	
Degenerative	
Lev's disease	Lenègre's disease
Coronary Artery Disease	
Acute MI	

Abbreviations: MCTD, mixed connective tissue disease; MI, myocardial infarction; OMIM, Online Mendelian Inheritance in Man (database; designations: #, phenotypic description, molecular basis known; %, phenotypic description); SLE, systemic lupus erythematosus.

Several infectious diseases have a predilection for the conducting system. Lyme disease may involve the heart in up to 50% of cases; 10% of patients with Lyme carditis develop AV conduction block, which is generally reversible but may require temporary pacing support. Chagas' disease, which is common in Latin America, and syphilis may produce more persistent AV conduction disturbances. Some autoimmune and infiltrative diseases may produce AV conduction block, including systemic lupus erythematosus (SLE), rheumatoid arthritis, mixed connective tissue disease, scleroderma, amyloidosis (primary and secondary), sarcoidosis, and hemochromatosis; rare malignancies also may impair AV conduction.

Idiopathic progressive fibrosis of the conduction system is one of the more common and degenerative causes of AV conduction block. Aging is associated with degenerative changes in the summit of the ventricular septum, central fibrous body, and aortic and mitral annuli and has been described as “sclerosis of the left cardiac skeleton.” The process typically begins in the fourth decade of life and may be accelerated by atherosclerosis, hypertension, and diabetes mellitus. Accelerated forms

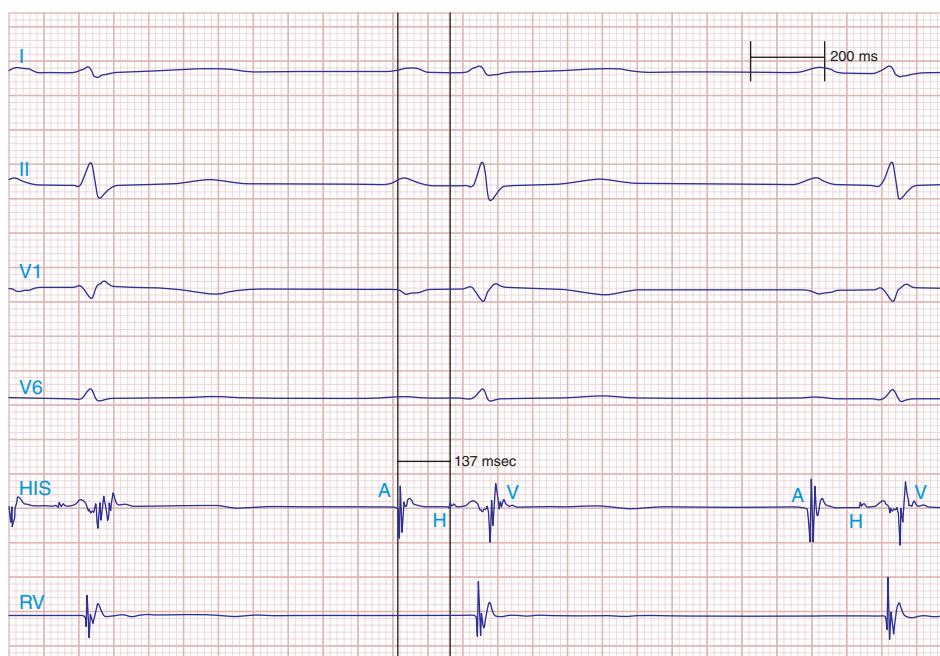


FIGURE 275-1 First-degree AV block with slowing of conduction in the AV node as indicated by the prolonged atrial-to-His bundle electrogram (AH) interval, in this case 157 ms. The His bundle-to-earliest ventricular activation on the surface ECG (HV) interval is normal. The normal HV interval suggests normal conduction below the AV node to the ventricle. I and V_1 are surface ECG leads, and HIS is the recording of the endocavitary electrogram at the His bundle position. A, H, and V are labels for the atrial, His bundle, and right ventricular electrograms, respectively.

of progressive familial heart block have been identified in families with mutations in the cardiac sodium channel gene (*SCN5A*) and other loci that have been mapped to chromosomes 1 and 19.

AV conduction block has been associated with heritable neuromuscular diseases, including the nucleotide repeat disease myotonic dystrophy, the mitochondrial myopathy Kearns-Sayre syndrome (Chap. 462e), and several of the monogenic muscular dystrophies. Congenital AV block may be observed in complex congenital cardiac anomalies (Chap. 282), such as transposition of the great arteries, ostium primum atrial septal defects (ASDs), ventricular septal defects (VSDs), endocardial cushion defects, and some single-ventricle defects. Congenital AV block in the setting of a structurally normal heart has been seen in children born to mothers with SLE. Iatrogenic AV block may occur during mitral or aortic valve surgery, rarely in the setting of thoracic radiation, and as a consequence of catheter ablation. AV block is a decidedly rare complication of the surgical repair of VSDs or ASDs but may complicate repairs of transposition of the great arteries.

Coronary artery disease may produce transient or persistent AV block. In the setting of coronary spasm, ischemia, particularly in the right coronary artery distribution, may produce transient AV block. In acute myocardial infarction (MI), AV block transiently develops in 10–25% of patients; most commonly, this is first- or second-degree AV block, but complete heart block (CHB) may also occur. Second-degree and higher-grade AV block tends to occur more often in inferior than in anterior acute MI; however, the level of block in inferior MI tends to be in the AV node with more stable, narrow escape rhythms. In contrast, acute anterior MI is associated with block in the distal AV

nodal complex, His bundle, or bundle branches and results in wide complex, unstable escape rhythms and a worse prognosis with high mortality rates.

ELECTROCARDIOGRAPHY AND ELECTROPHYSIOLOGY OF AV CONDUCTION BLOCK

AV conduction block typically is diagnosed electrocardiographically, which characterizes the severity of the conduction disturbance and allows one to draw inferences about the location of the block. AV conduction block manifests as slow conduction in its mildest forms and failure to conduct, either intermittent or persistently, in more severe varieties. First-degree AV block (PR interval >200 ms) is a slowing of conduction through the AV junction (Fig. 275-1). The site of delay is typically in the AV node but may be in the atria, bundle of His, or His-Purkinje system. A wide QRS is suggestive of delay in the distal conduction system, whereas a narrow QRS suggests delay in the AV node proper or, less commonly, in the bundle of His. In second-degree AV block there is an intermittent failure of electrical impulse conduction from atrium to ventricle. Second-degree AV block is subclassified as Mobitz type I (Wenckebach) or Mobitz type II. The periodic failure of conduction in Mobitz type I block is characterized by a progressively lengthening PR interval, shortening of the RR interval, and a pause that is less than two times the immediately preceding RR interval on the electrocardiogram (ECG). The ECG complex after the pause exhibits a shorter PR interval than that immediately preceding the pause (Fig. 275-2). This ECG pattern most often arises because of decremental conduction of electrical impulses in the AV node.



FIGURE 275-2 Mobitz type I second-degree AV block. The PR interval prolongs before the pause, as shown in the ladder diagram. The ECG pattern results from slowing of conduction in the AV node.



FIGURE 275-3 Paroxysmal AV block. Multiple nonconducted P waves after a period of sinus bradycardia with a normal PR interval. This implies significant conduction system disease, requiring permanent pacemaker implantation.

It is important to distinguish type I from type II second-degree AV nodal block because the latter has more serious prognostic implications. Type II second-degree AV block is characterized by intermittent failure of conduction of the P wave without changes in the preceding PR or RR intervals. When AV block is 2:1, it may be difficult to distinguish type I from type II block. Type II second-degree AV block typically occurs in the distal or infra-His conduction system, is often associated with intraventricular conduction delays (e.g., bundle branch block), and is more likely to proceed to higher grades of AV block than is type I second-degree AV block. Second-degree AV block (particularly type II) may be associated with a series of nonconducted P waves, referred to as *paroxysmal AV block* (Fig. 275-3), and implies significant conduction system disease and is an indication for permanent pacing. Complete failure of conduction from atrium to ventricle is referred to as complete or third-degree AV block. AV block that is intermediate between second degree and third degree is referred to as high-grade AV block and, as with CHB, implies advanced AV conduction system disease. In both cases, the block is most often distal to the AV node, and the duration of the QRS complex can be helpful in determining the level of the block. In the absence of a preexisting bundle branch block, a wide QRS escape rhythm (Fig. 275-4B) implies a block in the distal His or bundle branches; in contrast, a narrow QRS rhythm implies a block in the AV node or proximal His and an escape rhythm originating in the AV junction (Fig. 275-4A). Narrow QRS escape rhythms are typically faster and more stable than wide QRS escape rhythms and originate more proximally in the AV conduction system.

DIAGNOSTIC TESTING

Diagnostic testing in the evaluation of AV block is aimed at determining the level of conduction block, particularly in asymptomatic

patients, since the prognosis and therapy depend on whether the block is in or below the AV node. Vagal maneuvers, carotid sinus massage, exercise, and administration of drugs such as atropine and isoproterenol may be diagnostically informative. Owing to the differences in the innervation of the AV node and infranodal conduction system, vagal stimulation and carotid sinus massage slow conduction in the AV node but have less of an effect on infranodal tissue and may even improve conduction due to a reduced rate of activation of distal tissues. Conversely, atropine, isoproterenol, and exercise improve conduction through the AV node and impair infranodal conduction. In patients with congenital CHB and a narrow QRS complex, exercise typically increases heart rate; by contrast, those with acquired CHB, particularly with wide QRS, do not respond to exercise with an increase in heart rate.

Additional diagnostic evaluation, including electrophysiologic testing, may be indicated in patients with syncope and suspected high-grade AV block. This is particularly relevant if noninvasive testing does not reveal the cause of syncope or if the patient has structural heart disease with ventricular tachyarrhythmias as a cause of symptoms. Electrophysiologic testing provides more precise information regarding the location of AV conduction block and permits studies of AV conduction under conditions of pharmacologic stress and exercise. Recording of the His bundle electrogram by a catheter positioned at the superior margin of the tricuspid valve annulus provides information about conduction at all levels of the AV conduction axis. A properly recorded His bundle electrogram reveals local atrial activity, the His electrogram, and local ventricular activation; when it is monitored simultaneously with recorded body surface electrocardiographic traces, intraatrial, AV nodal, and infranodal conduction times can be assessed (Fig. 275-1). The time from the most rapid deflection of the

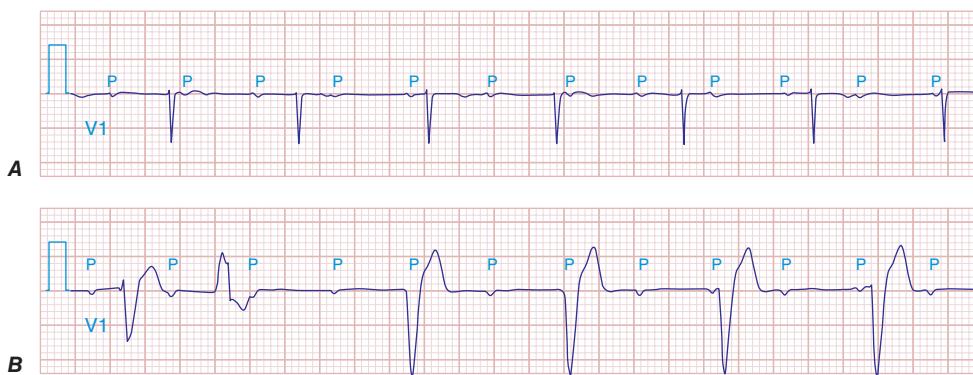


FIGURE 275-4 High-grade AV block. **A.** Multiple nonconducted P waves with a regular narrow complex QRS escape rhythm probably emanating from the AV junction. **B.** A wide complex QRS escape and a single premature ventricular contraction. In both cases, there is no consistent temporal relationship between the P waves and QRS complexes.



FIGURE 275-5 High-grade AV block below the His. The AH interval is normal and is not changing before the block. Atrial and His bundle electrograms are recorded consistent with block below the distal AV junction. I, II, III, and V₁, are surface ECG leads. HISp, HISd, and RVA are the proximal HIS, distal HIS, and right ventricular apical electrical recordings, respectively. A, H, and V represent the atrial, His, and ventricular electrograms on the His bundle recording, respectively. (Tracing courtesy of Dr. Joseph Marine; with permission.)

atrial electrogram in the His bundle recording to the His electrogram (*AH interval*) represents conduction through the AV node and is normally <130 ms. The time from the His electrogram to the earliest onset of the QRS on the surface ECG (*HV interval*) represents the conduction time through the His-Purkinje system and is normally ≤55 ms.

Rate stress produced by pacing can unveil abnormal AV conduction. Mobitz I second-degree AV block at short atrial paced cycle lengths is a normal response. However, when it occurs at atrial cycle lengths >500 ms (<120 beats/min) in the absence of high vagal tone, it is abnormal. Typically, type I second-degree AV block is associated with prolongation of the AH interval, representing conduction slowing and block in the AV node. AH prolongation occasionally is due to the effect of drugs (beta blockers, calcium channel blockers, digitalis) or increased vagal tone. Atropine can be used to reverse high vagal tone; however, if AH prolongation and AV block at long pacing cycle lengths persists, intrinsic AV node disease is likely. Type II second-degree block is typically infranodal, often in the His-Purkinje system. Block below the node with prolongation of the HV interval or a His bundle electrogram with no ventricular activation (Fig. 275-5) is abnormal unless it is elicited at fast pacing rates or short coupling intervals with extra stimulation. It is often difficult to determine the type of second-degree AV block when 2:1 conduction is present; however, the finding of a His bundle electrogram after every atrial electrogram indicates that block is occurring in the distal conduction system.

Intracardiac recording at electrophysiologic study that reveals prolongation of conduction through the His-Purkinje system (i.e., long HV interval) is associated with an increased risk of progression to higher grades of block and is generally an indication for pacing. In the setting of bundle branch block, the HV interval may reveal the condition of

the unblocked bundle and the prognosis for developing more advanced AV conduction block. Prolongation of the HV interval in patients with asymptomatic bundle branch block is associated with an increased risk of developing higher-grade AV block. The risk increases with greater prolongation of the HV interval such that in patients with an HV interval >100 ms, the annual incidence of complete AV block approaches 10%, indicating a need for pacing. In patients with acquired CHB, even if intermittent, there is little role for electrophysiologic testing, and pacemaker implantation is almost always indicated.

TREATMENT MANAGEMENT OF AV CONDUCTION BLOCK

Temporary or permanent artificial pacing is the most reliable treatment for patients with symptomatic AV conduction system disease. However, exclusion of reversible causes of AV block and the need for temporary heart rate support based on the hemodynamic condition of the patient are essential considerations in each patient. Correction of electrolyte derangements and ischemia, inhibition of excessive vagal tone, and withholding of drugs with AV nodal blocking properties may increase the heart rate. Adjunctive pharmacologic treatment with atropine or isoproterenol may be useful if the block is in the AV node. Since most pharmacologic treatment may take some time to initiate and become effective, temporary pacing may be necessary. The most expeditious technique is the use of transcutaneous pacing, where pacing patches are placed anteriorly over the cardiac apex (cathode) and posteriorly between the spine and the scapula or above the right nipple (anode). Acutely, transcutaneous pacing is highly effective, but its duration is limited by patient discomfort and longer-term failure to capture the ventricle owing to changes in lead impedance. If a patient requires more

TABLE 275-2 GUIDELINE SUMMARY FOR PACEMAKER IMPLANTATION IN ACQUIRED AV BLOCK**Class I**

1. Third-degree or high-grade AV block at any anatomic level associated with:
 - a. Symptomatic bradycardia
 - b. Essential drug therapy that produces symptomatic bradycardia
 - c. Periods of asystole >3 s or any escape rate <40 beats/min while awake, or an escape rhythm originating below the AV node
 - d. Postoperative AV block not expected to resolve
 - e. Catheter ablation of the AV junction
 - f. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy, regardless of the presence of symptoms
2. Second-degree AV block with symptomatic bradycardia
3. Type II second-degree AV block with a wide QRS complex with or without symptoms
4. Exercise-induced second- or third-degree AV block in the absence of ischemia
5. Atrial fibrillation with bradycardia and pauses >5 s

Class IIa

1. Asymptomatic third-degree AV block regardless of level
2. Asymptomatic type II second-degree AV block with a narrow QRS complex
3. Asymptomatic type II second-degree AV block with block within or below the His at electrophysiologic study
4. First- or second-degree AV block with symptoms similar to pacemaker syndrome

Class IIb

1. AV block in the setting of drug use/toxicity, when the block is expected to recur even with drug discontinuation
2. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy with any degree of AV block regardless of the presence of symptoms

Class III

1. Asymptomatic first-degree AV block
2. Asymptomatic type I second-degree AV block at the AV node level
3. AV block that is expected to resolve or is unlikely to recur (Lyme disease, drug toxicity)

Source: Modified from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008.

than a few minutes of pacemaker support, transvenous temporary pacing should be instituted. Temporary pacing leads can be placed from the jugular or subclavian venous system and advanced to the right ventricle, permitting stable temporary pacing for many days, if necessary. In most circumstances, in the absence of prompt resolution, conduction block distal to the AV node requires permanent pacemaking.

PACEMAKERS IN AV CONDUCTION DISEASE

There are no randomized trials that evaluate the efficacy of pacing in patients with AV block, as there are no reliable therapeutic alternatives for AV block and untreated high-grade AV block is potentially lethal. The consensus guidelines for pacing in acquired AV conduction block in adults provide a general outline for situations in which pacing is indicated (Table 275-2). Pacemaker implantation should be performed in any patient with symptomatic bradycardia and irreversible second- or third-degree AV block, regardless of the cause or level of block in the conducting system. Symptoms may include those directly related to bradycardia and low cardiac output or to worsening heart failure, angina, or intolerance to an essential medication. Pacing in patients with asymptomatic AV block should be individualized; situations in which pacing should be considered are patients with acquired CHB, particularly in the setting of cardiac enlargement; left ventricular dysfunction; and waking heart rates ≤40 beats/min. Patients who have asymptomatic second-degree AV block of either type should be considered for pacing if the block is demonstrated to be intra- or infra-His or is associated with a wide QRS complex. Pacing may be indicated in asymptomatic patients in special circumstances, in patients with profound first-degree AV block and left ventricular dysfunction in whom a shorter AV interval produces hemodynamic improvement, and in the setting of milder forms of AV conduction delay (first-degree AV block, intraventricular conduction delay) in patients with neuromuscular diseases that have

a predilection for the conduction system, such as myotonic dystrophy and other muscular dystrophies, and Kearns-Sayre syndrome.

PACEMAKER THERAPY IN MYOCARDIAL INFARCTION

AV block in acute MI is often transient, particularly in inferior infarction. The circumstances in which pacing is indicated in acute MI are persistent second- or third-degree AV block, particularly if symptomatic, and transient second- or third-degree AV block associated with bundle branch block (Table 275-3). Pacing is generally not indicated in the setting of transient AV block in the absence of intraventricular conduction delays or in the presence of fascicular block

TABLE 275-3 GUIDELINE SUMMARY FOR PACEMAKER IMPLANTATION IN AV CONDUCTION BLOCK IN ACUTE MYOCARDIAL INFARCTION (AMI)**Class I**

1. Persistent second-degree AV block in the His-Purkinje system with bilateral bundle branch block or third-degree block within or below the His after AMI
2. Transient advanced (second- or third-degree) infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiologic study may be necessary
3. Persistent and symptomatic second- or third-degree AV block

Class IIb

1. Persistent second- or third-degree AV block at the AV node level

Class III

1. Transient AV block in the absence of intraventricular conduction defects
2. Transient AV block in the presence of isolated left anterior fascicular block
3. Acquired left anterior fascicular block in the absence of AV block
4. Persistent first-degree AV block in the presence of bundle branch block that is old or age-indeterminate

Source: Modified from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008.

TABLE 275-4 INDICATIONS FOR PACEMAKER IMPLANTATION IN CHRONIC BIFASCICULAR AND TRIFASCICULAR BLOCK**Class I**

1. Intermittent third-degree AV block
2. Type II second-degree AV block
3. Alternating bundle branch block

Class IIa

1. Syncope not demonstrated to be due to AV block when other likely causes (e.g., ventricular tachycardia) have been excluded
2. Incidental finding at electrophysiologic study of a markedly prolonged HV interval (>100 ms) in asymptomatic patients
3. Incidental finding at electrophysiologic study of pacing-induced infra-His block that is not physiologic

Class IIb

1. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy with any degree of fascicular block regardless of the presence of symptoms, because there may be unpredictable progression of AV conduction disease

Class III

1. Fascicular block without AV block or symptoms
2. Fascicular block with first-degree AV block without symptoms

Source: Modified from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008.

or first-degree AV block that develops in the setting of preexisting bundle branch block. Fascicular blocks that develop in acute MI in the absence of other forms of AV block also do not require pacing (Table 275-3 and **Table 275-4**).

PACEMAKER THERAPY IN BIFASCICULAR AND TRIFASCICULAR BLOCK

Distal forms of AV conduction block may require pacemaker implantation in certain clinical settings. Patients with bifascicular or trifascicular block and symptoms, particularly syncope that is not attributable to other causes, should undergo pacemaker implantation. Pacemaking is indicated in asymptomatic patients with bifascicular or trifascicular block who experience intermittent third-degree, type II second-degree AV block or alternating bundle branch block. In patients with fascicular block who are undergoing electrophysiologic study, a markedly prolonged HV interval or block below the His at long cycle lengths also may constitute an indication for permanent pacing. Patients with fascicular block and the neuromuscular diseases previously described should also undergo pacemaker implantation (Table 275-4).

SELECTION OF PACING MODE

In general, a pacing mode that maintains AV synchrony reduces complications of pacing such as pacemaker syndrome and pacemaker-mediated tachycardia. This is particularly true in younger patients; the importance of dual-chamber pacing in the elderly, however, is not well established. Several studies have failed to demonstrate a difference in mortality rate in older patients with AV block treated with a single-(VVI) compared with a dual-(DDD) chamber pacing mode. In some of the studies that randomized pacing mode, the risk of chronic atrial fibrillation and stroke risk decreased with physiologic pacing. In patients with sinus rhythm and AV block, the very modest increase in risk with dual-chamber pacemaker implantation appears to be justified to avoid the possible complications of single-chamber pacing.

276**Supraventricular Tachyarrhythmias**

Gregory F. Michaud, William G. Stevenson

Supraventricular tachyarrhythmias originate from or are dependent on conduction through the atrium or atrioventricular (AV) node to the ventricles. Most produce narrow QRS-complex tachycardia (QRS duration <120 ms) characteristic of ventricular activation over the Purkinje system. Conduction block in the left or right bundle branch or activation of the ventricles from an accessory pathway produces a wide QRS complex during supraventricular tachycardia that must be distinguished from ventricular tachycardia (**Chap. 277**). Supraventricular tachyarrhythmia may be divided into physiologic sinus tachycardia and pathologic tachycardia (**Table 276-1**). The prognosis and treatment vary considerably depending on the mechanism and underlying heart disease.

Supraventricular tachycardia can be of brief duration, termed *nonsustained*, or can be sustained such that an intervention, such as cardioversion or drug administration, is required for termination. Episodes that occur with sudden onset and termination are referred to as *paroxysmal*. *Paroxysmal supraventricular tachycardia* (PSVT) refers to a family of tachycardias including AV node reentry, AV reentry using an accessory pathway, and atrial tachycardia.

CLINICAL PRESENTATION

Symptoms of supraventricular arrhythmia vary depending on the rate, duration, associated heart disease, and comorbidities and include palpitations, chest pain, dyspnea, diminished exertional capacity, and occasionally syncope. Rarely, a supraventricular arrhythmia precipitates cardiac arrest in patients with the Wolff-Parkinson-White syndrome or severe heart disease, such as hypertrophic cardiomyopathy.

Diagnosis requires obtaining an electrocardiogram (ECG) at the time of symptoms. For transient arrhythmia, ambulatory ECG recording is warranted (**see Table 277-1**). Exercise testing is useful for assessing exercise-related symptoms. Occasionally an invasive electrophysiology study is warranted to provoke the arrhythmia with pacing, confirm the mechanism, and often, perform catheter ablation.

Physiologic Sinus Tachycardia The sinus node is comprised of a group of cells dispersed within the superior aspect of the thick ridge of muscle known as the crista terminalis where the posterior smooth atrial wall derived from the sinus venosus meets the trabeculated anterior portion of the right atrium (**Fig. 276-1**). Sinus p waves are characterized by a frontal plane axis directed inferiorly and leftward, with positive p waves in leads II, III, and aVF; a negative p wave in aVR; and an initially positive biphasic p wave in V1. Normal sinus rhythm has a rate of 60–100 beats/min. Sinus tachycardia (>100 beats/min) typically occurs in response to sympathetic stimulation and vagal withdrawal, whereby the rate of spontaneous depolarization of the sinus node increases and the focus of earliest activation within the node typically shifts more leftward and closer to the superior septal aspect of the crista terminalis, thus producing taller p waves in the inferior limb leads when compared to normal sinus rhythm.

Sinus tachycardia is considered physiologic when it is an appropriate response to exercise, stress, or illness. Sinus tachycardia can be difficult to distinguish from focal atrial tachycardia (see below) that originates from a focus near the sinus node. A causative factor (such as exertion) and a gradual increase and decrease in rate favors sinus tachycardia, whereas an abrupt onset and offset favor atrial tachycardia. The distinction can be difficult and occasionally requires extended ECG monitoring or even invasive electrophysiology study. Treatment for physiologic sinus tachycardia is aimed at the underlying condition (**Table 276-2**).

Nonphysiologic Sinus Tachycardia *Inappropriate sinus tachycardia* is an uncommon condition in which the sinus rate increases spontaneously at rest or out of proportion to physiologic stress or exertion.

TABLE 276-1 SUPRAVENTRICULAR TACHYCARDIA**I. Physiologic sinus tachycardia**

Defining feature: normal sinus mechanism precipitated by exertion, stress, concurrent illness (Table 276-2)

II. Pathologic supraventricular tachycardia**A. Tachycardia originating from the atrium**

Defining feature: tachycardia may continue despite beats that fail to conduct to the ventricles, indicating that the AV node is not participating in the tachycardia circuit

1. Inappropriate sinus tachycardia

Defining feature: tachycardia from the normal sinus node area that occurs without an identifiable precipitating factor as a result of dysfunctional autonomic regulation

2. Focal atrial tachycardia

Defining feature: Regular atrial tachycardia with defined p wave; may be sustained, nonsustained, paroxysmal, or incessant. Frequent sites of origin occur along the valve annuli of left or right atrium, pulmonary veins, coronary sinus musculature, superior vena cava

3. Atrial flutter – macroreentrant atrial tachycardia

Defining feature: organized reentry creates organized atrial activity, commonly seen as sawtooth flutter waves at rates typically faster than 200 beats/min

- a. Common atrial flutter

- i. Right atrial reentry parallel to the tricuspid annulus and dependent on conduction through the isthmus between the inferior vena cava and tricuspid annulus

1. Counterclockwise (as viewed from the ventricular aspect)
2. Clockwise

- b. Atypical atrial flutter

- i. Usually due to reentry in left or right atrium associated with scars usually from prior surgery or catheter ablation for atrial fibrillation, but may be idiopathic

4. Atrial fibrillation

Defining feature: chaotic rapid atrial electrical activity with variable ventricular rate; the most common sustained cardiac arrhythmia in older adults

5. Multifocal atrial tachycardia

Defining feature: multiple discrete p waves often seen in patients with pulmonary disease during acute exacerbations of pulmonary insufficiency

B. AV nodal reentry tachycardia

Defining feature: paroxysmal regular tachycardia with P waves visible at the end of the QRS complex or not visible at all; the most common paroxysmal sustained tachycardia in healthy young adults; more common in women

C. Tachycardias associated with accessory atrioventricular pathways

- a. Orthodromic AV reentry tachycardia

Defining feature: paroxysmal sustained tachycardia similar to AV nodal reentry; during sinus rhythm, evidence of ventricular preexcitation may be present (Wolff-Parkinson-White syndrome) or absent (concealed accessory pathway)

- b. Preexcited tachycardia

Defining feature: wide QRS tachycardia with QRS morphology similar to VT

1. Antidromic AV reentry – regular paroxysmal tachycardia
2. Atrial fibrillation with preexcitation – irregular wide complex, or intermittently wide complex tachycardia, some with dangerously rapid rates faster than 250/min
3. Atrial tachycardia or flutter with preexcitation

Abbreviations: AV, atrioventricular; VT, ventricular tachycardia.

Affected individuals are often women in the third or fourth decade of life. Fatigue, dizziness, and even syncope may accompany palpitations, which can be disabling. Additional symptoms of chest pain, headaches, and gastrointestinal upset are common. It must be distinguished from appropriate sinus tachycardia and from focal atrial tachycardia, as discussed above. Misdiagnosis of physiologic sinus tachycardia with an anxiety disorder is common. Therapy is often ineffective or poorly tolerated. Careful titration of beta blockers and/or

or calcium channel blockers may reduce symptoms. Clonidine and serotonin reuptake inhibitors have also been used. Ivabradine, a drug that blocks the I_r current causing sinus node depolarization, is promising but is not approved for use in the United States. Catheter ablation of the sinus node has been used, but long-term control of symptoms is usually poor, and it often leaves young individuals with a permanent pacemaker.

When symptomatic sinus tachycardia occurs with postural hypotension, the syndrome is called *postural orthostatic tachycardia syndrome* (POTS). Symptoms are often similar to those in patients with inappropriate sinus tachycardia. POTS is sometimes due to autonomic dysfunction following a viral illness and may resolve spontaneously over 3–12 months. Volume expansion with salt supplementation, oral fludrocortisone, compression stockings, and the α -agonist midodrine, often in combination, can be helpful. Exercise training has also been purported to improve symptoms.

Focal Atrial Tachycardia Focal atrial tachycardia (AT) can be due to abnormal automaticity, triggered automaticity, or a small reentry circuit confined to the atrium or atrial tissue extending into a pulmonary vein, the coronary sinus, or vena cava. It can be sustained, nonsustained, paroxysmal, or incessant. Focal AT accounts for approximately 10% of PSVT referred for catheter ablation. Nonsustained AT is commonly observed on 24-h ambulatory ECG recordings, and the prevalence increases with age. Tachycardia can occur in the absence of structural heart disease or can be associated with any form of heart disease that affects the atrium. Sympathetic stimulation is a promoting factor such that AT can be a sign of underlying illness. AT with AV block can occur in digitalis toxicity. Symptoms are similar to other supraventricular tachycardias (SVTs). Incessant AT can cause tachycardia-induced cardiomyopathy.

AT typically presents as an SVT either with 1:1 AV conduction or with AV block that can be Wenckebach type conduction or fixed (e.g., 2:1 or 3:1) block. Because it is not dependent on AV nodal conduction, AT will not terminate with AV block, and the atrial rate will not be affected, which distinguishes AT from most AV nodal-dependent SVTs, such as AV nodal reentry and AV reentry using an accessory pathway (see below). An accelerated warm-up phase after initiation or cool-down phase prior to termination also favors AT rather than AV nodal-dependent SVT. P waves are often discrete, with an intervening isoelectric segment, in contrast to atrial flutter and macroreentrant AT (see below). When 1:1 conduction to the ventricles is present, the arrhythmia can resemble sinus tachycardia typically with a P-R interval shorter than the R-P interval (Fig. 276-2). It can be distinguished from sinus tachycardia by the p-wave morphology, which usually differs from sinus p waves depending on the location of the focus. Focal AT tends to originate in areas of complex atrial anatomy, such as the crista terminalis, valve annuli, atrial septum, and atrial muscle extending along cardiac thoracic veins (superior vena cava, coronary sinus, and pulmonary veins) (Fig. 276-3), and the location can often be estimated by the P-wave morphology. AT from the right atrium has a positive P-wave morphology in lead I and biphasic P-wave morphology in lead V_1 . AT from the atrial septum will frequently have a narrower P-wave duration than sinus rhythm. AT from the left atrium will usually have a monophasic, positive P wave in lead V_1 . AT that originates from superior atrial locations, such as the superior vena cava or superior pulmonary veins, will be positive in the inferior limb leads II, III, and aVF, whereas AT from a more inferior location, such as the ostium of the coronary sinus, will inscribe negative P waves in these same leads. When the focus is in the superior aspect of the crista terminalis, close to the sinus node, however, the p wave will resemble that of sinus tachycardia. Abrupt onset and offset then favor AT rather than sinus tachycardia. Depending on the atrial rate, the P wave may fall on top of the t wave or, during 2:1 conduction, may fall coincident with the QRS. Maneuvers that increase AV block, such as carotid sinus massage, Valsalva maneuver, or administration of AV nodal-blocking agents, such as adenosine, are useful to create AV block that will expose the p wave (Fig. 276-4).

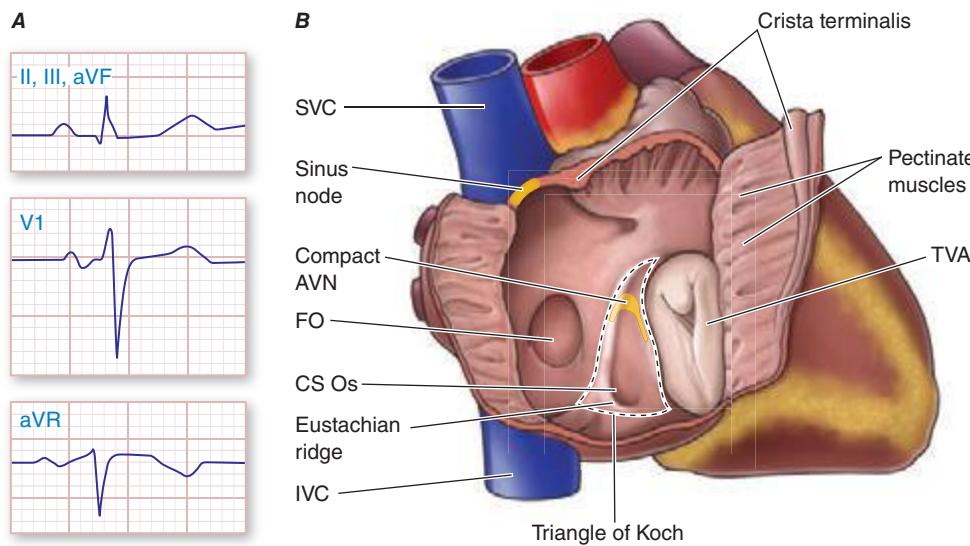


FIGURE 276-1 Right atrial anatomy pertinent to normal sinus rhythm and supraventricular tachycardia. **A.** Typical P-wave morphology during normal sinus rhythm based on standard 12-lead electrocardiogram. There is a positive P wave in leads II, III, and aVF; biphasic, initially positive P wave in V₁; and negative P wave in aVR. **B.** Right atrial anatomy seen from a right lateral perspective with the lateral wall opened to view the septum. AVN, atrioventricular node; CS Os, coronary sinus ostium; FO, fossa ovalis; IVC, inferior vena cava; SVC, superior vena cava; TVA, tricuspid valve annulus.

TABLE 276-2 COMMON CAUSES OF PHYSIOLOGIC SINUS TACHYCARDIA

1. Exercise
2. Acute illness with fever, infection, pain
3. Hypovolemia, anemia
4. Hyperthyroidism
5. Pulmonary insufficiency
6. Drugs that have sympathomimetic, vagolytic, or vasodilator properties, e.g., albuterol, theophylline, tricyclic antidepressants, nifedipine, hydralazine
7. Pheochromocytoma

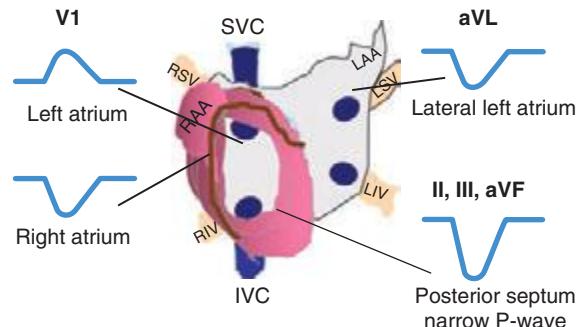
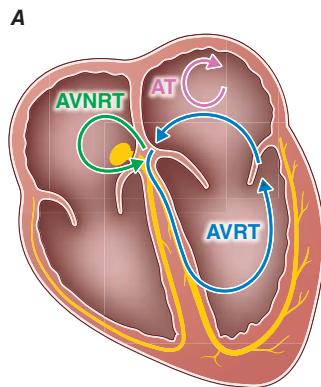


FIGURE 276-3 Location of focal atrial tachycardia focus estimated by P-wave morphology. LAA, left atrial appendage; LIV, left inferior pulmonary vein; LSV, left superior pulmonary vein; RAA, right atrial appendage; RIV, right inferior pulmonary vein; RSV, right superior pulmonary vein; SVC, superior vena cava.



- B.**
- No P-wave visible
 - AV node reentry
 - RP < PR
 - AV node reentry
 - AV reentry using an accessory pathway
 - RP < PR
 - Focal atrial tachycardia
 - AV reentry using an accessory pathway
 - AV node reentry uncommon form

FIGURE 276-2 Common mechanisms underlying paroxysmal supraventricular tachycardia along with typical R-P relationships.

A. Schematic showing a four-chamber view of the heart with atrioventricular node in green and an accessory pathway between the left atrium and left ventricle in yellow. Atrial tachycardia (AT; red circuit) is confined completely to atrial tissue. Atrioventricular nodal reentry tachycardia (AVNRT; blue circuit) uses atrioventricular (AV) nodal and perinodal atrial tissue. Atrioventricular reentry tachycardia (AVRT; black circuit) uses atrial and ventricular tissue, accessory pathway, AV node, and specialized conduction fibers (His-Purkinje) as part of the reentry circuit. **B.** Typical relation of the p wave to QRS, commonly described as the R-P to P-R relationships for the different tachycardia mechanisms.



FIGURE 276-4 Atrial tachycardia (AT) with 1:1 and 2:1 atrioventricular (AV) conduction. Arrows indicate p waves. **A.** AT with 1:1 AV relationship and R-P > P-R. **B.** Same AT with 2:1 AV relationship after AV nodal-blocking agent administered. (Adapted from F Marchlinski: The tachyarrhythmias. In Longo DL et al [eds]: *Harrison's Principles of Internal Medicine*, 18th ed. New York, McGraw-Hill, 2012, pp 1878–1900.)

Acute management of sudden-onset, sustained AT is the same as for PSVT (see below), but the response to pharmacologic therapy is variable, likely depending on the mechanism. For AT due to reentry, administration of adenosine or vagal maneuvers may transiently increase AV block without terminating tachycardia. Some ATs terminate with a sufficient dose of adenosine, consistent with triggered activity as the mechanism. Cardioversion can be effective in some, but fails in others, suggesting automaticity as the mechanism. Beta blockers and calcium channel blockers may slow the ventricular rate by increasing AV block, which can improve tolerance of the arrhythmias. Potential precipitating factors and intercurrent illness should be sought and corrected. Underlying heart disease should be considered and excluded.

For patients with recurrent episodes, beta blockers, the calcium channel blockers diltiazem or verapamil, and the antiarrhythmic drugs flecainide, propafenone, disopyramide, sotalol, and amiodarone can be effective, but potential toxicities and adverse effects often warrant avoiding these agents ([Tables 276-3, 276-4, and 276-5](#)). Catheter ablation targeting the AT

focus is effective in more than 80% of patients and is recommended for recurrent symptomatic AT when drugs fail or are not desired or for incessant AT causing tachycardia-induced cardiomyopathy.

Atrioventricular Nodal Reentry Tachycardia AV nodal reentry tachycardia (AVNRT) is the most common form of PSVT, representing approximately 60% of cases referred for catheter ablation. It most commonly manifests in the second to fourth decades of life, often in women. It is often well tolerated, but rapid tachycardia, particularly in the elderly, may cause angina, pulmonary edema, hypotension, or syncope. It is not usually associated with structural heart disease.

The mechanism is reentry involving the AV node and likely the perinodal atrium, made possible by the existence of multiple pathways for conduction from the atrium into the AV node ([Fig. 276-5](#)). In the most common form, a slowly conducting AV nodal pathway extends from the compact AV node near the bundle of His, inferiorly along the tricuspid annulus, adjacent to the coronary sinus os. The reentry wave-front propagates up this slow pathway to the compact AV node and then exits from the fast pathway at the top of the AV node. The path back to the slow pathway to complete the circuit is not defined. The conduction time from the compact AV node region to the atrium is similar to that from the compact node to the His bundle and ventricles, such that atrial activation occurs at about the same time as ventricular activation. The p wave is therefore inscribed during, slightly before, or slightly after the QRS and can be difficult to discern. Often the P wave is seen at the end of the QRS complex as a pseudo-r' in lead V₁ and pseudo-S waves in leads II, III, and aVF ([Fig. 276-5A](#)). The rate can vary with sympathetic tone. Simultaneous atrial and ventricular contraction results in atrial contraction against a closed tricuspid valve that produces cannon a waves visible in the jugular venous pulse and that the patient often perceives as a fluttering sensation in the neck. Elevated venous pressures may also lead to release of natriuretic peptides that cause posttachycardia diuresis. Less frequently, the AV nodal reentry circuit revolves in the opposite direction and gives rise to a tachycardia with an R-P interval longer than the P-R interval, similar to AT. The p wave will have the morphology noted above, and in contrast to ATs, maneuvers or medications that produce AV block terminate the arrhythmia.

Acute treatment is the same as for PSVT (discussed below). Whether ongoing therapy is warranted depends on the severity of symptoms and frequency of episodes. Reassurance and instruction as to performance of the Valsalva maneuver to terminate episodes are sufficient for many patients. Administration of an oral beta blocker, verapamil, or diltiazem at the onset of an episode has been used to

TABLE 276-3 COMMONLY USED ANTIARRHYTHMIC AGENTS—INTRAVENOUS DOSE RANGE/PRIMARY INDICATION

Drug	Loading	Maintenance	Primary Indication	Class ^a
Adenosine	6–18 mg (rapid bolus)	N/A	Terminate reentrant SVT involving AV node	—
Amiodarone	15 mg/min for 10 min, 1 mg/min for 6 h	0.5–1 mg/min	AF, AFL, SVT, VT/VF	III
Digoxin	0.25 mg q2h until 1 mg total	0.125–0.25 mg/d	AF/AFL rate control	—
Diltiazem	0.25 mg/kg over 3–5 min (max 20 mg)	5–15 mg/h	SVT, AF/AFL rate control	IV
Esmolol	500 µg/kg over 1 min	50 µg/kg per min	AF/AFL rate control	II
Ibutilide	1 mg over 10 min if over 60 kg	N/A	Terminate AF/AFL	III
Lidocaine	1–3 mg/kg at 20–50 mg/min	1–4 mg/min	VT	IB
Metoprolol	5 mg over 3–5 min × 3 doses	1.25–5 mg q6h	SVT, AF rate control; exercise-induced VT; long QT	II
Procainamide	15 mg/kg over 60 min	1–4 mg/min	Convert/prevent AF/VT	IA
Quinidine	6–10 mg/kg at 0.3–0.5 mg/kg per min	N/A	Convert/prevent AF/VT	IA
Verapamil	5–10 mg over 3–5 min	2.5–10 mg/h	SVT, AF rate control	IV

^aClassification of antiarrhythmic drugs: class I—agents that primarily block inward sodium current; class IA agents also prolong action potential duration; class II—antisympathetic agents; class III—agents that primarily prolong action potential duration; class IV—calcium channel-blocking agents.

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AV, atrioventricular; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 276-4 COMMONLY USED ANTIARRHYTHMIC AGENTS: CHRONIC ORAL DOSING/PRIMARY INDICATIONS

Drug	Dosing Oral, mg, Maintenance	Half-Life, h	Primary Route(s) of Metabolism/Elimination	Most Common Indication	Class ^a
Acebutolol	200–400 q12h	6–7	Renal/hepatic	AF rate control/SVT Long QT/RVOT VT	II
Amiodarone	100–400 qd	40–55 d	Hepatic	AF/VT prevention	III ^b
Atenolol	25–100 per d	6–9	Renal	AF rate control/SVT Long QT/RVOT VT	II
Digoxin	0.125–0.25 qd	38–48	Renal	AF rate control	—
Diltiazem	30–60 q6h	3–4.5	Hepatic	AF rate control/SVT	IV
Disopyramide	100–300 q6–8h	4–10	Renal 50%/hepatic	AF/SVT prevention	Ia
Dofetilide	0.125–0.5 q12h	10	Renal	AF prevention	III
Dronedarone	400 q12h	13–19	Hepatic	AF prevention	IIIb
Flecainide	50–200 q12h	7–22	Hepatic 75%/renal	AF/SVT/VT prevention	Ic
Metoprolol	25–100 q6h	3–8	Hepatic	AF rate control/SVT Long QT/RVOT VT	II
Mexiletine	150–300 q8–12h	10–14	Hepatic	VT prevention	Ib
Nadolol	40–240 per d	10–24	Renal	Same as metoprolol	II
Propafenone	150–300 q8h	2–8	Hepatic	AF/SVT/VT prevention	Ic
Quinidine	300–600 q6h	6–8	Hepatic 75%/renal	AF/SVT/VT prevention	Ia
Sotalol	80–160 q12h	12	Renal	AF/VT prevention	III
Verapamil	80–120 q6–8h	4.5–12	Hepatic/renal	AF rate control/RVOT VT Idiopathic LV VT	IV

^aClassification of antiarrhythmic drugs: class I—agents that primarily block inward sodium current; class II—antisympathetic agents; class III—agents that primarily prolong action potential duration; class IV—calcium channel-blocking agents. ^bAmiodarone and dronedarone both are grouped in class III, but both also have class I, II, and IV properties.

Abbreviations: AF, atrial fibrillation; LV, left ventricular; RVOT, right ventricular outflow tract; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

facilitate termination. Chronic therapy with these medications or flecainide is an option if prophylactic therapy is needed. Catheter ablation of the slow AV nodal pathway is recommended for patients with recurrent or severe episodes or when drug therapy is ineffective, not tolerated, or not desired by the patient. Catheter ablation is curative in over 95% of patients. The major risk is heart block requiring permanent pacemaker implantation, which occurs in less than 1% of patients.

Junctional Tachycardia Junctional ectopic tachycardia (JET) is due to automaticity within the AV node. It is rare in adults and more

frequently encountered as an incessant tachycardia in children, often in the perioperative period of surgery for congenital heart disease. It presents as a narrow QRS tachycardia, often with ventriculoatrial (VA) block, such that AV dissociation is present. JET can occur as a manifestation of increased adrenergic tone and may be seen after administration of isoproterenol. It may also occur for a short period of time after ablation for AVNRT.

Accelerated junctional rhythm is a junctional automatic rhythm between 50 and 100 beats/min. Initiation may occur with gradual acceleration in rate, suggesting an automatic focus, or after a premature

TABLE 276-5 COMMON AND PROARRHYTHMIC TOXICITIES OF ANTIARRHYTHMIC AGENTS

Drug	Potential Proarrhythmic Toxicities	Common Toxicities
Amiodarone	Sinus bradycardia, AV block, increase in defibrillation threshold. Rare: long QT and torsades des pointes, incessant slow VT in heart disease	Tremor, peripheral neuropathy, pulmonary fibrosis or inflammation, hypo- and hyperthyroidism, hepatitis, photosensitivity
Adenosine	Transient profound pauses, atrial fibrillation	Cough, flushing, chest pain, anxiety
Digoxin	AV block, fascicular tachycardia, accelerated junctional rhythm, atrial tachycardia with AV block	Anorexia, nausea, vomiting, visual changes
Disopyramide	Long QT and torsades des pointes, 1:1 ventricular response to atrial flutter	Anticholinergic effects, acute urinary retention (males), negative inotropy
Dofetilide	Long QT and torsades des pointes	Nausea
Dronedarone	Bradyarrhythmias and AV block, long QT and torsades des pointes (rare)	Gastrointestinal intolerance, exacerbation of heart failure
Flecainide	1:1 Ventricular response to atrial flutter; increased risk of ventricular tachycardias in patients with structural heart disease; sinus bradycardia	Dizziness, nausea, headache, decreased myocardial contractility
Ibutilide	Long QT and torsades des pointes	Nausea
Lidocaine	Slow VT in some patients with structural heart disease	Dizziness, confusion, delirium, seizures, coma
Mexiletine	Slow VT in patients with structural heart disease	Ataxia, tremor, gait disturbances, rash, nausea
Procainamide	Long QT and torsades des pointes, accelerated ventricular rate in AF or flutter	Lupus erythematosus-like syndrome (more common in slow acetylators), anorexia, nausea, neutropenia
Propafenone	1:1 Ventricular response to atrial flutter; increased risk ventricular tachycardias in patients with structural heart disease; sinus bradycardia	Taste disturbance, dyspepsia, nausea, vomiting
Quinidine	Long QT and torsades des pointes, accelerated ventricular rate in AF or flutter	Diarrhea, nausea, vomiting, cinchonism, thrombocytopenia
Sotalol	Long QT and torsades des pointes	Hypotension, bronchospasm from β-blocking effect

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; VT, ventricular tachycardia.

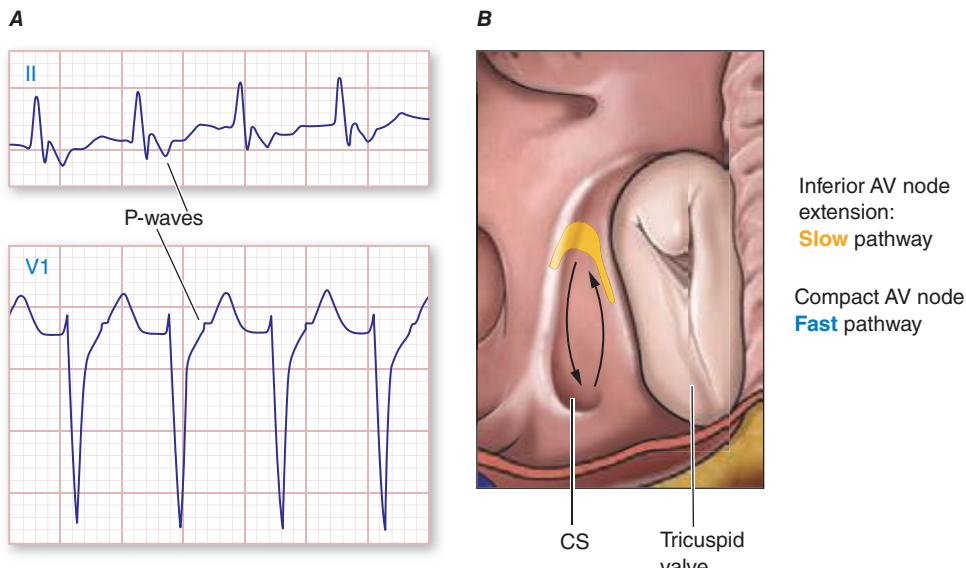


FIGURE 276-5 Atrioventricular (AV) node reentry. **A.** Leads II and V₁ are shown. P waves are visible at the end of the QRS complex and are negative in lead II, and may give the impression of S waves in the inferior limb leads II, III, and aVF and an R' in lead V₁. **B.** Stylized version of the AV nodal reentry circuit within the triangle of Koch (Fig. 276-1) that involves AV node and its extensions along with perinodal atrial tissue.

ventricular contraction, suggesting a focus of triggered automaticity. VA conduction is usually present, with p-wave morphology and timing such that it resembles slow AVNRT.

ACCESSORY PATHWAYS AND THE WOLFF-PARKINSON-WHITE SYNDROME

Accessory pathways (APs) occur in 1 in 1500–2000 people and are associated with a variety of arrhythmias including narrow-complex PSVT, wide-complex tachycardias, and, rarely, sudden death. Most patients have structurally normal hearts, but APs are associated with Ebstein's anomaly of the tricuspid valve and forms of hypertrophic cardiomyopathy including *PRKAG2* mutations, Danon's disease, and Fabry's disease.

APs are abnormal connections that allow conduction between the atrium and ventricles across the AV ring (Fig. 276-6). They are present from birth and are due to failure of complete partitioning of atrium and ventricle by the fibrous AV rings. They occur across either an AV valve annulus or the septum, most frequently between the left atrium and free wall of the left ventricle, followed by posteroseptal, right free wall, and anteroseptal locations. If the AP conducts from atrium to ventricle (antegrade) with a shorter conduction time than the AV node and His bundle, then the ventricles are preexcited during sinus rhythm, and the ECG shows a short P-R interval (<0.12 s), slurred initial portion of the QRS (delta wave), and prolonged QRS duration produced by slow conduction through direct activation of ventricular myocardium over the AP (Fig. 276-6A). The morphology of the QRS and delta wave is determined by the AP location (Fig. 276-7) and the degree of fusion between the excitation wavefronts from conduction over the AV node and conduction over the AP. Right-sided pathways preexcite the right ventricle, producing a left bundle branch block-like configuration in lead V₁, and often show marked preexcitation because of relatively close proximity of the AP to the sinus node (Fig. 276-7). Left-sided pathways preexcite the left ventricle and may produce a right bundle branch-like configuration in lead V₁ and a negative delta wave in aVL, indicating initial depolarization of the lateral portion of the left ventricle that can mimic q waves of lateral wall infarction (Fig. 276-7). Preexcitation due to an AP at the diaphragmatic surface of the heart, typically in the paraseptal region, produces delta waves that are negative in leads III and aVF, mimicking the q waves of inferior wall infarction (Fig. 276-7). Preexcitation can be intermittent and disappear during exercise as conduction over the AV node accelerates and takes over ventricular activation completely.

Wolff-Parkinson-White (WPW) syndrome is defined as a preexcited QRS during sinus rhythm and episodes of PSVT. There are a

number of variations of APs, which may not cause preexcitation and/or arrhythmias. Concealed APs allow only retrograde conduction, from ventricle to atrium, so no preexcitation is present during sinus rhythm, but SVT can occur. Fasciculoventricular connections between the His bundle and ventricular septum produce preexcitation but do not cause arrhythmia, nor do fibers such as atrio-Hisian connections, probably because the circuit is too short to promote reentry. Atriofascicular pathways, also known as Mahaim fibers, probably represent a duplicate AV node and His-Purkinje system that connect the right atrium to fascicles of the right bundle branch and conduct slowly only in the anterograde direction.

AV Reentry Tachycardia The most common tachycardia caused by an AP is the PSVT designated *orthodromic AV reentry*. The circulating reentry wavefront propagates from the atrium anterogradely over the AV node and His-Purkinje system to the ventricles and then reenters the atria via retrograde conduction over the AP (Fig. 276-6B). The QRS is narrow or may have typical right or left bundle branch block, but without preexcitation during tachycardia. Because excitation through the normal AV conduction system and AP are necessary, AV or VA block results in tachycardia termination. During sinus rhythm, preexcitation is seen if the pathway also allows anterograde conduction (Fig. 276-6A). Most commonly, during tachycardia the R-P interval is shorter than the P-R interval and can resemble AVNRT (Fig. 276-1). Unlike typical AVNRT, P-wave timing is never simultaneous with a narrow QRS complex because the ventricles must be activated before the reentry wavefront reaches the AP and conducts back to the atrium. The morphology of the P wave is determined by the pathway location, but can be difficult to assess because it is usually inscribed during the ST segment. The p wave in posteroseptal APs is negative in leads II, III, and aVF, similar to that of AV nodal reentry, but P-wave morphology differs from AV nodal reentry for pathways in other locations (Fig. 276-7).

Occasionally, an AP conducts extremely slowly in the retrograde direction, which results in tachycardia with a long R-P interval, similar to most ATs. These pathways are usually located in the septal region and have negative p waves in leads II, III, and aVF. Slow conduction facilitates reentry, often leading to nearly incessant tachycardia, known as *paroxysmal junctional reciprocating tachycardia* (PJRT). Tachycardia-induced cardiomyopathy can occur. Without an invasive electrophysiology study, it may be difficult to distinguish this form of orthodromic AV reentry from atypical AV nodal reentry or AT.

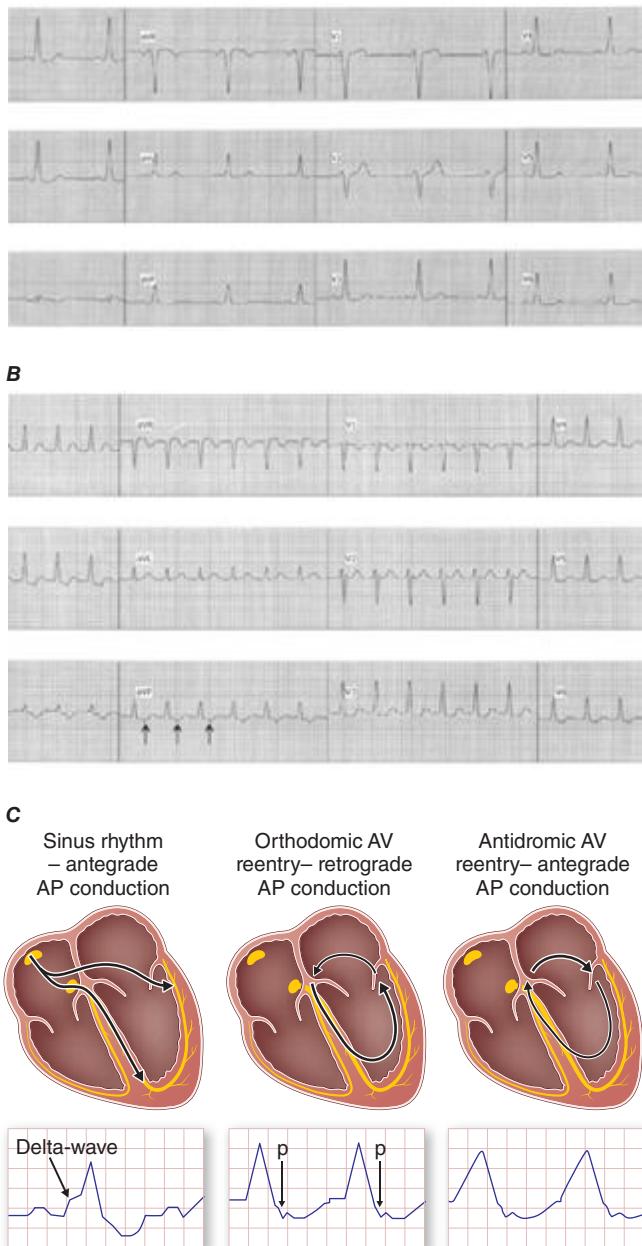


FIGURE 276-6 Wolff-Parkinson-White (WPW) syndrome. **A.** A 12-lead electrocardiogram in sinus rhythm (SR) of a patient with WPW demonstrating short P-R interval, delta waves, and widened QRS complex. This patient had an anteroseptal location of the AP. **B.** Orthodromic AV reentry in a patient with WPW syndrome using a posteroseptal AP. Note the P waves in the ST segment (arrows) seen in lead III and normal appearance of QRS complex. **C.** Three most common rhythms associated with WPW syndrome: sinus rhythm demonstrating antegrade conduction over the AP and AV node; orthodromic AVRT using retrograde conduction over the AP and antegrade conduction over the AV node; and antidromic AVRT using retrograde conduction over the AV node and antegrade conduction over the AP. AP, accessory pathway; AV, atrioventricular; AVRT, atrioventricular reentry tachycardia; WPW, Wolff-Parkinson-White.

Preexcited Tachycardias Preexcited tachycardia occurs when the ventricles are activated by antegrade conduction over the AP (Fig. 276-6C). The most common is *antidromic AV reentry* in which activation propagates from atrium to ventricle via the AP and then conducts retrogradely to the atria via the His-Purkinje system and the AV node (or rarely a

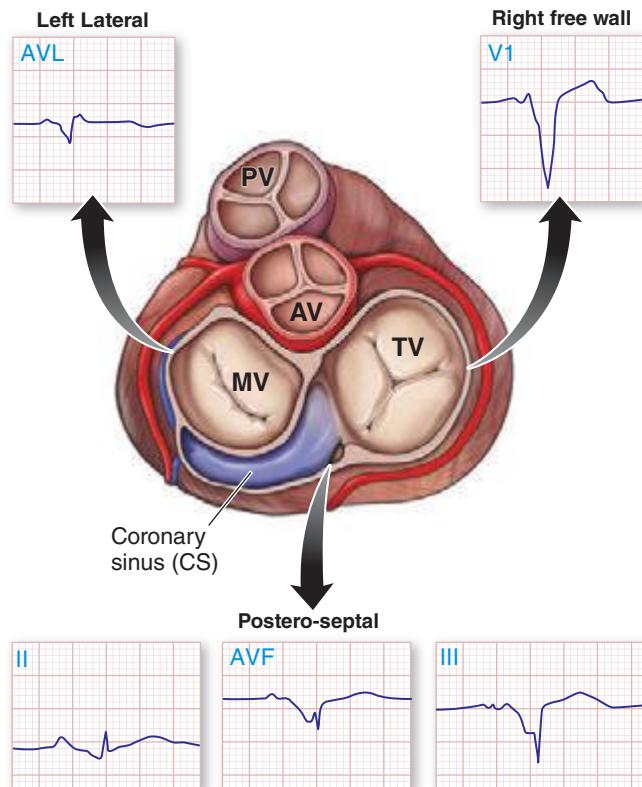


FIGURE 276-7 Potential locations for accessory pathways in patients with Wolff-Parkinson-White Syndrome and typical QRS appearance of delta waves that can mimic underlying structural heart disease such as myocardial infarction or bundle branch block. AV, atrioventricular valve; MV, mitral valve; PV, pulmonary valve; TV, tricuspid valve.

second AP). The wide QRS complex is produced entirely via ventricular excitation over the AP because there is no contribution of ventricular activation over more rapidly conducting specialized His-Purkinje fibers. This tachycardia is often indistinguishable from monomorphic ventricular tachycardia. The presence of preexcitation in sinus rhythm suggests the diagnosis.

Preexcited tachycardia also occurs if an AP allows antegrade conduction to the ventricles during AT, atrial flutter, atrial fibrillation (Fig. 276-8), or AV nodal reentry. Atrial fibrillation and atrial flutter are potentially life threatening if the AP allows very rapid repetitive conduction. Approximately 25% of APs causing preexcitation allow minimum R-to-R intervals of less than 250 ms during atrial fibrillation and are therefore associated with a risk of inducing ventricular fibrillation and sudden death. Preexcited atrial fibrillation presents as a wide-complex, very irregular rhythm. During atrial fibrillation, the ventricular rate is determined by the conduction properties of the AP and AV node. The QRS complex can appear quite bizarre and change on a beat-to-beat basis due to the variability in the degree of fusion from activation over the AV node and AP, or all beats may be due to conduction over the AP (Fig. 276-8). Ventricular activation from the Purkinje system may depolarize the ventricular end of the AP and prevent 1:1 atrial wavefront conduction over the AP. Slowing AV nodal conduction can thereby facilitate AP conduction and dangerously accelerate the ventricular rate. Administration of AV nodal-blocking agents including oral or intravenous verapamil, diltiazem, beta blockers, intravenous adenosine, and intravenous amiodarone are contraindicated. Preexcited tachycardias should be treated with electrical cardioversion or intravenous procainamide or ibutilide, which may terminate or slow the ventricular rate.

Management of Patients with Accessory Pathways Acute management of orthodromic AV reentry is discussed below for PSVT. Patients

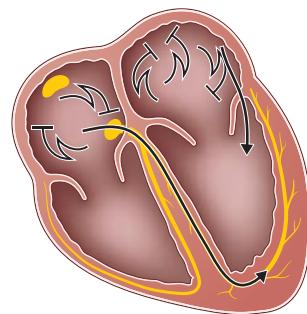


FIGURE 276-8 Preexcited atrial fibrillation (AF) due to conduction over a left free wall accessory pathway (AP). The electrocardiogram shows rapid irregular QRS complexes that represent fusion between conduction over the atrioventricular node and left free wall AP. Shortest R-R intervals between preexcited QRS complexes of less than 250 ms, as in this case, indicate a risk of sudden death with this arrhythmia.

with WPW syndrome may have wide-complex tachycardia due to antidiromic AV reentry, orthodromic AV with bundle branch block, or a preexcited tachycardia, and treatment depends on the underlying rhythm.

Initial patient evaluation should include assessment for aggravating factors, including intercurrent illness and factors that increase sympathetic tone. Examination should focus on excluding underlying heart disease. An echocardiogram is reasonable to exclude Ebstein's anomaly and hypertrophic cardiomyopathy.

Patients with preexcitation who have symptoms of arrhythmia are at risk for developing atrial fibrillation and sudden death if they have an AP with high-risk properties. The risk of cardiac arrest is in the range of 2 per 1000 patients in adults but is likely greater in children. An invasive electrophysiology study is warranted to determine if the AP is high enough risk to warrant potentially curative catheter ablation. For patients with concealed APs or known low-risk APs causing orthodromic AV reentry, chronic therapy is guided by symptoms and frequency of events. Vagal maneuvers may terminate episodes, as may a dose of beta blocker, verapamil, or diltiazem taken at the onset of an episode. Chronic therapy with these agents or flecainide can reduce the frequency of episodes in some patients. Catheter ablation is warranted for recurrent arrhythmias when drugs are ineffective, not tolerated, or not desired by the patient or if the AP is considered high risk (Fig. 276-8). Efficacy is in the range of 95% depending on the location of the AP. Serious complications occur in fewer than 3% of patients, but can include AV block, cardiac tamponade, thromboemboli, coronary artery injury, and vascular access complications. Mortality occurs in less than 1 in 1000 patients.

Adults who have preexcitation but no arrhythmia symptoms have a risk of sudden death estimated to be 1 per 1000 patient-years. Electrophysiology study is usually advised for people in occupations for which an arrhythmia occurrence would place them or others at risk, such as police, military, and pilots, or for individuals who desire evaluation for risk. Routine follow-up without therapy is reasonable in others. Children are at greater risk of sudden death, approximately 2 per 1000 patient-years.

TREATMENT

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

Acute management of narrow QRS PSVT is guided by the clinical presentation. Continuous ECG monitoring should be implemented and a 12-lead ECG should always be obtained when possible. In the presence of hypotension with unconsciousness or respiratory distress, QRS-synchronous direct current cardioversion is warranted, but this is rarely needed, because intravenous adenosine works promptly in most situations (see below). For stable individuals, initial therapy takes advantage of the fact that most PSVTs are dependent on AV nodal conduction (AV nodal reentry or orthodromic AV reentry) and therefore likely to respond to sympatholytic and vagotonic maneuvers and drugs (Fig. 276-9). As these are administered, the ECG should be continuously recorded, because the response can

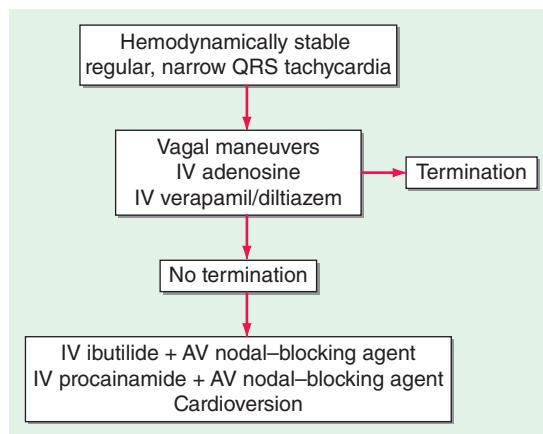


FIGURE 276-9 Treatment algorithm for patients presenting with hemodynamically stable paroxysmal supraventricular tachycardia. AV, atrioventricular.

1484 establish the diagnosis. AV block with only transient slowing of tachycardia may expose ongoing p waves, indicating AT or atrial flutter as the mechanism.

Carotid sinus massage is reasonable provided the risk of carotid vascular disease is low, as indicated by absence of carotid bruits and no prior history of stroke. A Valsalva maneuver should be attempted in cooperative individuals, and if effective, the patient can be taught to perform this maneuver as needed. If vagal maneuvers fail or cannot be performed, intravenous adenosine will terminate the vast majority of PSVT by transiently blocking conduction in the AV node. Adenosine may produce transient chest pain, dyspnea, and anxiety. It is contraindicated in patients with prior cardiac transplantation due to potential hypersensitivity. It can theoretically aggravate bronchospasm. Adenosine precipitates atrial fibrillation, which is usually brief, in up to 15% of patients, so it should be used cautiously in patients with WPW syndrome in whom AF may produce hemodynamic instability. Intravenous beta blockers and calcium channel blockers (verapamil or diltiazem) are also effective but may cause hypotension before and after arrhythmia termination and have a longer duration of action. These agents can also be given orally and can be taken by the patient on an as-needed basis to slow ventricular rate and facilitate termination by Valsalva maneuver.

The differential diagnosis of wide-complex tachycardia includes ventricular tachycardia (Chap. 277), PSVT with bundle branch block aberrancy, and preexcited tachycardia (see above). In general, these should be managed as ventricular tachycardia until proven otherwise. If the tachycardia is regular and the patient is stable, a trial of intravenous adenosine is reasonable. Very irregular wide-complex tachycardia should be managed with cardioversion, intravenous procainamide, or ibutilide, which presumes preexcited atrial fibrillation or flutter (see above). If the diagnosis of PSVT with aberrancy is unequivocal, as may be the case in patients with prior episodes, treatment for PSVT is reasonable. In all cases, continuous ECG monitoring should be implemented, and emergency cardioversion and defibrillation should be available.

COMMON ATRIAL FLUTTER AND MACRORENTRANT ATRIAL TACHYCARDIAS

Macrorentrant atrial tachycardia is due to a large reentry circuit, often associated with areas of scar in the atria. *Common or typical right atrial flutter* is due to a circuit that revolves around the tricuspid valve annulus, bounded anteriorly by the annulus and posteriorly by functional conduction block in the crista terminalis. The wavefront passes through an isthmus between the inferior vena cava and the tricuspid valve annulus, known as the sub-Eustachian or cavotricuspid isthmus, where it is susceptible to interruption by catheter ablation. Thus, common atrial flutter is *cavotricuspid isthmus-dependent atrial flutter*. This circuit most commonly revolves in a counterclockwise direction (as viewed looking toward the tricuspid annulus from the ventricular aspect), which produces the characteristic negative sawtooth flutter waves in leads II, III, and aVF and positive P waves in lead V₁ (Fig. 276-10). When the direction is reversed, clockwise rotation produces the opposite P-wave vector in those leads. The atrial rate is typically 240–300 beats/min but may be slower in the presence of atrial disease or antiarrhythmic drugs. It often conducts to the ventricles with 2:1 AV block, creating a regular tachycardia at 150 beats/min, with p waves that may be difficult to discern. Maneuvers that increase AV nodal block will typically expose flutter waves, allowing diagnosis.

Common right atrial flutter often occurs in association with atrial fibrillation and with atrial scar from senescence or prior cardiac surgery. Some patients with atrial fibrillation that is treated with an antiarrhythmic drug, particularly flecainide, propafenone, or amiodarone, will present with atrial flutter rather than fibrillation.

Macrorentrant ATs that are not dependent on conduction through the cavotricuspid isthmus are referred to as *atypical atrial flutters*. They can occur in either atrium and are usually associated with areas of scar. Left atrial flutter and perimitral left atrial flutter are commonly seen after extensive left atrial ablation for atrial fibrillation or atrial surgery. The clinical presentation is similar to common atrial flutter, but with different P-wave morphologies. They can be difficult to distinguish from focal AT, and in most cases, the mechanism can only be confirmed by an electrophysiology study.

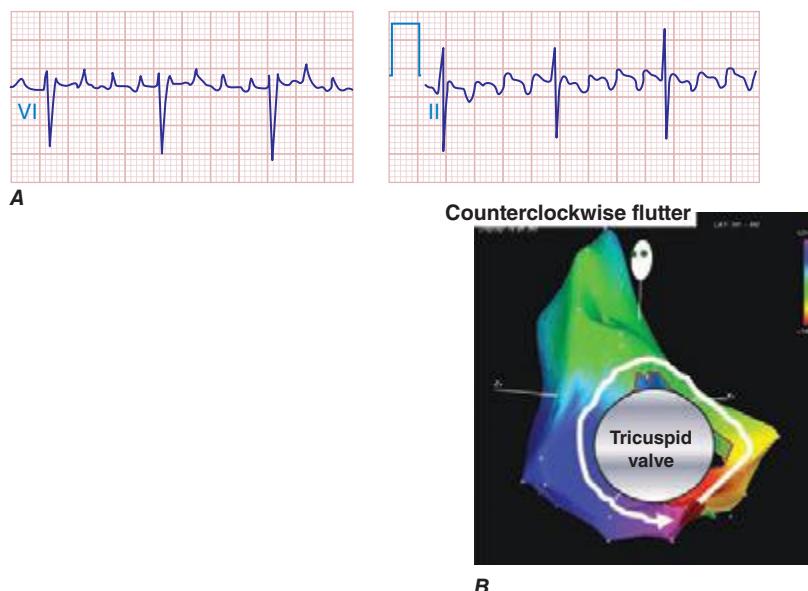


FIGURE 276-10 **A.** Common right atrial flutter, also known as cavotricuspid isthmus flutter, showing positive P waves in lead V₁ and negative "sawtooth" pattern in lead II typical of counterclockwise rotation relative to the tricuspid valve annulus. (*Adapted from F Marchlinski: The tachyarrhythmias. In Longo DL et al [eds]: Harrison's Principles of Internal Medicine, 18th ed. New York, McGraw-Hill, 2012, pp 1878–1900.*) **B.** A right atrial map of common counterclockwise flutter is shown. Colors indicate activation time, progressing from red to yellow to green, blue, and purple. The reentry path parallels the tricuspid annulus.

TREATMENT ATRIAL FLUTTER AND MACROREENTRANT ATRIAL TACHYCARDIAS

Initial management of atrial flutter is similar to that for atrial fibrillation, discussed in more detail below. Electrical cardioversion is warranted for hemodynamic instability or severe symptoms. Otherwise, rate control can be achieved with administration of AV nodal-blocking agents, but this is often more difficult than for atrial fibrillation. The risk of thromboembolic events is felt to be similar to that associated with atrial fibrillation. Anticoagulation is warranted prior to conversion for episodes more than 48 h in duration and chronically for patients at increased risk of thromboembolic stroke based on the CHA₂DS₂-VASc scoring system (Table 276-6).

For a first episode of atrial flutter, conversion to sinus rhythm with no antiarrhythmic drug therapy is reasonable. For recurrent episodes, antiarrhythmic drug therapy with sotalol, dofetilide, disopyramide, and amiodarone may be considered, but more than 70% of patients experience recurrences. For recurrent episodes of common atrial flutter, catheter ablation of the cavoatrial isthmus abolishes the arrhythmia in over 90% of patients with a low risk of complications that are largely related to vascular access and infrequent heart block. Approximately 50% of patients presenting with atrial flutter develop atrial fibrillation within the next 5 years.

MULTIFOCAL ATRIAL TACHYCARDIA

Multifocal AT (MAT) is characterized by at least three distinct P-wave morphologies with rates typically between 100 and 150 beats/min. Unlike atrial fibrillation, there are clear isoelectric intervals between P waves (Fig. 276-11). The mechanism is likely triggered automaticity from multiple atrial foci. It is usually encountered in patients with chronic pulmonary disease and acute illness.

TREATMENT MULTIFOCAL ATRIAL TACHYCARDIA

Therapy for MAT is directed at treating the underlying disease and correcting any metabolic abnormalities. Electrical cardioversion has no effect. The calcium channel blockers verapamil or diltiazem may slow the atrial and ventricular rate. Patients with severe pulmonary disease often do not tolerate beta-blocker therapy. MAT may respond to amiodarone, but long-term therapy with this agent is usually avoided due to its toxicities, particularly pulmonary fibrosis.

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is characterized by disorganized, rapid, and irregular atrial activation with loss of atrial contraction and with an irregular ventricular rate that is determined by AV nodal conduction (Fig. 276-12). In an untreated patient, the ventricular rate also tends

TABLE 276-6 CHA₂DS₂-VASc RISK ASSESSMENT AND ORAL ANTICOAGULANTS

Risk Factors	Points		CHA ₂ DS ₂ -VASc Score	Estimated Annual Stroke Rate ^a
C – congestive heart failure	1		0	0
H – hypertension	1		1	1.3%
A – age \geq 75 y	2		2	2.2%
D – diabetes mellitus	1		3	3.2%
S – stroke or TIA, embolus	2		4	4.0%
V – vascular disease	1		5	6.7%
A – age 65–75 y	1		6–9	>9%
Sex – female	1			
Anticoagulants	Mechanism	Excretion	Dosing Considerations	Risk/Benefit
Warfarin	Vitamin K antagonist	Liver	Adjusted to INR 2–3 Days to therapeutic effect Multiple drug/food interactions (e.g., amiodarone)	Major hemorrhage: 1% per year Intracranial hemorrhage: 0.1–0.6% per year Risk of bleeding increases with INR >3.5 Inexpensive
Dabigatran ^b	Thrombin inhibitor	Kidney	CCr >30 mL/min CCr 15–30 mL/min	Onset of action within hours No reversal agent for bleeding
			P-glycoprotein substrate (inducers – rifampin, reduce concentration) (inhibitors – amiodarone, verapamil, dronedarone, quinidine), Proton pump inhibitors may reduce absorption	
Rivaroxaban	Xa inhibitor	Kidney	CCr \geq 50 mL/min CCr 15–50 mL/min	P-glycoprotein substrate 20 mg daily 15 mg daily
				No reversal agent for bleeding
Apixaban	Xa inhibitor	Kidney and liver	Cr >1.5 mg/dL	P-glycoprotein substrate 2.5 mg bid
				No reversal agent for bleeding

^aModified from GY Lip et al: Lancet 379:648, 2012. ^bU.S. Food and Drug Administration recommended dosing; other regimens are available outside the United States.

Abbreviations: CCr, creatinine clearance; Cr, creatinine; INR, international normalized ratio; TIA, transient ischemic attack.



FIGURE 276-11 Multifocal atrial tachycardia. Rhythm strip obtained from a patient with severe pulmonary disease during an acute illness. Arrows note three distinct P-wave morphologies.

to be rapid and variable, between 120 and 160 beats/min, but in some patients, it may exceed 200 beats/min. Patients with high vagal tone or AV nodal conduction disease may have slow rates.

AF is the most common sustained arrhythmia and is a major public health problem. Prevalence increases with age, and more than 95% of AF patients are older than 60 years of age. The prevalence by age 80 is approximately 10%. The lifetime risk of developing AF for individuals 40 years old is approximately 25%. AF is slightly more common in men than women and more common in whites than blacks. Risk factors for developing AF in addition to age include hypertension, diabetes mellitus, cardiac disease, and sleep apnea. AF is a marker for heart disease, the severity of heart disease, and age, and it is therefore difficult to determine the extent to which AF itself contributes to associated increased mortality and morbidity. AF is associated with increased risk of developing heart failure. AF increases the risk of stroke by fivefold and is estimated to be the cause of 25% of strokes. It also increases the risk of dementia.

AF is occasionally associated with an acute precipitating factor such as hyperthyroidism, acute alcohol intoxication, or an acute illness

including myocardial infarction or pulmonary embolism. AF occurs in up to 30% of patients recovering from cardiac surgery, associated with inflammatory pericarditis.

The clinical type of AF suggests the underlying pathophysiology (Fig. 276-12). Paroxysmal AF is defined as episodes that start and stop spontaneously. It is often initiated by small reentrant or rapidly firing foci in sleeves of atrial muscle along the pulmonary veins. Catheter ablation that isolates these foci usually abolishes the AF. Persistent AF has a longer duration, exceeding 7 days, and, in many cases, will continue unless cardioversion is performed. Cardioversion can be followed by prolonged periods of sinus rhythm. Episodes may be initiated by rapidly firing foci, but persistence of the arrhythmia is likely due to single or multiple areas of reentry facilitated by structural and electrophysiologic atrial abnormalities. In patients with long-standing persistent AF (>1 year), significant structural changes are present in the atrium that support reentry and automaticity, making it difficult to restore and maintain sinus rhythm. Some patients progress over years from paroxysmal to persistent AF. Fibrosis that develops with

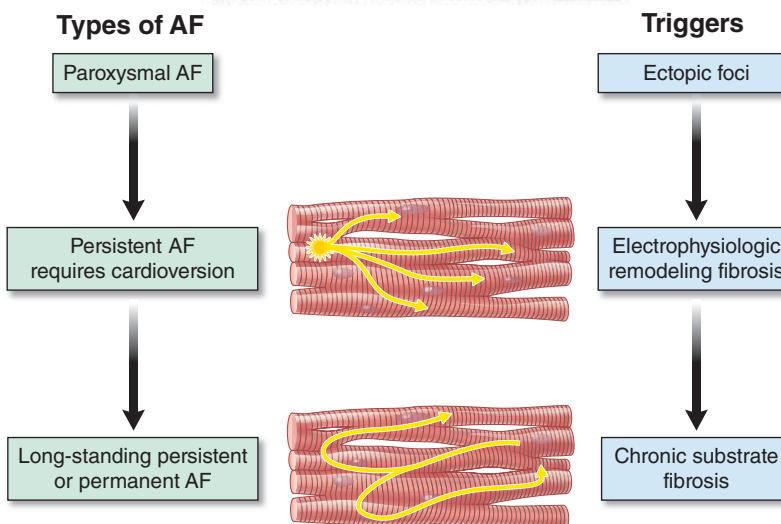
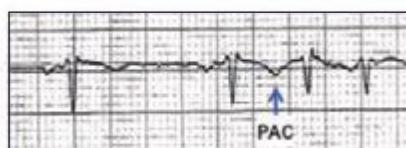
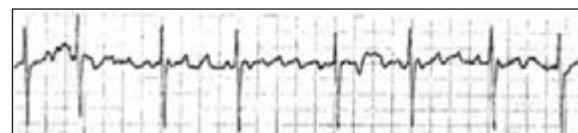


FIGURE 276-12 A rhythm strip of atrial fibrillation (AF) showing no distinct P-wave morphology and irregular ventricular response.

Diagram depicts atrial fibrillation types. Paroxysmal AF is initiated by premature beats, as shown in the rhythm strip (arrow) after two sinus beats. Triggering foci are often an important cause of this arrhythmia. Persistent AF is associated with atrial structural and electrophysiologic remodeling, as well as with triggering foci in many patients. Long-standing persistent AF is associated with greater structural remodeling with atrial fibrosis and electrophysiologic remodeling.

aging and atrial hypertrophy in response to hypertension and other cardiac disease may be an important promoting factor, although electrophysiologic changes to conduction and refractoriness occur as well in response to chronic tachycardia in the atrium.

Clinical consequences are related to rapid ventricular rates, loss of atrial contribution to ventricular filling, and predisposition to thrombus formation in the left atrial appendage with potential embolization. Presentations vary with the ventricular rate and underlying heart disease and comorbidities. Many patients are asymptomatic. Rapid rates may cause hemodynamic collapse or heart failure exacerbations particularly in patients with impaired cardiac function, hypertrophic cardiomyopathy, and heart failure with preserved systolic function. Exercise intolerance and easy fatigability are common. Occasionally, dizziness or syncope occurs due to pauses when AF terminates to sinus rhythm (Fig. 276-13).

TREATMENT ATRIAL FIBRILLATION

Treatment for AF is primarily guided by patients' symptoms, the hemodynamic effect of AF, the duration of AF if there are persistent risk factors for stroke, and underlying heart disease. Oral anticoagulation in high-risk patients with AF includes vitamin K antagonists or the newer anticoagulants such as thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban), but not antiplatelet agents (aspirin and clopidogrel), which have substantially less effect.

New-onset AF that produces severe hypotension, pulmonary edema, or angina should be electrically cardioverted starting with a QRS synchronous shock of 200 J, ideally after sedation or anesthesia is achieved. Greater shock energy and different electrode placements may be tried if the shock fails to terminate AF. If AF terminates and reinitiates, administration of an antiarrhythmic drug, such as ibutilide, and repeat cardioversion may be considered. If the patient is stable, immediate management involves rate control to alleviate or prevent

symptoms, anticoagulation if appropriate, and cardioversion to restore sinus rhythm if AF is persistent. Anticoagulation strategies for new-onset AF are debated. In the absence of contraindications, it is usually appropriate to initiate systemic anticoagulation with heparin immediately, while evaluation and other therapies are implemented.

CARDIOVERSION AND ANTICOAGULATION

Cardioversion within 48 h of the onset of AF is common practice in patients who have not been anticoagulated, provided that they are not at high risk for stroke due to a prior history of embolic events, rheumatic mitral stenosis, or hypertrophic cardiomyopathy with marked left atrial enlargement. These patients are usually at risk of recurrence, such that initiation of anticoagulation is considered based on the patient's individual risk for stroke, commonly assessed from the CHA₂DS₂-VASC score.

If the duration of AF exceeds 48 h or is unknown, there is greater concern for thromboembolism with cardioversion, even in patients considered low risk for stroke. There are two approaches to mitigate the risk related to cardioversion. One option is to anticoagulate continuously for 3 weeks before and a minimum of 4 weeks after cardioversion. A second approach is to start anticoagulation and perform a transesophageal echocardiogram to determine if thrombus is present in the left atrial appendage. If thrombus is absent, cardioversion can be performed and anticoagulation continued for a minimum of 4 weeks because recovery of atrial mechanical function after electrical or pharmacologic cardioversion may be delayed and thrombus can form and embolize days after cardioversion. Some patients may merit ongoing anticoagulation after cardioversion, depending on stroke risk profile.

RATE CONTROL

Acute rate control can be achieved with beta blockers and/or the calcium channel blockers verapamil and diltiazem administered either intravenously or orally, as warranted by the urgency of the clinical situation. Digoxin may be added, particularly in heart failure

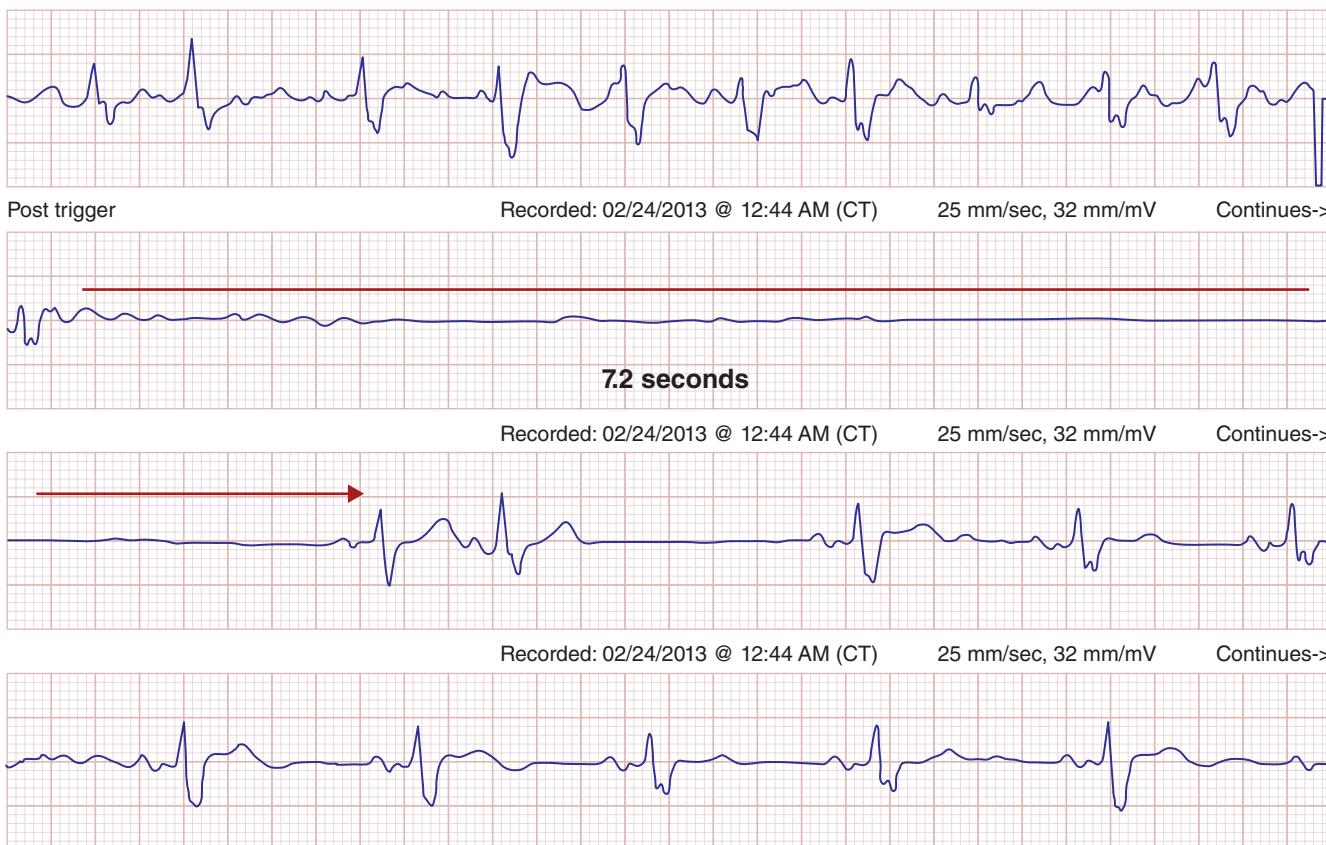


FIGURE 276-13 A continuous rhythm strip is shown. Atrial fibrillation is present at the top and abruptly terminates in the second tracing, with atrial and ventricular standstill for 7.2 s until resumption of sinus rhythm. The patient experienced syncope.

1488 patients, because it does not have negative inotropic effects, particularly if use of AV nodal-blocking agents is limited by poor tolerance or is contraindicated. Its effect is modest but synergistic with the other AV nodal-blocking agents, but it is particularly limited when sympathetic tone is elevated. Typically, the goal of acute rate control is to reduce the ventricular rate to less than 100/min, but the goal must be guided by the clinical situation.

CHRONIC RATE CONTROL

For patients who remain in AF chronically, the goal of rate control is to alleviate and prevent symptoms and prevent deterioration of ventricular function from excessive rates. β -Adrenergic blockers, calcium channel blockers, and digoxin are used, sometimes in combination. Rate should be assessed with exertion and medications adjusted accordingly. Exertion-related symptoms are often an indication of inadequate rate control. The initial goal is a resting heart rate of less than 80 beats/min that increases to less than 100 beats/min with light exertion, such as walking. If it is difficult to slow the ventricular rate to that degree, allowing a resting rate of up to 110 beats/min is acceptable provided it does not cause symptoms and ventricular function remains normal. Periodic assessment of ventricular function is warranted because some patients develop tachycardia-induced cardiomyopathy.

If adequate rate control in AF is difficult to achieve, further consideration should be given to restoring sinus rhythm. Catheter ablation of the AV junction to create heart block and implantation of a permanent pacemaker reliably achieve rate control without the need for AV nodal agents, but implement life-long permanent pacing. Right ventricular apical pacing induces dyssynchronous ventricular activation that can be symptomatic or depress ventricular function in some patients. Biventricular pacing may be used to minimize the degree of ventricular dyssynchrony.

STROKE PREVENTION IN ATRIAL FIBRILLATION

The majority of patients warrant chronic anticoagulation, but selection of therapy should be individualized based on patient profile and risks and benefits of individual agents. Anticoagulation with a vitamin K antagonist is warranted for all patients with AF who have rheumatic mitral stenosis or mechanical heart valves for whom the newer anticoagulants have not been tested. Anticoagulation with a vitamin K antagonist (warfarin) or the newer oral anticoagulants is warranted for patients who have had more than 48 h of AF and are undergoing cardioversion, for patients who have a prior history of stroke, or for patients with a CHA₂DS₂-VASc score of ≥ 2 , but it may be considered in patients with a risk score of 1. The approach to patients with paroxysmal AF is the same as for persistent AF. It is recognized that many patients who appear to have infrequent AF episodes often have asymptomatic episodes that put them at risk. Absence of AF during periodic monitoring is not sufficient to indicate low risk. The role of continuous monitoring with implanted recorders or pacemakers is not yet clear as a guide for anticoagulation in patients with a borderline risk profile. Bleeding is the major risk of anticoagulation. Major bleeding requiring transfusion or in a critical area (e.g., intracranial) occurs in approximately 1% of patients per year. Risk factors for bleeding include age $>65\text{--}75$ years, heart failure, history of anemia, and excessive alcohol or nonsteroidal anti-inflammatory drug use. Patients with coronary stents who require antiplatelet therapy with aspirin and a thienopyridine are at particularly high risk of bleeding.

Warfarin reduces the annual risk of stroke by 64% compared to placebo and by 37% compared to antiplatelet therapy. The newer anticoagulants, dabigatran, rivaroxaban, and apixaban, have been found to be noninferior to warfarin in individual trials, and analysis of pooled data suggests superiority to warfarin by small absolute margins of 0.4–0.7% in reduction of mortality, stroke, major bleeding, and intracranial hemorrhage. Warfarin is an inconvenient agent that requires several days to achieve a

therapeutic effect (prothrombin time [PT]/international normalized ratio [INR] >2), requires monitoring of PT/INR to adjust dose, and has many drug and food interactions, thus limiting patient compliance. The newer agents are easier to use and achieve reliable anticoagulation promptly without requiring dosage adjustment based on blood tests. Dabigatran, rivaroxaban, and apixaban have renal excretion, cannot be used with severe renal insufficiency, and require dose adjustment for modest renal impairment, which is of particular concern in the elderly, who are at increased bleeding risk. Excretion can also be influenced by P-glycoprotein inducers and inhibitors. Warfarin anticoagulation can be reversed by administration of fresh frozen plasma and vitamin K. Reversing agents for the newer anticoagulants are lacking (but in development), and bleeding must be managed with supportive care, with the expectation that clotting will improve over 12 h as the anticoagulant is excreted.

The antiplatelet agents aspirin and clopidogrel are inferior to warfarin for stroke prevention in AF and do not reduce the risk of bleeding. Clopidogrel combined with aspirin is better than aspirin alone but inferior to warfarin and has greater bleeding risk than aspirin alone.

Chronic anticoagulation is contraindicated in some patients due to bleeding risks. Because most atrial thrombi are felt to originate in the left atrial appendage, surgical removal of the appendage, combined with atrial maze surgery, may be considered for patients undergoing surgery, although removal of the appendage has not been unequivocally shown to reduce the risk of thromboembolism. Percutaneous devices that occlude or ligate the left atrial appendage are being studied for safety and efficacy.

RHYTHM CONTROL

The decision to administer antiarrhythmic drugs or perform catheter ablation to attempt maintenance of sinus rhythm (commonly referred to as the "rhythm control strategy") is mainly guided by patient symptoms and preferences regarding the benefits and risks of therapies. In general, patients who maintain sinus rhythm have better survival than those who continue to have AF. This is likely because continued AF is a marker of disease severity. In randomized trials, administration of antiarrhythmic medications to maintain sinus rhythm did not improve survival or symptoms compared to a rate control strategy, and the drug therapy group had more hospitalizations. Disappointing efficacy and toxicities of available antiarrhythmic drugs and patient selection bias may be factors that influenced the results of these trials. The impact of catheter ablation on mortality is not known. A rhythm control strategy is usually selected for patients with symptomatic paroxysmal AF, a first episode of symptomatic persistent AF, AF with difficult rate control, and AF that has resulted in depressed ventricular function or that aggravates heart failure. A rhythm control strategy is more likely to be favored in younger patients than in sedentary or elderly patients in whom rate control is usually easily achieved. Even if sinus rhythm is apparently maintained, anticoagulation is recommended according to the CHA₂DS₂-VASc stroke risk profile because asymptomatic episodes of AF are common. Following a first episode of persistent AF, a strategy using AV nodal-blocking agents, cardioversion, and anticoagulation is reasonable, in addition to addressing possible aggravating factors, including hypertension, heart failure, and sleep apnea. If recurrences are infrequent, periodic cardioversion is reasonable.

Pharmacologic Therapy for Maintaining Sinus Rhythm The goal of pharmacologic therapy is to maintain sinus rhythm or reduce episodes of AF. Drug therapy can be instituted once sinus rhythm has been established or in anticipation of cardioversion. β -Adrenergic blockers and calcium channel blockers help control ventricular rate, improve symptoms, and possess a low-risk profile, but have low efficacy for preventing AF episodes. Risks and side effects of antiarrhythmic drugs are a major consideration in selecting

therapy. Class I sodium channel-blocking agents (e.g., flecainide, propafenone, disopyramide) are options for subjects without significant structural heart disease, but they have negative inotropic and proarrhythmic effects that warrant avoidance in patients with coronary artery disease or heart failure. The class III agents sotalol and dofetilide can be administered to patients with coronary artery disease or structural heart disease but have approximately a 3% risk of inducing excessive QT prolongation and torsades des pointes. Dofetilide should be initiated only in a hospital with ECG monitoring, and many physicians take this approach with sotalol as well. Dronedarone increases mortality in patients with heart failure. All of these agents have modest efficacy in patients with paroxysmal AF, of whom approximately 30–50% will benefit. Amiodarone is more effective, maintaining sinus rhythm in approximately two-thirds of patients. It can be administered to patients with heart failure and coronary artery disease. Over 20% of patients experience toxicities during long-term therapy.

CATHETER AND SURGICAL ABLATION FOR ATRIAL FIBRILLATION

Catheter ablation avoids antiarrhythmic drug toxicities but has procedural risks and requires an experienced center. For patients with previously untreated but recurrent paroxysmal AF, catheter ablation has similar efficacy to antiarrhythmic drug therapy and is superior to antiarrhythmic drugs for patients who have recurrent AF despite drug treatment. The procedure involves cardiac catheterization, transatrial septal puncture, and radiofrequency ablation or cryoablation to electrically isolate the regions around the pulmonary veins, abolishing the effect of triggering foci to interact with the left atrial AF substrate. Extensive areas of ablation are required, and gaps in healed ablation areas necessitate a repeat procedure in 20–50% of patients. Sinus rhythm is maintained for more than 1 year after one procedure in approximately 60% of patients and in 70–80% of patients after multiple procedures. Some patients become more responsive to antiarrhythmic drugs.

There is a 2–7% risk of major complications, including stroke (0.5–1%), cardiac tamponade (1%), phrenic nerve paralysis, bleeding from femoral access sites, and fluid overload with heart failure, that can emerge 1–3 days after the procedure. It is important to recognize the potential for delayed presentation of some complications. Ablation within the pulmonary veins can lead to pulmonary vein stenosis, presenting weeks to months after the procedure with dyspnea or hemoptysis. Esophageal ulcers can form immediately after the procedure and may rarely lead to a fistula between the left atrium and esophagus (estimated incidence of 0.1%) that presents as endocarditis and stroke 10 days to 3 weeks after the procedure.

Catheter ablation is less effective for persistent AF. More extensive ablation is often required, including areas that likely support reentry in regions outside the pulmonary venous antra, but individual strategies are debated. More than one ablation procedure is often required to maintain sinus rhythm.

Surgical ablation of AF is typically performed concomitant with cardiac valve or coronary artery surgery and less commonly as a stand-alone procedure; however, for patients with persistent AF, surgical or hybrid procedures may have higher single-procedure efficacy. Risks include sinus node injury requiring pacemaker implantation. Surgical removal of the left atrial appendage may reduce stroke risk, although thrombus can form in the remnant of the appendage or if the appendage is not completely ligated.

ACKNOWLEDGMENT

Portions of this chapter were retained from the work of the previous author, Francis Marchlinski.

Arrhythmias that originate in the ventricular myocardium or His-Purkinje system include premature ventricular beats, ventricular tachycardias that can be sustained or nonsustained, and ventricular fibrillation. Arrhythmia may emerge from a focus of myocardial or Purkinje cells capable of automaticity, or triggered automaticity, or from reentry through areas of scar or a diseased Purkinje system. Ventricular arrhythmias are often associated with structural heart disease and are an important cause of sudden death (Chap. 327). They also occur in some structurally normal hearts, in which case they are usually benign. Evaluation and management are guided by the risk of arrhythmic death, which is assessed based on symptoms, type of arrhythmia, and associated underlying heart disease.

DEFINITIONS

Ventricular arrhythmias are characterized by their electrocardiographic appearance and duration. Conduction away from the ventricular focus through the ventricular myocardium is slower than activation of the ventricles over the Purkinje system. Hence, the QRS complex during ventricular arrhythmias will be wide, typically >0.12 s.

Premature ventricular beats (also referred to as *premature ventricular contractions* [PVCs]) are single ventricular beats that fall earlier than the next anticipated supraventricular beat (Fig. 277-1). PVCs that originate from the same focus will have the same QRS morphology and are referred to as unifocal (Fig. 277-1A). PVCs that originate from different ventricular sites have different QRS morphologies and are referred to as multifocal (Fig. 277-1B). Two consecutive ventricular beats are *ventricular couples*.

Ventricular tachycardia (VT) is three or more consecutive beats at a rate faster than 100 beats/min. Three or more consecutive beats at slower rates are designated an *idioventricular rhythm* (Fig. 277-1C). VT that terminates spontaneously within 30 s is designated *nonsustained* (Fig. 277-2), whereas *sustained* VT persists longer than 30 s or is terminated by an active intervention, such as administration of an intravenous medication, external cardioversion, or pacing or a shock from an implanted cardioverter-defibrillator.

Monomorphic VT has the same QRS complex from beat to beat, indicating that the activation sequence is the same from beat to beat and that each beat likely originates from the same source (Fig. 277-3A). The initial site of ventricular activation largely determines the sequence of ventricular activation. Therefore, the QRS morphology of PVCs and monomorphic VT provides an indication of the site of origin within the ventricles (Fig. 277-4). The likely origin often suggests whether an arrhythmia is idiopathic or associated with structural disease. Arrhythmias that originate from the right ventricle or septum result in late activation of much of the left ventricle, thereby producing a prominent S wave in V_1 referred to as a left bundle branch block-like configuration. Arrhythmias that originate from the free wall of the left ventricle have a prominent positive deflection in V_1 , thereby producing a right bundle branch block-like morphology in V_1 . The frontal plane axis of the QRS is also useful. An axis that is directed inferiorly, as indicated by dominant R waves in leads II, III, and AVF, suggests initial activation of the cranial portion of the ventricle, whereas a frontal plane axis that is directed superiorly (dominant S waves in II, III, and AVF) suggests initial activation at the inferior wall.

Very rapid monomorphic VT has a sinusoidal appearance, also called *ventricular flutter*, because it is not possible to distinguish the QRS complex from the T wave (Fig. 277-3B). Relatively slow *sinusoidal* VTs have a wide QRS indicative of slowed ventricular conduction (Fig. 277-3C). Hyperkalemia, toxicity from excessive effects of drugs that blocks sodium channels (e.g., flecainide, propafenone, or



FIGURE 277-1 Examples of types of premature ventricular contractions (PVCs). **A.** Unifocal PVCs follow every sinus beat in a bigeminal frequency. Trace shows electrocardiogram lead 1 and arterial pressure (Art. Pr.). Sinus rhythm beats are followed by normal arterial waveform. The arterial pressure following premature beats is attenuated (arrows) and imperceptible to palpation. The pulse in this patient is registered at half the heart rate. **B.** Multifocal PVCs. The two PVCs shown have different morphologies. **C.** Example of accelerated idioventricular rhythm. The second QRS is a normally conducted beat. All other QRS complexes on this rhythm strip are ventricular due to accelerated idioventricular rhythm.

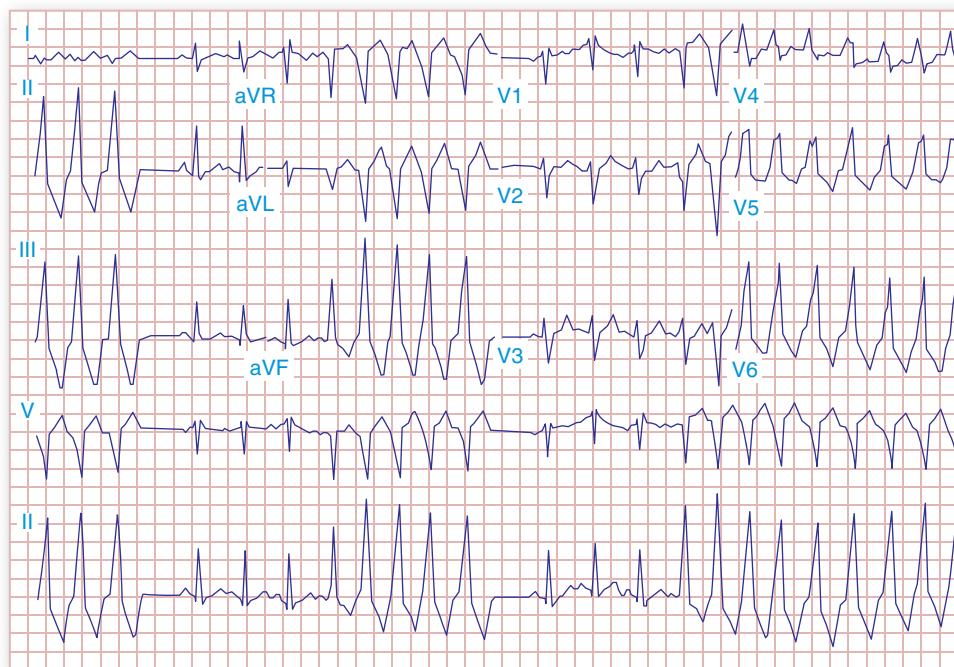


FIGURE 277-2 Repetitive monomorphic nonsustained ventricular tachycardia (VT) of right ventricular outflow tract origin. The VT has a left bundle branch block pattern with inferior axis with tall QRS complexes in the inferior leads.

tricyclic antidepressants), and severe global myocardial ischemia are causes.

Polymorphic VT has a continually changing QRS morphology indicating a changing ventricular activation sequence. Polymorphic VT that occurs in the context of congenital or acquired prolongation of the QT interval often has a waxing and waning QRS amplitude creating a “twisting about the points” appearance referred to as *Torsade de Pointes* (Fig. 277-3D).

Ventricular fibrillation (VF) has continuous irregular activation with no discrete QRS complexes (Fig. 277-3E). Monomorphic or polymorphic VT may transition to VF in susceptible patients.

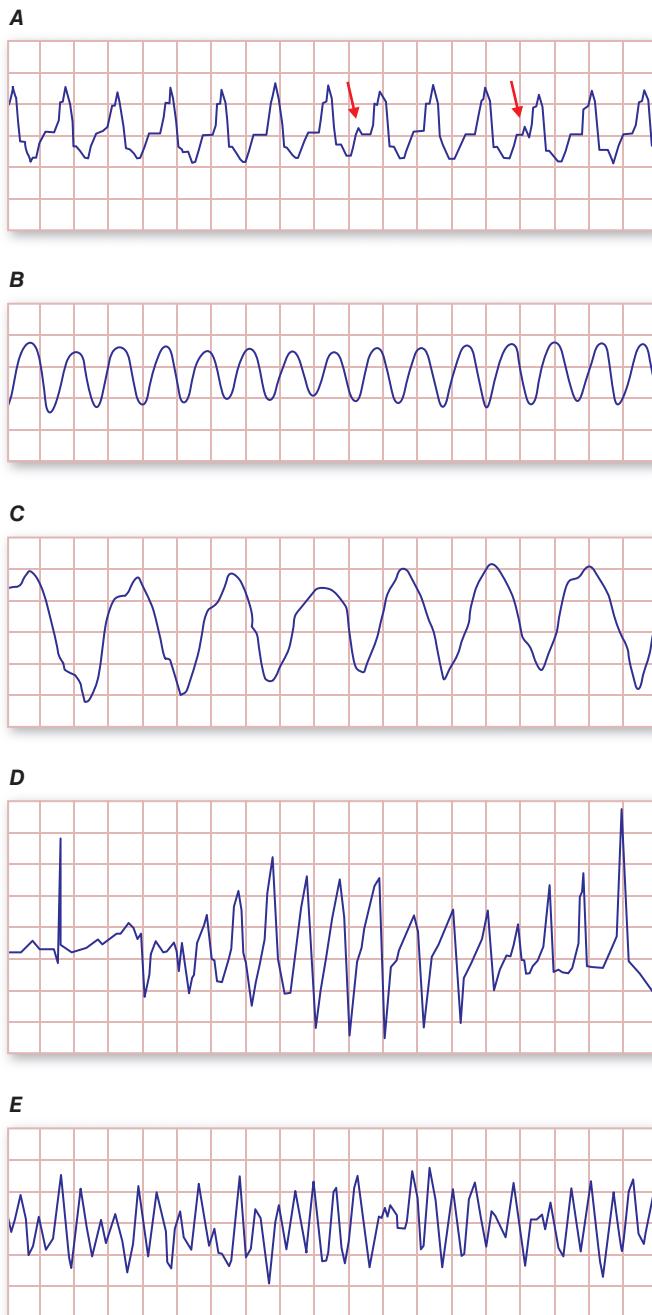


FIGURE 277-3 Examples of types of ventricular tachycardia (VT).

- A. Monomorphic VT with dissociated P waves (*short arrows*).
- B. Ventricular flutter.
- C. Sinusoidal VT due to electrolyte disturbance or drug effects.
- D. Polymorphic VT resulting from prolongation of QT interval (*torsade de pointes* VT).
- E. Ventricular fibrillation.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Common symptoms of ventricular arrhythmias include palpitations, dizziness, exercise intolerance, episodes of lightheadedness, syncope, or sudden death. These arrhythmias can be asymptomatic and encountered unexpectedly as an irregular pulse or heart sounds on examination, or seen on a routine electrocardiogram (ECG), exercise test, or cardiac ECG monitoring.

Syncope is a concerning symptom that can be due to an episode of VT with hypotension. Syncope due to a ventricular arrhythmia often indicates that there is a significant risk for subsequent cardiac arrest and sudden death with arrhythmia recurrence. Although benign causes of syncope, such as reflex-mediated neurocardiogenic (vasovagal) syncope and orthostatic hypotension, are generally more common, it is important to consider the possibility of heart disease or a genetic syndrome causing VT. When these are suspected, hospitalization for further evaluation and monitoring is often appropriate.

Sustained VT may present with cardiac arrest, often with degeneration of the VT to VF. Occasionally a sustained VT will be hemodynamically tolerated and present with diminished exercise capacity or exacerbation of heart failure. Many patients who are at risk for VT have known heart disease and may have an implantable cardioverter-defibrillator (ICD). In patients with an ICD, spontaneous episodes of VT may elicit an episode of transient lightheadedness, palpitations, or syncope that may be followed by a shock from the ICD (see below).

The diagnosis of ventricular arrhythmias is established by recording of the arrhythmia on an ECG or, in some cases, initiation of the arrhythmia during an electrophysiologic study (Table 277-1). A 12-lead ECG of the arrhythmia should be obtained when possible and often provides clues to the potential site of origin and possible presence of underlying heart disease (see above). When the arrhythmia is intermittent with days to weeks between symptoms, prolonged ambulatory monitoring to capture the ECG at the time of symptoms is required to make the diagnosis. Continuous ambulatory monitoring or looping event recording monitors are options. Exercise testing should be considered in patients with exercise-induced symptoms.

APPROACH TO THE PATIENT: Documented or Suspected Ventricular Arrhythmias

Initial assessment focuses on hemodynamic stability and evaluation for underlying heart disease. A family history of sudden death or cardiomyopathy suggests the possibility of a genetic basis for the arrhythmia and greater risk. The electrocardiogram can provide important clues. Patients with benign idiopathic arrhythmias usually have a completely normal ECG during sinus rhythm.

Cardiac imaging is warranted to assess ventricular function and look for evidence of depressed ventricular function indicative of a cardiomyopathy or ventricular hypertrophy that may indicate hypertrophic cardiomyopathy. Cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement can detect areas of ventricular scar, which are usually present in patients who are at risk for sustained monomorphic VT (Fig. 277-5). Evaluation to exclude atherosclerotic coronary artery disease should be performed in patients at risk, guided by age and other risk factors.

SPECIFIC ARRHYTHMIAS

PVCs and Nonsustained VT Ventricular extrasystoles (Fig. 277-1A) can be due to automaticity or reentry (Chap. 278e). PVCs can be a sign of increased sympathetic tone; myocardial ischemia; hypoxia; electrolyte abnormalities, particularly hypokalemia; or underlying heart disease. During myocardial ischemia or in association with other heart disease, PVCs can be a harbinger of sustained VT or

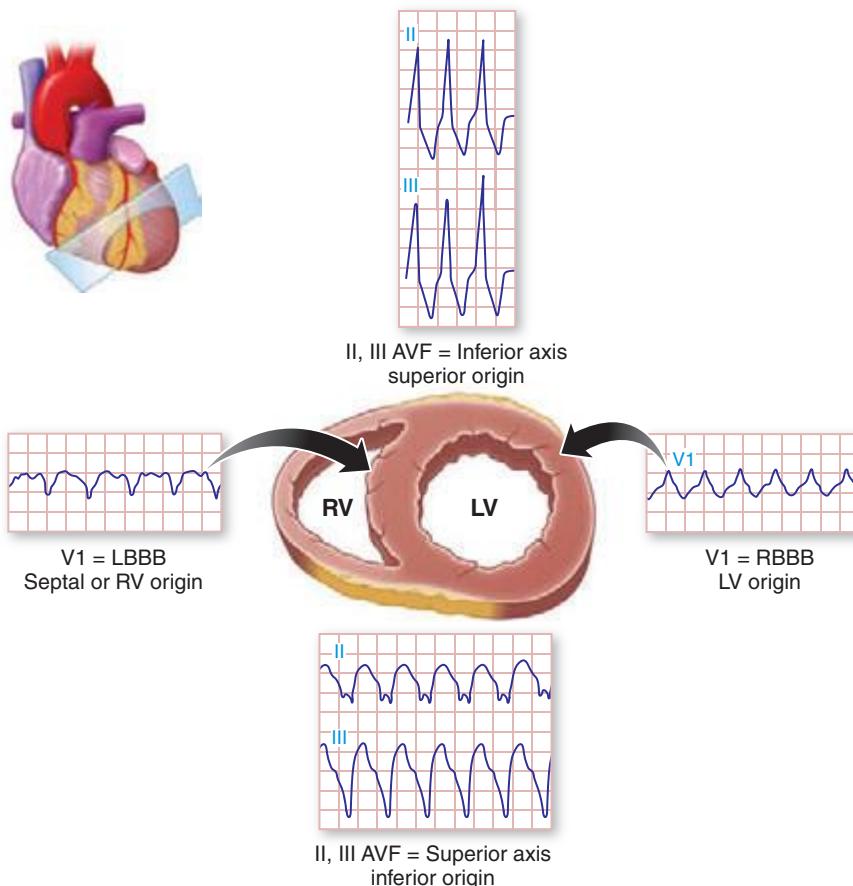


FIGURE 277-4 Site of VT origin based on QRS morphology. LBBB, left bundle branch block; LV, left ventricle; RBBB, right bundle branch block; RV, right ventricle.

TABLE 277-1 DIAGNOSTIC TESTS FOR VENTRICULAR ARRHYTHMIAS

- I. 12-Lead ECG
 - A. Should be obtained for PVCs, nonsustained VT, and monomorphic VT when possible
 - B. QRS morphology suggests ventricular region of origin
 - V1 – dominant S = septum or RV
 - V1 – dominant R = LV
 - Superior axis = inferior wall origin
 - Inferior axis = outflow region or anterior wall
- II. Ambulatory monitoring
 - A. 24- to 48-h continuous Holter monitor
 - Useful for evaluation of daily symptoms to quantitate PVCs
 - B. Event recorder: can be used for weeks at a time
 - Useful for evaluation of infrequent symptoms
 - Some require patient activation and will miss asymptomatic arrhythmias
- III. Exercise testing
 - A. Useful for evaluating exercise-induced arrhythmias and symptoms
 - B. QT interval response to exercise may be abnormal in long QT syndrome
- IV. Invasive electrophysiology study
 - A. Can establish definitive diagnosis of VT versus supraventricular tachycardia with aberrancy or ventricular preexcitation
 - B. Can provoke some arrhythmias that are otherwise infrequent
 - C. Allows potential catheter ablation
 - D. Procedural risks determined by vascular access, whether ablation is performed, and the location of the arrhythmia substrate

Abbreviation: RV, right ventricle. See text for other abbreviations.

VF. In patients with heart disease, a higher frequency of ectopy and complexity (couplets and nonsustained VT) are associated with more severe disease and, in those with heart failure, with increased mortality. However, suppression of these arrhythmias with antiarrhythmic drugs does not improve survival. In the absence of cardiac disease, PVCs and nonsustained VT generally have a benign prognosis. PVCs that occur at a bigeminal frequency may not generate sufficient cardiac output for a radial pulse and hence may register at rates half that of the heart rate (Fig. 277-1A). Very frequent PVCs can depress ventricular function (see below).

EVALUATION AND MANAGEMENT When encountered during acute illness or as a new finding, evaluation should focus on detection and correction of potential aggravating factors and causes, specifically myocardial ischemia, ventricular dysfunction, and electrolyte abnormalities, most commonly hypokalemia. Underlying heart disease should be defined.

The ECG characteristics of the arrhythmia are often suggestive of whether structural heart disease is present. PVCs with smooth uninterrupted contours and sharp QRS deflections suggest an ectopic focus in relatively normal myocardium, whereas broad notching and slurred QRS deflections suggest a diseased myocardial substrate. The most frequent site of origin for idiopathic ventricular arrhythmias is the right ventricular outflow tract, giving rise to PVCs or VT that have a left bundle branch block configuration, with an inferiorly directed frontal plane axis as discussed below (Fig. 277-2). However, QRS

morphology alone is not reliable as an indicator of disease or subsequent risk. Nonsustained VT is usually monomorphic with rates less than 200 beats/min and typically lasts less than 8 beats (Fig. 277-2). Nonsustained VT that is very rapid, polymorphic, or with a first beat that occurs prior to the peak of the T wave (“short-coupled”) is uncommon and should prompt careful evaluation for underlying disease or genetic syndromes associated with sudden death.

A family history of sudden death should prompt evaluation for genetic syndromes associated with sudden death, including cardiomyopathy, long QT syndrome, and arrhythmogenic right ventricular cardiomyopathy (see below). Any abnormality on the 12-lead ECG warrants further evaluation (Fig. 277-6). Repolarization abnormalities are seen in a number of genetically determined syndromes associated with sudden death, including the long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy (ARVC), and hypertrophic cardiomyopathy. An echocardiogram is often necessary to assess ventricular function, wall motion abnormalities, and valvular heart disease. Cardiac magnetic resonance (CMR) imaging is also useful for this purpose and for the detection of ventricular scarring that is the substrate for sustained VT (Fig. 277-5). Exercise stress testing should be performed in patients with effort-related symptoms and in those at risk for coronary artery disease.

IDIOPATHIC PVCs AND NONSUSTAINED VT For PVC and nonsustained VT in the absence of structural heart disease or a genetic sudden death syndrome, no specific therapy is needed unless the patient has significant symptoms or evidence that frequent PVCs are depressing ventricular function (see below). Reassurance that the arrhythmia is benign is often sufficient to allow the patient to cope with the symptoms, which will often wax and wane in frequency over years. Avoiding stimulants, such as caffeine, is helpful in some patients. If symptoms require treatment, β -adrenergic blockers and nondihydropyridine calcium channel blockers (verapamil and diltiazem) are sometimes helpful (see Table 276-3). If these fail, more potent antiarrhythmic drugs or catheter

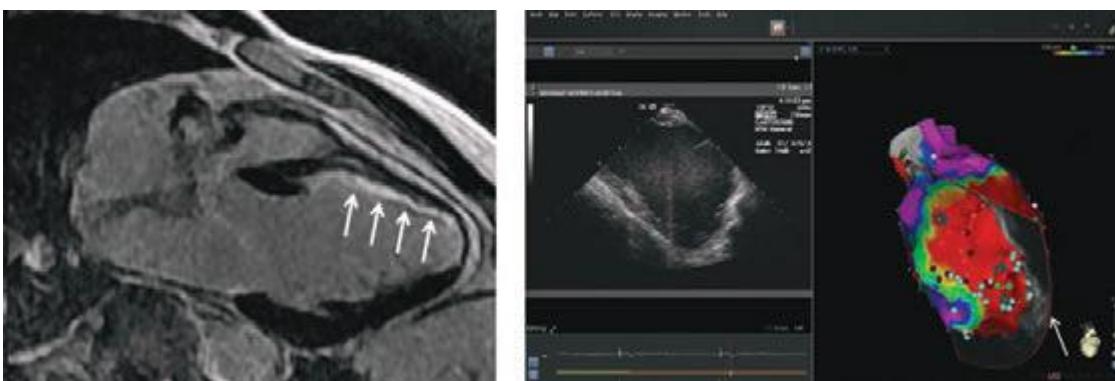


FIGURE 277-5 Imaging studies of the left ventricle (LV) used to assist ablation for ventricular tachycardia (VT). Left panel is a magnetic resonance image of a longitudinal section demonstrating thinning of the anterior wall and late gadolinium enhancement in a subendocardial scar (white arrows). The middle panel shows a two-dimensional image of the LV in long axis corresponding to the sector through the mid LV (arrow, right panel) obtained by an intracardiac echo probe positioned in the right ventricle. An electroanatomic three-dimensional map of the LV in the left anterior oblique projection is displayed in the right panel. The purple color depicts areas of normal voltage (>1.5 mV). Blue, green, and yellow represent progressively lower voltages with the red areas indicating scar (<0.5 mV). Channels of viable myocardium with slow conduction within the scar are identified with the light blue dots. Areas of ablation delivered to regions involved in reentrant VT are indicated by maroon dots.

ablation can be considered. The antiarrhythmic agents flecainide, propafenone, mexiletine, and amiodarone can be effective, but the potential for side effects warrants careful consideration. Catheter ablation can be effective if the arrhythmia occurs with sufficient frequency or is readily provoked such that its origin can be identified for ablation in a similar manner to that for idiopathic monomorphic VT as discussed below. Benefit must be carefully weighed against the procedure-related risks (see below).

PVCs AND NONSUSTAINED VT ASSOCIATED WITH ACUTE CORONARY SYNDROMES

During and early after acute myocardial infarction (MI), PVCs and nonsustained VT are common and can be an early manifestation of ischemia and a harbinger of subsequent VF. Treatment with β -adrenergic blockers and correction of hypokalemia and hypomagnesemia reduce the risk of VF. Routine administration of the

antiarrhythmic drugs such as lidocaine has not been shown to reduce mortality and is not indicated for suppression of PVCs or asymptomatic nonsustained VT.

Following recovery from acute MI, frequent PVCs (typically >10 PVCs per hour), repetitive PVCs with couplets, and nonsustained VT are markers for depressed ventricular function and increased mortality, but routine antiarrhythmic drug therapy to suppress these arrhythmias is not warranted. Treatment with the sodium channel blocker flecainide increased mortality. Amiodarone therapy reduces sudden death, but does not improve total mortality. Therefore, amiodarone is an option for treatment of symptomatic arrhythmias in this population when the potential benefit outweighs its potential toxicities. β -Adrenergic blockers reduce sudden death but have limited effect on spontaneous arrhythmias.

For survivors of an acute MI, an ICD reduces mortality in certain high-risk groups: patients who have survived >40 days after the acute MI and have a left ventricular (LV) ejection fraction of ≤ 0.30 or who have an ejection fraction <0.35 and have symptomatic heart failure (functional class II or III); and patients >5 days after MI who have a reduced LV ejection fraction, nonsustained VT, and inducible sustained VT or VF on electrophysiologic testing. ICDs do not reduce mortality when routinely implanted soon after MI or in patients after recent coronary artery revascularization surgery.

PVCs AND NONSUSTAINED VT ASSOCIATED WITH DEPRESSED VENTRICULAR FUNCTION AND HEART FAILURE

PVCs and nonsustained VT are common in patients with depressed ventricular function and heart failure and are markers for disease severity and increased mortality, but antiarrhythmic drug therapy to suppress these arrhythmias has not been shown to improve survival. Antiarrhythmic drugs whose major action is blockade of the cardiac sodium channel (flecainide, propafenone, mexiletine, quinidine, and disopyramide) are avoided in patients with structural heart disease because of a risk of proarrhythmia, negative inotropic effects, and increased mortality. Therapy with the potassium channel blockers, e.g., dofetilide, does not reduce mortality. Amiodarone suppresses ventricular ectopy and reduces sudden death but does not improve overall survival. ICDs are the major

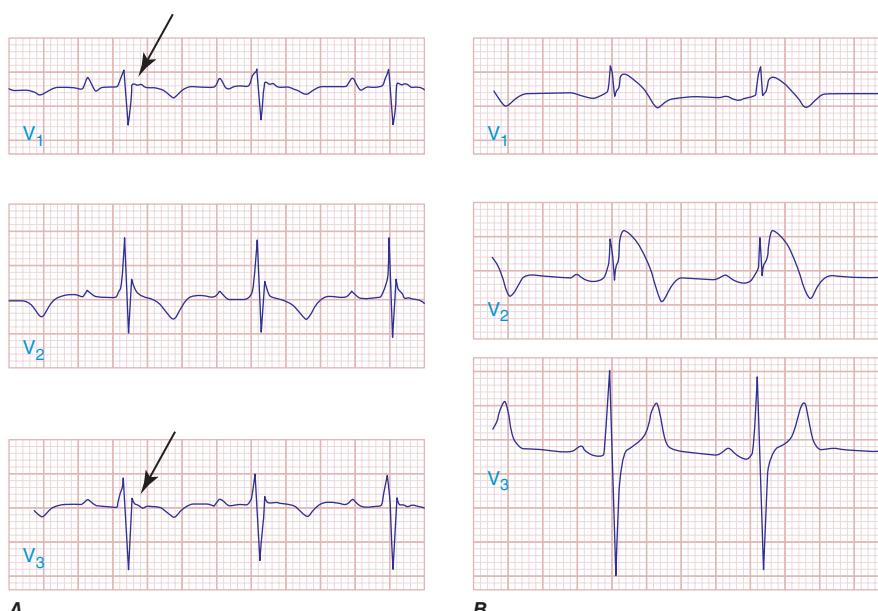


FIGURE 277-6 Precordial chest leads V_1 – V_3 showing typical abnormalities of arrhythmogenic right ventricular cardiomyopathy (ARVC) (A) and Brugada syndrome (B). In ARVC, there is T inversion and delayed ventricular activation manifest as epsilon waves (arrows). Panel B shows ST elevation in V_1 and V_2 typical of the Brugada syndrome. (Figures reproduced from F Marchlinski: The tachyarrhythmias. In Longo DL et al [eds]: Harrison's Principles of Internal Medicine, 18th edition. New York, McGraw-Hill, 2012, pp 1878–1900.)

1494 therapy to protect against sudden death in patients at high risk and are recommended for those with LV ejection fraction <0.35 and New York Heart Association class II and III heart failure, in whom they reduce mortality by 20%, from 36% to 29%, over 5 years.

OTHER CARDIAC DISEASES Ventricular ectopy is associated with increased mortality in patients with *hypertrophic cardiomyopathy* (Chap. 287) or with *congenital heart disease* (Chap. 282) associated with right ventricular or LV dysfunction. In these patients, management is similar to that for patients with ventricular dysfunction. Pharmacologic suppression of the arrhythmia has not been shown to improve mortality. ICDs are indicated for patients considered at high risk for sudden cardiac death.

PVC-INDUCED VENTRICULAR DYSFUNCTION Very frequent ventricular ectopy and repetitive nonsustained VT (Fig. 277-2) can depress ventricular function, possibly through an effect similar to chronic tachycardia or by inducing ventricular dyssynchrony. Depression of ventricular function rarely occurs unless PVCs account for more than 10–20% of total beats over a 24-h period. Often the PVCs are idiopathic and unifocal, most commonly originating from the LV papillary muscles or outflow tract regions where they can be targeted for ablation. The distinction between PVC-induced ventricular dysfunction as compared to a cardiomyopathic process causing ventricular dysfunction and arrhythmia is difficult and in some cases can be made only retrospectively by observing an improvement in ventricular function after the arrhythmia is suppressed with an antiarrhythmic drug, such as amiodarone, or by catheter ablation.

Idioventricular Rhythms Three or more ventricular beats at a rate slower than 100 beats/min are termed *idioventricular rhythm* (Fig. 277-1C). Automaticity is the likely mechanism. Idioventricular rhythms are common during acute MI (Chap. 295) and may emerge during sinus bradycardia. Atropine may be administered to increase the sinus rates if the loss of atrioventricular synchrony leads to hemodynamic compromise. This rhythm is also common in patients with cardiomyopathies or sleep apnea. It can also be idiopathic, often emerging when the sinus rate slows during sleep. Therapy should target any underlying cause and correction of bradycardia. Specific therapy for asymptomatic idioventricular rhythm is not necessary.

Sustained Monomorphic VT Sustained monomorphic VT presents as a wide QRS tachycardia that has the same QRS configuration from beat to beat, indicating an identical sequence of ventricular depolarization for each beat (Fig. 277-3A). VT originates from a stable focus or reentry circuit. In structural heart disease, the substrate is often an area of patchy replacement fibrosis due to infarction, inflammation, or prior cardiac surgery that creates anatomical or functional reentry pathways (Fig. 277-5). Less commonly, VT is related to reentry or automaticity in a diseased Purkinje system. In the absence of structural heart disease, idiopathic VT can present as sustained monomorphic VTs that are due to focal automaticity or reentry involving a portion of the Purkinje system.

The clinical presentation can vary depending on the rate of the arrhythmia, underlying cardiac function, and autonomic adaptation in response to the arrhythmia. Whereas patients with normal cardiac function might tolerate rapid VTs, those with severe LV dysfunction often experience symptoms of hypotension, even if VT is not particularly fast. Monomorphic VT may deteriorate to VF, which may be the initial cardiac rhythm recorded at the time of resuscitation.

DIAGNOSIS Sustained monomorphic VT has to be distinguished from other causes of uniform wide QRS tachycardia. These include supraventricular tachycardia with left or right bundle branch block aberrant conduction, supraventricular tachycardias conducted to the ventricles over an accessory pathway (Chap. 276), and rapid cardiac pacing in a patient with a pacemaker or defibrillator. In the presence of known heart disease, VT is the most likely diagnosis of a wide QRS tachycardia. Hemodynamic stability during the arrhythmia does not exclude VT. A number of ECG criteria have been evaluated. The presence of AV dissociation is usually a reliable marker for VT (Fig. 277-7), but P waves can be difficult to define. A P wave following each QRS does not

VT versus Supraventricular Tachycardia with Aberrancy

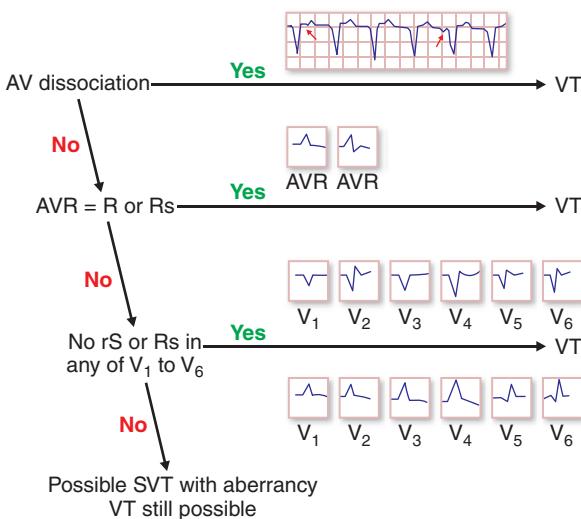


FIGURE 277-7 Algorithm for differentiation of ventricular tachycardia (VT) from supraventricular tachycardia (SVT) with aberrancy. AV, atrioventricular.

exclude VT because 1:1 conduction from ventricle to atrium can occur. A monophasic R wave or Rs complex in AVR or concordance from V_1 to V_6 of monophasic R or S waves is also relatively specific for VT (Fig. 277-7). Other QRS morphology criteria have also been described, but all have limitations and are not very reliable in patients with severe heart disease. In patients with known bundle branch block, the same QRS morphology during tachycardia as during sinus rhythm suggests supraventricular tachycardia rather than VT, but is not absolutely reliable. An electrophysiologic study is sometimes required for definitive diagnosis. Rarely, noise and movement artifacts on telemetry recordings can simulate VT; prompt recognition can avoid unnecessary tests and interventions.

When LV function is depressed or there is evidence of structural myocardial disease, scar-related reentry is the most likely diagnosis. Scars are suggested by pathologic Q waves on the ECG, segmental left or right ventricular wall motion abnormalities on echocardiogram or nuclear imaging, and areas of delayed gadolinium enhancement during MRI (Fig. 277-5).

TREATMENT AND PROGNOSIS Initial management follows Advanced Cardiac Life Support (ACLS) guidelines. If hypotension, impaired consciousness, or pulmonary edema is present, QRS synchronous electrical cardioversion should be performed, ideally after sedation if the patient is conscious. For stable tachycardia, a trial of adenosine is reasonable, as this may clarify a supraventricular tachycardia with aberrancy (Chap. 276). Intravenous amiodarone is the drug of choice if heart disease is present. Following restoration of sinus rhythm, hospitalization and evaluation to define underlying heart disease are required. Assessment of cardiac biomarkers for evidence of MI is appropriate, but acute MI is rarely a cause of sustained monomorphic VT, and elevations in troponin or creatine kinase (CK)-MB are more likely to indicate myocardial damage that is secondary to hypotension and ischemia from the VT. Subsequent management is determined by the underlying heart disease and frequency of VT. If VT recurs frequently or is incessant, administration of antiarrhythmic medications or catheter ablation may be required to restore stability. More commonly, sustained monomorphic VT occurs as an isolated episode, but with a risk of recurrence. ICDs are usually considered for VT associated with structural heart disease.

Sustained Monomorphic VT in Specific Diseases • CORONARY ARTERY DISEASE Patients who present with sustained VT associated with coronary artery disease typically have a history of prior large MI and present years after

the acute infarct with a remodeled ventricle and markedly depressed LV function. Even when there is biomarker evidence of acute MI, a preexisting scar from previous MI should be suspected as the cause of the VT. Infarct scars provide a durable substrate for sustained VT, and up to 70% of patients have a recurrence of the arrhythmia within 2 years. Scar-related reentry is not dependent on recurrent acute myocardial ischemia, so coronary revascularization cannot be anticipated to prevent recurrent VT, even when it may be appropriate for other indications. Depressed ventricular function, which is a risk factor for sudden death, is usually present. Implantation of an ICD is warranted for most patients provided that there is a reasonable expectation of survival with acceptable functional status for the next year after recovery from the VT episode. ICDs reduce annual mortality from 12.3% to 8.8% and lower arrhythmic deaths by 50% in patients with hemodynamically significant sustained VT or a history of cardiac arrest compared with pharmacologic therapy. Chronic amiodarone therapy may be considered for patients who are not candidates for or who decline ICD placement.

Following ICD implantation, patients remain at risk for heart failure, recurrent ischemic events, and recurrent VT, with a 5-year mortality that exceeds 30%. Attention to therapies with survival benefit, including β -adrenergic blocking agents, angiotensin-converting enzyme inhibitors, and statins, is important. Patients with frequent symptomatic recurrences of VT require antiarrhythmic drug therapy or catheter ablation.

NONISCHEMIC DILATED CARDIOMYOPATHY Sustained monomorphic VT associated with nonischemic cardiomyopathy is usually due to scar-related reentry. The etiology of scar is often unclear, but progressive replacement fibrosis is the likely cause. On cardiac MRI, scars are detectable as areas of delayed gadolinium enhancement and are more often intramural or subepicardial in location as compared with patients with prior MI. Scars that cause VT are often located adjacent to a valve annulus and can occur in either ventricle. Any cardiomyopathic process can cause scars and VT, but cardiac sarcoidosis (**Chap. 390**) and Chagas' disease (**Chap. 252**) are particularly associated with monomorphic VT (**Table 277-2**). An ICD is usually indicated with additional drugs or ablation for control of recurrent VT.

MONOMORPHIC VT IN ARVC ARVC (**Chap. 287**) is a rare genetic disorder most commonly due to mutations in genes encoding for cardiac desmosomal proteins. Approximately 50% have a familial transmission with autosomal dominant inheritance. A less common, autosomal recessive form is associated with cardiocutaneous syndromes that include Naxos disease and Carvajal syndrome. Patients typically present between the second and fifth decade with palpitations, syncope, or cardiac arrest owing to sustained monomorphic VT, although polymorphic VT can also occur. Fibrosis and fibro-fatty replacement most commonly involve the right ventricular myocardium and provide the substrate for reentrant VT that usually has a left bundle branch block-like configuration, consistent with the right ventricular origin. The sinus rhythm ECG suggests the disease in more than 85% of patients, most often showing T-wave inversions in V_1-V_3 (**Fig. 277-6**). Delayed activation of the right ventricle may cause a widened QRS (≥ 110 ms) in the right precordial leads and a prolonged S-wave upstroke in those leads, and occasionally a deflection at the end of the QRS known as an *epsilon wave* (**Fig. 277-6**). Cardiac imaging may show right ventricular enlargement or areas of abnormal motion or reveal areas of scar on CMR imaging with gadolinium. The monomorphic VT of early ARVC can sometimes be difficult to differentiate from idiopathic right ventricular outflow tract VT.

LV involvement can occur and occasionally precede manifest right ventricular disease. Heart failure is rare except in late stages, and survival to advanced age can be anticipated provided that VT can be controlled. An ICD is recommended. When VT is exercise-induced, it may respond to β -adrenergic blockers and limiting exercise. Sotalol, amiodarone, and catheter ablation have been used to reduce recurrences. Ablation targets are often located in the subepicardium of the RV.

TETRALOGY OF FALLOT VT occurs in 3–14% of patients late after repair of tetralogy of Fallot (**Chap. 282**) and contributes to a 2% per decade risk of

TABLE 277-2 VENTRICULAR ARRHYTHMIAS ASSOCIATED WITH DIFFERENT FORMS OF HEART DISEASE

- I. Idiopathic VT without structural heart disease
 - A. Outflow tract origin
 - 1. RV outflow tract: left bundle branch block pattern with inferior axis (tall QRS in inferior leads) and late transition in the precordial leads
 - 2. LV outflow tract: prominent R in V_1 with inferior axis
 - B. Left posterior fascicular VT
 - 1. Right bundle branch block pattern with left axis deviation (most common)
- II. Ischemic cardiomyopathy
 - A. Monomorphic VT is common with prior large myocardial infarction
 - B. Polymorphic VT and VF should prompt ischemia evaluation
- III. Nonischemic cardiomyopathy
 - A. Polymorphic VT and VF more common but fibrotic scars can cause monomorphic VT especially with sarcoidosis and Chagas' disease
- IV. Arrhythmogenic right ventricular cardiomyopathy
 - A. Monomorphic VT usually of right ventricular origin (left bundle branch morphology)
 - B. Polymorphic VT and VF can occur independently or through degeneration of monomorphic VT
- V. Repaired tetralogy of Fallot
 - A. Monomorphic VT of right ventricular origin (usually left bundle branch morphology)
- VI. Hypertrophic cardiomyopathy
 - A. Polymorphic VT or ventricular fibrillation
 - B. Less commonly, monomorphic VT associated with myocardial scars
- VIII. Genetic arrhythmia syndromes
 - A. Long QT syndrome: torsade de pointes VT
 - B. Brugada syndrome: VF
 - C. Catecholaminergic polymorphic VT: polymorphic VT or bidirectional VT
 - D. Short QT syndrome: ventricular fibrillation
 - E. Early repolarization syndrome: polymorphic VT or VF

Abbreviation: RV, right ventricle. See text for other abbreviations.

sudden death. Monomorphic VT is due to reentry around areas of surgically created scar in the RV (**Table 277-2**). Factors associated with VT risk include age >5 years at the time of repair, high-grade ventricular ectopy, inducible VT on an electrophysiologic study, abnormal right ventricular hemodynamics, and sinus rhythm QRS duration >180 ms. An ICD is usually warranted for patients who have a spontaneous episode of VT, but criteria for a prophylactic ICD in other patients have not been established. Catheter ablation is used to control recurrent episodes.

BUNDLE BRANCH REENTRY VT Reentry through the Purkinje system occurs in approximately 5% of patients with monomorphic VT in the presence of structural heart disease. The reentry circuit typically revolves retrograde via the left bundle and anterograde down the right bundle, thereby producing VT that has a left bundle branch block configuration. Catheter ablation of the right bundle branch abolishes this VT. Bundle branch reentry is usually associated with severe underlying heart disease. Other scar-related VTs are often present and often require additional therapy or ICD implantation.

IDIOPATHIC MONOMORPHIC VT Idiopathic VT in patients without structural heart disease usually presents with palpitations, lightheadedness, and occasionally syncope, often provoked by sympathetic stimulation during exercise or emotional upset. The QRS morphology of the arrhythmia suggests the diagnosis (see below). The sinus rhythm ECG is normal. Cardiac imaging shows normal ventricular function and no evidence of ventricular scar. Occasionally a patient with structural heart disease is found to have concomitant idiopathic VT, unrelated to the structural disease. Sudden death is rare.

Outflow tract VTs originate from a focus, usually with features consistent with triggered automaticity. The arrhythmia may present with

TABLE 277-3 CAUSES OF QT PROLONGATION AND TORSADE DE POINTES VENTRICULAR TACHYCARDIA

1. Congenital long QT syndromes (see text for details)	Antihistamines (histamine 1-receptor antagonists)
Long QT syndrome type 1: Reduced repolarizing current I_{K_s} due to mutation in <i>KCNQ1</i> gene	Terfenadine, astemizole, diphenhydramine, hydroxyzine
Long QT syndrome type 2: Reduced repolarizing current I_{K_r} due to mutation in <i>KCNH2</i> gene	Cholinergic antagonists: Cisapride, organophosphates
Long QT syndrome type 3: Delayed inactivation of the I_{Na} due to mutations in <i>SCN5A</i> gene	Citrate (massive blood transfusions)
Others: Several other types of long QT syndromes have been described; long QT types 1, 2, and 3 account for 80–90% of cases	Cocaine
2. Acquired prolongation of QT interval	Methadone
Electrolyte abnormalities	Fluoxetine (in conjunction with other drugs that prolong QT)
Hypokalemia	Cardiac conditions
Hypomagnesemia	Myocardial ischemia and infarction
Hypocalcemia	Myocarditis
Drugs	Marked bradycardia
Antiarrhythmic drugs	Stress cardiomyopathy
Class IA: Quinidine, disopyramide, procainamide	Endocrine disorders
Class III: Sotalol, amiodarone (QT prolongation common but torsade ventricular tachycardia is rare), ibutilide, dofetilide, almokalant	Hypothyroidism
Antibiotics	Hyperparathyroidism
Macrolides: Erythromycin, clarithromycin, azithromycin	Pheochromocytoma
Fluoroquinolones: Levofloxacin, moxifloxacin, gatifloxacin	Hyperaldosteronism
Trimethoprim-sulfamethoxazole	Intracranial disorders
Clindamycin	Subarachnoid hemorrhage
Pentamidine	Thalamic hematoma
Chloroquine	Cerebrovascular accident
Antifungals: Ketoconazole, itraconazole	Encephalitis
Antivirals: Amantadine	Head injury
Antipsychotics	Nutritional disorders
Haloperidol, phenothiazines, thioridazine, trifluoperazine, sertindole, zimelidine, ziprasidone	Anorexia nervosa
Tricyclic and tetracyclic antidepressants	Starvation
	Liquid protein diets
	Gastroplasty and ileojejunral bypass
	Celiac disease

sustained VT, nonsustained VT, or PVCs often provoked by exercise or emotional upset. Repeated bursts of nonsustained VTs, which may occur incessantly, are known as repetitive monomorphic VTs and can cause tachycardia-induced cardiomyopathy with depressed ventricular function that recovers after suppression of the arrhythmia (Fig. 277-2). Most originate in the right ventricular outflow tract, which gives rise to VT that has a left bundle branch block configuration in V_1 and an axis that is directed inferiorly, with tall R waves in leads II, III, and AVF (Fig. 277-2). Idiopathic VT can also arise in the LV outflow tract or in sleeves of myocardium that extend along the aortic root. LV origin is suspected when lead V_1 or V_2 has prominent R waves. Although this typical outflow tract QRS morphology favors idiopathic VT, some cardiomyopathies, notably ARVC, can cause PVCs or VT from this region. Excluding these diseases is an initial focus of evaluation.

LV intrafascicular VT presents with sustained VT that has a right bundle branch block-like configuration. It is often exercise-induced and occurs more often in men than women. The mechanism is reentry in or near the septal ramifications of the LV Purkinje system. This VT can be terminated by intravenous administration of verapamil.

MANAGEMENT OF IDIOPATHIC VT Treatment is required for symptoms or when frequent or incessant arrhythmias depress ventricular function. β -Adrenergic blockers are first-line therapy. Nondihydropyridine calcium channel blockers (diltiazem and verapamil) are sometimes effective. Catheter ablation is warranted for severe symptoms or when beta blockers or calcium channel blockers are not effective or not desired. Efficacy and risks of catheter ablation vary with the specific site of origin of the VT, being most favorable for arrhythmias originating in the right ventricular outflow tract.

LV fascicular VT can be terminated by intravenous administration of verapamil, although chronic therapy with oral verapamil is not

always effective. Catheter ablation is recommended if β -adrenergic blockers or calcium channel blockers are ineffective or not desired.

Polymorphic VT Sustained polymorphic VT can be seen with any form of structural heart disease (Table 277-2). However, unlike sustained monomorphic VT, polymorphic VT does not always indicate a structural abnormality or focus of automaticity. Reentry with continually changing reentrant paths, spiral wave reentry, and multiple automatic foci are potential mechanisms (Chap. 278e). Sustained polymorphic VT usually degenerates into VF. Polymorphic VT is typically seen in association with acute MI or myocardial ischemia, ventricular hypertrophy, and a number of genetic mutations that affect cardiac ion channels (Table 277-3).

POLYMORPHIC VT ASSOCIATED WITH ACUTE MI/MYOCARDIAL ISCHEMIA Acute MI or ischemia is a common cause of polymorphic VT and should be the initial consideration in management. Approximately 10% of patients with acute MI develop VT that degenerates to VF, related to reentry through the infarct border zone. The risk is greatest in the first hour of acute MI. Following resuscitation as per the ACLS guidelines, management is as for acute MI (Chap. 295). β -Adrenergic blockers, correction of electrolyte abnormalities, and prompt myocardial reperfusion are required. Repeated episodes of polymorphic VT suggest ongoing myocardial ischemia and warrant assessment of adequacy of myocardial reperfusion. Polymorphic VT and VF that occur within the first 48 h of acute MI are associated with greater in-hospital mortality, but those who survive past hospital discharge are not at increased risk for arrhythmic sudden death. Long-term therapy for postinfarct ventricular arrhythmia is determined by residual LV function, with an ICD being indicated for persistent severe LV dysfunction (LV ejection fraction <0.35).

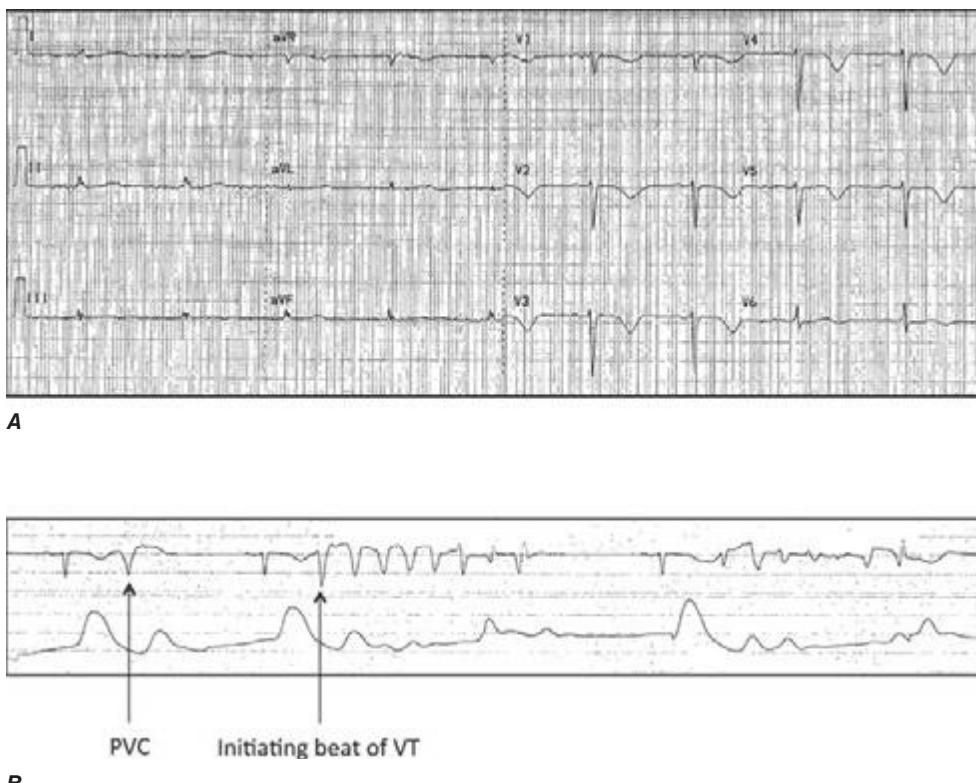


FIGURE 277-8 Electrocardiogram (ECG) of a patient with prolonged QT and episodes of torsade de pointes ventricular tachycardia (VT). **A.** Twelve-lead ECG showing a heart rate of 54, anterior wall T inversion, and QT interval of 600 ms. The corrected QT interval (QTc) is 585 ms. **B.** Telemetry ECG tracing with digital pulse waveform demonstrating bursts of torsade de pointes VT. The initiating sequence of the VT is characteristic, with a PVC inducing a pause followed by a sinus beat that had a longer QT and interruption of the T wave by a PVC that is the first beat of VT. The VT is self-terminating in this case.

REPOLARIZATION ABNORMALITIES AND GENETIC ARRHYTHMIA SYNDROMES • Acquired long QT

Abnormal prolongation of the QT interval is associated with the polymorphic VT Torsade de Pointes (Fig. 277-8). The VT often has a characteristic initiation sequence of a premature ventricular beat that induces a pause, followed by a sinus beat that has a longer QT interval and interruption of the T wave by the PVC that is the first beat of the polymorphic VT. This characteristic initiation is termed “pause-dependent” (Fig. 277-8). Causes of QT prolongation include electrolyte abnormalities, bradycardia, and a number of medications that block repolarizing potassium currents, notably the antiarrhythmic drugs sotalol, dofetilide, and ibutilide, but also a number of other medications used for noncardiac diseases, including erythromycin, pentamidine, haloperidol, phenothiazines, and methadone (Table 277-3). Individual susceptibility may be related to genetic polymorphisms or mutations that influence repolarization.

Patients typically present with near-syncope, syncope, or cardiac arrest. Sustained episodes degenerate to VF requiring defibrillation. PVCs and nonsustained VT often precede episodes of sustained VT. Intravenous administration of 1–2 g of magnesium sulphate usually suppresses recurrent episodes. If magnesium alone is ineffective, increasing heart rate with isoproterenol infusion or pacing, to a rate of 100–120 beats/min as required to suppress PVCs, usually suppresses VT recurrences. These maneuvers allow time for correction of associated electrolyte disturbance (hypokalemia and hypocalcemia) and bradycardia and removal of any causative drugs (Table 277-3). Drug interactions that elevate levels of the offending agent are often a precipitating factor. Patients who experience a polymorphic VT induced by QT prolongation should be considered to have a susceptibility to the arrhythmia and should avoid all future exposure to medications known to prolong the QT interval.

selective agents nadolol or propranolol) are sufficient protection from arrhythmia episodes. Markers of increased risk include QTc interval exceeding 0.5 s, female gender, and a history of syncope or cardiac arrest. Recurrent syncope despite beta blocker therapy or a high-risk profile merits consideration of an ICD. Avoidance of QT-prolonging drugs is critical for all patients with LQTS, including those who are genotype positive but have normal QT intervals.

Short QT syndrome Short QT syndrome is very rare compared to LQTS. The QTc is shorter than 0.36 s, and usually less than 0.3 s. The genetic abnormality causes a gain of function of the potassium channel (I_{Kr}) or reduced inward depolarizing currents. The abnormality is associated with atrial fibrillation, polymorphic VT, and sudden death.

Brugada syndrome Brugada syndrome is a rare syndrome characterized by >0.2 mV of ST-segment elevation with a coved ST segment and negative T wave in more than one anterior precordial lead (V_1-V_3) (Fig. 277-6) and episodes of syncope or cardiac arrest due to polymorphic VT in the absence of structural heart disease. Cardiac arrest may occur during sleep or be provoked by febrile illness. Males are more commonly affected than females. Mutations involving cardiac sodium channels are identified in approximately 25% of cases. Distinction from patients with similar ST elevation owing to LV hypertrophy, pericarditis, myocardial ischemia or MI hyperkalemia, hypothermia, right bundle branch block, and ARVC is often difficult. Furthermore, the characteristic ST-segment elevation can wax and wane over time and may become pronounced during acute illness and fever. Administration of the sodium channel blocking drug flecainide, ajmaline, or procainamide can augment or unmask ST elevation in affected individuals. An ICD is indicated for individuals who have had unexplained syncope or been resuscitated from cardiac arrest.

Congenital long QT syndrome The congenital long QT syndrome (LQTS) is caused by mutations in genes coding for cardiac ion channels responsible for ventricular repolarization. The corrected QT (QTc) is typically prolonged to greater than 440 ms in men and 460 ms in women. Symptoms are due to Torsade de Pointes VT (Fig. 277-8). Several forms of congenital LQTS have been identified, but three groups of mutations that lead to LQTS type 1 (LQTS-1), LQTS type 2 (LQTS-2), or LQTS type 3 (LQTS-3) account for 90% of cases. The most frequently encountered mutations, *LQTS1* and *LQTS2*, are due to abnormalities of potassium channels, but mutations affecting the sodium channel (*LQTS3*) and calcium channels have also been described (Table 277-3).

Patients often present with syncope or cardiac arrest, usually during childhood. In LQTS-1, episodes tend to occur during exertion, particularly swimming. In LQTS-2, sudden auditory stimuli or emotional upset predispose to events. In LQTS-3, sudden death during sleep is a notable feature. Asymptomatic patients may be discovered in the course of family screening or on a routine ECG. Genotyping can be helpful for family screening and to provide reassurance regarding the diagnosis. Correlations of genotype with risk and response to therapy are beginning to emerge. In most patients with LQTS-1 or LQTS-2, adequate doses of beta blocker therapy (the non-

- 1498** Quinidine has been used successfully to suppress frequent episodes of VT.

Early repolarization syndrome Patients resuscitated from VF who have no structural heart disease or other identified abnormality have a higher prevalence of J-point elevation with notching in the terminal QRS. A family history of sudden death is present in some patients, suggesting a potential genetic basis. J-point elevation is also seen in some patients with the Brugada syndrome and associated with a higher risk of arrhythmias. An ICD is recommended for those who have had prior cardiac arrest. It should be noted that J-point elevation is commonly seen as a normal variant, and in the absence of specific symptoms, the clinical relevance is not known.

Catecholaminergic polymorphic VT This rare familial syndrome is due to mutations in the cardiac ryanodine receptor and, less commonly, the sarcoplasmic calcium binding protein, calsequestrin 2. These mutations result in abnormal sarcoplasmic calcium handling and polymorphic ventricular arrhythmias that resemble those seen with digitalis toxicity. The VT is polymorphic or has a characteristic alternating QRS morphology termed bidirectional VT. Patients usually present during childhood with exercise- or emotion-induced palpitations, syncope, or cardiac arrest. β -Adrenergic blockers (e.g., nadolol and propranolol) and an ICD are recommended. Verapamil, flecainide, or surgical left cardiac sympathetic denervation reduces or prevents recurrent VT in some patients.

Hypertrophic cardiomyopathy (HCM) HCM is the most common genetic cardiovascular disorder, occurring in 1 in 500 individuals, and is a prominent cause of sudden death before the age of 35 years (Chap. 287). Sudden death can be due to polymorphic VT/VF. Rarely, sustained monomorphic VT occurs related to areas of ventricular scar. Risk factors include young age, nonsustained VT, failure of blood pressure to increase during exercise, recent (within 6 months) syncope, ventricular wall thickness >3 cm, and possibly the severity of LV outflow obstruction. An ICD is generally indicated for high-risk patients, but the specific risk profile warranting an ICD continues to be debated. Surgical myectomy, performed to relieve outflow obstruction, has been associated with a sudden death rate of less than 1% per year. The reported annual rate of sustained VT or sudden death after transcoronary ethanol septal ablation done to relieve outflow obstruction has been reported to range between 1 and 5%.

Genetic dilated cardiomyopathies Genetic dilated cardiomyopathies account for 30–40% of cases of nonischemic dilated cardiomyopathies. Some are associated with muscular dystrophy. Autosomal dominant, recessive, X-linked, and mitochondrial inheritance patterns are recognized. Mutations in genes coding for structural proteins of the nuclear lamina (lamin A and C) and the SCN5A gene are particularly associated with conduction system disease and ventricular arrhythmias. Patients can experience polymorphic VT and cardiac arrest or develop areas of scar causing sustained monomorphic VT. ICDs are recommended for those who have had a sustained VT or are at high risk due to significantly depressed ventricular function (LV ejection fraction of ≤ 0.35 and associated with heart failure) or a malignant family history of sudden death.

Ventricular Fibrillation VF is characterized by disordered electrical ventricular activation without identifiable QRS complexes (Fig. 277-3E). Spiral wave reentry and multiple circulating reentry wavefronts are possible mechanisms. Sustained polymorphic or monomorphic VT that degenerates to VF is a common cause of out-of-hospital cardiac arrest. Treatment follows ACLS guidelines with defibrillation to restore sinus rhythm. If resuscitation is successful, further evaluation is performed to identify and treat underlying heart disease and potential causes of the arrhythmia, including the possibility that monomorphic or polymorphic VT could have initiated VF. If a transient reversible cause such as acute MI is not identified, therapy to reduce the risk of sudden death with an ICD is often warranted. Chronic amiodarone therapy may be considered for individuals who are not ICD candidates.

Incessant VT and Electrical Storm VT is incessant when it continues to recur shortly after electrical, pharmacologic, or spontaneous conversion to sinus rhythm. “VT storm” or “electrical storm” refers to three or more separate episodes of VT within 24 h, most commonly encountered in patients with ICDs. Slow incessant VT is sometimes asymptomatic, but can cause heart failure or tachycardia-induced cardiomyopathy. More commonly, these presentations are life-threatening and require emergent therapy. Measures to reduce sympathetic tone, including β -adrenergic blockade, sedation, and general anesthesia, have been used effectively. Intravenous administration of amiodarone and lidocaine can be effective for suppression. Urgent catheter ablation can be lifesaving.

TREATMENT VENTRICULAR ARRHYTHMIAS

ANTIARRHYTHMIC DRUGS

Use of antiarrhythmic drugs is based on consideration of the risks and potential benefit for the individual patient. The potential to increase the frequency of VT or cause a new VT, an undesirable effect known as “proarrhythmia,” is a potential risk. Many drugs have multiple effects, often blocking more than one channel. **Drug doses, metabolism, and adverse effects are summarized in Chap. 277.**

β -Adrenergic Blockers Many ventricular arrhythmias are sensitive to sympathetic stimulation, and β -adrenergic stimulation also diminishes the electrophysiologic effects of many antiarrhythmic drugs. The safety of β -blocking agents makes them the first choice of therapy for most ventricular arrhythmias. They are particularly useful for exercise-induced arrhythmias and idiopathic arrhythmias, but have limited efficacy for most arrhythmias associated with heart disease. Bradyarrhythmias are the major cardiac toxicity.

Calcium Channel Blockers The nondihydropyridine calcium channel blockers diltiazem and verapamil can be effective for some idiopathic VTs. The risk of proarrhythmia is low, but they have negative inotropic and vasodilatory effects that can aggravate hypotension.

Sodium Channel-Blocking Agents Drugs whose major effect is mediated through sodium channel blockade include mexiletine, quinidine, disopyramide, flecainide, and propafenone, which are available for chronic oral therapy (Table 277-3). Lidocaine, quinidine, and procainamide are available as intravenous formulations. Quinidine, disopyramide, and procainamide also have potassium channel-blocking effects that prolong the QT interval. These agents have potential proarrhythmic effects and, with the possible exception of quinidine, also have negative inotropic effects that may contribute to increased mortality observed in patients with prior MI. Long-term therapy is generally avoided in patients with structural heart disease but may be used to reduce symptomatic arrhythmias in patients with ICDs.

Potassium Channel-Blocking Agents Sotalol and dofetilide block the delayed rectifier potassium channel I_{Kr} , thereby prolonging the QT interval. Sotalol also has nonselective β -adrenergic blocking activity. It has a modest effect on reducing ICD shocks due to ventricular and atrial arrhythmias. Proarrhythmia with Torsade de Pointes due to QT prolongation occurs in 3–5% of patients. Both sotalol and dofetilide are excreted via the kidneys, necessitating dose adjustment or avoidance in renal insufficiency. These drugs must be avoided in patients with other risk factors for Torsade de Pointes, including QT prolongation, hypokalemia, and significant bradycardia.

Amiodarone and Dronedarone Amiodarone, which blocks multiple cardiac ionic currents and has sympatholytic activity, suppresses a variety of ventricular arrhythmias. It is administered intravenously for life-threatening arrhythmias. During chronic oral therapy, electrophysiologic effects develop over several days. It is more effective than sotalol in reducing ICD shocks and is the preferred drug for ventricular arrhythmias in patients with heart

disease who are not candidates for an ICD. Bradyarrhythmias are the major cardiac adverse effect. Ventricular proarrhythmia can occur, but Torsade de Pointes VT is rare. Noncardiac toxicities are a major problem and contribute to drug discontinuation in approximately a third of patients during long-term therapy. Pneumonitis or pulmonary fibrosis occurs in approximately 1% of patients. Photosensitivity is common, and neuropathy and ocular toxicity can occur. Systematic monitoring is recommended during chronic therapy, including assessment for thyroid and liver toxicity every 6 months and lung toxicity with a chest radiograph and/or determination of lung diffusing capacity annually. Dronedarone has structural similarities to amiodarone but without the iodine moiety. Efficacy for ventricular arrhythmias is poor, and it increases mortality in patients with heart failure.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

ICDs are highly effective for termination of VT and VF and also provide bradycardia pacing. ICDs decrease mortality in patients at risk for sudden death due to structural heart diseases. In all cases, ICDs are recommended only if there is also expectation for survival of at least a year with acceptable functional capacity. The exception is in cases of patients with end-stage heart disease who are awaiting cardiac transplantation outside the hospital, or who have left bundle branch block QRS prolongation such that they are likely to have improvement in ventricular function with cardiac resynchronization therapy from a biventricular ICD.

ICDs can often terminate monomorphic VT by a burst of rapid pacing faster than the VT, known as antitachycardia pacing (ATP) (Fig. 277-9A). If ATP fails or is not a programmed treatment, as is often the case for rapid VT or VF, a shock is delivered (Fig. 277-9B). Shocks are painful if the patient is conscious. The most common ICD complication is the delivery of unnecessary therapy (either ATP or shocks) in response to a rapid supraventricular tachycardia or

electrical noise as a result of an ICD lead fracture. Interrogation of the ICD, which can be performed remotely and communicated via Internet, is critical after an ICD shock to determine the arrhythmia diagnosis and exclude an unnecessary therapy. Device infection occurs in approximately 1% of patients.

Despite prompt termination of VT or VF by an ICD, the occurrence of these arrhythmias predicts subsequent increased mortality and risk of heart failure. Occurrence of VT or VF should therefore prompt assessment for potential causes including worsening heart failure, electrolyte abnormalities, and ischemia. Repeated shocks, even if appropriate, often induce posttraumatic stress disorder. Antiarrhythmic drugs mostly in the form of amiodarone or catheter ablation are often required for suppression of recurrent arrhythmias. Antiarrhythmic drug therapy can alter the VT rate and the energy required for defibrillation, thereby necessitating programming changes in the ICD's algorithms for detection and therapy.

CATHETER ABLATION FOR VT

Catheter ablation is performed by guiding an electrode catheter to the arrhythmia origin and producing a thermal injury with radiofrequency current. The size and location of the arrhythmia substrate determine the ease and likely effectiveness of the procedure, as well as potential complications. The most common complications, which occur in <5% of patients, are related to vascular access, including bleeding, femoral hematomas, arteriovenous fistulae, and pseudoaneurysms.

Catheter ablation is a reasonable first-line therapy for many patients with symptomatic idiopathic VTs. Success rates for those originating from a focus in the right ventricular outflow tract are in the range of 80–90% but lower for idiopathic VTs arising in less common locations such as from the LV outflow tract or aortic root, along the atrioventricular valve annuli, and from the papillary muscles. Failure of ablation is often due to inability to induce the

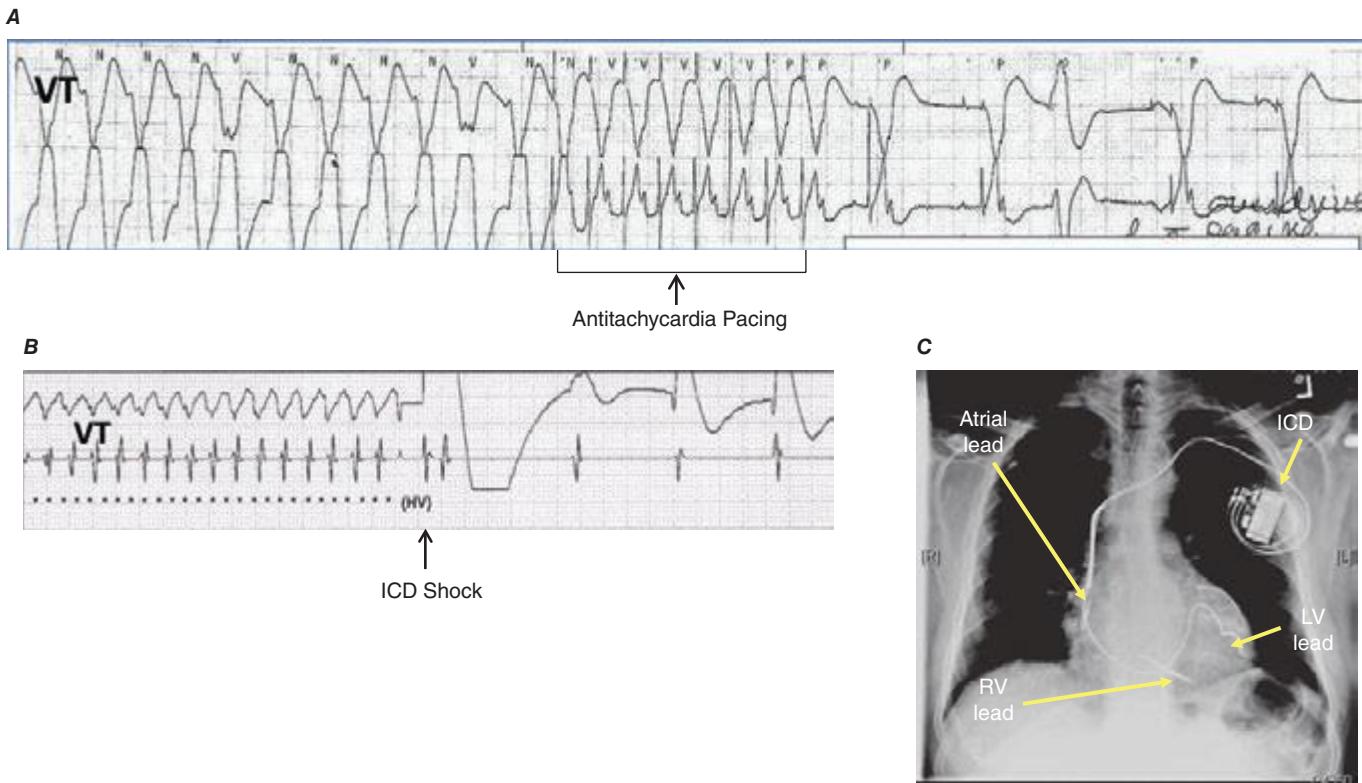


FIGURE 277-9 Implantable cardioverter-defibrillator (ICD) and therapies for ventricular arrhythmias. **A.** A monomorphic ventricular tachycardia (VT) is terminated by a burst of pacing impulses at a rate faster than VT (antitachycardia pacing). **B.** A rapid VT is converted with a high-voltage shock (arrow). The chest x-ray in panel **C** shows the components of an ICD capable of biventricular pacing. ICD generator in the subcutaneous tissue of the left upper chest, pacing leads in the right atrium and the left ventricular (LV) branch of the coronary sinus (LV lead), and a pacing/defibrillating lead in the right ventricle (RV lead) are shown.

1500 arrhythmia for precise localization or because the origin of the VT is from a site that is inaccessible or in close proximity to a coronary artery. Complications are infrequent but can include perforation with cardiac tamponade, atrioventricular block due to injury to the conduction system, and coronary artery injury for foci in proximity to a coronary vessel.

In patients with scar-related VT due to prior infarction or cardiomyopathy, ablation targets abnormal regions in the scar. Because these scars often contain multiple reentry circuits over relatively large regions, extensive areas of ablation are required, and these areas are often identified as regions of low voltage displayed on anatomic reconstructions of the ventricle (Fig. 277-5). If the circuits are not confined to the subendocardial scar, epicardial mapping and ablation can be performed via a subxiphoid pericardial puncture, similar to a pericardiocentesis. Epicardial mapping and ablation are often required for VTs due to nonischemic cardiomyopathy, but also have potentially greater risks of bleeding, coronary injury, and post-procedure pericarditis, which is usually transient. For drug-refractory VT due to prior MI, ablation abolishes VT in approximately half of patients and reduces the frequency of VT in an additional 20%. More than one procedure is necessary in up to 30% of patients. Ablation can be lifesaving for patients with very frequent or incessant VT. Procedure-related mortality is in the range of 3%, with most mortality due to continued uncontrollable VT when the procedure fails. In nonischemic heart disease, the arrhythmia substrate locations are more variable and outcomes are less well defined.

Catheter ablation can also be lifesaving for rare patients with recurrent polymorphic VT and VF that is repeatedly initiated by a uniform PVC. The initiating ectopic beat often originates from the Purkinje system or the right ventricular outflow tract and can be targeted for ablation.

When antiarrhythmic drug therapy and catheter ablation fail or are not options, surgical cryoablation, often combined with aneurysmectomy, can be effective therapy for recurrent VT due to prior MI and has also been used successfully in a few patients with nonischemic heart disease. Few centers now maintain the expertise for this therapy. Injection of absolute ethanol into the coronary arterial blood supply of the arrhythmia substrate has also been used for ablation in a small number of patients who have failed catheter ablation and drugs.

SUMMARY

Patients with ventricular arrhythmias fall into three general groups. The first are those who have associated structural heart disease that must be detected. The risk of life-threatening arrhythmias causing sudden death is indicated by the nature of the arrhythmia—sustained (or causing cardiac arrest) or nonsustained, in which case the risk of life-threatening arrhythmias is assessed from the severity of the heart disease, usually the severity of ventricular dysfunction. ICDs provide the most protection from sudden arrhythmic death. The second group comprises those who do not have recognizable structural heart disease, but have a genetic syndrome associated with increased risk of sudden death. A family history of sudden death and abnormal electrocardiogram most frequently suggest the diagnosis. The third group includes individuals with benign idiopathic arrhythmias who may require therapy to control symptoms, but who are not at significant risk for life-threatening arrhythmias. The appropriate recognition of these patients is facilitated by thoughtful application of ECG and cardiac imaging. High-risk individuals benefit from specialized care for consideration of ICDs, catheter ablation, and antiarrhythmic drug therapy.

278e Atlas of Cardiac Arrhythmias

Ary L. Goldberger

The electrocardiograms in this atlas supplement those illustrated in Chaps. 274 and 276. The interpretations emphasize findings of specific teaching value.

All of the figures are adapted from cases in ECG Wave-Maven, Copyright 2003, Beth Israel Deaconess Medical Center, <http://ecg.bidmc.harvard.edu>.

The abbreviations used in this chapter are as follows:

- AF—atrial fibrillation
- AV—atrioventricular
- LBBB—left bundle branch block
- LV—left ventricular
- LVH—left ventricular hypertrophy
- MI—myocardial infarction
- NSR—normal sinus rhythm
- RBBB—right bundle branch block
- VT—ventricular tachycardia
- WPW—Wolff-Parkinson-White

CHAPTER 278e

Atlas of Cardiac Arrhythmias

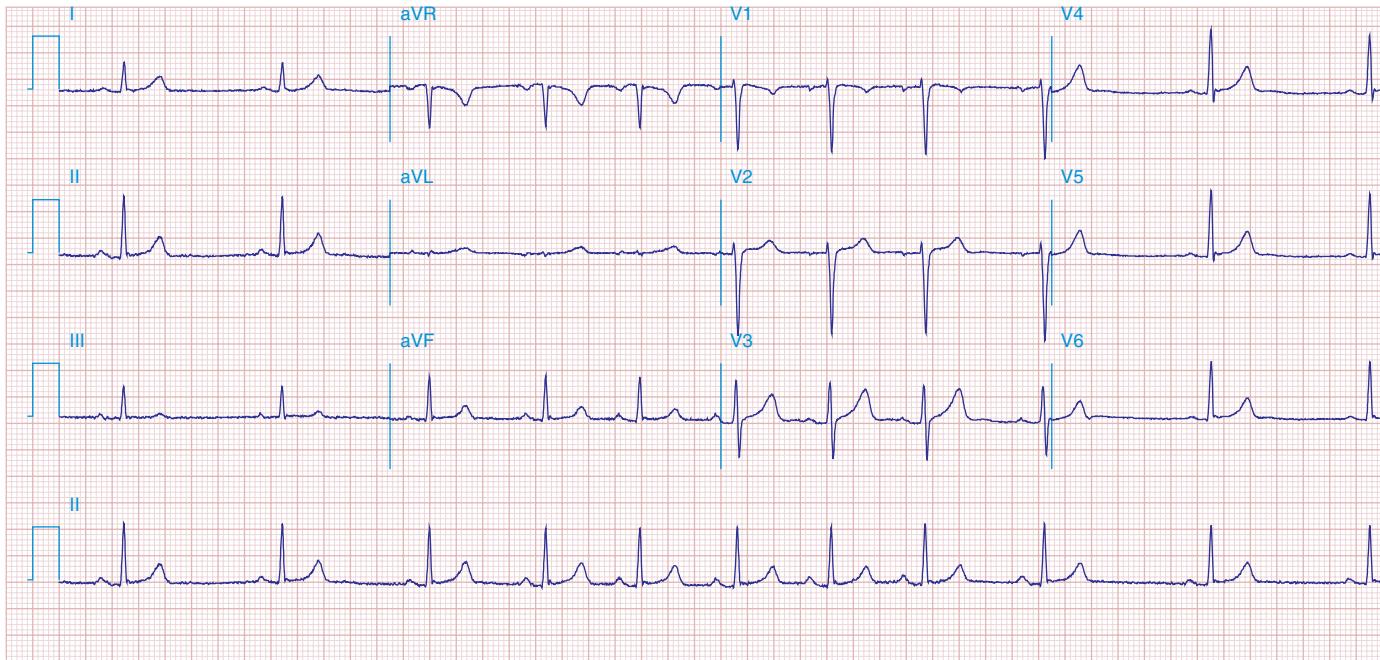


FIGURE 278e-1 Respiratory sinus arrhythmia, a physiologic finding in a healthy young adult. The rate of the sinus pacemaker is relatively slow at the beginning of the strip during expiration, then accelerates during inspiration and slows again with expiration. Changes are due to cardiac vagal tone modulation with breathing.

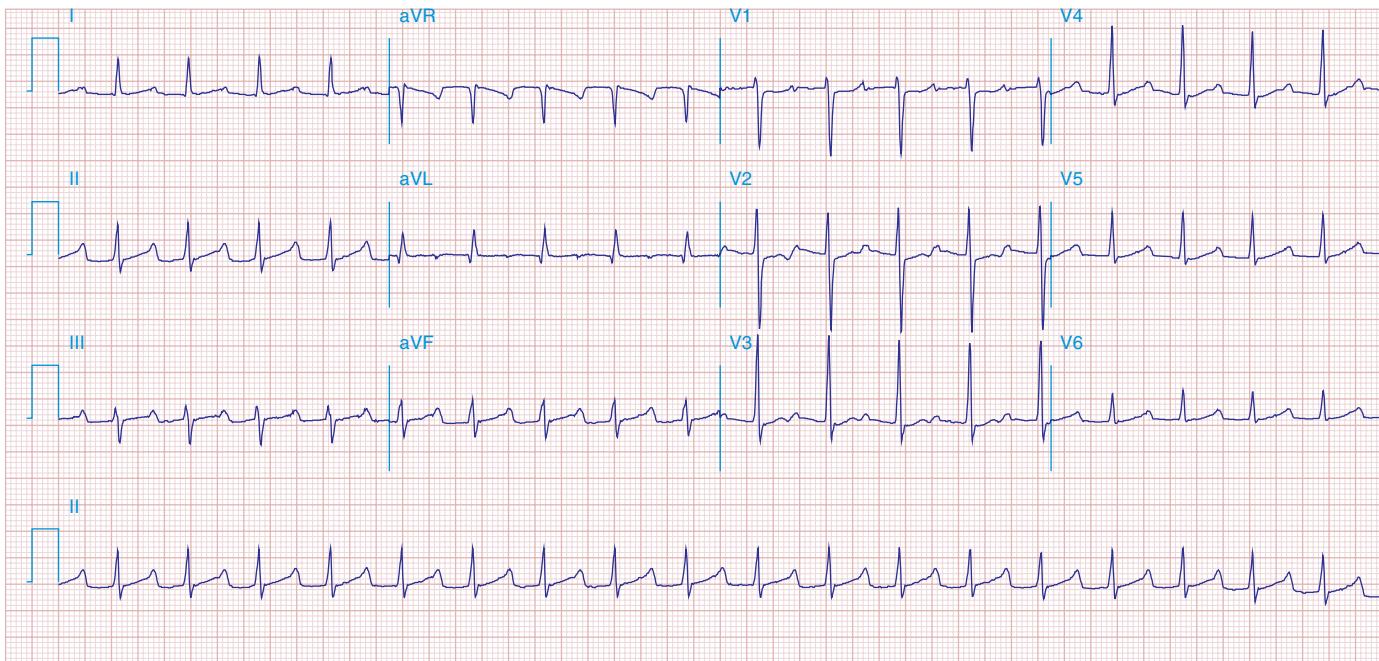


FIGURE 278e-2 Sinus tachycardia (110/min) with first-degree AV “block” (conduction delay) with PR interval = 0.28 s. The P wave is visible after the ST-T wave in V_1-V_3 and superimposed on the T wave in other leads. Atrial (nonsinus) tachycardias may produce a similar pattern, but the rate is usually faster.

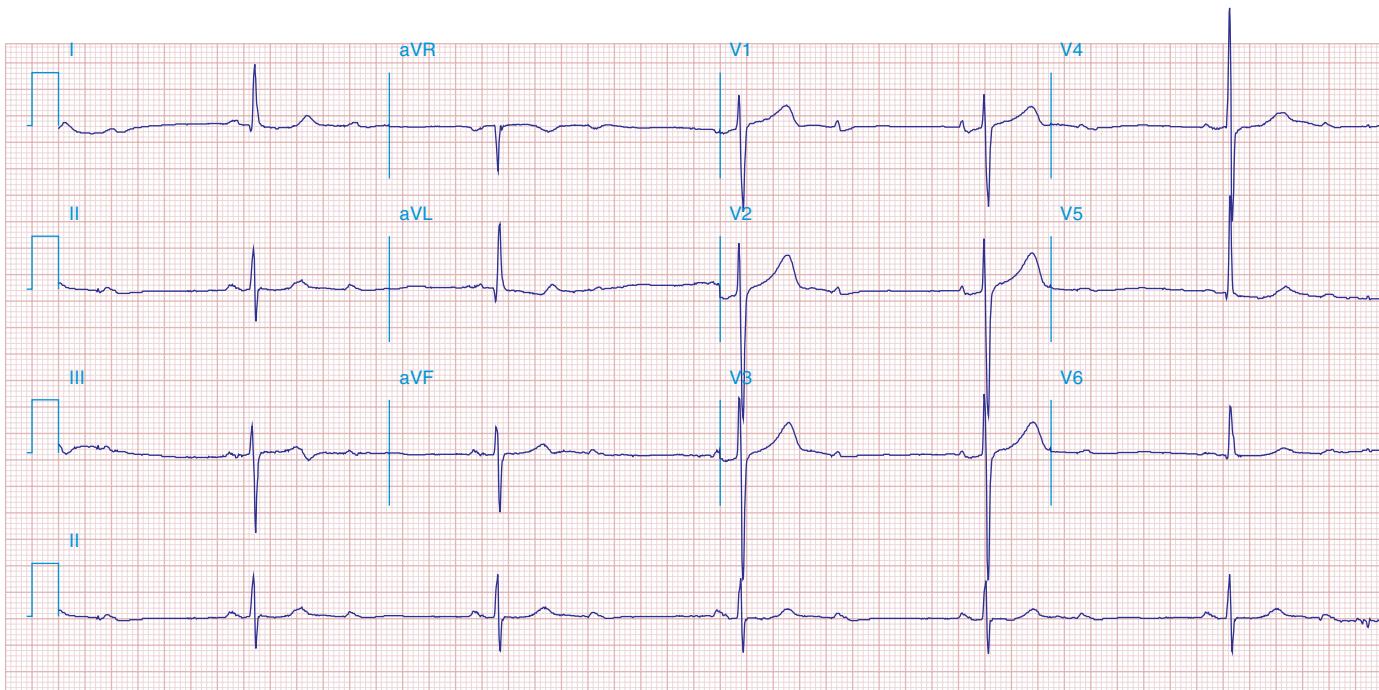


FIGURE 278e-3 Sinus rhythm (P wave rate about 60/min) with 2:1 AV (second-degree) block causing marked bradycardia (ventricular rate of about 30/min). LVH is also present, along with left atrial abnormality.

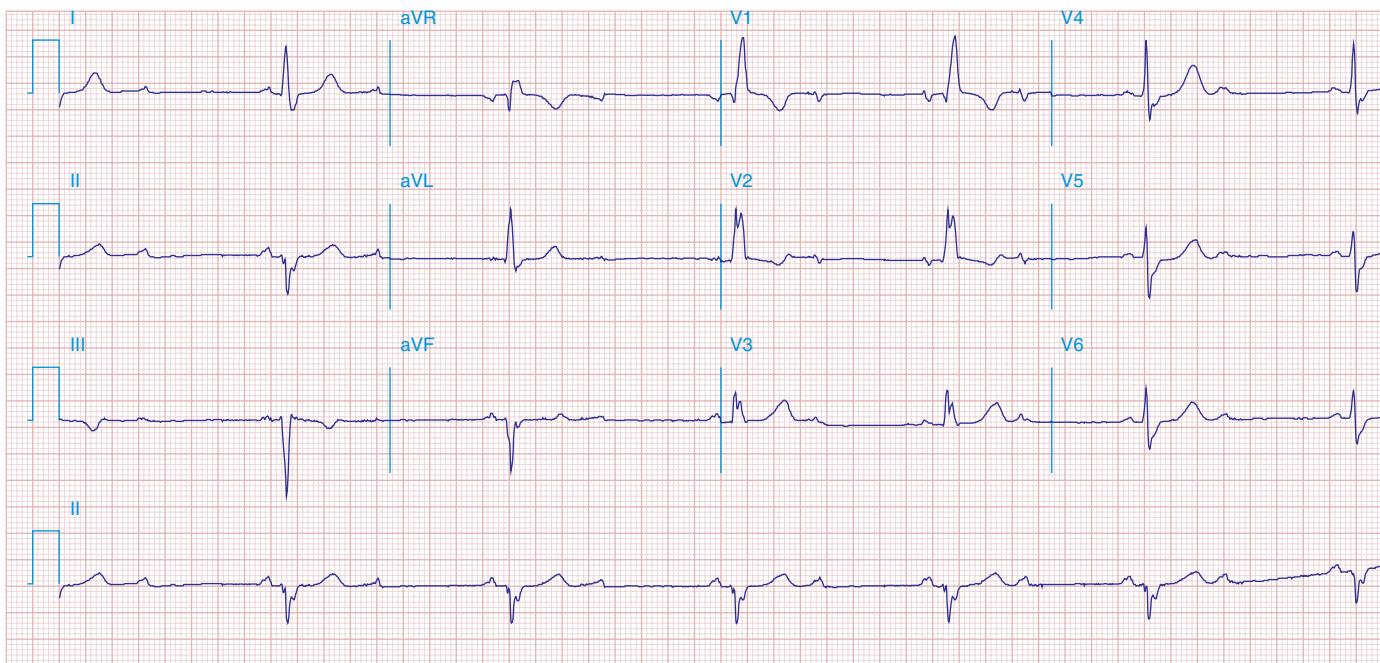


FIGURE 278e-4 Sinus rhythm (P wave rate about 60/min) with 2:1 (second-degree) AV block yielding a ventricular (pulse) rate of about 30/min. Left atrial abnormality. RBBB with left anterior fascicular block. Possible inferior MI.

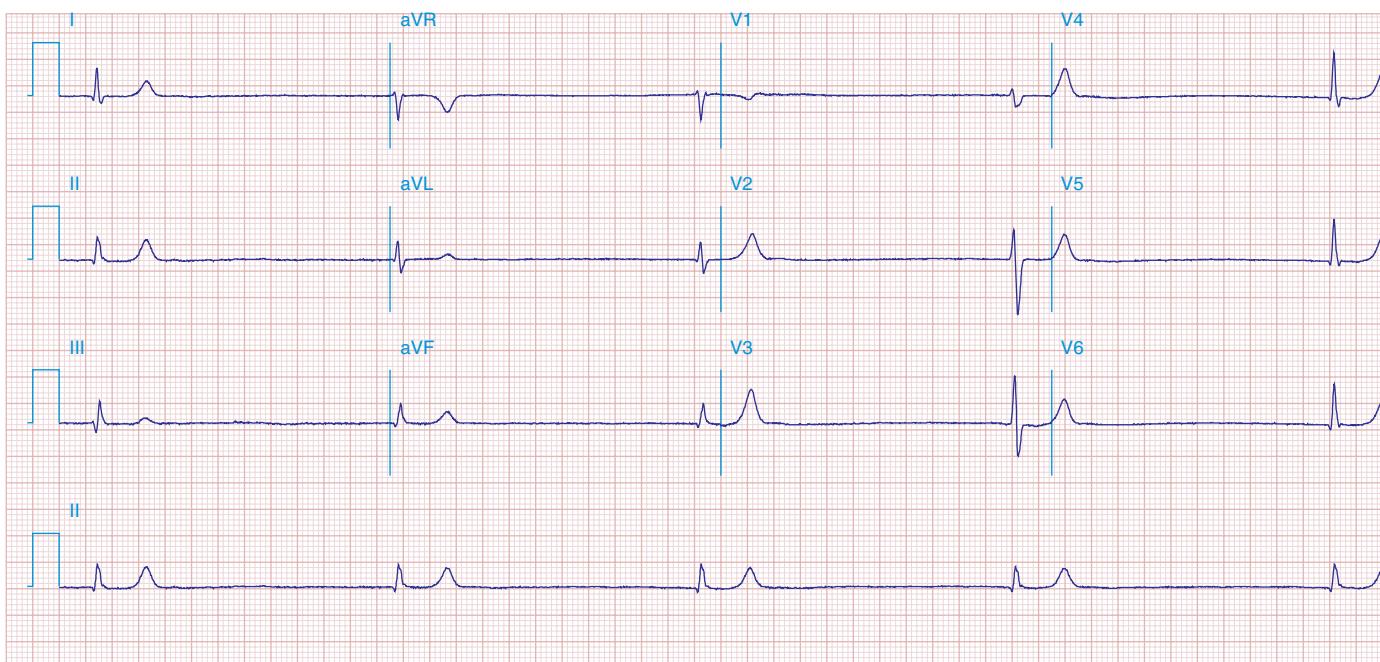


FIGURE 278e-5 Marked junctional bradycardia (25 beats/min). Rate is regular with a flat baseline between narrow QRS complexes, without evident P waves. Patient was on atenolol, with possible underlying sick sinus syndrome. The serum potassium was slightly elevated at 5.5 mEq/L.

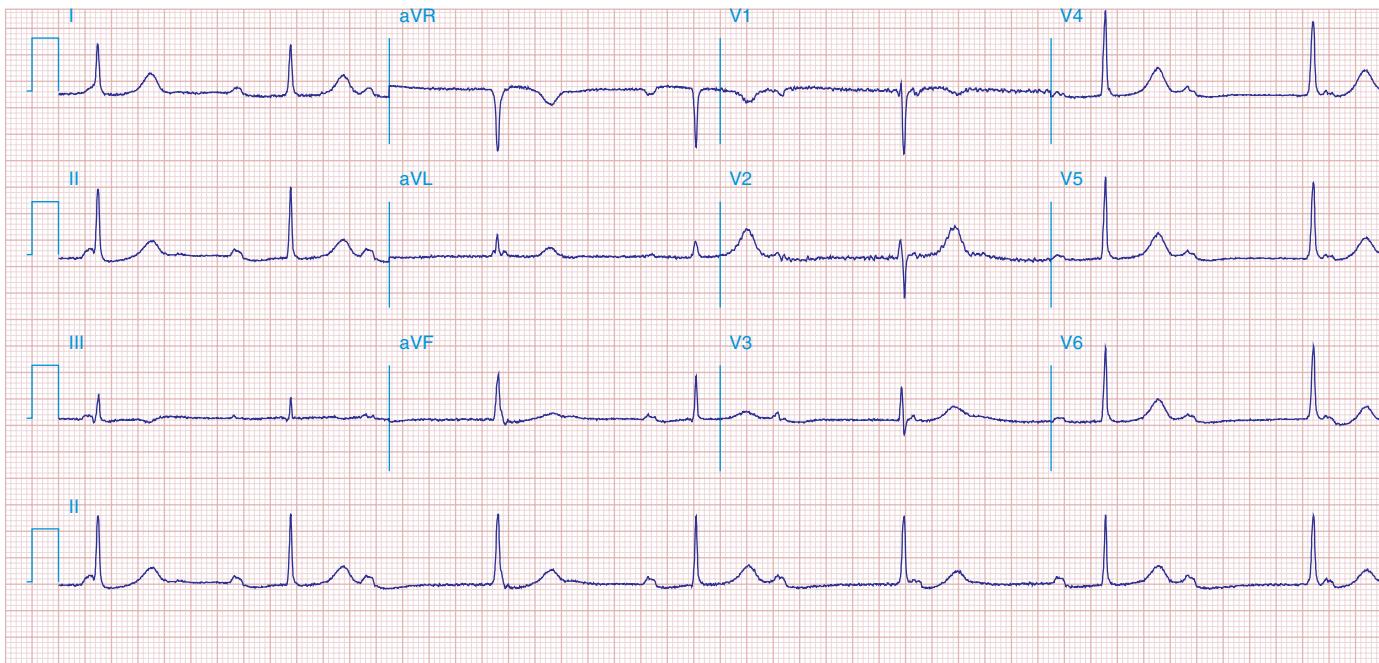


FIGURE 278e-6 Sinus rhythm at a rate of 64/min (P wave rate) with third-degree (complete) AV block yielding an effective heart (pulse) rate of 40/min. The slow, narrow QRS complexes indicate an AV junctional escape pacemaker. Left atrial abnormality.

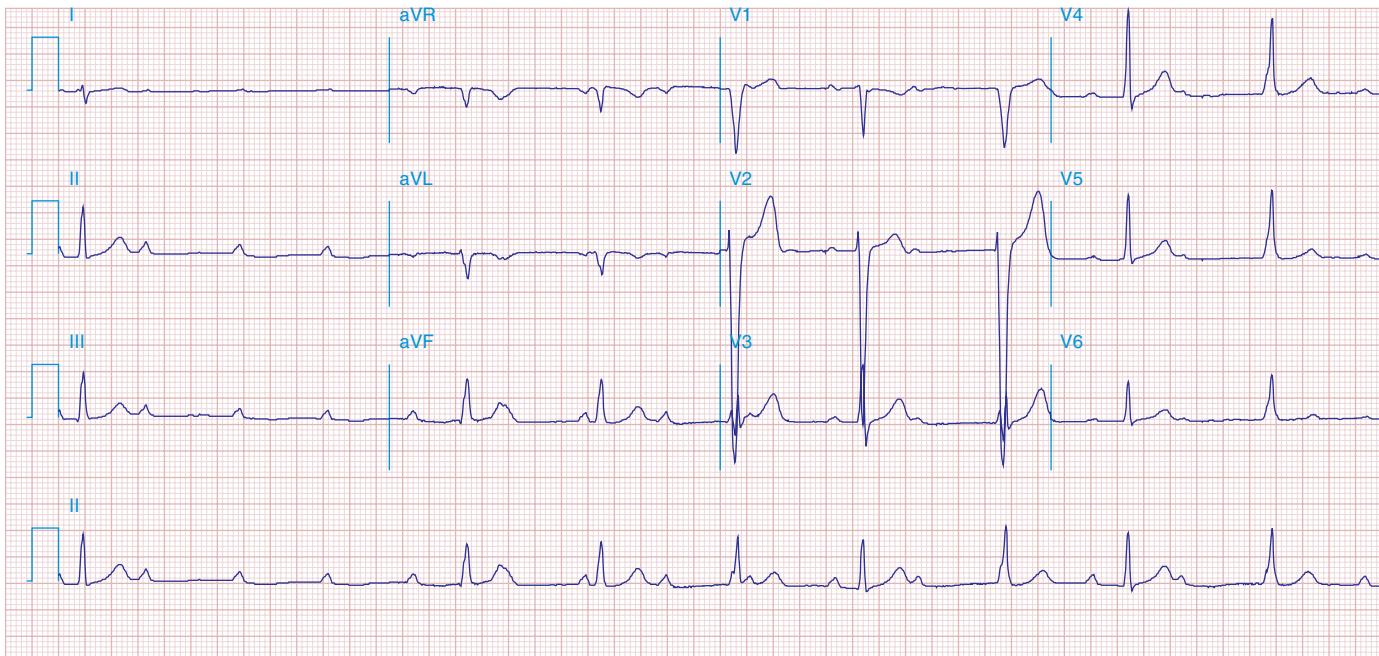


FIGURE 278e-7 Sinus rhythm at a rate of 90/min with advanced second-degree AV block and possible transient complete heart block with Lyme carditis.

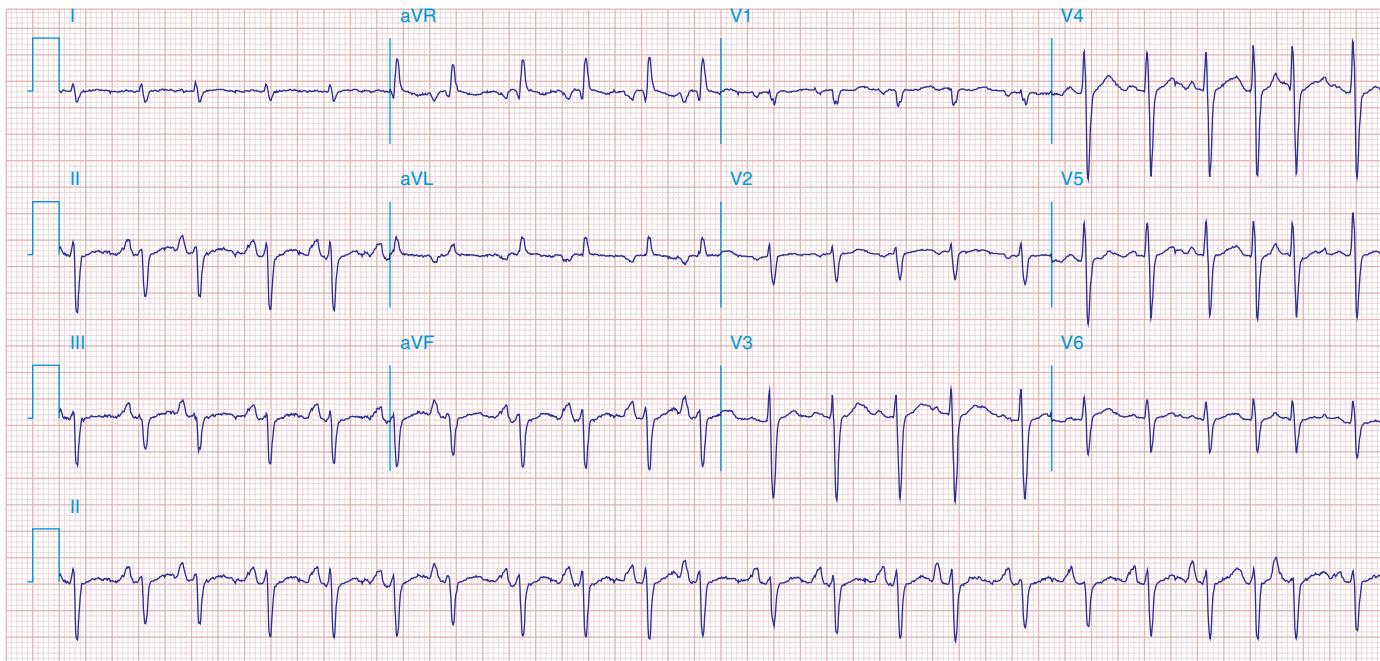


FIGURE 278e-8 Multifocal atrial tachycardia with varying P-wave morphologies and P-P intervals; right atrial overload with peaked P waves in II, III, and aVF (with vertical P-wave axis); superior QRS axis; slow R-wave progression with delayed transition in precordial leads in patient with severe chronic obstructive lung disease.

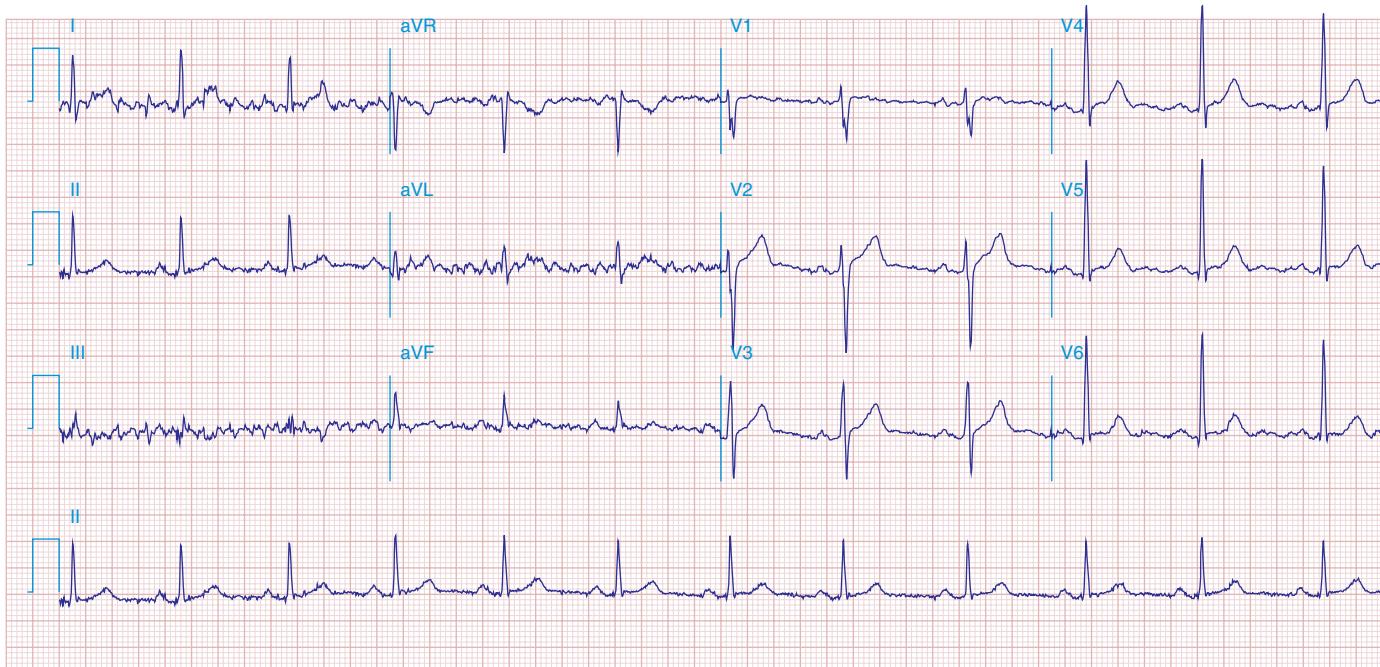


FIGURE 278e-9 NSR in a patient with Parkinson's disease. Tremor artifact, best seen in limb leads. This tremor artifact may sometimes be confused with atrial flutter/fibrillation. Borderline voltage criteria for LVH are present.

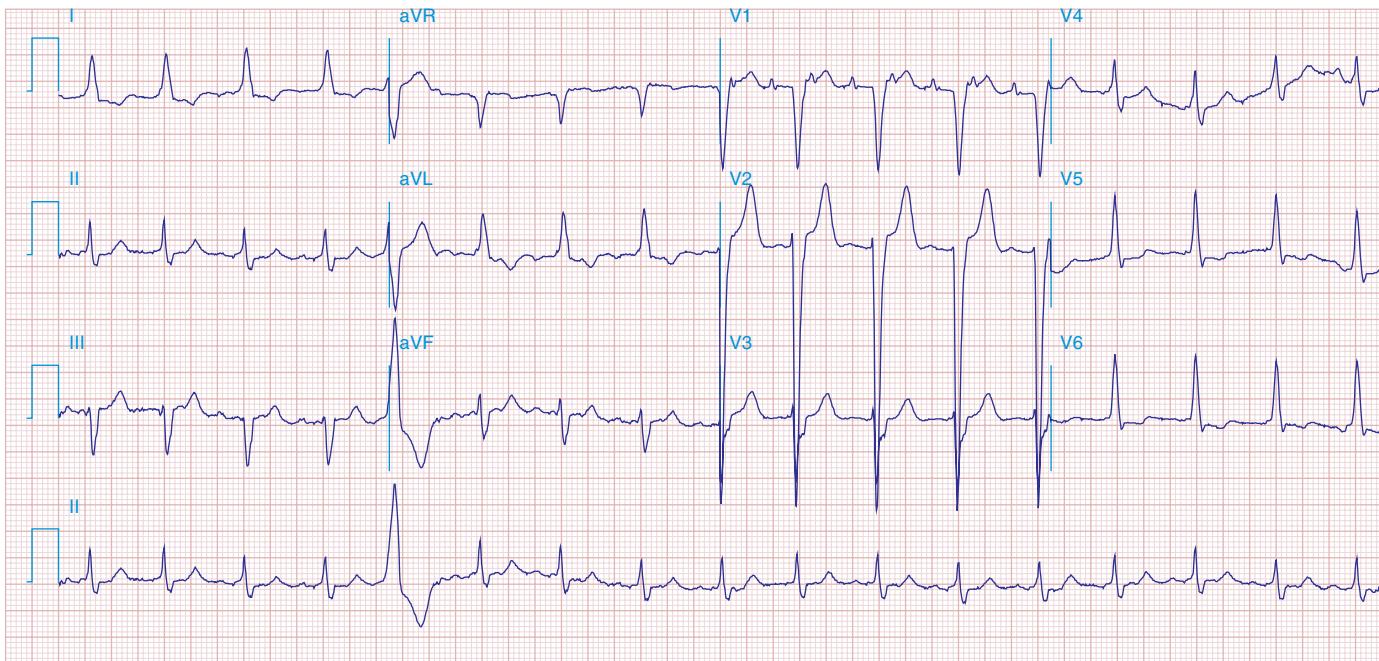


FIGURE 278e-10 Atrial tachycardia with atrial rate of about 200/min (note lead V₁), 2:1 AV block (conduction), and one premature ventricular complex. Also present: LVH with intraventricular conduction delay and slow precordial R-wave progression (cannot rule out prior anterior MI).

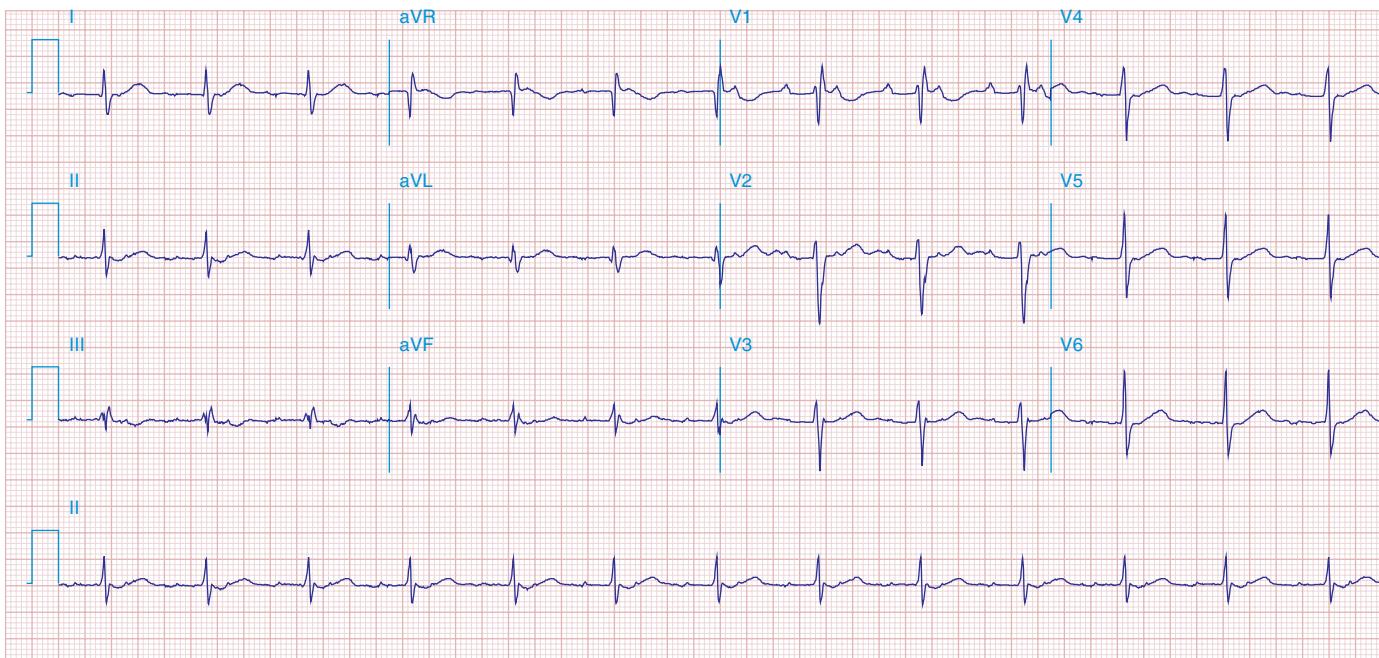


FIGURE 278e-11 Atrial tachycardia with 2:1 block. P-wave rate is about 150/min, with ventricular (QRS) rate of about 75/min. The nonconducted ("extra") P waves just after the QRS complex are best seen in lead V₁. Also, note incomplete RBBB and borderline QT prolongation.

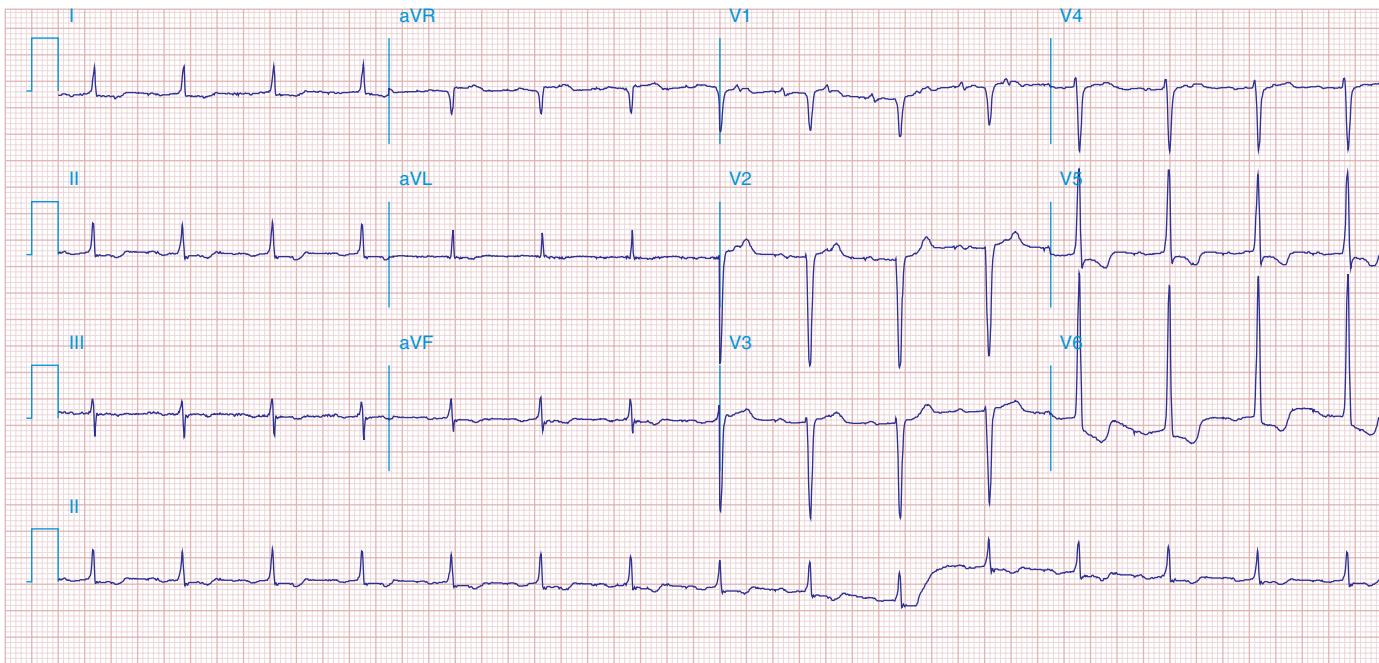


FIGURE 278e-12 Atrial tachycardia (180/min with 2:1 AV block [see lead V₁]). LVH by precordial voltage and nonspecific ST-T changes. Slow R-wave progression (V₁-V₄) raises consideration of prior anterior MI.

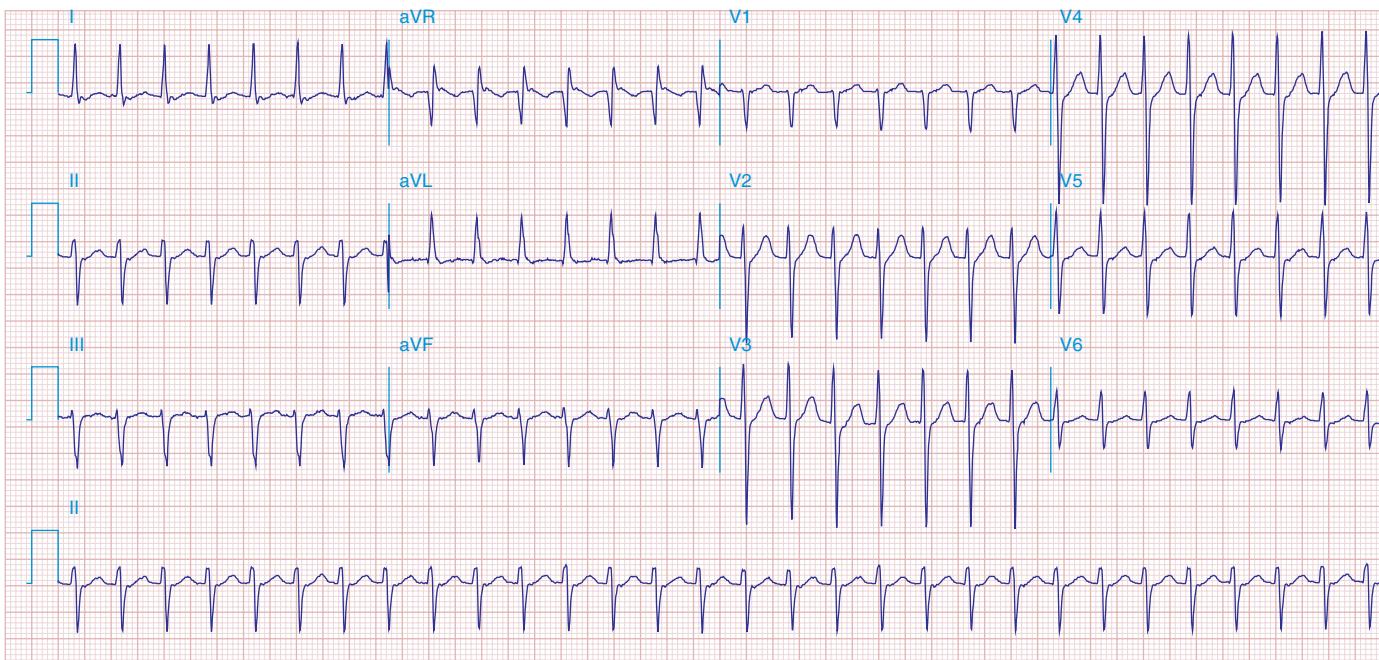


FIGURE 278e-13 AV nodal reentrant tachycardia (AVNRT) at a rate of 150/min. Note subtle "pseudo" R waves in lead aVR due to retrograde atrial activation, which usually occurs nearly simultaneous with ventricles in AVNRT. Left-axis deviation consistent with left anterior fascicular block (hemiblock) is also present.

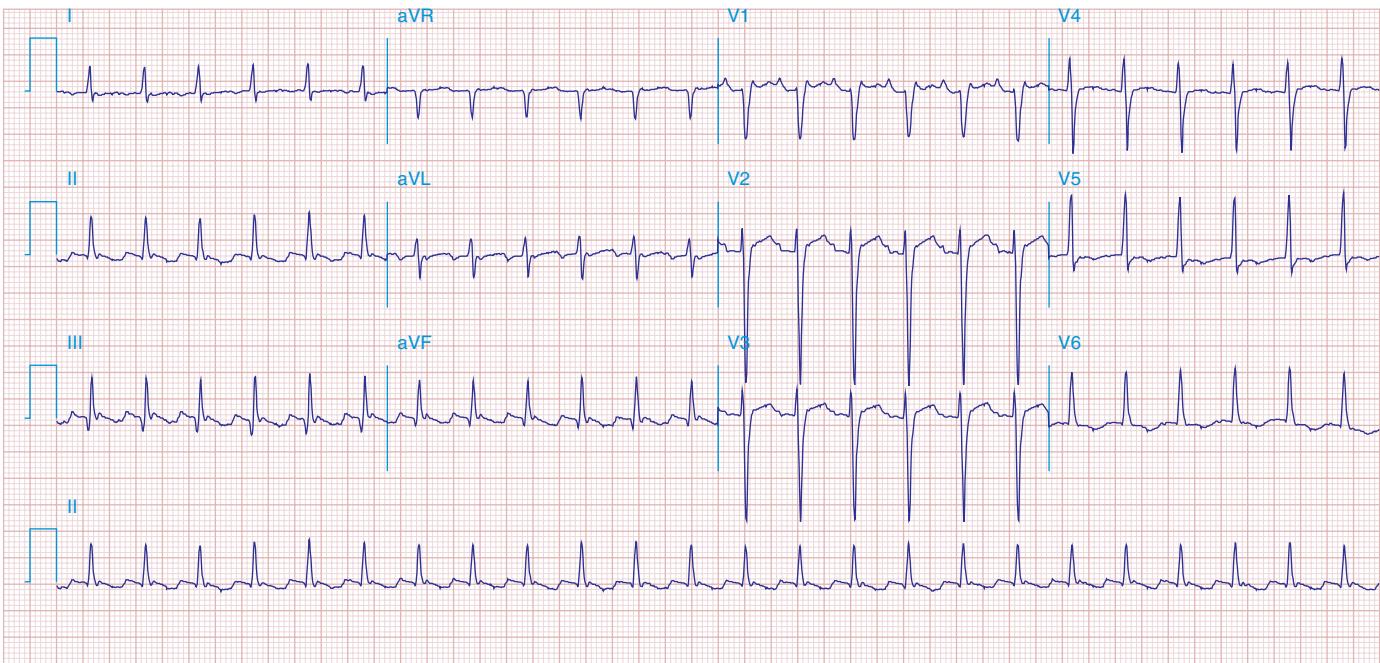


FIGURE 278e-14 Atrial flutter with 2:1 AV conduction. Note typical atrial flutter waves, partly hidden in the early ST segment, seen, for example, in leads II and V₁.

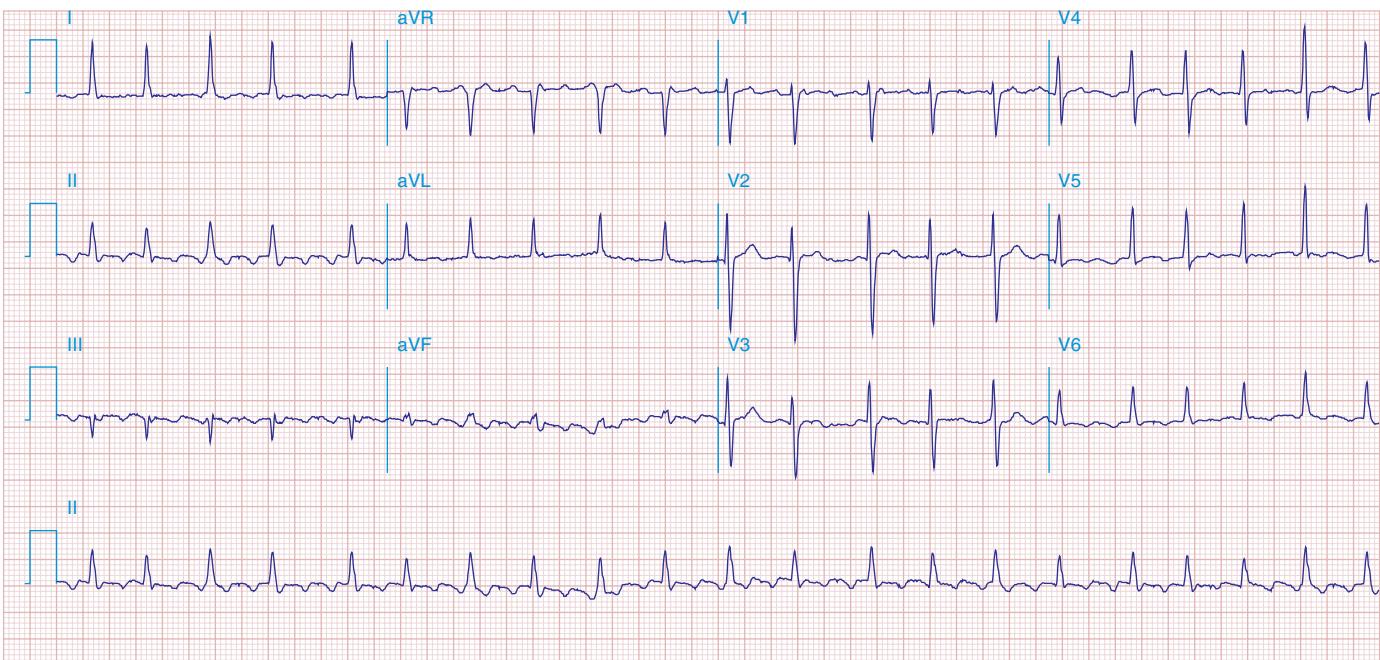


FIGURE 278e-15 Atrial flutter with atrial rate 300/min and variable (predominant 2:1 and 3:1) AV conduction. Typical flutter waves are best seen in lead II.

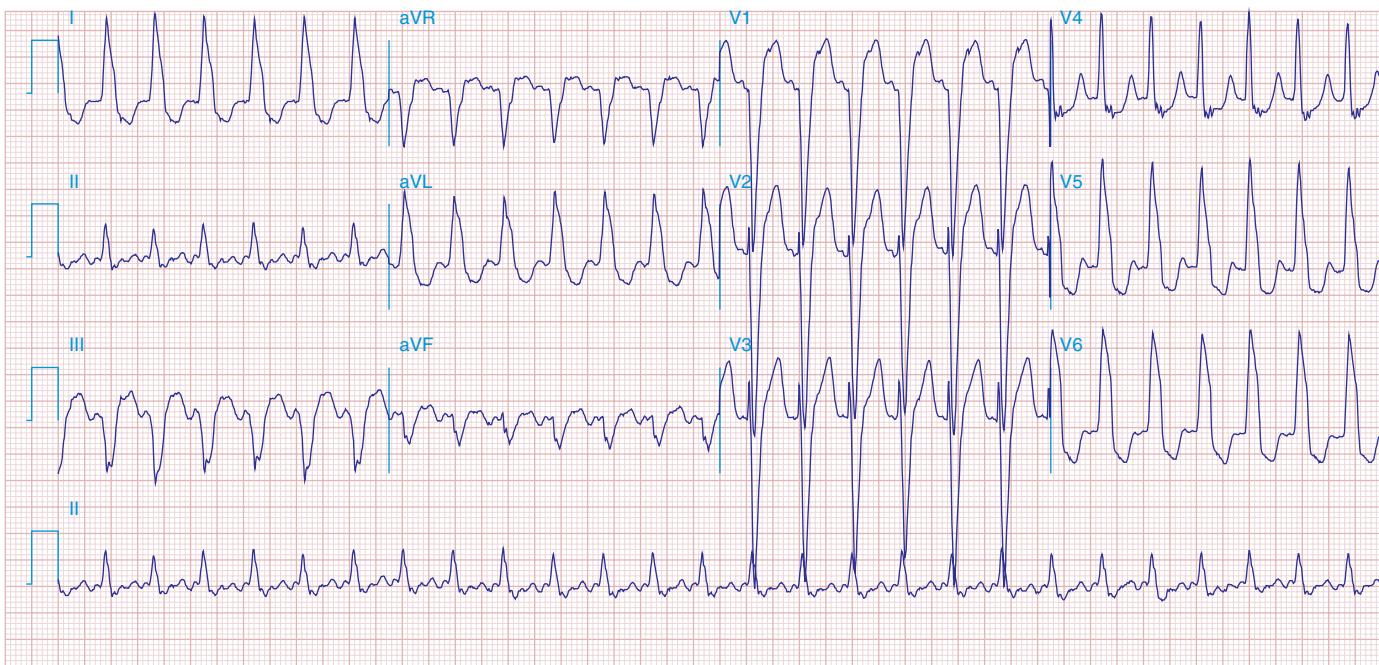


FIGURE 278e-16 Wide complex tachycardia. Atrial flutter with 2:1 AV conduction (block) and LBBB, not to be mistaken for VT. Typical atrial flutter activity is clearly present in lead II, at a cycle rate of about 320/min, yielding an effective ventricular rate of about 160/min.

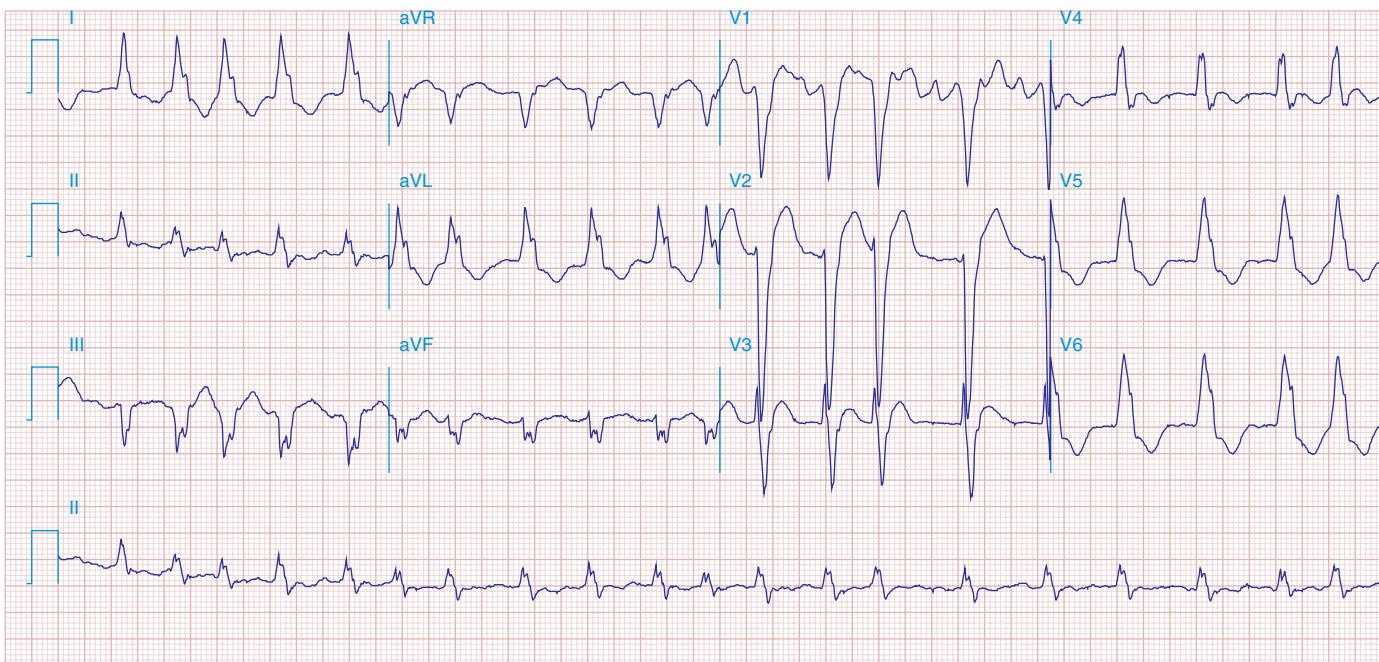


FIGURE 278e-17 AF with LBBB. The ventricular rhythm is erratically irregular. Coarse fibrillary waves are best seen in lead V₁, with a typical LBBB pattern.

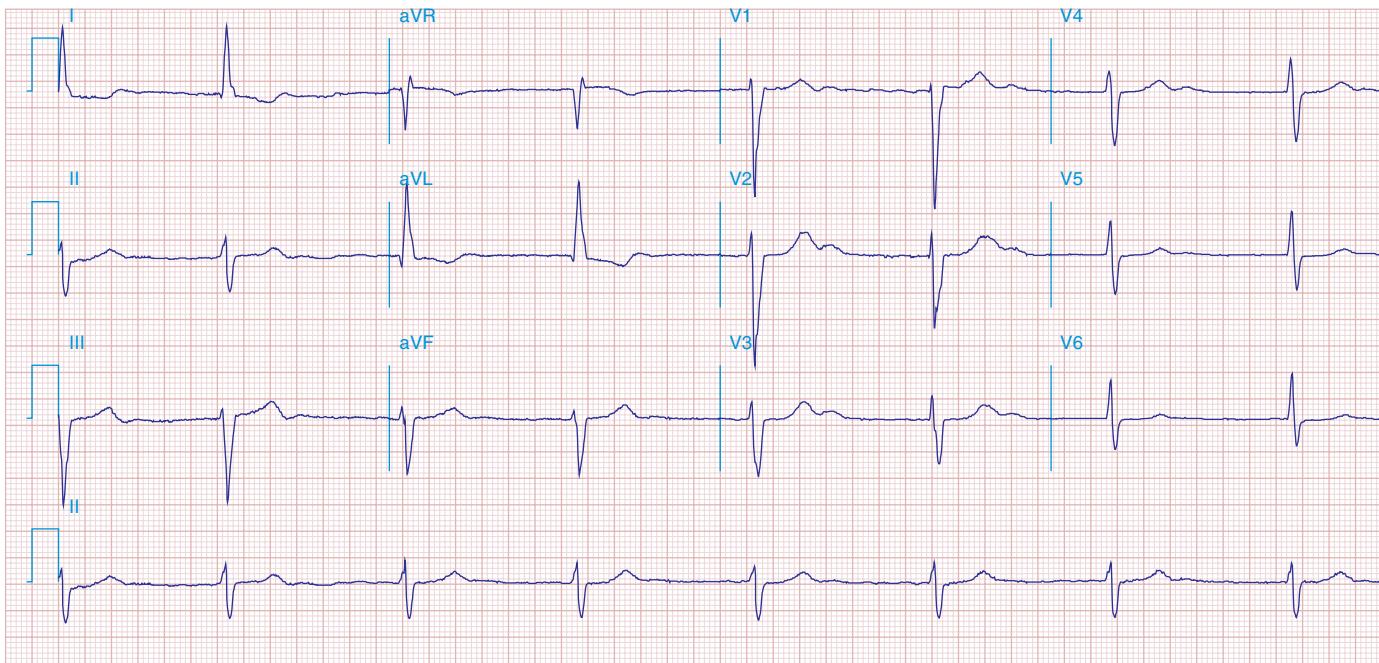


FIGURE 278e-18 AF with complete heart block and a junctional escape mechanism causing a slow regular ventricular response (45/min). The QRS complexes show an intraventricular conduction delay with left-axis deviation and LVH. Q-T (U) prolongation is also present.

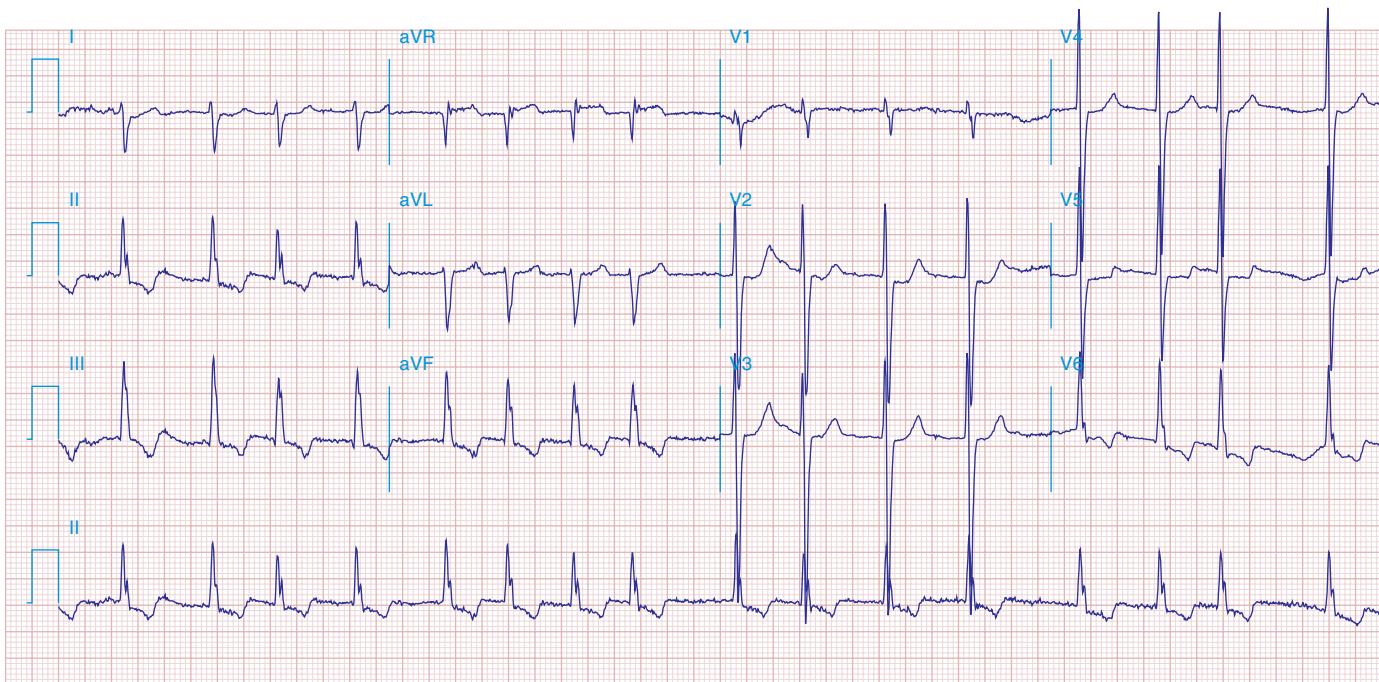


FIGURE 278e-19 AF with right-axis deviation and LVH. Tracing suggests biventricular hypertrophy in a patient with mitral stenosis and aortic valve disease.

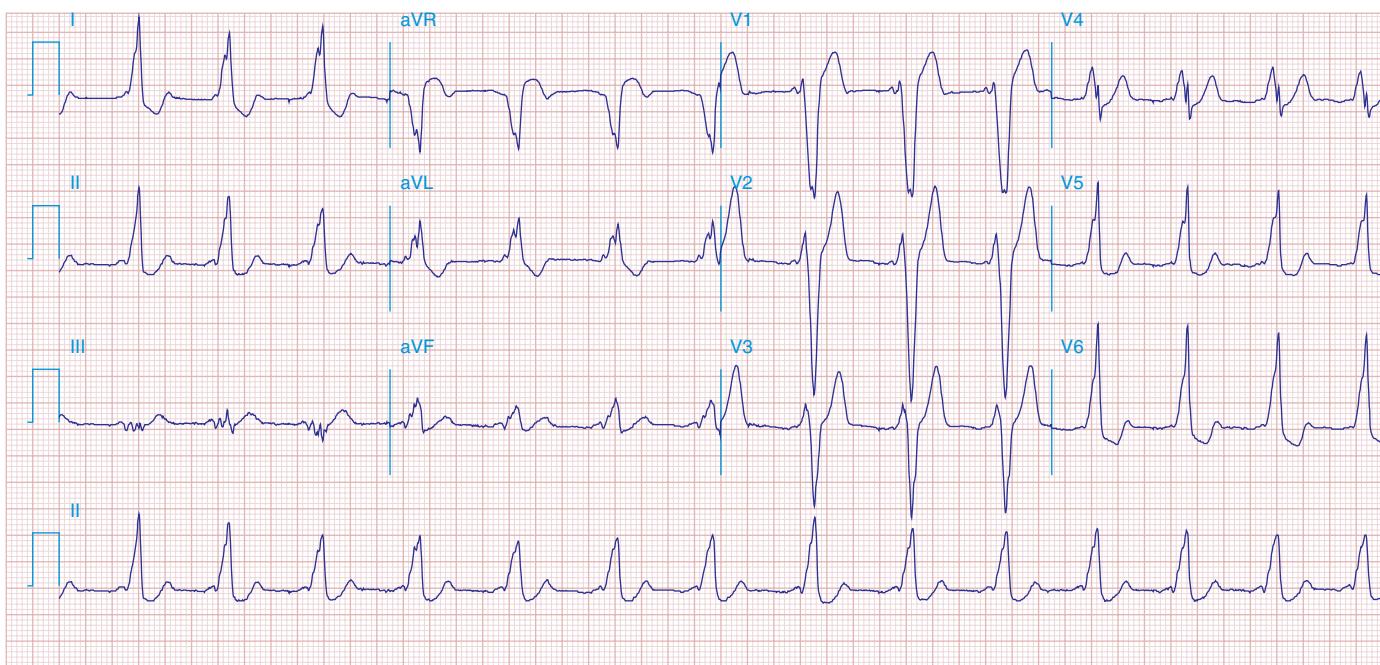


FIGURE 278e-20 WPW preexcitation pattern, with triad of short PR, wide QRS, and delta waves. Polarity of the delta waves (slightly positive in leads V_1 and V_2 and most positive in lead II and lateral chest leads) is consistent with a right-sided bypass tract.



FIGURE 278e-21 AF in patient with the WPW syndrome and antegrade conduction down the bypass tract leading to a wide complex tachycardia. Rhythm is “irregularly irregular,” and rate is extremely rapid (about 230/min). Not all beats are preexcited.

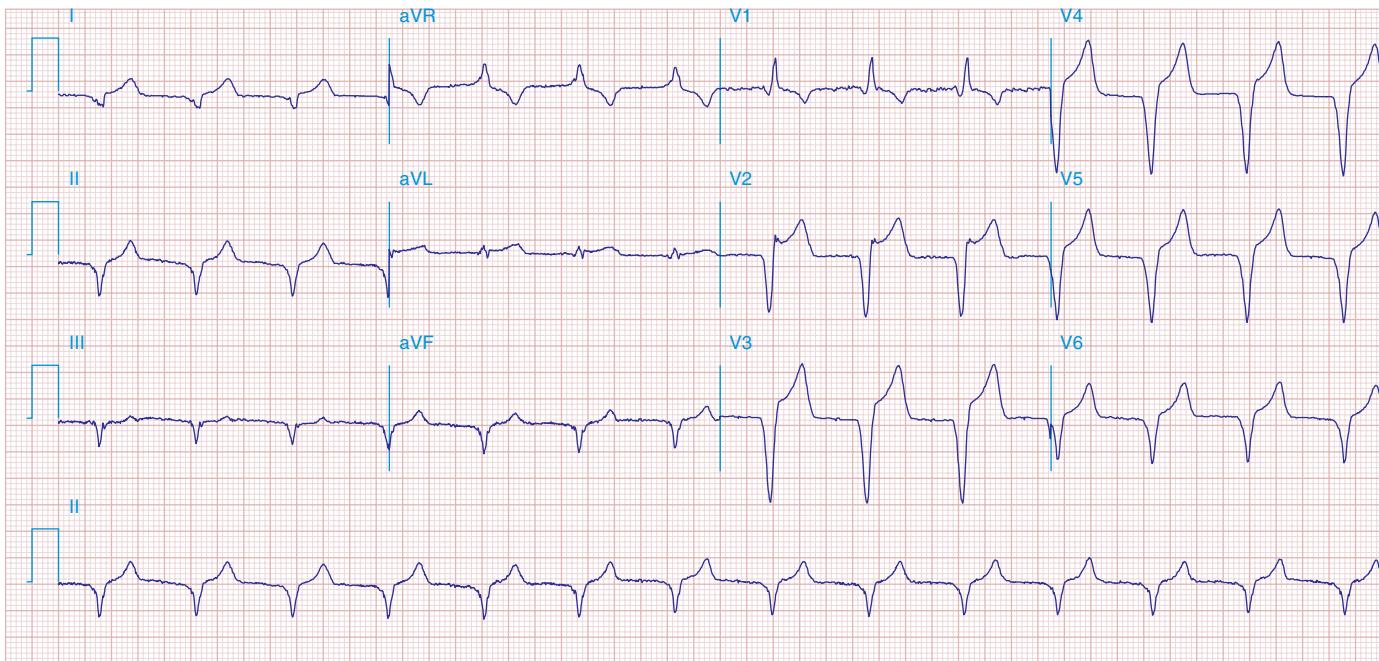


FIGURE 278e-22 Accelerated idioventricular rhythm (AIVR) originating from the LV and accounting for RBBB morphology. ST elevations in the precordial leads from underlying acute MI.

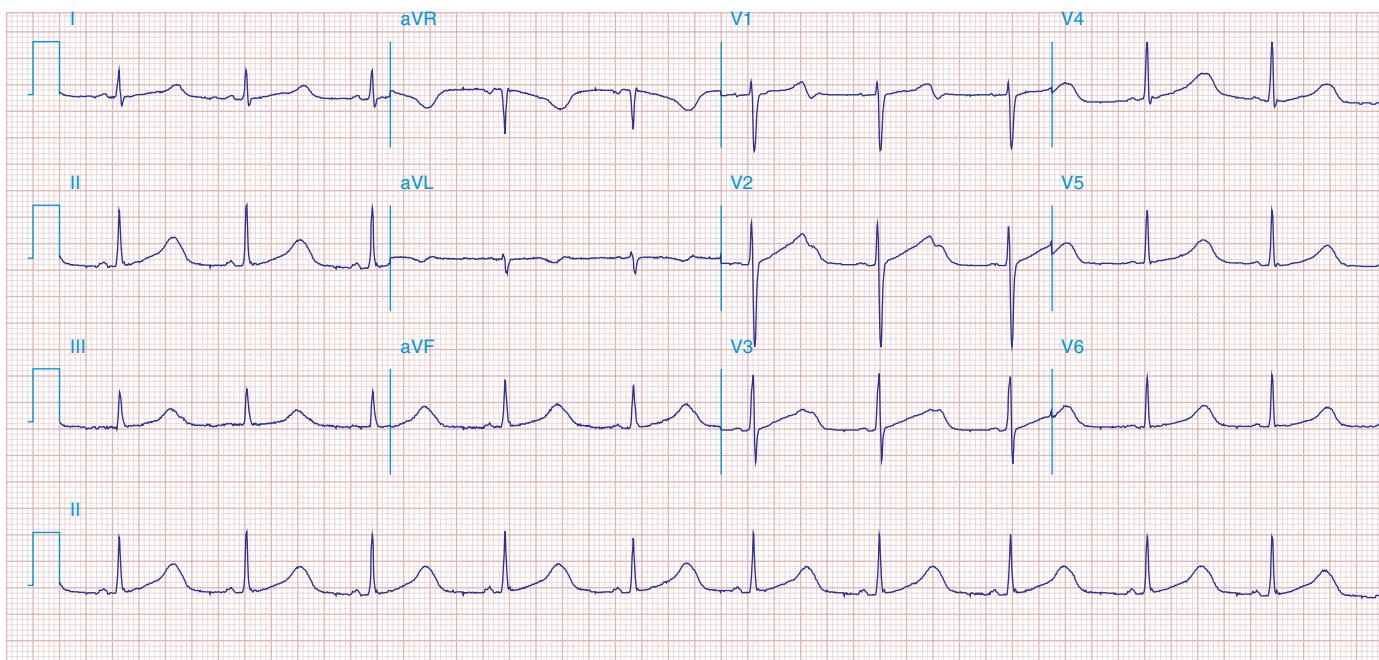


FIGURE 278e-23 Prolonged (0.60 s) QT interval in a patient with a hereditary long QT syndrome.



FIGURE 278e-24 Monomorphic VT at rate of 170/min. The RBBB morphology in V_1 and the R:S ratio <1 in V_6 are both suggestive of VT. The morphology of the VT is suggestive of origin from the left side of the heart, near the base (RBBB with inferior/rightward axis). Baseline artifact is present in leads V_1 - V_3 .

SECTION 4 DISORDERS OF THE HEART

279 Heart Failure: Pathophysiology and Diagnosis

Douglas L. Mann, Murali Chakinala

HEART FAILURE

DEFINITION

Despite repeated attempts to develop a mechanistic definition that encompasses the heterogeneity and complexity of heart failure (HF), no single conceptual paradigm has withstood the test of time. The current American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines define HF as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which in turn leads to the cardinal clinical symptoms of dyspnea and fatigue and signs of HF, namely edema and rales. Because many patients present without signs

or symptoms of volume overload, the term “heart failure” is preferred over the older term “congestive heart failure.”

EPIDEMIOLOGY

 HF is a burgeoning problem worldwide, with more than 20 million people affected. The overall prevalence of HF in the adult population in developed countries is 2%. HF prevalence follows an exponential pattern, rising with age, and affects 6–10% of people over age 65. Although the relative incidence of HF is lower in women than in men, women constitute at least one-half the cases of HF because of their longer life expectancy. In North America and Europe, the lifetime risk of developing HF is approximately one in five for a 40-year-old. The overall prevalence of HF is thought to be increasing, in part because current therapies for cardiac disorders, such as myocardial infarction (MI), valvular heart disease, and arrhythmias, are allowing patients to survive longer. Very little is known about the prevalence or risk of developing HF in emerging nations because of the lack of population-based studies in those countries. HF was once thought to arise primarily in the setting of a

depressed left ventricular (LV) ejection fraction (EF); however, epidemiologic studies have shown that approximately one-half of patients who develop HF have a normal or preserved EF (EF $\geq 50\%$). Accordingly, the historical terms “systolic” and “diastolic” HF have been abandoned, and HF patients are now broadly categorized into HF with a reduced EF (HFrEF; formerly *systolic failure*) or HF with a preserved EF (HRpEF; formerly *diastolic failure*).

Etiology

As shown in **Table 279-1**, any condition that leads to an alteration in LV structure or function can predispose a patient to developing HF. Although the etiology of HF in patients with a preserved EF differs from that of patients with depressed EF, there is considerable overlap between the etiologies of these two conditions. In industrialized countries, coronary artery disease (CAD) has become the predominant cause in men and women and is responsible for 60–75% of cases of HF. Hypertension contributes to the development of HF in 75% of patients, including most patients with CAD. Both CAD and hypertension interact to augment the risk of HF, as does diabetes mellitus.

In 20–30% of the cases of HF with a depressed EF, the exact etiologic basis is not known. These patients are referred to as having nonischemic, dilated, or idiopathic cardiomyopathy if the cause is unknown (**Chap. 287**). Prior viral infection or toxin exposure (e.g., alcoholic or chemotherapeutic) also may lead to a dilated cardiomyopathy. Moreover, it is becoming increasingly clear that a large number of cases of dilated cardiomyopathy are secondary to specific genetic defects, most notably those in the cytoskeleton. Most forms of familial dilated cardiomyopathy are inherited in an autosomal dominant fashion. Mutations of genes that encode cytoskeletal proteins (desmin, cardiac myosin, vinculin) and nuclear membrane proteins (laminin) have been identified thus far. Dilated cardiomyopathy also is associated with Duchenne’s, Becker’s, and limb-girdle muscular dystrophies. Conditions that lead to a high cardiac output (e.g., arteriovenous fistula, anemia) are seldom responsible for the development of HF in a normal heart; however, in the presence of underlying structural heart disease, these conditions can lead to overt HF.

TABLE 279-1 ETIOLOGIES OF HEART FAILURE

Depressed Ejection Fraction (<40%)	
Coronary artery disease	Nonischemic dilated cardiomyopathy
Myocardial infarction ^a	Familial/genetic disorders
Myocardial ischemia ^a	Infiltrative disorders ^a
Chronic pressure overload	Toxic/drug-induced damage
Hypertension ^a	Metabolic disorder ^a
Obstructive valvular disease ^a	Viral
Chronic volume overload	Chagas’ disease
Regurgitant valvular disease	Disorders of rate and rhythm
Intracardiac (left-to-right) shunting	Chronic bradyarrhythmias
Extracardiac shunting	Chronic tachyarrhythmias
Chronic lung disease	
Cor pulmonale	
Pulmonary vascular disorders	
Preserved Ejection Fraction (>40–50%)	
Pathologic hypertrophy	Restrictive cardiomyopathy
Primary (hypertrophic cardiomyopathies)	Infiltrative disorders (amyloidosis, sarcoidosis)
Secondary (hypertension)	Storage diseases (hemochromatosis)
Aging	Fibrosis
	Endomyocardial disorders
High-Output States	
Metabolic disorders	Excessive blood flow requirements
Thyrotoxicosis	Systemic arteriovenous shunting
Nutritional disorders (beriberi)	Chronic anemia

^aIndicates conditions that can also lead to heart failure with a preserved ejection fraction.

TABLE 279-2 NEW YORK HEART ASSOCIATION CLASSIFICATION

Functional Capacity	Objective Assessment
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: Adapted from New York Heart Association, Inc., *Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis*, 6th ed. Boston, Little Brown, 1964, p. 114.

GLOBAL CONSIDERATIONS

Rheumatic heart disease remains a major cause of HF in Africa and Asia, especially in the young. Hypertension is an important cause of HF in the African and African-American populations. Chagas’ disease is still a major cause of HF in South America. Not surprisingly, anemia is a frequent concomitant factor in HF in many developing nations. As developing nations undergo socio-economic development, the epidemiology of HF is becoming similar to that of Western Europe and North America, with CAD emerging as the single most common cause of HF. Although the contribution of diabetes mellitus to HF is not well understood, diabetes accelerates atherosclerosis and often is associated with hypertension.

PROGNOSIS

Despite many recent advances in the evaluation and management of HF, the development of symptomatic HF still carries a poor prognosis. Community-based studies indicate that 30–40% of patients die within 1 year of diagnosis and 60–70% die within 5 years, mainly from worsening HF or as a sudden event (probably because of a ventricular arrhythmia). Although it is difficult to predict prognosis in an individual, patients with symptoms at rest (New York Heart Association [NYHA] class IV) have a 30–70% annual mortality rate, whereas patients with symptoms with moderate activity (NYHA class II) have an annual mortality rate of 5–10%. Thus, functional status is an important predictor of patient outcome (**Table 279-2**).

PATHOGENESIS

Figure 279-1 provides a general conceptual framework for considering the development and progression of HFrEF. As shown, HF may be viewed as a progressive disorder that is initiated after an *index event* either damages the heart muscle, with a resultant loss of functioning cardiac myocytes, or, alternatively, disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally. This index event may have an abrupt onset, as in the case of an MI; it may have a gradual or insidious onset, as in the case of hemodynamic pressure or volume overloading; or it may be hereditary, as in the case of many of the genetic cardiomyopathies. Regardless of the nature of the inciting event, the feature that is common to each of these index events is that they all in some manner produce a decline in the pumping capacity of the heart. In most instances, patients remain asymptomatic or minimally symptomatic after the initial decline in pumping capacity of the heart or develop symptoms only after the dysfunction has been present for some time.

Although the precise reasons why patients with LV dysfunction may remain asymptomatic is not certain, one potential explanation is that a number of compensatory mechanisms become activated in the presence of cardiac injury and/or LV dysfunction allowing patients

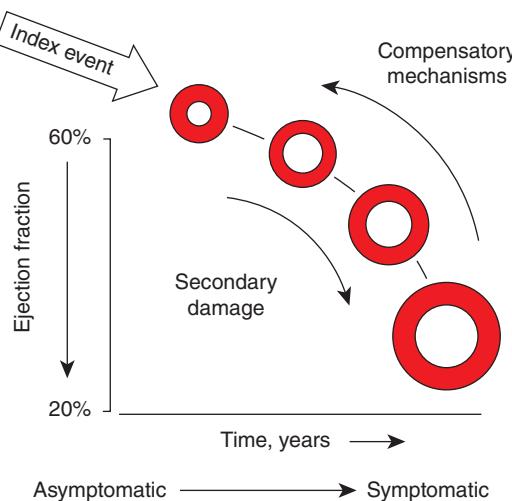


FIGURE 279-1 Pathogenesis of heart failure with a depressed ejection fraction. Heart failure begins after an index event produces an initial decline in the heart's pumping capacity. After this initial decline in pumping capacity, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin-angiotensin-aldosterone system, and the cytokine system. In the short term, these systems are able to restore cardiovascular function to a normal homeostatic range with the result that the patient remains asymptomatic. However, with time, the sustained activation of these systems can lead to secondary end-organ damage within the ventricle, with worsening left ventricular remodeling and subsequent cardiac decompensation. (From D Mann: *Circulation* 100:999, 1999.)

to sustain and modulate LV function for a period of months to years. The compensatory mechanisms that have been described thus far include (1) activation of the renin-angiotensin-aldosterone (RAA) and adrenergic nervous systems, which are responsible, respectively, for maintaining cardiac output through increased retention of salt and water (Fig. 279-2), and (2) increased myocardial contractility. In addition, there is activation of a family of countervailing vasodilatory molecules, including the atrial and brain natriuretic peptides (ANP and BNP), prostaglandins (PGE_2 and PGI_2), and nitric oxide (NO), that offsets the excessive peripheral vascular vasoconstriction. Genetic background, sex, age, or environment may influence these compensatory mechanisms, which are able to modulate LV function within a physiologic/homeostatic range so that the functional capacity of the patient is preserved or is depressed only minimally. Thus, patients may remain asymptomatic or minimally symptomatic for a period of years; however, at some point patients become overtly symptomatic, with a resultant striking increase in morbidity and mortality rates. Although the exact mechanisms that are responsible for this transition are not known, as will be discussed below, the transition to symptomatic HF is accompanied by increasing activation of neurohormonal, adrenergic, and cytokine systems that lead to a series of adaptive changes within the myocardium collectively referred to as *LV remodeling*.

In contrast to our understanding of the pathogenesis of HF with a depressed EF, our understanding of the mechanisms that contribute to the development of HF with a preserved EF is still evolving. That is, although diastolic dysfunction (see below) was thought to be the only mechanism responsible for the development of HF with a preserved EF, community-based studies suggest that additional extracardiac mechanisms may be important, such as increased vascular stiffness and impaired renal function.

BASIC MECHANISMS OF HEART FAILURE

Heart Failure with a Reduced Ejection Fraction LV remodeling develops in response to a series of complex events that occur at the cellular and molecular levels (Table 279-3). These changes include (1) myocyte hypertrophy; (2) alterations in the contractile properties of the myocyte; (3) progressive loss of myocytes through necrosis,

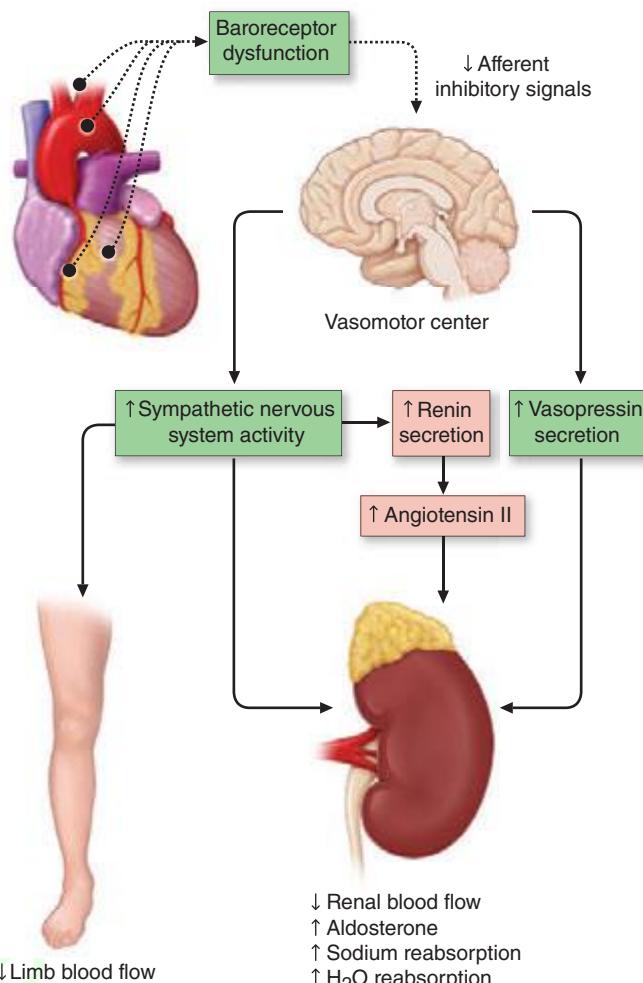


FIGURE 279-2 Activation of neurohormonal systems in heart failure.

The decreased cardiac output in heart failure (HF) patients results in an "unloading" of high-pressure baroreceptors (circles) in the left ventricle, carotid sinus, and aortic arch. This unloading of the peripheral baroreceptors leads to a loss of inhibitory parasympathetic tone to the central nervous system (CNS), with a resultant generalized increase in efferent sympathetic tone, and nonosmotic release of arginine vasopressin (AVP) from the pituitary. AVP (or antidiuretic hormone [ADH]) is a powerful vasoconstrictor that increases the permeability of the renal collecting ducts, leading to the reabsorption of free water. These afferent signals to the CNS also activate efferent sympathetic nervous system pathways that innervate the heart, kidney, peripheral vasculature, and skeletal muscles.

Sympathetic stimulation of the kidney leads to the release of renin, with a resultant increase in the circulating levels of angiotensin II and aldosterone. The activation of the renin-angiotensin-aldosterone system promotes salt and water retention and leads to vasoconstriction of the peripheral vasculature, myocyte hypertrophy, myocyte cell death, and myocardial fibrosis. Although these neurohormonal mechanisms facilitate short-term adaptation by maintaining blood pressure, and hence perfusion to vital organs, the same neurohormonal mechanisms are believed to contribute to end-organ changes in the heart and the circulation and to the excessive salt and water retention in advanced HF. (Modified from A Nohria et al: Neurohormonal, renal and vascular adjustments, in *Atlas of Heart Failure: Cardiac Function and Dysfunction*, 4th ed, WS Colucci [ed]. Philadelphia, Current Medicine Group 2002, p. 104.)

apoptosis, and autophagic cell death; (4) β -adrenergic desensitization; (5) abnormal myocardial energetics and metabolism; and (6) reorganization of the extracellular matrix with dissolution of the organized structural collagen weave surrounding myocytes and subsequent replacement by an interstitial collagen matrix that does not

TABLE 279-3 OVERVIEW OF LEFT VENTRICULAR REMODELING**Alterations in Myocyte Biology**

- Excitation-contraction coupling
- Myosin heavy chain (fetal) gene expression
- β -Adrenergic desensitization
- Hypertrophy
- Myocytolysis
- Cytoskeletal proteins

Myocardial Changes

- Myocyte loss
- Necrosis
- Apoptosis
- Autophagy
- Alterations in extracellular matrix
- Matrix degradation
- Myocardial fibrosis

Alterations in Left Ventricular Chamber Geometry

- Left ventricular (LV) dilation
- Increased LV sphericity
- LV wall thinning
- Mitral valve incompetence

Source: Adapted from D. Mann: Pathophysiology of heart failure, in *Braunwald's Heart Disease*, 8th ed, PL Libby et al (eds). Philadelphia, Elsevier, 2008, p. 550.

provide structural support to the myocytes. The biologic stimuli for these profound changes include mechanical stretch of the myocyte, circulating neurohormones (e.g., norepinephrine, angiotensin II), inflammatory cytokines (e.g., tumor necrosis factor [TNF]), other peptides and growth factors (e.g., endothelin), and reactive oxygen species (e.g., superoxide). The sustained overexpression of these biologically active molecules is believed to contribute to the progression of HF by virtue of the deleterious effects they exert on the heart and the circulation. Indeed, this insight forms the clinical rationale for using pharmacologic agents that antagonize these systems (e.g., angiotensin-converting enzyme [ACE] inhibitors and beta blockers) in treating patients with HF ([Chap. 280](#)).

To understand how the changes that occur in the failing cardiac myocyte contribute to depressed LV systolic function in HF, it is instructive first to review the biology of the cardiac muscle cell ([Chap. 265e](#)). Sustained neurohormonal activation and mechanical overload result in transcriptional and posttranscriptional changes in the genes and proteins that regulate excitation-contraction coupling and cross-bridge interaction (see [Figs. 265e-6 and 265e-7](#)). The changes that regulate excitation-contraction include decreased function of sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase (SERCA2A), resulting in decreased calcium uptake into the sarcoplasmic reticulum (SR), and hyperphosphorylation of the ryanodine receptor, leading to calcium leakage from the SR. The changes that occur in the cross-bridges include decreased expression of α -myosin heavy chain and increased expression of β -myosin heavy chain, myocytolysis, and disruption of the cytoskeletal links between the sarcomeres and the extracellular matrix. Collectively, these changes impair the ability of the myocyte to contract and therefore contribute to the depressed LV systolic function observed in patients with HF.

Myocardial relaxation is an adenosine triphosphate (ATP)-dependent process that is regulated by uptake of cytoplasmic calcium into the SR by SERCA2A and extrusion of calcium by sarcolemmal pumps (see [Fig. 265e-7](#)). Accordingly, reductions in ATP concentration, as occurs in ischemia, may interfere with these processes and lead to slowed myocardial relaxation. Alternatively, if LV filling is delayed because LV compliance is reduced (e.g., from hypertrophy or fibrosis), LV filling pressures will similarly remain elevated at end diastole (see [Fig. 265e-11](#)). An increase in heart rate disproportionately shortens the time for diastolic filling, which may lead to elevated LV filling

pressures, particularly in noncompliant ventricles. Elevated LV end-diastolic filling pressures result in increases in pulmonary capillary pressures, which can contribute to the dyspnea experienced by patients with diastolic dysfunction. In addition to impaired myocardial relaxation, increased myocardial stiffness secondary to cardiac hypertrophy and increased myocardial collagen content may contribute to diastolic failure. Importantly, diastolic dysfunction can occur alone or in combination with systolic dysfunction in patients with HF.

Left Ventricular Remodeling Ventricular remodeling refers to the changes in LV mass, volume, and shape and the composition of the heart that occur after cardiac injury and/or abnormal hemodynamic loading conditions. LV remodeling may contribute independently to the progression of HF by virtue of the mechanical burdens that are engendered by the changes in the geometry of the remodeled LV. In addition to the increase in LV end-diastolic volume, LV wall thinning occurs as the left ventricle begins to dilate. The increase in wall thinning, along with the increase in afterload created by LV dilation, leads to a functional *afterload mismatch* that may contribute further to a decrease in stroke volume. Moreover, the high end-diastolic wall stress might be expected to lead to (1) hypoperfusion of the subendocardium, with resultant worsening of LV function; (2) increased oxidative stress, with the resultant activation of families of genes that are sensitive to free radical generation (e.g., TNF and interleukin 1 β); and (3) sustained expression of stretch-activated genes (angiotensin II, endothelin, and TNF) and/or stretch activation of hypertrophic signaling pathways. Increasing LV dilation also results in tethering of the papillary muscles with resulting incompetence of the mitral valve apparatus and functional mitral regurgitation, which in turn leads to further hemodynamic overloading of the ventricle. Taken together, the mechanical burdens that are engendered by LV remodeling contribute to the progression of HF. Recent studies have shown that LV remodeling can be reversed following medical and device therapy and that reverse LV remodeling is associated with improved clinical outcomes in patients with HFrEF. Indeed, one of the goals of therapy for HF is to prevent and/or reverse LV remodeling.

CLINICAL MANIFESTATIONS

Symptoms The cardinal symptoms of HF are fatigue and shortness of breath. Although fatigue traditionally has been ascribed to the low cardiac output in HF, it is likely that skeletal-muscle abnormalities and other noncardiac comorbidities (e.g., anemia) also contribute to this symptom. In the early stages of HF, dyspnea is observed only during exertion; however, as the disease progresses, dyspnea occurs with less strenuous activity, and it ultimately may occur even at rest. The origin of dyspnea in HF is probably multifactorial ([Chap. 47e](#)). The most important mechanism is pulmonary congestion with accumulation of interstitial or intra-alveolar fluid, which activates juxtagapillary J receptors, which in turn stimulate the rapid, shallow breathing characteristic of cardiac dyspnea. Other factors that contribute to dyspnea on exertion include reductions in pulmonary compliance, increased airway resistance, respiratory muscle and/or diaphragm fatigue, and anemia. Dyspnea may become less frequent with the onset of right ventricular (RV) failure and tricuspid regurgitation.

ORTHOPNEA Orthopnea, which is defined as dyspnea occurring in the recumbent position, is usually a later manifestation of HF than is exertional dyspnea. It results from redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation during recumbency, with a resultant increase in pulmonary capillary pressure. Nocturnal cough is a common manifestation of this process and a frequently overlooked symptom of HF. Orthopnea generally is relieved by sitting upright or sleeping with additional pillows. Although orthopnea is a relatively specific symptom of HF, it may occur in patients with abdominal obesity or ascites and patients with pulmonary disease whose lung mechanics favor an upright posture.

PAROXYSMAL NOCTURNAL DYSPNEA (PND) This term refers to acute episodes of severe shortness of breath and coughing that generally occur at night and awaken the patient from sleep, usually 1–3 h after the

patient retires. PND may manifest as coughing or wheezing, possibly because of increased pressure in the bronchial arteries leading to airway compression, along with interstitial pulmonary edema that leads to increased airway resistance. Whereas orthopnea may be relieved by sitting upright at the side of the bed with the legs in a dependent position, patients with PND often have persistent coughing and wheezing even after they have assumed the upright position. *Cardiac asthma* is closely related to PND, is characterized by wheezing secondary to bronchospasm, and must be differentiated from primary asthma and pulmonary causes of wheezing.

CHEYNE-STOKES RESPIRATION Also referred to as periodic respiration or cyclic respiration, Cheyne-Stokes respiration is present in 40% of patients with advanced HF and usually is associated with low cardiac output. Cheyne-Stokes respiration is caused by an increased sensitivity of the respiratory center to arterial PCO_2 . There is an apneic phase, during which arterial PO_2 falls and arterial PCO_2 rises. These changes in the arterial blood gas content stimulate the respiratory center, resulting in hyperventilation and hypocapnia, followed by recurrence of apnea. Cheyne-Stokes respirations may be perceived by the patient or the patient's family as severe dyspnea or as a transient cessation of breathing.

ACUTE PULMONARY EDEMA *See Chap. 326*

Other Symptoms Patients with HF also may present with gastrointestinal symptoms. Anorexia, nausea, and early satiety associated with abdominal pain and fullness are common complaints and may be related to edema of the bowel wall and/or a congested liver. Congestion of the liver and stretching of its capsule may lead to right upper-quadrant pain. Cerebral symptoms such as confusion, disorientation, and sleep and mood disturbances may be observed in patients with severe HF, particularly elderly patients with cerebral arteriosclerosis and reduced cerebral perfusion. Nocturia is common in HF and may contribute to insomnia.

PHYSICAL EXAMINATION

A careful physical examination is always warranted in the evaluation of patients with HF. The purpose of the examination is to help determine the cause of HF as well as to assess the severity of the syndrome. Obtaining additional information about the hemodynamic profile and the response to therapy and determining the prognosis are important additional goals of the physical examination.

General Appearance and Vital Signs In mild or moderately severe HF, the patient appears to be in no distress at rest except for feeling uncomfortable when lying flat for more than a few minutes. In more severe HF, the patient must sit upright, may have labored breathing, and may not be able to finish a sentence because of shortness of breath. Systolic blood pressure may be normal or high in early HF, but it generally is reduced in advanced HF because of severe LV dysfunction. The pulse pressure may be diminished, reflecting a reduction in stroke volume. Sinus tachycardia is a nonspecific sign caused by increased adrenergic activity. Peripheral vasoconstriction leading to cool peripheral extremities and cyanosis of the lips and nail beds is also caused by excessive adrenergic activity.

Jugular Veins (*See also Chap. 267*) Examination of the jugular veins provides an estimation of right atrial pressure. The jugular venous pressure is best appreciated with the patient lying recumbent, with the head tilted at 45°. The jugular venous pressure should be quantified in centimeters of water (normal ≤ 8 cm) by estimating the height of the venous column of blood above the sternal angle in centimeters and then adding 5 cm. In the early stages of HF, the venous pressure may be normal at rest but may become abnormally elevated with sustained (~15 seconds) pressure on the abdomen (positive abdominojugular reflux). Giant v waves indicate the presence of tricuspid regurgitation.

Pulmonary Examination Pulmonary crackles (rales or crepitations) result from the transudation of fluid from the intravascular space into

the alveoli. In patients with pulmonary edema, rales may be heard widely over both lung fields and may be accompanied by expiratory wheezing (cardiac asthma). When present in patients without concomitant lung disease, rales are specific for HF. Importantly, rales are frequently absent in patients with chronic HF, even when LV filling pressures are elevated, because of increased lymphatic drainage of alveolar fluid. Pleural effusions result from the elevation of pleural capillary pressure and the resulting transudation of fluid into the pleural cavities. Since the pleural veins drain into both the systemic and the pulmonary veins, pleural effusions occur most commonly with biventricular failure. Although pleural effusions are often bilateral in HF, when they are unilateral, they occur more frequently in the right pleural space.

Cardiac Examination Examination of the heart, although essential, frequently does not provide useful information about the severity of HF. If cardiomegaly is present, the point of maximal impulse (PMI) usually is displaced below the fifth intercostal space and/or lateral to the midclavicular line, and the impulse is palpable over two interspaces. Severe LV hypertrophy leads to a sustained PMI. In some patients, a third heart sound (S_3) is audible and palpable at the apex. Patients with enlarged or hypertrophied right ventricles may have a sustained and prolonged left parasternal impulse extending throughout systole. An S_3 (or *protodiastolic gallop*) is most commonly present in patients with volume overload who have tachycardia and tachypnea, and it often signifies severe hemodynamic compromise. A fourth heart sound (S_4) is not a specific indicator of HF but is usually present in patients with diastolic dysfunction. The murmurs of mitral and tricuspid regurgitation are frequently present in patients with advanced HF.

Abdomen and Extremities Hepatomegaly is an important sign in patients with HF. When it is present, the enlarged liver is frequently tender and may pulsate during systole if tricuspid regurgitation is present. Ascites, a late sign, occurs as a consequence of increased pressure in the hepatic veins and the veins draining the peritoneum. Jaundice, also a late finding in HF, results from impairment of hepatic function secondary to hepatic congestion and hepatocellular hypoxemia and is associated with elevations of both direct and indirect bilirubin.

Peripheral edema is a cardinal manifestation of HF, but it is nonspecific and usually is absent in patients who have been treated adequately with diuretics. Peripheral edema is usually symmetric and dependent in HF and occurs predominantly in the ankles and the pretibial region in ambulatory patients. In bedridden patients, edema may be found in the sacral area (*presacral edema*) and the scrotum. Long-standing edema may be associated with indurated and pigmented skin.

Cardiac Cachexia With severe chronic HF, there may be marked weight loss and cachexia. Although the mechanism of cachexia is not entirely understood, it is probably multifactorial and includes elevation of the resting metabolic rate; anorexia, nausea, and vomiting due to congestive hepatomegaly and abdominal fullness; elevation of circulating concentrations of cytokines such as TNF; and impairment of intestinal absorption due to congestion of the intestinal veins. When present, cachexia augurs a poor overall prognosis.

DIAGNOSIS

The diagnosis of HF is relatively straightforward when the patient presents with classic signs and symptoms of HF; however, the signs and symptoms of HF are neither specific nor sensitive. Accordingly, the key to making the diagnosis is to have a high index of suspicion, particularly for high-risk patients. When these patients present with signs or symptoms of HF, additional laboratory testing should be performed.

Routine Laboratory Testing Patients with new-onset HF and those with chronic HF and acute decompensation should have a complete blood count, a panel of electrolytes, blood urea nitrogen, serum creatinine, hepatic enzymes, and a urinalysis. Selected patients should have assessment for diabetes mellitus (fasting serum glucose or oral glucose

tolerance test), dyslipidemia (fasting lipid panel), and thyroid abnormalities (thyroid-stimulating hormone level).

Electrocardiogram (ECG) A routine 12-lead ECG is recommended. The major importance of the ECG is to assess cardiac rhythm and determine the presence of LV hypertrophy or a prior MI (presence or absence of Q waves) as well as to determine QRS width to ascertain whether the patient may benefit from resynchronization therapy (see below). A normal ECG virtually excludes LV systolic dysfunction.

Chest X-Ray A chest x-ray provides useful information about cardiac size and shape, as well as the state of the pulmonary vasculature, and may identify noncardiac causes of the patient's symptoms. Although patients with acute HF have evidence of pulmonary hypertension, interstitial edema, and/or pulmonary edema, the majority of patients with chronic HF do not. The absence of these findings in patients with chronic HF reflects the increased capacity of the lymphatics to remove interstitial and/or pulmonary fluid.

Assessment of LV Function Noninvasive cardiac imaging (Chap. 270e) is essential for the diagnosis, evaluation, and management of HF. The most useful test is the two-dimensional (2-D) echocardiogram/Doppler, which can provide a semiquantitative assessment of LV size and function as well as the presence or absence of valvular and/or regional wall motion abnormalities (indicative of a prior MI). The presence of left atrial dilation and LV hypertrophy, together with abnormalities of LV diastolic filling provided by pulse-wave and tissue Doppler, is useful for the assessment of HF with a preserved EF. The 2-D echocardiogram/Doppler is also invaluable in assessing RV size and pulmonary pressures, which are critical in the evaluation and management of cor pulmonale (see below). Magnetic resonance imaging (MRI) also provides a comprehensive analysis of cardiac anatomy and function and is now the gold standard for assessing LV mass and volumes. MRI also is emerging as a useful and accurate imaging modality for evaluating patients with HF, both in terms of assessing LV structure and for determining the cause of HF (e.g., amyloidosis, ischemic cardiomyopathy, hemochromatosis).

The most useful index of LV function is the EF (stroke volume divided by end-diastolic volume). Because the EF is easy to measure by noninvasive testing and easy to conceptualize, it has gained wide acceptance among clinicians. Unfortunately, the EF has a number of limitations as a true measure of contractility, since it is influenced by alterations in afterload and/or preload. Nonetheless, with the exceptions indicated above, when the EF is normal ($\geq 50\%$), systolic function is usually adequate, and when the EF is significantly depressed ($< 30\text{--}40\%$), contractility is usually depressed.

Biomarkers Circulating levels of natriuretic peptides are useful and important adjunctive tools in the diagnosis of patients with HF. Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), which are released from the failing heart, are relatively sensitive markers for the presence of HF with depressed EF; they also are elevated in HF patients with a preserved EF, albeit to a lesser degree. In ambulatory patients with dyspnea, the measurement of BNP or NT-proBNP is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty. Moreover, the measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF and can be useful to achieve optimal dosing of medical therapy in select clinically euvolemic patients. However, it is important to recognize that natriuretic peptide levels increase with age and renal impairment, are more elevated in women, and can be elevated in right HF from any cause. Levels can be falsely low in obese patients. Other biomarkers, such as soluble ST-2 and galectin-3, are newer biomarkers that can be used for determining the prognosis of HF patients.

Exercise Testing Treadmill or bicycle exercise testing is not routinely advocated for patients with HF, but either is useful for assessing the need for cardiac transplantation in patients with advanced HF

(Chap. 281). A peak oxygen uptake (vo_2) $< 14 \text{ mL/kg per min}$ is associated with a relatively poor prognosis. Patients with a $\text{vo}_2 < 14 \text{ mL/kg per min}$ have been shown, in general, to have better survival when transplanted than when treated medically.

DIFFERENTIAL DIAGNOSIS

HF resembles but should be distinguished from (1) conditions in which there is circulatory congestion secondary to abnormal salt and water retention but in which there is no disturbance of cardiac structure or function (e.g., renal failure), and (2) noncardiac causes of pulmonary edema (e.g., acute respiratory distress syndrome). In most patients who present with classic signs and symptoms of HF, the diagnosis is relatively straightforward. However, even experienced clinicians have difficulty differentiating the dyspnea that arises from cardiac and pulmonary causes (Chap. 47e). In this regard, noninvasive cardiac imaging, biomarkers, pulmonary function testing, and chest x-ray may be useful. A very low BNP or NT-proBNP may be helpful in excluding a cardiac cause of dyspnea in this setting. Ankle edema may arise secondary to varicose veins, obesity, renal disease, or gravitational effects. When HF develops in patients with a preserved EF, it may be difficult to determine the relative contribution of HF to the dyspnea that occurs in chronic lung disease and/or obesity.

COR PULMONALE

DEFINITION

Cor pulmonale, often referred to as *pulmonary heart disease*, can be defined as altered RV structure and/or function in the context of chronic lung disease and is triggered by the onset of pulmonary hypertension. Although RV dysfunction is also an important sequela of HFrEF and HFrEF, this is not considered as cor pulmonale.

ETIOLOGY AND EPIDEMIOLOGY

Cor pulmonale develops in response to acute or chronic changes in the pulmonary vasculature and/or the lung parenchyma that are sufficient to cause pulmonary hypertension. The true prevalence of cor pulmonale is difficult to ascertain. First, not all patients with chronic lung disease will develop cor pulmonale, which may be subclinical in compensated individuals. Second, our ability to diagnose pulmonary hypertension and cor pulmonale by routine physical examination and laboratory testing is relatively insensitive. However, advances in 2-D echo/Doppler imaging and biomarkers (BNP) can make it easier to identify cor pulmonale.

Once patients with chronic pulmonary or pulmonary vascular disease develop cor pulmonale, the prognosis worsens. Although chronic obstructive pulmonary disease (COPD) and chronic bronchitis are responsible for approximately 50% of the cases of cor pulmonale in North America (Chap. 314), any disease that affects the pulmonary vasculature (Chap. 304) or parenchyma can lead to cor pulmonale (Table 279-4). Primary pulmonary vascular disorders are relatively rare causes of cor pulmonale, but cor pulmonale is extremely common with these conditions, given the magnitude of pulmonary hypertension present.

PATHOPHYSIOLOGY AND BASIC MECHANISMS

Although many conditions can lead to cor pulmonale, the common pathophysiologic mechanism is pulmonary hypertension that is sufficient to alter RV structure (i.e., dilation with or without hypertrophy) and function. Normally, pulmonary artery pressures are only $\sim 15 \text{ mmHg}$ and do not increase even with multiples of resting cardiac output, because of vasodilation and blood vessel recruitment of the pulmonary circulatory bed. But, in the setting of parenchymal lung diseases, primary pulmonary vascular disorders, or chronic (alveolar) hypoxia, the circulatory bed undergoes varying degrees of vascular remodeling, vasoconstriction, and destruction. As a result, pulmonary artery pressures and RV afterload increase, setting the stage for cor pulmonale (Table 279-4). The systemic consequences of cor pulmonale relate to alterations in cardiac output as well as salt and

TABLE 279-4 ETIOLOGY OF CHRONIC COR PULMONALE**Diseases of the Lung Parenchyma**

- Chronic obstructive pulmonary disease
- Emphysema
- Chronic bronchitis
- Cystic fibrosis
- Idiopathic interstitial pneumonitis
- Idiopathic pulmonary fibrosis
- Nonspecific interstitial pneumonitis
- Sarcoidosis
- Bronchiectasis
- Pulmonary Langerhans cell histiocytosis
- Lymphangioleiomyomatosis

Disorders of Chronic (Alveolar) Hypoxia

- Alveolar hypoventilation syndromes
- Obesity hypoventilation syndrome
- Central hypoventilation syndrome
- Neuromuscular respiratory failure
- Chest wall disorders
 - Kyphoscoliosis
- Living at high altitude

Diseases of the Pulmonary Vasculature

- Pulmonary arterial hypertension (PAH)
- Idiopathic PAH
 - Heritable PAH
 - Associated PAH
 - Venoocclusive disease
- Chronic thromboembolic pulmonary hypertension
- Pulmonary tumor thrombotic microangiopathy

water homeostasis. Anatomically, the RV is a thin-walled, compliant chamber that is better suited to handle volume overload than pressure overload. Thus, the sustained pressure overload imposed by pulmonary hypertension and increased pulmonary vascular resistance eventually causes the RV to fail.

The response of the RV to pulmonary hypertension depends on the acuteness and severity of the pressure overload. Acute cor pulmonale occurs after a sudden and severe stimulus (e.g., massive pulmonary embolus), with RV dilatation and failure but no RV hypertrophy ([Chap. 300](#)). Chronic cor pulmonale, however, is associated with a more slowly evolving and progressive pulmonary hypertension that leads to initial modest RV hypertrophy and subsequent RV dilation. Acute decompensation of previously compensated chronic cor pulmonale is a common clinical occurrence. Triggers include worsening hypoxia from any cause (e.g., pneumonia), acidemia (e.g., exacerbation of COPD), acute pulmonary embolus, atrial tachyarrhythmia, hypervolemia, and mechanical ventilation that leads to compressive forces on alveolar blood vessels.

CLINICAL MANIFESTATIONS

Symptoms The symptoms of chronic cor pulmonale generally are related to the underlying pulmonary disorder. Dyspnea, the most common symptom, is usually the result of the increased work of

breathing secondary to changes in elastic recoil of the lung (fibrosing lung diseases), altered respiratory mechanics (e.g., overinflation with COPD), or inefficient ventilation (e.g., primary pulmonary vascular disease). Orthopnea and PND are rarely symptoms of isolated right HF and usually point toward concurrent left heart dysfunction. Rarely, these symptoms reflect increased work of breathing in the supine position resulting from compromised diaphragmatic excursion. Abdominal pain and ascites that occur with cor pulmonale are similar to the right HF that ensues in chronic HF. Lower-extremity edema may occur secondary to neurohormonal activation, elevated RV filling pressures, or increased levels of carbon dioxide and hypoxemia, which can lead to peripheral vasodilation and edema formation.

Signs Many of the signs encountered in cor pulmonale are also present in HF patients with a depressed EF, including tachypnea, elevated jugular venous pressures, hepatomegaly, and lower-extremity edema. Patients may have prominent *v* waves in the jugular venous pulse as a result of tricuspid regurgitation. Other cardiovascular signs include an RV heave palpable along the left sternal border or in the epigastrium. The increase in intensity of the holosystolic murmur of tricuspid regurgitation with inspiration ("Carvallo's sign") may be lost eventually as RV failure worsens. Cyanosis is a late finding in cor pulmonale and is secondary to a low cardiac output with systemic vasoconstriction and ventilation-perfusion mismatches in the lung.

DIAGNOSIS

The most common cause of right HF is not pulmonary parenchymal or vascular disease but left HF. Therefore, it is important to evaluate the patient for LV systolic and diastolic dysfunction. The ECG in severe pulmonary hypertension shows P pulmonale, right axis deviation, and RV hypertrophy. Radiographic examination of the chest may show enlargement of the main central pulmonary arteries and hilar vessels. Spirometry and lung volumes can identify obstructive and/or restrictive defects indicative of parenchymal lung diseases; arterial blood gases can demonstrate hypoxemia and/or hypercapnia. Spiral computed tomography (CT) scans of the chest are useful in diagnosing acute thromboembolic disease; however, ventilation-perfusion lung scanning remains best suited for diagnosing *chronic thromboembolic disease* ([Chap. 300](#)). A high-resolution CT scan of the chest can identify interstitial lung disease.

Two-dimensional echocardiography is useful for measuring RV thickness and chamber dimensions. Location of the RV behind the sternum and its crescent shape challenge assessment of RV function by echocardiography, especially when parenchymal lung disease is present. Calculated measures of RV function (e.g., tricuspid annular plane systolic excursion [TAPSE] or the Tei Index) supplement more subjective assessments of RV function. The interventricular septum may move paradoxically during systole in the presence of pulmonary hypertension. As noted, Doppler echocardiography can be used to assess pulmonary artery pressures. MRI is also useful for assessing RV structure and function, particularly in patients who are difficult to image with 2-D echocardiography because of severe lung disease. Right-heart catheterization is useful for confirming the diagnosis of pulmonary hypertension and for excluding elevated left-heart pressures (measured as the pulmonary capillary wedge pressure) as a cause for right HF. BNP and N-terminal BNP levels are elevated in patients with cor pulmonale secondary to RV myocardial stretch and may be dramatically elevated in acute pulmonary embolism.

Distinctive phenotypes of presentation with diverse management targets exemplify the vast syndrome of heart failure. These range from chronic heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF), acute decompensated heart failure (ADHF), and advanced heart failure. Early management evolved from symptom control to disease-modifying therapy in HFrEF with the advent of renin-angiotensin-aldosterone system (RAAS)-directed therapy, beta receptor antagonists, mineralocorticoid receptor antagonists, cardiac resynchronization therapy, and implantable cardio-defibrillators. However, similar advances have been elusive in the syndromes of HFpEF and ADHF, which have remained devoid of convincing therapeutic advances to alter their natural history. In advanced heart failure, a stage of disease typically encountered in HFrEF, the patient remains markedly symptomatic with demonstrated refractoriness or inability to tolerate full-dose neurohormonal antagonism, often requires escalating doses of diuretics, and exhibits persistent hyponatremia and renal insufficiency with frequent episodes of heart failure decompensation requiring recurrent hospitalizations. Such individuals are at the highest risk of sudden or progressive pump failure-related deaths (*Chap. 281*). In contrast, early-stage asymptomatic left ventricular dysfunction is amenable to preventive care, and its natural history is modifiable by neurohormonal antagonism (not further discussed).

HEART FAILURE WITH PRESERVED EJECTION FRACTION

GENERAL PRINCIPLES

Therapeutic targets in HFpEF include control of congestion, stabilization of heart rate and blood pressure, and efforts at improving exercise tolerance. Addressing surrogate targets, such as regression of ventricular hypertrophy in hypertensive heart disease, and use of lusitropic agents, such as calcium channel blockers and beta receptor antagonists, have been disappointing. Experience has demonstrated that lowering blood pressure alleviates symptoms more effectively than targeted therapy with specific agents.

CLINICAL TRIALS IN HFpEF

The Candesartan in Heart Failure—Assessment of Mortality and Morbidity (CHARM) Preserved study showed a statistically significant reduction in hospitalizations but no difference in all-cause mortality in patients with HFpEF who were treated with the angiotensin receptor blocker (ARB), candesartan. Similarly, the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial demonstrated no differences in meaningful endpoints in such patients treated with irbesartan. An earlier analysis of a subset of the Digitalis Investigation Group (DIG) trial found no role for digoxin in the treatment of HFpEF. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial of nebivolol, a vasodilating beta blocker, the subgroup of elderly patients with prior hospitalization and HFpEF did not appear to benefit in terms of all-cause or cardiovascular mortality. Much smaller mechanistic studies in the elderly with the angiotensin-converting enzyme inhibitor (ACEI) enalapril showed no effect on peak exercise oxygen consumption, 6-minute walk distance, aortic distensibility, left ventricular mass, or peripheral neurohormone expression.

NOVEL TARGETS

A small trial demonstrated that the phosphodiesterase-5 inhibitor *sildenafil* improved filling pressures and right ventricular function in a cohort of HFpEF patients with pulmonary venous hypertension. This finding led to the phase II trial, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX), in HFpEF patients (left ventricular ejection fraction [LVEF] >50%) with New York Heart Association (NYHA) functional

class II or III symptoms, who received sildenafil at 20 mg three times daily for 3 months, followed by 60 mg three times daily for another 3 months, compared with a placebo. There was no improvement in functional capacity, quality of life, or other clinical and surrogate parameters. Conceptually targeting myocardial fibrosis in HFpEF, the large-scale Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart Failure (TOPCAT) trial has been completed. This trial demonstrated no improvement in the primary composite end-point, but did show a secondary signal of benefit on HF hospitalizations, counterbalanced, however, by an increase in adverse effects, particularly hyperkalemia. However, pessimism has been generated by the negative outcome of the Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) study wherein *spironolactone* improved echocardiographic indices of diastolic dysfunction but failed to improve exercise capacity, symptoms, or quality-of-life measures. A unique molecule that hybridizes an ARB with an *endopeptidase inhibitor*, LCZ696, increases the generation of myocardial cyclic guanosine 3',5'-monophosphate, enhances myocardial relaxation, and reduces ventricular hypertrophy. This dual blocker has been shown to reduce circulating natriuretic peptides and reduce left atrial size to a significantly greater extent than valsartan alone in patients with HFpEF.

CLINICAL PEARLS

Even as efforts to control hypertension in HFpEF are critical, evaluation for and correction of underlying ischemia may be beneficial. Appropriate identification and treatment of sleep-disordered breathing should be strongly considered. Excessive decrease in preload with vasodilators may lead to underfilling the ventricle and subsequent hypotension and syncope. Some investigators have suggested that the exercise intolerance in HFpEF is a manifestation of chronotropic insufficiency and that such aberrations could be corrected with use of rate responsive pacemakers, but this remains an inadequately investigated contention (*Fig. 280-1*).

ACUTE DECOMPENSATED HEART FAILURE

GENERAL PRINCIPLES

ADHF is a heterogeneous clinical syndrome most often resulting in need for hospitalization due to confluence of interrelated abnormalities of decreased cardiac performance, renal dysfunction, and alterations in vascular compliance. Admission with a diagnosis of ADHF is associated with excessive morbidity and mortality, with nearly half of these patients readmitted for management within 6 months, and a high short-term (5–8% in-hospital) and long-term mortality (20% at 1 year). Importantly, long-term aggregate outcomes remain poor, with a combined incidence of cardiovascular deaths, heart failure hospitalizations, myocardial infarction, strokes, or sudden death reaching 50% at 12 months after hospitalization. The management of these patients has remained difficult and principally revolves around volume control and decrease of vascular impedance while maintaining attention to end-organ perfusion (coronary and renal).

The first principle of management of these patients is to identify and tackle known precipitants of decompensation. Identification and management of medication nonadherence and use of prescribed medicines such as nonsteroidal anti-inflammatory drugs, cold and flu preparations with cardiac stimulants, and herbal preparations, including licorice, ginseng, and ma huang (an herbal form of ephedrine now banned in most places), are required. Active infection and overt or covert pulmonary thromboembolism should be sought, identified, and treated when clinical clues suggest such direction. When possible, arrhythmias should be corrected by controlling heart rate or restoring sinus rhythm in patients with poorly tolerated rapid atrial fibrillation and by correcting ongoing ischemia with coronary revascularization or by correcting offenders such as ongoing bleeding in demand-related ischemia. A parallel step in management involves stabilization of hemodynamics in those with instability. The routine use of a pulmonary artery catheter is not recommended and should be restricted to those who respond poorly to diuresis or experience hypotension or signs and symptoms suggestive of a low cardiac output where therapeutic targets are unclear. Analysis of in-hospital registries has identified several

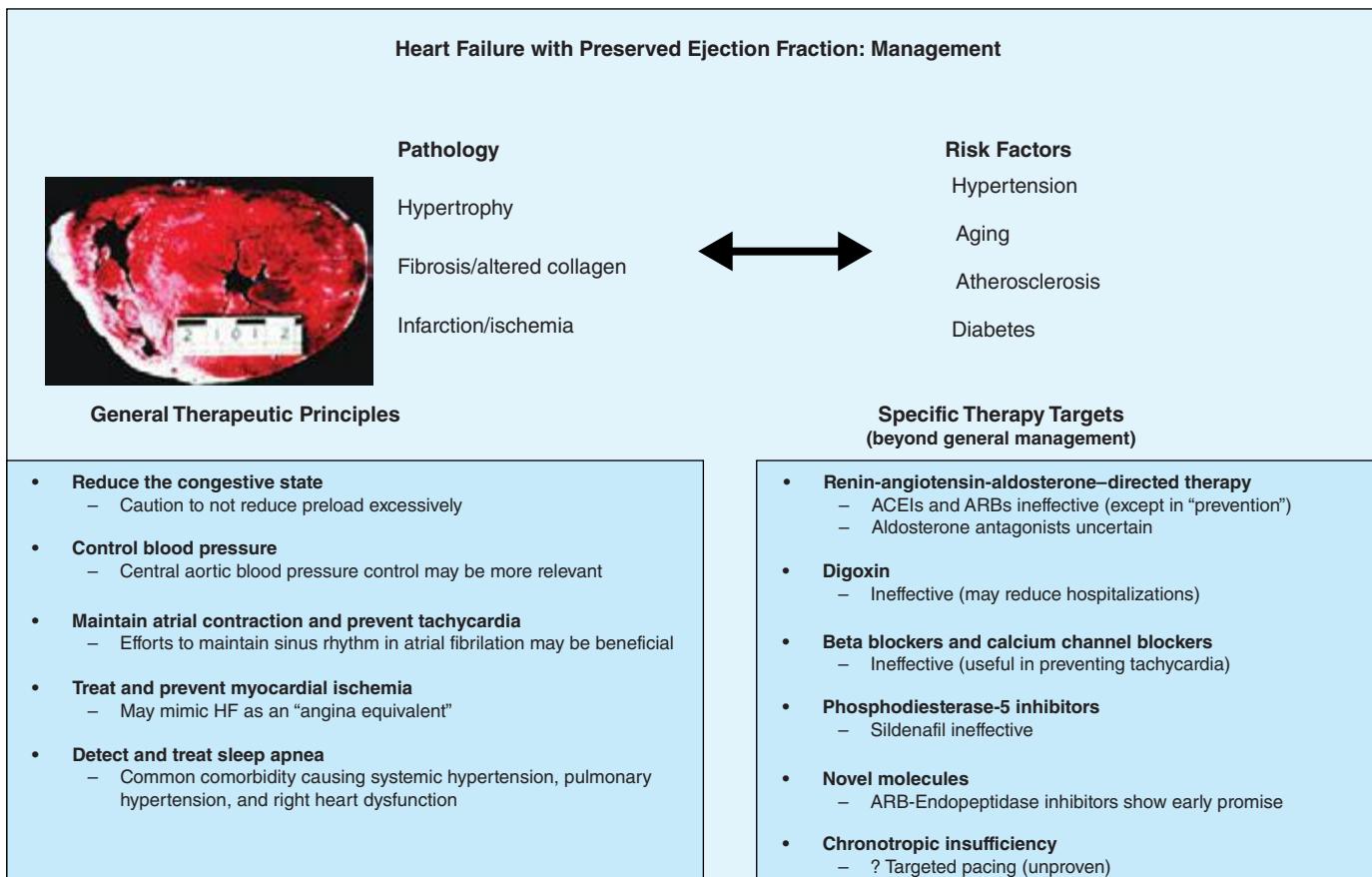


FIGURE 280-1 Pathophysiologic correlations, general therapeutic principles, and results of specific "directed" therapy in heart failure (HF) with preserved ejection fraction. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

parameters associated with worse outcomes: a blood urea nitrogen level greater than 43 mg/dL (to convert to mmol/L, multiply by 0.357), systolic blood pressure less than 115 mmHg, a serum creatinine level greater than 2.75 mg/dL (to convert to $\mu\text{mol}/\text{L}$, multiply by 88.4), and an elevated troponin I level. A useful clinical schema to identify treatment targets for the various phenotypic presentations and management goals in ADHF is depicted in Fig. 280-2.

VOLUME MANAGEMENT

Intravenous Diuretic Agents Intravenous diuretic agents rapidly and effectively relieve symptoms of congestion and are essential when oral drug absorption is impaired. When high doses of diuretic agents are required or when the effect is suboptimal, a continuous infusion may be needed to reduce toxicity and maintain stable serum drug levels. Randomized clinical trials of high-versus low-dose or bolus versus continuous infusion diuresis have not provided clear justification for the best diuretic strategy in ADHF, and as such, the use of diuretic regimens remains an art rather than science. Addition of a thiazide diuretic agent such as metolazone in combination provides a synergistic effect and is often required in patients receiving long-term therapy with loop diuretic agents. Change in weight is often used as a surrogate for adequate diuresis, but this objective measure of volume status may be surprisingly difficult to interpret, and weight loss during hospitalization does not necessarily correlate closely with outcomes. It is generally advisable to continue diuresis until euolemia has been achieved. Physical examination findings, specifically the jugular venous pressure coupled with biomarker trends, are useful in timing discharge planning.

The Cardiorenal Syndrome The cardiorenal syndrome is being recognized increasingly as a complication of ADHF. Multiple definitions have been proposed for the cardiorenal syndrome, but at its simplest, it can be thought to reflect the interplay between abnormalities of heart and kidney function, with deteriorating function of one organ

while therapy is administered to preserve the other. Approximately 30% of patients hospitalized with ADHF exhibit abnormal renal function at baseline, and this is associated with longer hospitalizations and increased mortality. However, mechanistic studies have been largely unable to find correlation between deterioration in renal function, cardiac output, left-sided filling pressures, and reduced renal perfusion; most patients with cardiorenal syndrome demonstrate a preserved cardiac output. It is hypothesized that in patients with established heart failure, this syndrome represents a complex interplay of neurohormonal factors, potentially exacerbated by "backward failure" resulting from increased intra-abdominal pressure and impairment in return of renal venous blood flow. Continued use of diuretic therapy may be associated with a reduction in glomerular filtration rate and a worsening of the cardiorenal syndrome when right-sided filling pressures remain elevated. In patients in the late stages of disease characterized by profound low cardiac output state, inotropic therapy or mechanical circulatory support has been shown to preserve or improve renal function in selected individuals in the short term until more definitive therapy such as assisted circulation or cardiac transplantation is implemented.

Ultrafiltration Ultrafiltration (UF) is an invasive fluid removal technique that may supplement the need for diuretic therapy. Proposed benefits of UF include controlled rates of fluid removal, neutral effects on serum electrolytes, and decreased neurohormonal activity. This technique has also been referred to as aquapheresis in recognition of its electrolyte depletion-sparing effects. Current UF systems function with two large-bore, peripherally inserted venous lines. In a pivotal study evaluating UF versus conventional therapy, fluid removal was improved and subsequent heart failure hospitalizations and urgent clinic visits were reduced with UF; however, no improvement in renal function and no subjective differences in dyspnea scores or adverse outcomes were noted. More recently, in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial,

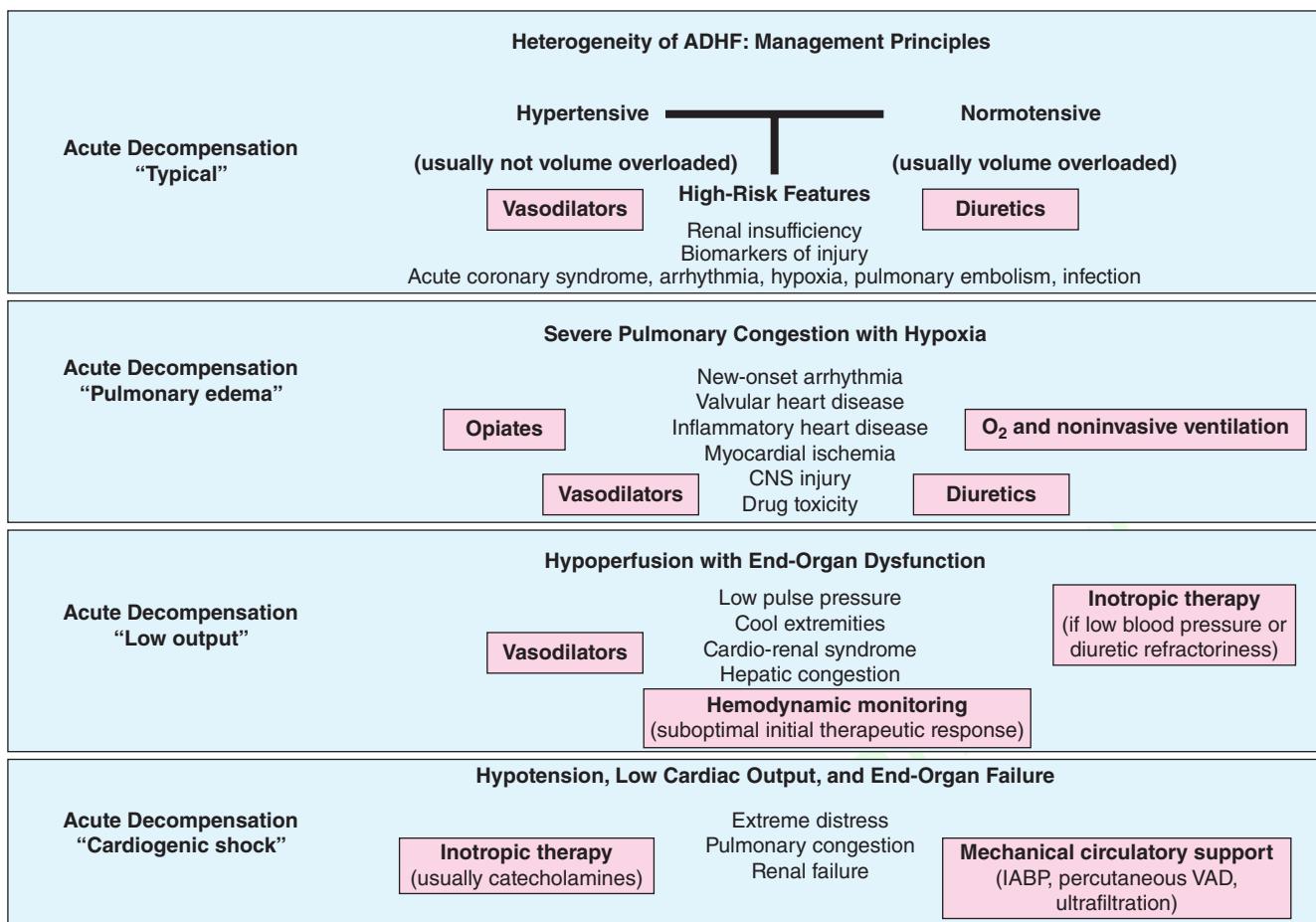


FIGURE 280-2 The distinctive phenotypes of acute decompensated heart failure (ADHF), their presentations, and suggested therapeutic routes. (Unique causes of ADHF, such as isolated right heart failure and pericardial disease, and rare causes, such as aortic and coronary dissection or ruptured valve structures or sinuses of Valsalva, are not delineated and are covered elsewhere.) IABP, intraaortic balloon pump; VAD, ventricular assist device.

188 patients with ADHF and worsening renal failure were randomized to stepped pharmacologic care or UF. The primary endpoint was a change in serum creatinine and change in weight (reflecting fluid removal) at 96 hours. Although similar weight loss occurred in both groups (approximately 5.5 kg), there was worsening in creatinine in the UF group. Deaths and hospitalizations for heart failure were no different between groups, but there were more severe adverse events in the UF group, mainly due to kidney failure, bleeding complications, and intravenous catheter-related complications. This investigation argues against using UF as a primary strategy in patients with ADHF who are nonetheless responsive to diuretics. Whether UF is useful in states of diuretic unresponsiveness remains an open question, and this strategy continues to be employed judiciously in such situations.

VASCULAR THERAPY

Vasodilators including *intravenous nitrates*, *nitroprusside*, and *nesiritide* (a recombinant brain-type natriuretic peptide) have been advocated for upstream therapy in an effort to stabilize ADHF. The latter agent was introduced in a fixed dose for therapy after a comparison with intravenous nitrates suggested more rapid and greater reduction in pulmonary capillary wedge pressure. Enthusiasm for nesiritide waned due to concerns within the pivotal trials for development of renal insufficiency and an increase in mortality. To address these concerns, a large-scale morbidity and mortality trial, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) study was completed in 2011 and randomly enrolled 7141 patients with ADHF to nesiritide or placebo for 24 to 168 hours in addition to standard care. Nesiritide was not associated with an increase or a decrease in the rates of death and rehospitalization and had a clinically insignificant benefit on dyspnea. Renal function did

not worsen, but increased rates of hypotension were noted. Although this trial established the safety for this drug, the routine use cannot be advocated due to lack of significant efficacy. *Recombinant human relaxin-2*, or serelaxin, is a peptide upregulated in pregnancy and examined in ADHF patients with a normal or elevated blood pressure. In the Relaxin in Acute Heart Failure (RELAX-AHF) trial, serelaxin or placebo was added to a regimen of standard therapy in 1161 patients hospitalized with ADHF, evidence of congestion, and systolic pressure >125 mmHg. Serelaxin improved dyspnea, reduced signs and symptoms of congestion, and was associated with less early worsening of HF. Exploratory endpoints of hard outcomes at 6 months suggested positive signals in favor of mortality reduction. This agent is being tested in a large, more confirmatory trial setting.

INOTROPIC THERAPY

Impairment of myocardial contractility often accompanies ADHF, and pharmacologic agents that increase intracellular concentration of cyclic adenosine monophosphate via direct or indirect pathways, such as sympathomimetic amines (dobutamine) and phosphodiesterase-3 inhibitors (milrinone), respectively, serve as positive inotropic agents. Their activity leads to an increase in cytoplasmic calcium. Inotropic therapy in those with a low-output state augments cardiac output, improves perfusion, and relieves congestion acutely. Although milrinone and dobutamine have similar hemodynamic profiles, milrinone is slower acting and is renally excreted and thus requires dose adjustments in the setting of kidney dysfunction. Since milrinone acts downstream from the β_1 -adrenergic receptor, it may provide an advantage in patients receiving beta blockers when admitted to the hospital. Studies are in universal agreement that long-term inotropic therapy increases mortality. However, the short-term use of inotropic agents in ADHF

1510 is also associated with increased arrhythmia, hypotension, and no beneficial effects on hard outcomes. Inotropic agents are currently indicated as bridge therapy (to either left ventricular assist device support or to transplant) or as selectively applied palliation in end-stage heart failure.

Novel inotropic agents that leverage the concept of myofilament calcium sensitization rather than increasing intracellular calcium levels have been introduced. *Levosimendan* is a calcium sensitizer that provides inotropic activity, but also possesses phosphodiesterase-3 inhibition properties that are vasodilators in action. This makes the drug unsuitable in states of low output in the setting of hypotension. Two trials, the second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) and Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE), have tested this agent in ADHF. SURVIVE compared levosimendan with dobutamine, and despite an initial reduction in circulating B-type natriuretic peptide levels in the levosimendan group compared with patients in the dobutamine group, this drug did not reduce all-cause mortality at 180 days or affect any secondary clinical outcomes. The second trial compared levosimendan against traditional noninotropic therapy and found a modest improvement in symptoms with worsened short-term mortality and ventricular arrhythmias. Another drug that functions as a selective myosin activator, *omecamtiv mecarbil*, prolongs the ejection period and increases fractional shortening. Distinctively, the force of contraction is not increased, and as such, this agent does not increase myocardial oxygen demand. In a 600-patient trial called ATOMIC-HF

(A Trial of Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure), this agent showed improvement in dyspnea scores in the highest dose cohort, but not across all enrolled patients. How this agent performs in broader populations remains uncertain. Other inotropic agents that increase myocardial calcium sensitivity through mechanisms that reduce cTnI phosphorylation or inhibit protein kinase A are being developed. (Table 280-1 depicts typical inotropic, vasodilator, and diuretic drugs used in ADHF.)

NEUROHORMONAL ANTAGONISTS

Other trials testing unique agents have yielded disappointing results in the situation of ADHF. The Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial of selective adenosine antagonism and the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial of an oral selective vasopressin-2 antagonist in ADHF were both negative with respect to hard outcomes.

In patients who fail to respond adequately to medical therapy, mechanical assist devices may be required. This is covered in more detail in Chap. 281.

HEART FAILURE WITH REDUCED EJECTION FRACTION

The past 50 years have witnessed great strides in the management of HFrEF. The treatment of symptomatic heart failure that evolved from a renocentric (diuretics) and hemodynamic therapy model

TABLE 280-1 INTRAVENOUS THERAPY IN ACUTE DECOMPENSATED HEART FAILURE

Drug Class	Generic Drug	Usual Dosing	Special Caution	Comments
Inotropic therapy				
Dobutamine	2–20 µg/kg per min	Increased myocardial oxygen demand, arrhythmia		Use in hypotension, end-organ hypoperfusion, or shock states
Milrinone	0.375–0.75 µg/kg per min	Hypotension, arrhythmia		Short acting, an advantage; variable efficacy in presence of beta blockers (requires higher doses); clinical tolerance to prolonged infusions; concerns with hypersensitivity carditis (rare)
Levosimendan	0.1 µg/kg per min, range, 0.05–0.2 µg/kg per min	Hypotension, arrhythmia		Decrease dose in renal insufficiency; avoid initial bolus; effectiveness retained in presence of beta blockers
Omecamtiv Mecarbil	N/A	*In trials		Long acting; should not be used in presence of low blood pressure; similar effectiveness as dobutamine but effectiveness retained in presence of beta blockers
Serelaxin	N/A (tested at 30 µg/kg per d)	Baseline blood pressure should be >125 mmHg		Increases contractility without increasing myocardial oxygen demand; in confirmatory trials
Vasodilators				
Nitroglycerine	10–20 µg/min, increase up to 200 µg/min	Headache, flushing, tolerance		Use in presence of pulmonary congestion for rapid relief of dyspnea, in presence of a preserved blood pressure
Nesiritide	Bolus 2 µg/kg and infusion at 0.01 µg/kg per min	Hypotension		Most common vasodilator but often underdosed; effective in higher doses
Nitroprusside	0.3 µg/kg per min titrated to 5 µg/kg per min	Thiocyanate toxicity in renal insufficiency (>72 hours)		Decrease in blood pressure may reduce renal perfusion pressure; bolus may be avoided since it increases hypotension predilection
Serelaxin	N/A (tested at 30 µg/kg per d)	Baseline blood pressure should be >125 mmHg		Requires arterial line placement for titration for precise blood pressure management and prevention of hypotension
Diuretics				
Furosemide	20–240 mg daily	Monitor for electrolyte loss		Not widely commercially available; undergoing confirmatory trials
Torsemide	10–100 mg daily	Monitor for electrolyte loss		First line of therapy in volume overload with congestion; may use bolus or continuous dosing; initial low dose (1× home dose) or high dose (2.5 × home dose) equally effective with higher risk of renal worsening with higher dose
Bumetanide	0.5–5 mg daily	Monitor for electrolyte loss		In severe congestion, use intravenously and consider continuous infusion (not trial supported)
Adjuvant diuretics for augmentation	n/a	Metolazone, chlorthalidone, spironolactone, acetazolamide		High bioavailability, can be given orally; anecdotally more effective in advanced heart failure states if furosemide less bioavailable (due to gut congestion)

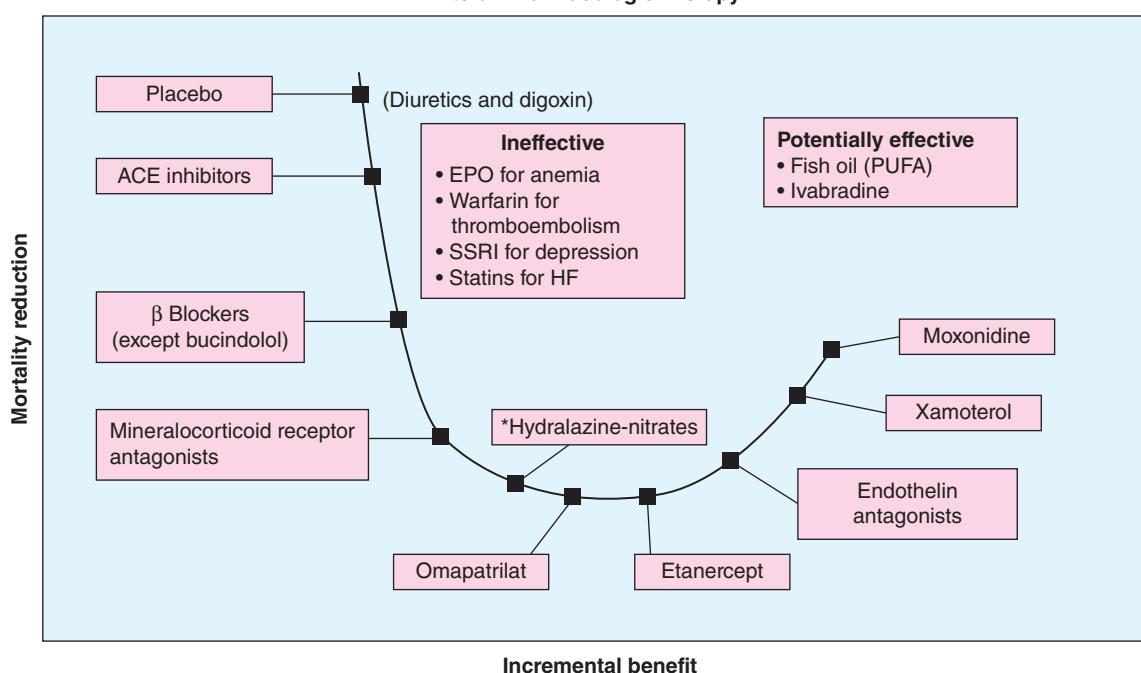


FIGURE 280-3 Progressive decline in mortality with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta blockers, mineralocorticoid receptor antagonists, and balanced vasodilators (*selected populations such as African Americans); further stack-on neurohormonal therapy is ineffective or results in worse outcome; management of comorbidity is of unclear efficacy. EPO, erythropoietin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; PUFA, polyunsaturated fatty acid; SSRI, selective serotonin reuptake inhibitor.

(digoxin, inotropic therapy) ushered in the era of disease-modifying therapy with neurohormonal antagonism. In this regard, ACEIs and beta blockers form the cornerstone of pharmacotherapy and lead to attenuation of decline and improvement in cardiac structure and function with consequent reduction in symptoms, improvement in quality of life, decreased burden of hospitalizations, and a decline in mortality from both pump failure and arrhythmic deaths (Fig. 280-3).

NEUROHORMONAL ANTAGONISM

Meta-analyses suggest a 23% reduction in mortality and a 35% reduction in the combination endpoint of mortality and hospitalizations for heart failure in patients treated with ACEIs. Patients treated with beta blockers provide a further 35% reduction in mortality on top of the benefit provided by ACEIs alone. Increased experience with both agents in a broad range of patients with HFrEF has demonstrated the safety of ACEIs in treating patients with mild renal insufficiency and the tolerability of beta blockers in patients with moderately controlled diabetes, asthma, and obstructive lung disease. The benefits of ACEIs and beta blockers extend to advanced symptoms of disease (NYHA class IIIb–IV). However, a substantial number of patients with advanced heart failure may not be able to achieve optimal doses of neurohormonal inhibitors and require cautious reduction in dose exposure to maintain clinical stability. Such individuals with lower exposure to ACEIs and beta blockers represent a high-risk cohort with poor prognosis.

Class Effect and Sequence of Administration ACEIs exert their beneficial effects in HFrEF as a class; however, the beneficial effects of beta blockers are thought to be limited to specific drugs. Beta blockers with intrinsic sympathomimetic activity (xamoterol) and other agents, including bucindolol, have not demonstrated a survival benefit. On the basis of investigations, beta blocker use in HFrEF should be restricted to carvedilol, bisoprolol, and metoprolol succinate—agents tested and proven to improve survival in clinical trials. Whether beta blockers or ACEIs should be started first was answered by the Cardiac Insufficiency Bisoprolol Study (CIBIS) III, in which outcomes did not vary when either agent was initiated first. Thus, it matters little which agent is initiated first; what does matter is that optimally titrated doses of both ACEIs and beta blockers be established in a timely manner.

Dose and Outcome A trial has indicated that higher tolerated doses of ACEIs achieve greater reduction in hospitalizations without materially improving survival. Beta blockers demonstrate a dose-dependent improvement in cardiac function and reductions in mortality and hospitalizations. Clinical experience suggests that, in the absence of symptoms to suggest hypotension (fatigue and dizziness), pharmacotherapy may be up-titrated every 2 weeks in hemodynamically stable and euvolemic ambulatory patients as tolerated.

MINERALOCORTICOID ANTAGONISTS

Aldosterone antagonism is associated with a reduction in mortality in all stages of symptomatic NYHA class II to IV HFrEF. Elevated aldosterone levels in HFrEF promote sodium retention, electrolyte imbalance, and endothelial dysfunction and may directly contribute to myocardial fibrosis. The selective agent eplerenone (tested in NYHA class II and post-myocardial infarction heart failure) and the nonselective antagonist spironolactone (tested in NYHA class III and IV heart failure) reduce mortality and hospitalizations, with significant reductions in sudden cardiac death (SCD). Hyperkalemia and worsening renal function are concerns, especially in patients with underlying chronic kidney disease, and renal function and serum potassium levels must be closely monitored.

RAAS THERAPY AND NEUROHORMONAL “ESCAPE”

Neurohormonal “escape” has been witnessed in patients with HFrEF by the finding that circulating levels of angiotensin II return to pretreatment levels with long-term ACEI therapy. ARBs blunt this phenomenon by binding competitively to the AT₁ receptor. A large meta-analysis of 24 randomized trials showed the superiority of ARBs to placebo in patients with intolerable adverse effects with ACEIs and their noninferiority in all-cause mortality or hospitalizations when compared with ACEIs. The Valsartan Heart Failure Trial (Val-HeFT) suggested that addition of valsartan in patients already receiving treatment with ACEIs and beta blockers was associated with a trend toward worse outcomes. Similarly, adding valsartan to captopril in patients with heart failure after myocardial infarction who were receiving background beta blocker therapy was associated with an increase in adverse events without any added benefit compared with

1512 monotherapy for either group. Thus, the initial clinical strategy should be to use a two-drug combination first (ACEI and beta blocker; if beta blocker intolerant, then ACEI and ARB; if ACEI intolerant, then ARB and beta blocker). In symptomatic patients (NYHA class II–IV), an aldosterone antagonist should be strongly considered, but four-drug therapy should be avoided.

A recent trial called the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) tested a direct renin inhibitor, aliskiren, in addition to other heart failure medications, within a week after discharge from a hospitalization for decompensated HFrEF. No significant difference in cardiovascular death or hospitalization at 6 or 12 months was noted. Aliskiren was associated with a reduction in circulating natriuretic peptides, but any disease-modifying effect was overcome by excessive adverse events including hyperkalemia, hypotension, and renal dysfunction.

ARTERIOVENOUS VASODILATION

The combination of hydralazine and nitrates has been demonstrated to improve survival in HFrEF. Hydralazine reduces systemic vascular resistance and induces arterial vasodilatation by affecting intracellular calcium kinetics; nitrates are transformed in smooth muscle cells into nitric oxide, which stimulates cyclic guanosine monophosphate production and consequent arterial-venous vasodilation. This combination improves survival, but not to the magnitude evidenced by ACEIs or ARBs. However, in individuals with HFrEF unable to tolerate renin-angiotensin-aldosterone-based therapy for reasons such as renal insufficiency or hyperkalemia, this combination is preferred as a disease-modifying approach. A trial conducted in self-identified African Americans, the African-American Heart Failure Trial (A-Heft), studied a fixed dose of isosorbide dinitrate with hydralazine in patients with advanced symptoms of HFrEF who were receiving standard background therapy. The study demonstrated benefit in survival and hospitalization recidivism in the treatment group. Adherence to this regimen is limited by the thrice-daily dosing schedule. **Table 280-2** lists the common neurohormonal and vasodilator regimens for HFrEF.

HEART RATE MODIFICATION

Ivabradine, an inhibitor of the I_f current in the sinoatrial node, slows the heart rate without a negative inotropic effect. The Systolic Heart Failure Treatment with Ivabradine Compared with Placebo Trial

(SHIFT) was conducted in patients with class II or III HFrEF, a heart rate >70 beats/min, and history of hospitalization for heart failure during the previous year. Ivabradine reduced hospitalizations and the combined endpoint of cardiovascular-related death and heart failure hospitalization. The study population was not necessarily representative of North American patients with HFrEF since, with a few exceptions, most did not receive internal cardioverter-defibrillation or cardiac resynchronization therapy and 40% did not receive a mineralocorticoid receptor antagonist. Although 90% received beta blockers, only a quarter were on full doses. Whether this agent, now available outside the United States, would have been effective in patients receiving robust, guideline-recommended therapy for heart failure remains enigmatic. In the 2012 European Society of Cardiology guidelines for the treatment of heart failure, ivabradine was suggested as second-line therapy before digoxin is considered in patients who remain symptomatic after guideline-based ACEIs, beta blockers, and mineralocorticoid receptor antagonists and with residual heart rate >70 beats/min. Another group in whom potential benefit may be expected includes those unable to tolerate beta blockers.

DIGOXIN

Digitalis glycosides exert a mild inotropic effect, attenuate carotid sinus baroreceptor activity, and are sympathoinhibitory. These effects decrease serum norepinephrine levels, plasma renin levels, and possibly aldosterone levels. The DIG trial demonstrated a reduction in heart failure hospitalizations in the treatment group but no reduction in mortality or improvement in quality of life. Importantly, treatment with digoxin resulted in a higher mortality rate in women than men. Furthermore, the effects of digoxin in reducing hospitalizations were lower in women than in men. It should be noted that low doses of digoxin are sufficient to achieve any potentially beneficial outcomes, and higher doses breach the therapeutic safety index. Although digoxin levels should be checked to minimize toxicity and although dose reductions are indicated for higher levels, no adjustment is made for low levels. Generally, digoxin is now relegated as therapy for patients who remain profoundly symptomatic despite optimal neurohormonal blockade and adequate volume control.

ORAL DIURETICS

Neurohormonal activation results in avid salt and water retention. Loop diuretic agents are often required because of their increased potency,

TABLE 280-2 PHARMACOLOGIC THERAPY AND TARGET DOSES IN HEART FAILURE WITH REDUCED EJECTION FRACTION

Drug Class	Generic Drug	Mean Daily Dose in Clinical Trials (mg)	Initiation (mg)	Target Dose (mg)
Angiotensin-Converting Enzyme Inhibitors				
	Lisinopril	4.5–33	2.5–5 qd	20–35 qd
	Enalapril	17	2.5 bid	10–20 bid
	Captopril	123	6.25 tid	50 tid
	Trandolapril	N/A	0.5–1 qd	4 qd
Angiotensin Receptor Blockers				
	Losartan	129	50 qd	150 qd
	Valsartan	254	40 bid	160 bid
	Candesartan	24	4–8 qd	32 qd
Aldosterone Antagonists				
	Eplerenone	42.6	25 qd	50 qd
	Spirostanolactone	26	12.5–25 qd	25–50 qd
Beta Blockers				
	Metoprolol succinate CR/XL	159	12.5–25 qd	200 qd
	Carvedilol	37	3.125 bid	25–50 bid
	Bisoprolol	8.6	1.25 qd	10 qd
Arteriovenous Vasodilators				
	Hydralazine isosorbide dinitrate	270/136	37.5/20 tid	75/40 tid
	Fixed-dose hydralazine/isosorbide dinitrate	143/76	37.5/20 qid	75/40 qid

and frequent dose adjustments may be necessary because of variable oral absorption and fluctuations in renal function. Importantly, clinical trial data confirming efficacy are limited, and no data suggest that these agents improve survival. Thus, diuretic agents should ideally be used in tailored dosing schedules to avoid excessive exposure. Indeed, diuretics are essential at the outset to achieve volume control before neurohormonal therapy is likely to be well tolerated or titrated.

CALCIUM CHANNEL ANTAGONISTS

Amlodipine and felodipine, second-generation calcium channel-blocking agents, safely and effectively reduce blood pressure in HFrEF but do not affect morbidity, mortality, or quality of life. The first-generation agents, including verapamil and diltiazem, may exert negative inotropic effects and destabilize previously asymptomatic patients. Their use should be discouraged.

NOVEL NEUROHORMONAL ANTAGONISM

Despite an abundance of animal and clinical data demonstrating deleterious effects of activated neurohormonal pathways beyond the RAAS and sympathetic nervous system, targeting such pathways with incremental blockade has been largely unsuccessful. As an example, the endothelin antagonist bosentan is associated with worsening heart failure in HFrEF despite demonstrating benefits in right-sided heart failure due to pulmonary arterial hypertension. Similarly, the centrally acting sympatholytic agent moxonidine worsens outcomes in left heart failure. The combined drug omapatrilat hybridizes an ACEI with a neutral endopeptidase inhibitor, and this agent was tested in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial. This drug did not favorably influence the primary outcome measure of the combined risk of death or hospitalization for heart failure requiring intravenous treatment. The risk of angioedema was notably higher with omapatrilat than ACEIs alone. LCZ696 and ARB with an endopeptidase inhibitor have shown benefit in a large trial versus ARB alone.

INFLAMMATION

Targeting inflammatory cytokines such as tumor necrosis factor α (TNF- α) by using anticytokine agents such as infliximab and etanercept has been unsuccessful and associated with worsening heart failure. Nonspecific immunomodulation has been tested in the large Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy (ACCLAIM-HF) trial of 2426 HFrEF patients with NYHA functional class II to IV symptoms. Ex vivo exposure of a blood sample to controlled oxidative stress initiates apoptosis of leukocytes soon after intramuscular gluteal injection of the treated sample. The physiologic response to apoptotic cells results in a reduction in inflammatory cytokine production and upregulation of anti-inflammatory cytokines. This promising hypothesis was not proven, although certain subgroups (those with no history of previous myocardial infarction and those with mild heart failure) showed signals in favor of immunomodulation. Use of intravenous immunoglobulin therapy in nonischemic etiology of heart failure has not been shown to result in beneficial outcomes.

STATINS

Potent lipid-altering and pleiotropic effects of statins reduce major cardiovascular events and improve survival in non-heart failure populations. Once heart failure is well established, this therapy may not be as beneficial and theoretically could even be detrimental by depleting ubiquinone in the electron transport chain. Two trials, Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiac (GISSI-HF), have tested low-dose rosuvastatin in patients with HFrEF and demonstrated no improvement in aggregate clinical outcomes. If statins are required to treat progressive coronary artery disease in the background setting of heart failure, then they should be employed. However, no rationale appears to exist for routine statin therapy in nonischemic heart failure.

ANTICOAGULATION AND ANTIPLATELET THERAPY

HFrEF is accompanied by a hypercoagulable state and therefore a high risk of thromboembolic events, including stroke, pulmonary embolism, and peripheral arterial embolism. Although long-term oral anticoagulation is established in certain groups, including patients with atrial fibrillation, the data are insufficient to support the use of warfarin in patients in normal sinus rhythm without a history of thromboembolic events or echocardiographic evidence of left ventricular thrombus. In the large Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, 2305 patients with HFrEF were randomly allocated to either full-dose aspirin or international normalized ratio-controlled warfarin with follow-up for 6 years. Among patients with reduced LVEF who were in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. Aspirin blunts ACEI-mediated prostaglandin synthesis, but the clinical importance of this finding remains unclear. Current guidelines support the use of aspirin in patients with ischemic cardiomyopathy.

FISH OIL

Treatment with long-chain omega-3 polyunsaturated fatty acids (ω -3 PUFAs) has been shown to be associated with modestly improved clinical outcomes in patients with HFrEF. This observation from the GISSI-HF trial was extended to measurements of ω -3 PUFAs in plasma phospholipids at baseline and after 3 months. Three-month treatment with ω -3 PUFAs enriched circulating eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Low EPA levels are inversely related to total mortality in patients with HFrEF.

MICRONUTRIENTS

A growing body of evidence suggests an association between heart failure and micronutrient status. Reversible heart failure has been described as a consequence of severe thiamine and selenium deficiency. Thiamine deficiency has received attention in heart failure due to the fact that malnutrition and diuretics are prime risk factors for thiamine loss. Small exploratory randomized studies have suggested a benefit of supplementation of thiamine in HFrEF with evidence of improved cardiac function. This finding is restricted to chronic heart failure states and does not appear to be beneficial in the ADHF phenotype. Due to the preliminary nature of the evidence, no recommendations for routine supplementation or testing for thiamine deficiency can be made.

ENHANCED EXTERNAL COUNTERPULSATION (EECP)

Peripheral lower extremity therapy using graded external pneumatic compression at high pressure is administered in 1-hour sessions for 35 treatments (7 weeks) and has been proposed to reduce angina symptoms and extend time to exercise-induced ischemia in patients with coronary artery disease. The Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH) study assessed the benefits of enhanced external counterpulsation in the treatment of patients with mild-to-moderate heart failure. This randomized trial improved exercise tolerance, quality of life, and NYHA functional classification but without an accompanying increase in peak oxygen consumption. A placebo effect due to the nature of the intervention simply cannot be excluded.

EXERCISE

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study investigated short-term (3-month) and long-term (12-month) effects of a supervised exercise training program in patients with moderate HFrEF. Exercise was safe, improved patients' sense of well-being, and correlated with a trend toward mortality reduction. Maximal changes in 6-minute walk distance were evident at 3 months with significant improvements in cardiopulmonary exercise time and peak oxygen consumption persisting at 12 months. Therefore, exercise training is recommended as an adjunctive treatment in patients with heart failure.

Sleep-disordered breathing is common in HF and particularly in HFrEF. A range of presentations exemplified by obstructive sleep apnea, central sleep apnea, and its extreme form of Cheyne-Stokes breathing are noted. Frequent periods of hypoxia and repeated micro- and macro-arousals trigger adrenergic surges, which can worsen hypertension and impair systolic and diastolic function. A high index of suspicion is required, especially in patients with difficult-to-control hypertension or with predominant symptoms of fatigue despite reverse remodeling in response to optimal medical therapy. Worsening of right heart function with improvement of left ventricular function noted on medical therapy should immediately trigger a search for underlying sleep-disordered breathing or pulmonary complications such as occult embolism or pulmonary hypertension. Treatment with nocturnal positive airway pressure improves oxygenation, LVEF, and 6-minute walk distance. However, no conclusive data exist to support this therapy as a disease-modifying approach with reduction in mortality.

Anemia is common in heart failure patients, reduces functional status and quality of life, and is associated with increased proclivity for hospital admissions and mortality. Anemia in heart failure is more common in the elderly, in those with advanced stages of HFrEF, in the presence of renal insufficiency, and in women and African Americans. The mechanisms include iron deficiency, dysregulation of iron metabolism, and occult gastrointestinal bleeding. Intravenous iron using either iron sucrose or carboxymaltose (Ferric Carboxymaltose Assessment in Patients with Iron Deficiency and Chronic Heart Failure [FAIR-HF] trial) has been shown to correct anemia and improve functional capacity. Erythropoiesis-regulating agents such as erythropoietin analogues have been studied with disappointing results. The Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial evaluated 2278 mild-to-moderate anemia patients with HFrEF and demonstrated that treatment with darbepoetin alfa did not improve clinical outcomes in patients with systolic heart failure.

Depression is common in HFrEF, with a reported prevalence of one in five patients, and is associated with a poor quality of life, limited functional status, and increased risk of morbidity and mortality in this population. Antidepressants may improve depression, promote vascular health, and decrease systemic inflammation in HFrEF. However, the largest randomized study of depression in HFrEF, the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) trial, showed that sertraline was safe, but did not provide greater reduction in depression or improve cardiovascular status among patients with heart failure and depression compared with nurse-driven multidisciplinary management.

Atrial arrhythmias, especially atrial fibrillation, are common and serve as a harbinger of worse prognosis in patients with heart failure. When rate control is inadequate or symptoms persist, pursuing a rhythm control strategy is reasonable. Rhythm control may be achieved via pharmacotherapy or by percutaneous or surgical techniques, and referral to practitioners or centers experienced in these modalities is recommended. Antiarrhythmic drug therapy should be restricted to amiodarone and dofetilide, both of which have been shown to be safe and effective but do not alter the natural history of the underlying disease. The Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) studied the effects of the novel antiarrhythmic agent dronedarone and found an increased mortality due to worsening heart failure. Catheter ablation and pulmonary vein isolation appear to be safe and effective in this high-risk cohort and compare favorably with the more established practice of atrioventricular node ablation and biventricular pacing.

CARDIAC RESYNCHRONIZATION THERAPY

Nonsynchronous contraction between the walls of the left ventricle (intraventricular) or between the ventricular chambers (interventricular) impairs systolic function, decreases mechanical efficiency of contraction, and adversely affects ventricular filling. Mechanical

dyssynchrony results in an increase in wall stress and worsens functional mitral regurgitation. The single most important association of extent of dyssynchrony is a widened QRS interval on the surface electrocardiogram, particularly in the presence of a left bundle branch block pattern. With placement of a pacing lead via the coronary sinus to the lateral wall of the ventricle, cardiac resynchronization therapy (CRT) enables a more synchronous ventricular contraction by aligning the timing of activation of the opposing walls. Early studies showed improved exercise capacity, reduction in symptoms, and evidence of reverse remodeling. The Cardiac Resynchronization in Heart Failure Study (CARE-HF) trial was the first study to demonstrate a reduction in all-cause mortality with CRT placement in patients with HFrEF on optimal therapy with continued moderate-to-severe residual symptoms of NYHA class III or IV heart failure. More recent clinical trials have demonstrated disease-modifying properties of CRT in even minimally symptomatic patients with HFrEF, including the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), both of which sought to use CRT in combination with an implantable defibrillator. Most benefit in mildly symptomatic HFrEF patients accrues from applying this therapy in those with a QRS width of >149 ms and a left bundle branch block pattern. Attempts to further optimize risk stratification and expand indications for CRT using modalities other than electrocardiography have proven disappointing. In particular, echocardiographically derived measures of dyssynchrony vary tremendously, and narrow QRS dyssynchrony has not proven to be a good target for treatment. Uncertainty surrounds the benefits of CRT in those with ADHF, a predominant right bundle branch block pattern, atrial fibrillation, and evidence of scar in the lateral wall, which is the precise location where the CRT lead is positioned.

SUDDEN CARDIAC DEATH PREVENTION IN HEART FAILURE

SCD due to ventricular arrhythmias is the mode of death in approximately half of patients with heart failure and is particularly proportionally prevalent in HFrEF patients with early stages of the disease. Patients who survive an episode of SCD are considered to be at very high risk and qualify for placement of an implantable cardioverter-defibrillator (ICD). Although primary prevention is challenging, the degree of residual left ventricular dysfunction despite optimal medical therapy ($\leq 35\%$) to allow for adequate remodeling and the underlying etiology (post-myocardial infarction or ischemic cardiomyopathy) are the two single most important risk markers for stratification of need and benefit. Currently, patients with NYHA class II or III symptoms of heart failure and an LVEF $< 35\%$, irrespective of etiology of heart failure, are appropriate candidates for ICD prophylactic therapy. In patients with a myocardial infarction and optimal medical therapy with residual LVEF $\leq 30\%$ (even when asymptomatic), placement of an ICD is appropriate. In patients with a terminal illness and a predicted life span of less than 6 months or in those with NYHA class IV symptoms who are refractory to medications and who are not candidates for transplant, the risks of multiple ICD shocks must be carefully weighed against the survival benefits. If a patient meets the QRS criteria for CRT, combined CRT with ICD is often employed (Table 280-3).

SURGICAL THERAPY IN HEART FAILURE

Coronary artery bypass grafting (CABG) is considered in patients with ischemic cardiomyopathy with multivessel coronary artery disease. The recognition that hibernating myocardium, defined as myocardial tissue with abnormal function but maintained cellular function, could recover after revascularization led to the notion that revascularization with CABG would be useful in those with living myocardium. Revascularization is most robustly supported in individuals with ongoing angina and left ventricular failure. Revascularizing those with left ventricular failure in the absence of angina remains controversial. The Surgical Treatment for Ischemic Heart Failure (STICH) trial enrolled 1212 patients with an ejection fraction of 35% or less and coronary artery disease amenable to CABG and randomly assigned them to

TABLE 280-3 PRINCIPLES OF ICD IMPLANTATION FOR PRIMARY PREVENTION OF SUDDEN DEATH

Principle	Comment
Arrhythmia–sudden death mismatch	Sudden death in heart failure patients is generally due to progressive LVD, not a focal arrhythmia substrate (except in patients with post-MI HF)
Diminishing returns with advanced disease	Intervention at early stages of HF most successful since sudden death diminishes as cause of death with advanced HF
Timing of benefits	LVEF should be evaluated on optimal medical therapy or after revascularization before ICD therapy is employed; no benefit to ICD implant within 40 days of an MI (unless for secondary prevention)
Estimation of benefits and prognosis	Patients and clinicians often overestimate benefits of ICDs; an ICD discharge is not equivalent to an episode of sudden death (some ventricular arrhythmias terminate spontaneously); appropriate ICD discharges are associated with a worse near-term prognosis

Abbreviations: HF, heart failure; ICD, implantable cardioverter-defibrillator; LVD, left ventricular disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

medical therapy alone or medical therapy plus CABG. There was no significant difference between groups with respect to the primary endpoint of death from any cause. Patients assigned to CABG had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes. An ancillary study of this trial also determined that the detection of hibernation pre-revascularization did not materially influence the efficacy of this approach, nor did it help to define a population unlikely to benefit if hibernation was not detected.

Surgical ventricular restoration (SVR), a technique characterized by infarct exclusion to remodel the left ventricle by reshaping it surgically in patients with ischemic cardiomyopathy and dominant anterior left ventricular dysfunction, has been proposed. However, in a 1000-patient trial in patients with HFrEF who underwent CABG alone or CABG plus SVR, the addition of SVR to CABG had no disease-modifying effect. Cardiac symptoms and exercise tolerance improved from baseline to a similar degree in both study groups. SVR resulted in lower left ventricular volumes at 4 months after operation. However, left ventricular aneurysm surgery is still advocated in those with refractory heart failure, ventricular arrhythmias, or thromboembolism arising from an akinetic aneurysmal segment of the ventricle. Other remodeling procedures, such as use of an external mesh-like net attached around the heart to limit further enlargement, have not been shown to provide hard clinical benefits, although favorable cardiac remodeling was noted.

Mitral regurgitation (MR) occurs with varying degrees in patients with HFrEF and dilated ventricles. Annular dilatation and leaflet non-coaptation in the setting of anatomically normal papillary muscles, chordal structures, and valve leaflets characterize functional MR. In patients who are not candidates for surgical coronary revascularization, mitral valve repair remains controversial. Ischemic MR (or infarct-related MR) is typically associated with leaflet tethering and displacement related to abnormal left ventricular wall motion and geometry. No evidence to support the use of surgical or percutaneous valve correction for functional MR exists as disease-modifying therapy even though MR can be corrected.

CELLULAR AND GENE-BASED THERAPY

The cardiomyocyte is no longer considered a terminally differentiated cell and possesses regenerative capacity. Such renewal is accelerated

under conditions of stress and injury, such as an ischemic event or heart failure. Investigations that use either bone marrow-derived precursor cells or autologous cardiac-derived cells have gained traction. A number of small- and moderate-scale trials of such therapy have focused on post-myocardial infarction patients and have used autologous bone marrow-derived progenitor or stem cells. These trials have had variable results, with most demonstrating modest improvements in parameters of cardiac structure and remodeling. More promising, however, are cardiac-derived stem cells. Two preliminary pilot trials delivering cells via an intracoronary approach have been reported. In one, autologous c-kit-positive cells isolated from the atria obtained from patients undergoing CABG were cultured and reinfused. In another, cardiosphere-derived cells grown from endomyocardial biopsy specimens were used. These small trials demonstrated improvements in left ventricular function but require far more work to usher in a clinical therapeutic success. The appropriate route of administration, the quantity of cells to achieve a minimal therapeutic threshold, the constitution of these cells (single source or mixed), the mechanism by which benefit accrues, and short- and long-term safety remain to be elucidated.

Targeting molecular aberrations using gene transfer therapy, mostly with an adenoviral vector, is emerging in HFrEF. Several methods of gene delivery have been developed, including direct intramyocardial injection, coronary artery or venous infusion, and injection into the pericardial space. Cellular targets under consideration include β_2 -adrenergic receptors and calcium cycling proteins such as inhibitors of phospholamban. SERCA2a is deficient in patients with HFrEF and is primarily responsible for reincorporating calcium into the sarcoplasmic reticulum during diastole. A phase II randomized, double-blind, placebo-controlled trial called CUPID (Efficacy and Safety Study of Genetically Targeted Enzyme Replacement Therapy for Advanced Heart Failure) was completed. This study used coronary arterial infusion of adeno-associated virus type 1 carrying the gene for SERCA2a and demonstrated that natriuretic peptides were decreased, reverse remodeling was noted, and symptomatic improvements were forthcoming. Stromal-derived factor 1 enhances myocardial repair and facilitates “homing” of stem cells to the site of tissue injury. Strategies using intramyocardial injections to deploy this gene at sites of injury are being studied.

More advanced therapies for late-stage heart failure such as left ventricular assist devices and cardiac transplantation are covered in detail in Chap. 281.

DISEASE MANAGEMENT AND SUPPORTIVE CARE

Despite stellar outcomes with medical therapy, admission rates following heart failure hospitalization remain high, with nearly half of all patients readmitted to hospital within 6 months of discharge. Recurrent heart failure and related cardiovascular conditions account for only half of readmissions in patients with heart failure, whereas other comorbidity-related conditions account for the rest. The key to achieving enhanced outcomes must begin with the attention to transitional care at the index hospitalization with facilitated discharge through comprehensive discharge planning, patient and caregiver education, appropriate use of visiting nurses, and planned follow-up. Early postdischarge follow-up, whether by telephone or clinic-based, may be critical to ensuring stability because most heart failure-related readmissions tend to occur within the first 2 weeks after discharge. Although routinely advocated, intensive surveillance of weight and vital signs with use of telemonitoring has not decreased hospitalizations. Intrathoracic impedance measurements have been advocated for the identification of early rise in filling pressure and worsened hemodynamics so that preemptive management may be employed. However, this has not been successful and may worsen outcomes in the short term. Implantable pressure monitoring systems do tend to provide signals for early decompensation, and in patients with moderately advanced symptoms, such systems have been shown to provide information that can allow implementation of therapy to avoid hospitalizations by as much as 39% (in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart

- 1516** Failure Patients [CHAMPION] trial). Once heart failure becomes advanced, regularly scheduled review of the disease course and options with the patient and family is recommended including discussions surrounding end-of-life preferences when patients are comfortable in an outpatient setting. As the disease state advances further, integrating care with social workers, pharmacists, and community-based nursing may be critical in improving patient satisfaction with the therapy, enhancing quality of life, and avoiding heart failure hospitalizations. Equally important is attention to seasonal influenza vaccinations and periodic pneumococcal vaccines that may obviate non–heart failure hospitalizations in these ill patients. When nearing end of life, facilitating a shift in priorities to outpatient and hospice palliation is key, as are discussions around advanced therapeutics and continued use of ICD prophylaxis, which may worsen quality of life and prolong death.

PART 10

Disorders of the Cardiovascular System

GLOBAL CONSIDERATIONS

Substantial differences exist in the practice of heart failure therapeutics and outcomes by geographic location. International guidelines produced by the American College of Cardiology/American Heart Association, European Society of Cardiology, and National Institute for Health and Clinical Excellence (United Kingdom) differ in their approach to evaluation of evidence and prioritization of therapy. The penetrance of CRT and ICD is higher in the United States than in Europe. Conversely, therapy unavailable in the United States, such as ivabradine and levosimendan, is designated as useful in Europe. Although ACEIs appear to be similarly effective across populations, variation in the benefits of beta blockers based on world region remains an area of controversy. In oral pharmacologic therapy trials of HFrEF, patients from southwest Europe have a lower incidence of ischemic cardiomyopathy and those in North America tend to have more diabetes and prior coronary revascularization. There is also regional variation in medication use even after accounting for indication. In trials of ADHF, patients in Eastern Europe tend to be younger, with higher ejection fractions and lower natriuretic peptide levels. Patients from South America tend to have the lowest rates of comorbidities, revascularization, and device use. In contrast, patients from North America have the highest comorbidity burden with high revascularization and device use rates. Given geographic differences in baseline characteristics and clinical outcomes, the generalizability of therapeutic outcomes in patients in the United States and Western Europe may require verification.

options for such patients. Currently, both of the latter approaches are considered to be experimental.

CARDIAC TRANSPLANTATION



Surgical techniques for orthotopic transplantation of the heart were devised in the 1960s and taken into the clinical arena in 1967. The procedures did not gain widespread clinical acceptance until the introduction of “modern” and more effective immunosuppression in the early 1980s. By the 1990s, the demand for transplantable hearts met, and then exceeded, the available donor supply and leveled off at about 4000 heart transplants annually worldwide, according to data from the Registry of the International Society for Heart and Lung Transplantation (ISHLT). Subsequently, heart transplantation activity in the United States has remained stable at ~2200 per year, but worldwide activity reported to this registry has decreased somewhat. This apparent decline in numbers may be a result of the fact that reporting is legally mandated in the United States but not elsewhere, and several countries have started their own databases.

SURGICAL TECHNIQUE

Donor and recipient hearts are excised in virtually identical operations with incisions made across the atria and atrial septum at the mid-atrial level (with the posterior walls of the atria left in place) and across the great vessels just above the semilunar valves. The donor heart is generally “harvested” by a separate surgical team, transported from the donor hospital in a bag of iced saline solution, and reanastomosed into the waiting recipient in the orthotopic or normal anatomic position. The only change in surgical technique since this method was first described has been a movement in recent years to move the right atrial anastomosis back to the level of the superior and inferior vena cavae to better preserve right atrial geometry and prevent atrial arrhythmias. Both methods of implantation leave the recipient with a surgically denervated heart that does not respond to any direct sympathetic or parasympathetic stimuli but does respond to circulating catecholamines. The physiologic responses of the denervated heart to the demands of exercise are atypical but quite adequate for continuation of normal physical activity.

DONOR ALLOCATION SYSTEM

In the United States, the allocation of donor organs is accomplished under the supervision of the United Network for Organ Sharing, a private organization under contract to the federal government. The United States is divided geographically into eleven regions for donor heart allocation. Allocation of donor hearts within a region is decided according to a system of priority that takes into account (1) the severity of illness, (2) the geographic distance from the donor, and (3) the patient’s time on the waiting list. A physiologic limit of ~3 h of “ischemic” (out-of-body) time for hearts precludes a national sharing of hearts. This allocation system design is reissued annually and is responsive to input from a variety of constituencies, including both donor families and transplantation professionals.

At the current time, the highest priority according to severity of illness is assigned to patients requiring hospitalization at the transplantation center for IV inotropic support, with a pulmonary artery catheter in place for hemodynamic monitoring, or to patients requiring mechanical circulatory support—i.e., use of an intra-aortic balloon pump or a right or left ventricular assist device (RVAD, LVAD), extracorporeal membrane oxygenation, or mechanical ventilation. The second highest priority is given to patients requiring ongoing inotropic support, but without a pulmonary artery catheter in place. All other patients are assigned a priority according to time accrued on the waiting list, and matching generally is based only on compatibility in terms of ABO blood group and gross body size.

While HLA matching of donor and recipient would be ideal, the relatively small numbers of patients as well as the time constraints involved make such matching impractical. However, some patients who are “presensitized” and have preexisting antibodies to human leukocyte antigens (HLAs) undergo prospective cross-matching with the

281 Cardiac Transplantation and Prolonged Assisted Circulation

Sharon A. Hunt, Hari R. Mallidi

Advanced or end-stage heart failure is an increasingly frequent sequela of many types of heart disease, as progressively more effective palliation for the earlier stages of heart disease and prevention of sudden death associated with heart disease become more widely recognized and employed ([Chap. 279](#)). When patients with end-stage or refractory heart failure are identified, the physician is faced with the decision of advising compassionate end-of-life care or choosing to recommend extraordinary life-extending measures. For the occasional patient who is relatively young and without serious comorbidities, the latter may represent a reasonable option. Current therapeutic options are limited to cardiac transplantation (with the option of mechanical cardiac assistance as a “bridge” to transplantation) or permanent mechanical assistance of the circulation. In the future, it is possible that genetic modulation of ventricular function or cell-based cardiac repair will be

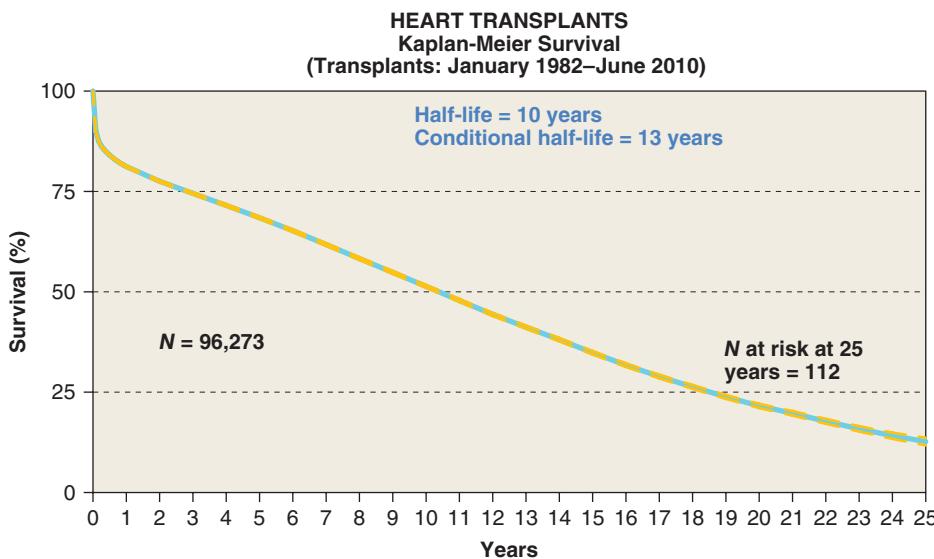


FIGURE 281-1 Global survival rates after heart transplantation since 1982. Rates were calculated by the Kaplan-Meier method, which incorporates information from all transplant recipients for whom any follow-up has been provided. Because many patients are still alive and some patients have been lost to follow-up, the survival rates are estimates rather than exact figures because the time of death is not known for all patients. Therefore, 95% confidence limits are provided. (From J Stehlik et al: *J Heart Lung Transplant* 31:1052, 2012.)

donor; these patients are commonly multiparous women or patients who have received multiple transfusions.

INDICATIONS/CONTRAINDICATIONS

Heart failure is an increasingly common cause of death, particularly in the elderly. Most patients who reach what has recently been categorized as stage D, or refractory end-stage heart failure, are appropriately treated with compassionate end-of-life care. A subset of such patients who are younger and without significant comorbidities can be considered as candidates for heart transplantation. Exact criteria vary in different centers but generally take into consideration the patient's physiologic age and the existence of comorbidities such as peripheral or cerebrovascular disease, obesity, diabetes, cancer, or chronic infection.

RESULTS

 A registry organized by the ISHLT has tracked worldwide and U.S. survival rates after heart transplantation since 1982. The most recent update reveals survival rates of 83% and 76% 1 and 3 years after transplantation, respectively, or a posttransplantation "half-life" of 10.00 years (Fig. 281-1). The quality of life of survivors is generally excellent, with well over 90% of patients in the registry returning to normal and unrestricted function after transplantation.

IMMUNOSUPPRESSION

Medical regimens employed to suppress the normal immune response to a solid organ allograft vary from center to center and are in a constant state of evolution, as more effective agents with improved side-effect profiles and less toxicity are introduced. All currently used regimens are nonspecific, providing general hyporeactivity to foreign antigens rather than donor-specific hyporeactivity and also causing the attendant, and unwanted, susceptibility to infections and malignancy. Most cardiac transplantation programs currently use a three-drug regimen that includes a calcineurin inhibitor (cyclosporine or tacrolimus), an inhibitor of T cell proliferation or differentiation (azathioprine, mycophenolate mofetil, or sirolimus), and at least a short initial course of glucocorticoids. Many programs also include an initial "induction" course of polyclonal or monoclonal antibodies to T cells in the perioperative period to decrease the frequency or severity of early posttransplantation rejection. Most recently introduced have been monoclonal antibodies (daclizumab and basiliximab) that block

the interleukin 2 receptor and may prevent allograft rejection without additional global immunosuppression.

Cardiac allograft rejection is usually diagnosed by endomyocardial biopsy conducted either on a surveillance basis or in response to clinical deterioration. Biopsy surveillance is performed on a regular basis in most programs for the first year postoperatively (or the first 5 years in many programs). Therapy consists of augmentation of immunosuppression, the intensity and duration of which are dictated by the severity of rejection.

LATE POSTTRANSPLANTATION MANAGEMENT ISSUES

Increasing numbers of heart transplant recipients are surviving for years following transplantation and constitute a population of patients with a number of long-term management issues.

Allograft Coronary Artery Disease Despite usually having young donor hearts, cardiac allograft recipients are prone to develop coronary artery disease (CAD). This CAD is generally a diffuse, concentric, and longitudinal process that is quite different from "ordinary" atherosclerotic CAD, which is more focal and often eccentric. The underlying etiology most likely is primarily immunologic injury of the vascular endothelium, but a variety of risk factors influence the existence and progression of CAD, including nonimmunologic factors such as dyslipidemia, diabetes mellitus, and cytomegalovirus (CMV) infection. It is hoped that newer and improved immunosuppressive modalities will reduce the incidence and impact of these devastating complications, which currently account for the majority of late posttransplantation deaths. Thus far, the immunosuppressive agents mycophenolate mofetil and the mammalian target of the rapamycin (mTOR) inhibitors sirolimus and everolimus have been shown to be associated with short-term lower incidence and extent of coronary intimal thickening; in anecdotal reports, institution of sirolimus was associated with some reversal of CAD. The use of statins also is associated with a reduced incidence of this vasculopathy, and these drugs are now used almost universally in transplant recipients unless contraindicated. Palliation of CAD with percutaneous interventions is probably safe and effective in the short term, although the disease often advances relentlessly. Because of the denervated status of the organ, patients rarely experience angina pectoris, even in advanced stages of disease.

Retransplantation is the only definitive form of therapy for advanced allograft CAD. However, the scarcity of donor hearts makes the

1518 decision to pursue retransplantation in an individual patient difficult and ethically complex.

Malignancy An increased incidence of malignancy is a well-recognized sequela of any program of chronic immunosuppression, and organ transplantation is no exception. Lymphoproliferative disorders are among the most frequent posttransplantation complications and, in most cases, seem to be driven by Epstein-Barr virus. Effective therapy includes reduction of immunosuppression (a clear “double-edged sword” in the setting of a life-sustaining organ), administration of antiviral agents, and traditional chemo- and radiotherapy. Most recently, specific antilymphocyte (CD20) therapy has shown great promise. Cutaneous malignancies (both basal cell and squamous cell carcinomas) also occur with increased frequency among transplant recipients and can follow aggressive courses. The role of decreasing immunosuppression in the treatment of these cancers is far less clear.

Infections The use of currently available nonspecific immunosuppressive modalities to prevent allograft rejection naturally results in increased susceptibility to infectious complications in transplant recipients. Although the incidence has decreased since the introduction of cyclosporine, infections with unusual and opportunistic organisms are still the major cause of death during the first postoperative year and remain a threat to the chronically immunosuppressed patient throughout life. Effective therapy depends on careful surveillance for early signs and symptoms of opportunistic infection, an extremely aggressive approach to obtaining a specific diagnosis, and expertise in recognizing the more common clinical presentations of infections caused by CMV, *Aspergillus*, and other opportunistic agents.

PROLONGED ASSISTED CIRCULATION

The modern era of mechanical circulatory support can be traced back to 1953, when cardiopulmonary bypass was first used in a clinical setting and ushered in the possibility of brief periods of circulatory support to permit open-heart surgery. Subsequently, a variety of extracorporeal pumps to provide circulatory support for brief periods have been developed. The use of a mechanical device to support the circulation for more than a few hours initially progressed slowly, with the implantation of a total artificial heart in 1969 in Texas by Cooley. This patient survived for 60 h until a donor organ became available, at which point he underwent transplantation. Unfortunately, the patient died of pulmonary complications after transplantation. The entire field of mechanical replacement of the heart then took a decade-long hiatus until the 1980s, when total artificial hearts were reintroduced with much publicity; however, they failed to produce the hoped-for treatment of end-stage heart disease. Starting in the 1970s, in parallel with the development of the total artificial heart, intense research had addressed the development of ventricular assist devices, which provide mechanical assistance for (rather than replacing) the failing ventricle.

Although conceived of initially as alternatives to biologic replacement of the heart, LVADs were introduced—and are still employed primarily—as temporary “bridges” to heart transplantation in candidates in whom medical therapy begins to fail before a donor heart becomes available. Several devices are approved by the U.S. Food and Drug Administration (FDA) and are in widespread use (see later). Those that are implantable within the body are compatible with hospital discharge and offer the patient a chance for life at home during a wait for a donor heart. However successful such “bridging” is for the individual patient, it does nothing to alleviate the scarcity of donor hearts; the ultimate goal in the field remains that of providing a reasonable alternative to biologic replacement of the heart—one that is widely and easily available and cost-effective.

CURRENT INDICATIONS AND APPLICATIONS OF VENTRICULAR ASSIST DEVICES

Currently, there are two major indications for ventricular assistance. First, patients at risk of imminent death from cardiogenic shock are eligible for mechanical support. These patients are generally managed with temporary cardiac assist devices. Second, if patients have a left ventricular ejection fraction <25% or a peak VO_2 <14 mL/kg per min

or are dependent on inotropic therapy or support with intra-aortic balloon counterpulsation, they may be eligible for mechanical support. If they are eligible for heart transplantation, the mechanical circulatory assistance is termed the “bridge to transplantation.” By contrast, if the patient has a contraindication to heart transplantation, the use of the device is deemed to constitute “destination” left ventricular assistance therapy.

BASIC CONCEPTS

Pulsatile vs. Nonpulsatile Devices *Pulsatile* devices are ventricular assist devices whose mechanism of action mandates the alternating filling and emptying of a volume chamber within the device that mimics the mechanism of action of the natural heart. *Nonpulsatile* devices have a mechanism of action that results in continuous blood flow through the device, eliminating the need for pulsatility. The pulsatile devices are larger, bulkier, and associated with greater energy requirements and higher rates of complications than the nonpulsatile devices. However, pulsatile devices provide greater degrees of support and may even be capable of replacing the function of the heart entirely in the form of a total artificial heart. Because of the bulkiness of these devices, many patients are too small to be supported with intracorporeal pulsatile pumps. However, paracorporeal versions are available. These devices are versatile and can be used for right, left, or biventricular assistance/replacement.

Continuous-flow (nonpulsatile) devices are further categorized on the basis of impeller design and mechanism. The older designs have tended to be axial-flow pumps, which operate on the Archimedes screw principle. These devices have an impeller that is in line with the direction of blood flow, and the inlet direction of blood is the same as the outlet direction. Continuous-flow devices have been dependent on the presence of blood-washed bearings within the pump housing and may be associated with an increased risk of blood and platelet activation. The newer devices are centrifugal in design; the blood flow takes a 90° turn between the inlet section of the pump and the outlet section. Another major difference in the newer devices is the absence of blood-washed bearings (with most devices having magnetically levitated impellers). This design allows the construction of smaller pumps with less blood-element activation than the axial-flow designs.

Available Devices In the United States, there are currently four FDA-approved devices that are used as bridges to transplantation in adults. Of these four devices, one is also approved for use as destination therapy or as long-term mechanical support of the heart. A number of other devices are approved only for short-term support in post–cardiac surgery shock or in cardiogenic shock secondary to acute myocardial infarction or fulminant myocarditis; these will not be considered here. So far, no long-term device is totally implantable, and, because of the need for transcutaneous connections, all share a common problem with infectious complications. Likewise, all share some tendency to thromboembolic complications and are subject to the possibility of mechanical failure common to any machine.

The total artificial heart (TAH) (Syncardia, Tucson, AZ) is a pneumatic, biventricular, orthotopically implanted ventricular assist device with an externalized driveline connecting it to its console. The TAH is currently the only FDA-approved device for use in patients who have severe biventricular failure.

The Thoratec LVAD (Thoratec Corp., Pleasanton, CA) is an extracorporeal pump that takes blood from a large cannula placed in the left ventricular apex and propels it forward through an outflow cannula inserted into the ascending aorta. The extracorporeal nature of this pump allows its use in small adults for whom intracorporeal pumps would be too large. This device provides not only left but also right ventricular assistance and can be utilized for biventricular support within the same patient (BiVentricular Assist Device).

The HeartMate II LVAD (Thoratec) similarly uses a drainage cannula in the left ventricular apex to drain blood into a small chamber, where the blood is driven by an electrically powered motor that spins a rotor, accelerating blood outflow into the ascending aorta (Fig. 281-2). This device is currently the only FDA-approved axial-flow pump that can be used both as a bridge to transplantation and as destination therapy.

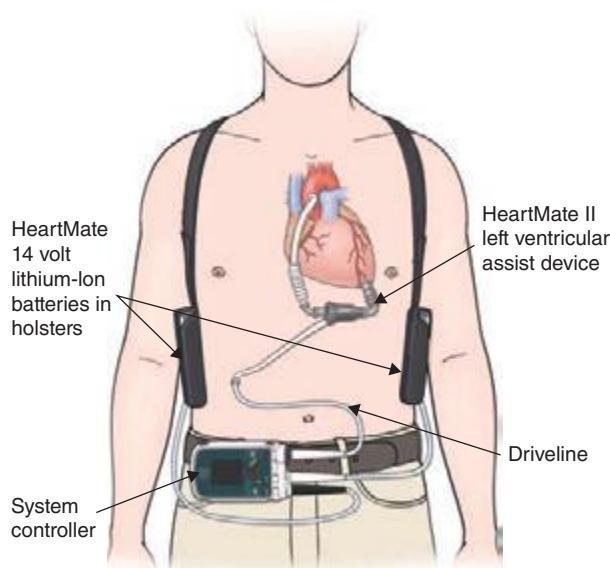


FIGURE 281-2 Diagram of HeartMate II left ventricular assist device (LVAD). (Reprinted with permission from Thoratec Corp., Pleasanton, CA.)

The HeartWare Ventricular Assist System with the HVAD pump (HeartWare Inc., Framingham, MA) is the first third-generation device to be granted FDA approval for use in patients as a bridge to transplantation. The device is a centrifugal pump that is housed completely within the patient's pericardial cavity and provides adequate support for many patients.

RESULTS

The use of these devices in the United States is limited mainly to patients with post-cardiac surgery shock and to those who are bridged to transplantation. The results of bridging to transplantation with the available devices are quite good, with nearly 75% of younger patients receiving a transplant by 1 year and having excellent posttransplantation survival rates.

Publication of the REMATCH (Randomized Evaluation of Mechanical Assistance in the Treatment of Heart Failure) trial in 2001 documented a somewhat improved survival rate in patients who had end-stage heart disease, were not candidates for transplantation, and were randomized to a pulsatile LVAD (albeit with a high rate of complications, especially neurologic issues) as opposed to continued medical therapy. This result led to renewed interest in use of the devices for nonbiologic permanent replacement of heart function as well. Subsequently, this device was supplanted by the HeartMate II axial-flow device, which has dramatically improved the survival of patients with severe end-stage heart disease in whom medical therapy has failed. The patients who had this device implanted had a 2-year survival rate of 58%, whereas the survival rate for patients in the medically treated arm of the original REMATCH trial was only 8%. More recent experience has shown that the mean survival period of patients with a continuous-flow LVAD for destination therapy is approaching 5 years.

Several studies have evaluated the benefit of LVAD therapy as a bridge to transplantation. The most recent data come from a series of 140 patients who underwent implantation of a HeartWare HVAD. Of these patients, 94% achieved the principal outcome (defined as survival to transplantation, recovery of heart function, or ongoing device support) at 180 days. With increased experience and improved outcomes using LVADs as a bridge to transplantation, the ability to maintain end-organ function and limit the progression of pulmonary hypertension—or even to decrease pulmonary vascular resistance—makes mechanical unloading a more attractive option than continued inotropic support. The early bridge-to-transplantation experience demonstrated reduced posttransplantation survival compared with medical management; however, more recent experience has shown equivalent outcomes following transplantation. This result is likely secondary to a trend toward earlier device implantation—i.e., prior to the onset of irreversible end-organ damage.

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Congenital Heart Disease in the Adult

Jamil A. Aboulhosn, John S. Child

Over a hundred years ago, Sir William Osler, in his classic textbook *The Principles and Practice of Medicine* (New York, Appleton & Co, 1892, pp 659–663), devoted only five pages to “Congenital Affections of the Heart,” with the first sentence declaring that “[t]hese [disorders] have only limited clinical interest, as in a large proportion of cases the anomaly is not compatible with life, and in others nothing can be done to remedy the defect or even to relieve symptoms.” Fortunately, in the intervening century, considerable progress has been made in understanding the basis for these disorders and their effective treatment.

The most common birth defects are cardiovascular in origin. These malformations are due to complex multifactorial genetic and environmental causes. Recognized chromosomal aberrations and mutations of single genes account for <10% of all cardiac malformations. Congenital heart disease (CHD) complicates ~1% of all live births in the general population—about 40,000 births/year—but occurs more frequently in the offspring (about 4–10%, depending on maternal CHD type) of women with CHD. Owing to the remarkable surgical advances over the last 60 years, >90% of afflicted neonates and children now reach adulthood; women with CHD may now frequently successfully bear children after competent repairs. As such, the population with CHD is steadily increasing. Women with CHD are at increased risk for peri- and postpartum complications, but maternal CHD is generally not considered an absolute contraindication to pregnancy unless the mother has certain high-risk features (e.g., cyanosis, pulmonary hypertension, decompensated heart failure, arrhythmias, aortic aneurysm, among others). Consultation with an adult CHD expert is warranted for all females with CHD who desire to become pregnant.

Nearly one and a half million adults with operated or unoperated CHD live in the United States today; there are now more adults than children with CHD in the United States. Because true surgical cures are rare, and all repairs—be they palliative or corrective—may leave residua, sequelae, or complications, most require some degree of lifetime expert surveillance. The anatomic and physiologic changes in the heart and circulation due to any specific CHD lesion are not static but, rather, progress from prenatal life to adulthood. Malformations that are benign or escape detection in childhood may become clinically significant in the adult. Unfortunately, the growing number of adults with CHD has not been paralleled by an adequate increase in the number of specialists and

1520 specialty centers that are trained and equipped to manage this challenging population. Ongoing efforts to increase awareness, resources, and advocacy are essential for the necessary growth of this specialty.

CARDIAC DEVELOPMENT

(See also Chap. 265e) CHD is generally the result of aberrant embryonic development of a normal structure or failure of such a structure to progress beyond an early stage of embryonic or fetal development. This brief section serves to introduce the reader to normal development so that defects may be better understood; by necessity, it is not exhaustive. Cardiogenesis is a finely tuned process with transcriptional control of a complex group of regulatory proteins that activate or inhibit their gene targets in a location- and time-dependent manner. At about 3 weeks of embryonic development, two cardiac cords form and become canalized; at that point, the primordial cardiac tube develops from two sources (cardiac crescent or the first heart field, pharyngeal mesoderm or the second heart field); by 21 days, these fuse into a single cardiac tube beginning at the cranial end. The cardiac tube then elongates and develops discrete constrictions with the following segments from caudal to cranial location: sinus venosus receives the umbilical, vitelline, and common cardinal veins; atrium, ventricle, bulbus cordis, truncus arteriosus, aortic sac, and the aortic arches. The cardiac tube is fixed at the sinus venosus and arterial ends.

Subsequently, in the next few weeks, differential growth of cells causes the tube to elongate and loop as an “S” with the bulboventricular portion moving rightward and the atrium and sinus venosus moving posterior to the ventricle. The primitive atrium and ventricle communicate via the atrioventricular canal from which the endocardial cushion develops into two parts (ventrally and dorsally). The cushions fuse and divide the atrioventricular canal into two atrioventricular inlets and also migrate to help form the ventricular septum. The primitive atrium is divided first by a septum primum membrane, which grows down from the superior wall to the cushions; as this fusion occurs, the mid-portion resorbs in the center forming the ostium secundum. Rightward of the septum primum, a second septum secundum membrane grows down from the ventral-cranial wall toward—but not reaching—the cushions, and covering most, but not all, of the ostium secundum, resulting in a flap of the foramen ovale. The primitive ventricle is partitioned by a finely tuned set of events. The interventricular septum grows up toward the cushions, and the cushions form an upper inlet septum; between the two portions is a hole called the interventricular foramen. The left and right ventricles begin to develop side by side, and the atria and their respective inlet valves align over their ventricles. Finally, these two parts of the septum fuse with the bulboventricular ridges, which, once having septated the truncus arteriosus, extend into the ventricle. The bulbocordis divides into a subaortic portion as the muscular conus resorbs, whereas the subpulmonary section has elongation of its muscular conus. Spiral division of the common truncus arteriosus rotates and aligns the pulmonary artery and aortic portions over their respective outflow tracts, the aortic valve moving posterior over the left ventricle (LV) outflow tract and the pulmonary valve moving anterior over the right ventricle (RV) outflow tract, with a wraparound relationship of the two great arteries.

Early on, the venous systems are bilateral and symmetric and enter two horns of the sinus venosus. Ultimately, except for the coronary sinus, most of the left-sided portions and the left sinus–venosus horn regress, and the systemic venous system empties into the right horn via the inferior and superior vena cavae. The pulmonary venous system, initially connecting to the systemic venous system, develops as buds from the developing lungs, which fuse together in the pulmonary venous confluence, at which point the connection to the systemic system regresses. Simultaneously, a projection from the back wall of the left atrium (the common pulmonary vein) grows posteriorly to merge with the confluence, which then becomes a part of the posterior left atrial wall.

The truncus arteriosus and aortic sac initially develop six paired symmetric arches, which curve posteriorly and become the paired dorsal aortae. The detailed description of the selective regression of some of the arches is not presented in this chapter. In brief summary,

TABLE 282-1 SIMPLE ADULT CONGENITAL HEART DISEASE

Native disease
Uncomplicated congenital aortic valve disease
Mild congenital mitral valve disease (e.g., except parachute valve, cleft leaflet)
Uncomplicated small atrial septal defect
Uncomplicated small ventricular septal defect
Mild pulmonic stenosis
Repaired conditions
Previously ligated or occluded ductus arteriosus
Repaired secundum or sinus venosus atrial septal defect without residua
Repaired ventricular septal defect without residua

this process results in the development of arch 3 as the internal carotid arteries, left arch 4 as the aortic arch and right subclavian artery, and part of arch 6 as the patent ductus arteriosus. The two dorsal thoracic aortae fuse in the abdomen with persistence of the left dorsal aorta.

SPECIFIC CARDIAC DEFECTS

Tables 282-1, 282-2, and 282-3 list CHD malformations as simple, intermediate, or complex. Simple defects generally are single lesions with a shunt or a valvular malformation. Intermediate defects may have two or more simple defects. Complex defects generally have components of an intermediate defect plus more complex cardiac and vascular anatomy, often with cyanosis, and frequently with transposition complexes. The goal of these tables is to suggest when cardiology consultation or advanced CHD specialty care is needed. Patients with complex CHD (which includes most “named” surgeries that usually involve complex CHD) should virtually always be managed in conjunction with an experienced specialty adult CHD center. Patients with intermediate lesions should have an initial consultation and subsequent occasional intermittent follow-up with an adult CHD specialist. Patients with simple lesions often may be managed by a well-informed internist or general cardiologist, although consultation with a specifically trained adult congenital cardiologist is occasionally advisable.

ATRIAL SEPTAL DEFECT

Atrial septal defect (ASD) is a common cardiac anomaly that may be first encountered in the adult and occurs more frequently in females. Sinus venosus ASD occurs high in the atrial septum near the entry of the superior vena cava into the right atrium and is associated frequently with anomalous pulmonary venous connection from the right lung to the superior vena cava or right atrium (Fig. 282-1). Ostium primum ASDs lie adjacent to the atrioventricular valves, either of which may be deformed and regurgitant. Ostium primum ASDs are common in Down’s syndrome, often as part of complex atrioventricular septal defects with a common atrioventricular valve and a posterior defect of the basal portion of the interventricular septum. The most common ostium secundum ASD involves the fossa ovalis and is mid-septal in location; this should not be confused with a patent foramen

TABLE 282-2 INTERMEDIATE COMPLEXITY CONGENITAL HEART DISEASE

Ostium primum or sinus venosus atrial septal defect
Anomalous pulmonary venous drainage, partial or total
Atrioventricular canal defects (partial or complete)
Ventricular septal defect, complicated (e.g., absent or abnormal valves or with associated obstructive lesions, aortic regurgitation)
Coarctation of the aorta
Pulmonic valve stenosis (moderate to severe)
Infundibular right ventricular outflow obstruction of significance
Pulmonary valve regurgitation (moderate to severe)
Patent ductus arteriosus (nonclosed)—moderate to large
Sinus of Valsalva fistula/aneurysm
Subvalvular or supravalvular aortic stenosis

TABLE 282-3 COMPLEX ADULT CONGENITAL HEART DISEASE

Cyanotic congenital heart diseases (all forms)
Eisenmenger's syndrome
Ebstein's anomaly
Tetralogy of Fallot or pulmonary atresia (all forms)
Transposition of the great arteries
Single ventricle; tricuspid or mitral atresia
Double-outlet ventricle
Truncus arteriosus
Fontan or Rastelli procedures

ovale. Anatomic obliteration of the foramen ovale ordinarily follows its functional closure soon after birth, but residual "probe patency" is a common normal variant; ASD denotes a true deficiency of the atrial septum and implies functional and anatomic patency. The magnitude of the left-to-right shunt depends on the ASD size, ventricular diastolic properties, and the relative impedance in the pulmonary and systemic circulations. The left-to-right shunt causes diastolic overloading of the RV and increased pulmonary blood flow. Patients with ASD are usually asymptomatic in early life, although there may be some physical underdevelopment and an increased tendency for respiratory infections; cardiorespiratory symptoms occur in many older patients. Beyond the fourth decade, a significant number of patients develop atrial arrhythmias, pulmonary arterial hypertension, and right heart failure. Patients exposed to the chronic environmental hypoxemia of high altitude tend to develop pulmonary hypertension at younger ages. In older patients, left-to-right shunting across the ASD increases as progressive systemic hypertension and/or coronary artery disease (CAD) result in reduced compliance of the LV.

Physical Examination Examination usually reveals a prominent RV impulse and palpable pulmonary artery pulsation. The first heart sound is normal or split, with accentuation of the tricuspid valve closure sound. Increased flow across the pulmonic valve is responsible for a midsystolic pulmonary outflow murmur. The second heart sound is widely split and is fixed in relation to respiration. A mid-diastolic rumbling murmur, loudest at the fourth intercostal space and along the left sternal border, reflects increased flow across the tricuspid valve. In ostium primum ASD, an apical holosystolic murmur indicates associated mitral or tricuspid regurgitation or a ventricular septal defect (VSD).

These findings are altered when increased pulmonary vascular resistance causes diminution of the left-to-right shunt. Both the pulmonary outflow and tricuspid inflow murmurs decrease in intensity, the pulmonic component of the second heart sound and a systolic ejection sound are accentuated, the two components of the second heart sound may fuse, and a diastolic murmur of pulmonic regurgitation appears. Cyanosis and clubbing accompany the development of a right-to-left shunt (see "Ventricular Septal Defect" later in this chapter). In adults with an ASD and atrial fibrillation, the physical findings may be confused with mitral stenosis with pulmonary hypertension because the tricuspid diastolic flow murmur and widely split second heart sound may be mistakenly thought to represent the diastolic murmur of mitral stenosis and the mitral "opening snap," respectively.

Electrocardiogram In ostium secundum ASD, electrocardiogram (ECG) usually shows right-axis deviation and an rSr' pattern in the right precordial leads representing enlargement of the RV outflow tract. An ectopic atrial pacemaker or first-degree heart block may occur with the sinus venous ASD. In ostium primum ASD, the RV conduction defect is accompanied by left superior axis deviation and counterclockwise rotation of the frontal plane QRS loop. Varying degrees of RV and right atrial (RA) enlargement or hypertrophy may occur with each type of defect, depending on the presence and degree of pulmonary hypertension. Chest x-ray shows an enlarged RA and RV, and pulmonary artery and its branches; increased pulmonary vascular markings of left-to-right shunt vascularity will diminish if pulmonary vascular disease develops.

Echocardiogram Echocardiography reveals pulmonary arterial and RV and RA dilatation with abnormal (paradoxical) ventricular septal motion in the presence of a significant right heart volume overload. The ASD may be visualized directly by two-dimensional imaging, color-flow imaging, or echocontrast. Echocardiography and Doppler examination have supplanted cardiac catheterization. Transesophageal echocardiography is indicated if the transthoracic echocardiogram is ambiguous, which is often the case with sinus venosus defects, or for guiding catheter device closure (Fig. 282-2). Cardiac catheterization is performed if inconsistencies exist in the clinical data, if significant pulmonary hypertension or associated malformations are suspected, if CAD is a possibility, or when attempting transcatheter closure of the ASD.

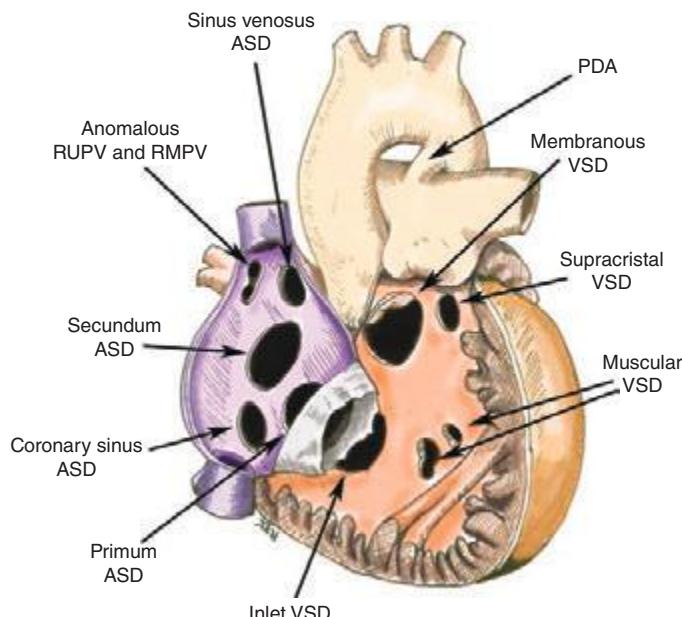


FIGURE 282-1 Types and locations of congenital cardiac defects. ASD, atrial septal defect; PDA, patent ductus arteriosus; RMPV, right middle pulmonary vein; RUPV, right upper pulmonary vein; VSD, ventricular septal defect.

TREATMENT ATRIAL SEPTAL DEFECT

Operative repair, usually with a patch of pericardium or of prosthetic material or percutaneous transcatheter device closure, if the ASD is of an appropriate size and shape, should be advised for all patients with uncomplicated secundum ASD with significant left-to-right shunting, i.e., pulmonary-to-systemic flow ratios $\geq 1.5:1$. Excellent results may be anticipated, at low risk, even in patients >40 years, in the absence of severe pulmonary hypertension. In ostium primum ASD, cleft mitral valves may require repair in addition to patch closure of the ASD. Closure is not usually carried out in patients with small defects and trivial left-to-right shunts or in those with severe pulmonary vascular disease without a significant left-to-right shunt. However, the use of pulmonary vasodilators with resultant reduction in pulmonary artery pressure and resistance may allow closure of ASD in patients with pulmonary vascular disease.

Patients with sinus venosus or ostium secundum ASDs rarely die before the fifth decade. During the fifth and sixth decades, the incidence of progressive symptoms, often leading to severe disability, increases substantially. Medical management should include prompt treatment of respiratory tract infections; antiarrhythmic medications for atrial fibrillation or supraventricular tachycardia; and the usual measures for hypertension, coronary disease, or heart failure (Chap. 279), if these complications occur. The risk of infective endocarditis is low, and antibiotic prophylaxis is not recommended (Chap. 155).

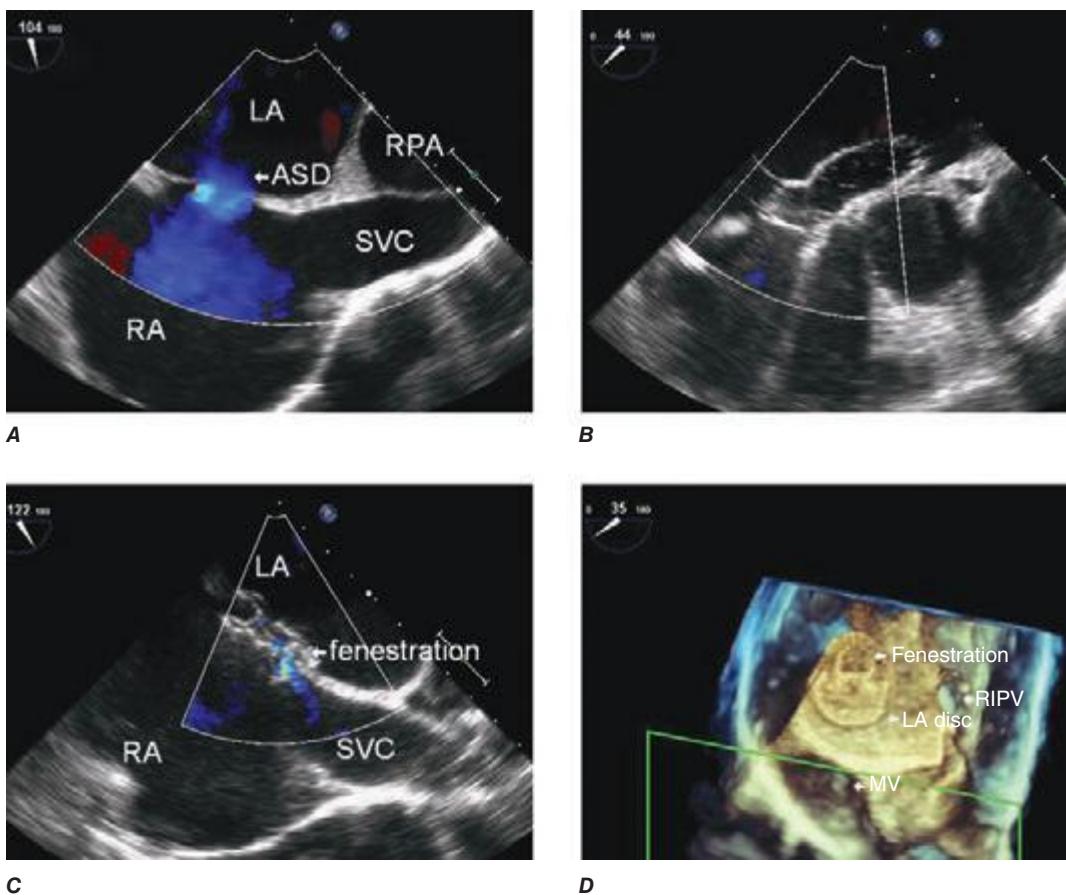


FIGURE 282-2 **A.** Transesophageal echocardiogram demonstrating a secundum-type atrial septal defect (ASD) with shunting from the left atrium (LA) to the right atrium (RA). The right pulmonary artery (RPA) and superior vena cava (SVC) are labeled. **B.** Transcatheter balloon sizing of the ASD. **C.** Atrial septal occluder placement with a small manually created “fenestration” within the device that continues to allow a small amount of flow from the LA to the RA; this is used as a means of preventing left atrial hypertension after ASD closure. Left atrial hypertension may occur in older patients with decreased left ventricular compliance. **D.** Three-dimensional image of the septal occluder en-face; note the fenestration in the LA disc. The mitral valve (MV) and right inferior pulmonary vein (RIPV) are labeled.

VENTRICULAR SEPTAL DEFECT

VSD is one of the most common of all cardiac birth defects, either as an isolated defect or as a component of a combination of anomalies (Fig. 282-1). The VSD is usually single and situated in the membranous or midmuscular portion of the septum. The functional disturbance depends on its size and on the status of the pulmonary vascular bed. Only small- or moderate-size VSDs are seen initially in adulthood, as most patients with an isolated large VSD come to medical or surgical attention early in life.

A wide spectrum exists in the natural history of VSD, ranging from spontaneous closure to congestive cardiac failure and death in infancy. Included within this spectrum is the possible development of pulmonary vascular obstruction, RV outflow tract obstruction, aortic regurgitation, or infective endocarditis. Spontaneous closure is more common in patients born with a small VSD, which occurs in early childhood in most. The pulmonary vascular bed is often a principal determinant of the clinical manifestations and course of a given VSD and feasibility of surgical repair. Increased pulmonary arterial pressure results from increased pulmonary blood flow and/or resistance, the latter usually the result of obstructive, obliterative structural changes within the pulmonary vascular bed. It is important to quantitate and compare pulmonary-to-systemic flows and resistances in patients with severe pulmonary hypertension. The term Eisenmenger's syndrome is applied to patients with a large communication between the two circulations at the aortopulmonary, ventricular, or atrial levels and bidirectional or predominantly right-to-left shunts because of high resistance and obstructive pulmonary hypertension.

Patients with large VSDs and pulmonary hypertension are at greatest risk for developing pulmonary vascular disease. Large VSDs should

be corrected early in life when pulmonary vascular disease is not severely elevated. In patients with Eisenmenger's syndrome, symptoms in adult life consist of exertional dyspnea, chest pain, syncope, and hemoptysis (see below). The degree to which pulmonary vascular resistance is elevated before operation is a critical factor determining prognosis. If the pulmonary vascular resistance is one-third or less of the systemic value, progression of pulmonary vascular disease after operation is unusual; however, if a moderate to severe increase in pulmonary vascular resistance exists preoperatively, either no change or a progression of pulmonary vascular disease is common postoperatively. Pregnancy is contraindicated in Eisenmenger's syndrome. The mother's health is most at risk if she has a cardiovascular lesion associated with pulmonary vascular disease and pulmonary hypertension (e.g., Eisenmenger's physiology or mitral stenosis) or severe LV outflow tract obstruction (e.g., aortic stenosis), but she is also at risk of death with any malformation that may cause heart failure or a hemodynamically important arrhythmia. The fetus is most at risk with maternal cyanosis, heart failure, or pulmonary hypertension.

RV outflow tract obstruction develops in ~5–10% of patients who present in infancy with a moderate to large left-to-right shunt. With time, as subvalvular RV outflow tract obstruction progresses, the findings in these patients whose VSD remains sizable begin to resemble more closely those of the cyanotic tetralogy of Fallot. In ~5% of patients, aortic valve regurgitation results from insufficient cusp tissue or prolapse of the cusp through the interventricular defect; the aortic regurgitation then complicates and dominates the clinical course. Echocardiography with spectral and color Doppler examination defines the number and location of defects in the ventricular septum

and associated anomalies and the hemodynamic physiology of the defect(s). Hemodynamic and angiographic study may be occasionally required to assess the status of the pulmonary vascular bed and clarify details of the altered anatomy. Cross-sectional imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) are useful in delineating complex anatomy and assessing extra-cardiac structures.

TREATMENT VENTRICULAR SEPTAL DEFECT

Closure is not recommended for patients with normal pulmonary arterial pressures with small shunts (pulmonary-to-systemic flow ratios of <1.5:1). Operative correction or transcatheter closure is indicated when there is a moderate to large left-to-right shunt with a pulmonary-to-systemic flow ratio >1.5:1, in the absence of prohibitively high levels of pulmonary vascular resistance (pulmonary arterial resistance is less than two-thirds of systemic arterial resistance).

In patients with Eisenmenger's VSD, pulmonary arterial vasodilators and both single- or double-lung transplantation with intracardiac defect repair or heart/lung transplantation show promise for improvement in symptoms ([Chaps. 281 and 320e](#)). Chronic hypoxemia in cyanotic CHD results in secondary erythrocytosis due to increased erythropoietin production ([Chap. 49](#)). The term polycythemia is a misnomer; white cell counts are normal, and platelet counts are normal to decreased. Compensated erythrocytosis with iron-replete equilibrium hematocrits rarely results in symptoms of hyperviscosity at hematocrits <65% and occasionally not even with hematocrits ≥70%. For this reason, therapeutic phlebotomy is rarely required in compensated erythrocytosis. In contrast, patients with decompensated erythrocytosis fail to establish equilibrium with unstable, rising hematocrits and recurrent hyperviscosity symptoms. Therapeutic phlebotomy, a two-edged sword, allows temporary relief of symptoms but limits oxygen delivery, begets instability of the hematocrit, and compounds the problem by iron depletion. Iron-deficiency symptoms are usually indistinguishable from those of hyperviscosity; progressive symptoms after recurrent phlebotomy are usually due to iron depletion with hypochromic microcytosis. Iron depletion results in a larger number of smaller (microcytic) hypochromic red cells that are less capable of carrying oxygen and less deformable in the microcirculation; with more of them relative to plasma volume, viscosity is greater than for an equivalent hematocrit with fewer, larger, iron-replete, deformable cells. As such, iron-depleted erythrocytosis results in increasing symptoms due to decreased oxygen delivery to the tissues.

Hemostasis is abnormal in cyanotic CHD, due, in part, to the increased blood volume and engorged capillaries, abnormalities in platelet function, and sensitivity to aspirin or nonsteroidal anti-inflammatory agents, as well as abnormalities of the extrinsic and intrinsic coagulation system. Oral contraceptives are often contraindicated for cyanotic women because of the enhanced risk of vascular thrombosis. Symptoms of hyperviscosity can be produced in any cyanotic patient with erythrocytosis if dehydration reduces plasma volume. Phlebotomy for symptoms of hyperviscosity not due to dehydration or iron deficiency is a simple outpatient removal of 500 mL of blood over 45 min with isovolumetric replacement with isotonic saline. Acute phlebotomy without volume replacement is contraindicated. Iron repletion in decompensated iron-depleted erythrocytosis reduces iron-deficiency symptoms, but must be done gradually to avoid an excessive rise in hematocrit and resulting hyperviscosity.

PATENT DUCTUS ARTERIOSUS

The ductus arteriosus is a vessel leading from the bifurcation of the pulmonary artery to the aorta just distal to the left subclavian artery ([Fig. 282-1](#)). Normally, the vascular channel is open in the fetus but closes immediately after birth. The flow across the ductus is determined by the pressure and resistance relationships between the systemic and pulmonary circulations and by the cross-sectional area and length of the ductus. In most adults with this anomaly, pulmonary pressures are normal, and a gradient and shunt from aorta to pulmonary artery

persist throughout the cardiac cycle, resulting in a characteristic thrill and a continuous "machinery" murmur with late systolic accentuation at the upper left sternal edge. In adults who were born with a large left-to-right shunt through the ductus arteriosus, pulmonary vascular obstruction (Eisenmenger's syndrome) with pulmonary hypertension, right-to-left shunting, and cyanosis have usually developed. Severe pulmonary vascular disease results in reversal of flow through the ductus; unoxygenated blood is shunted to the descending aorta; and the toes—but not the fingers—become cyanotic and clubbed, a finding termed differential cyanosis ([Fig. 282-3](#)). The leading causes of death in adults with patent ductus arteriosus are cardiac failure and infective endocarditis; occasionally, severe pulmonary vascular obstruction may cause aneurysmal dilatation, calcification, and rupture of the ductus.

TREATMENT PATENT DUCTUS ARTERIOSUS

In the absence of severe pulmonary vascular disease and predominant left-to-right shunting of blood, the patent ductus should be surgically ligated or divided. Transcatheter closure has become common for appropriately shaped defects. Operation should be deferred for several months in patients treated successfully for infective endocarditis because the ductus may remain somewhat edematous and friable.

AORTIC ROOT-TO-RIGHT-HEART SHUNTS

The three most common causes of aortic root-to-right-heart shunts are congenital aneurysm of an aortic sinus of Valsalva with fistula, coronary arteriovenous fistula, and anomalous origin of the left coronary artery from the pulmonary trunk. Aneurysm of an aortic sinus of Valsalva consists of a separation or lack of fusion between the media of the aorta and the annulus of the aortic valve. Rupture usually occurs in the third or fourth decade of life; most often, the aortocardiac fistula is between the right coronary cusp and the RV; but occasionally, when the noncoronary cusp is involved, the fistula drains into the RA. Abrupt rupture causes chest pain, bounding pulses, a continuous murmur accentuated in diastole, and volume overload of the heart. Diagnosis is confirmed by two-dimensional and Doppler echocardiographic studies; cardiac catheterization quantitates the left-to-right shunt, and thoracic aortography visualizes the fistula. Medical management is directed at cardiac failure, arrhythmias, or endocarditis. At operation, the aneurysm is closed and amputated, and the aortic wall is reunited with the heart, either by direct suture or with a patch or prosthesis. Transcatheter device closure is a less invasive and effective alternative to surgery.

Coronary arteriovenous fistula, an unusual anomaly, consists of a communication between a coronary artery and another cardiac chamber, usually the coronary sinus, RA, or RV. The shunt is usually of small magnitude, and myocardial blood flow is not usually compromised; if the shunt is large, there may be a coronary "steal" syndrome with myocardial ischemia and possible angina or ventricular arrhythmias. Potential complications include infective endocarditis; thrombus formation with occlusion or distal embolization with myocardial infarction; rupture of an aneurysmal fistula; and, rarely, pulmonary hypertension and congestive failure. A loud, superficial, continuous murmur at the lower or midsternal border usually prompts a further evaluation of asymptomatic patients. Doppler echocardiography demonstrates the site of drainage; if the site of origin is proximal, it may be detectable by two-dimensional echocardiography. Angiography (classic catheterization, CT, or magnetic resonance angiography) permits identification of the size and anatomic features of the fistulous tract, which may be closed by suture or transcatheter obliteration.

The third anomaly causing a shunt from the aortic root to the right heart is anomalous origin of the left coronary artery from the pulmonary artery. In this condition, oxygenated blood from the aortic root flows via a dilated right coronary artery and collaterals to the left coronary artery and retrograde to the lower pressure pulmonary artery circulation via the anomalous left main coronary artery (which emerges from the pulmonary artery). Myocardial infarction and

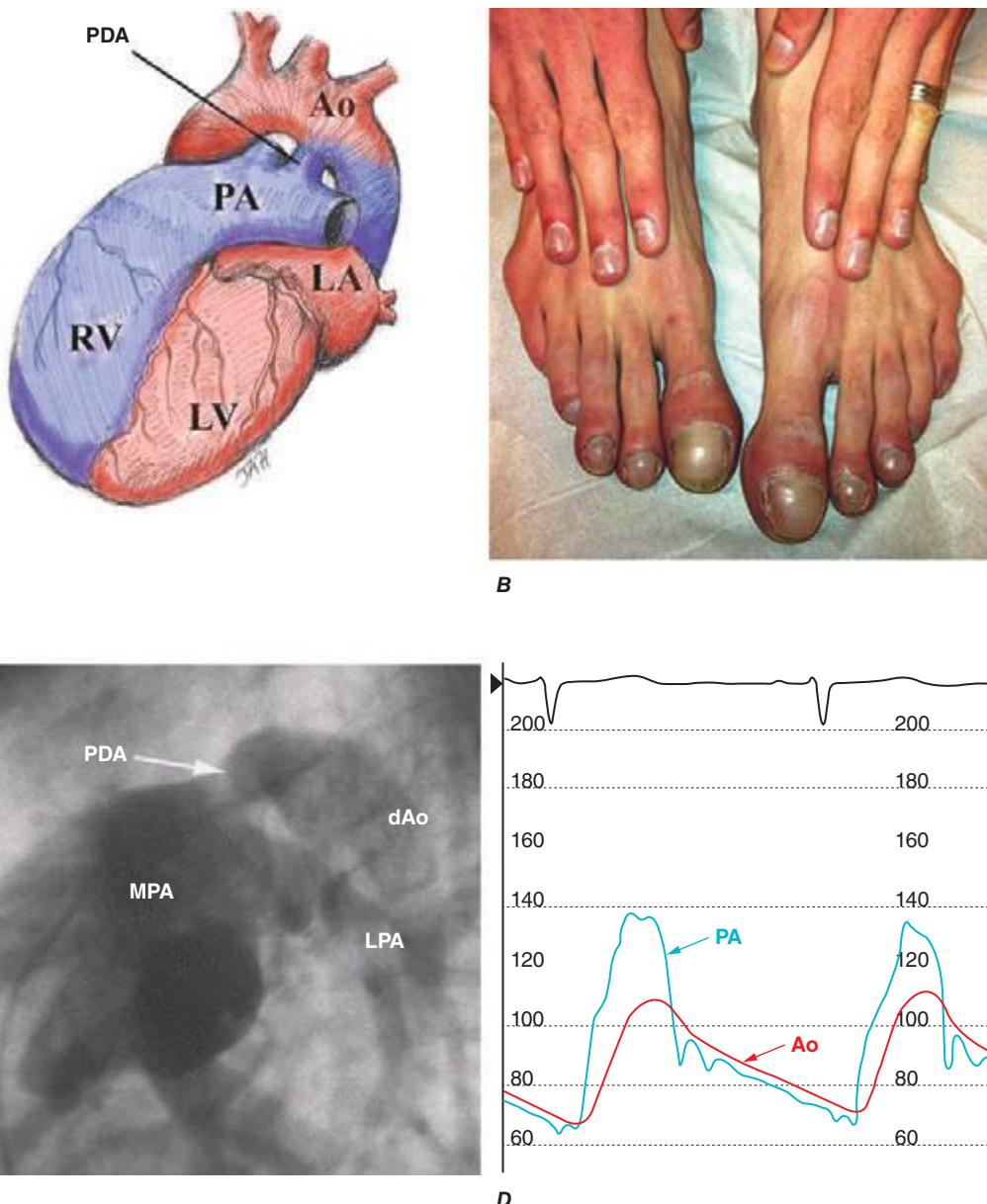


FIGURE 282-3 **A.** Patent ductus arteriosus (PDA) in a patient with severe pulmonary hypertension (Eisenmenger's syndrome). Due to the suprasystemic pulmonary arterial resistance, deoxygenated (cyanotic) blood from the right ventricle (RV) and pulmonary artery (PA) is shunted across the PDA to the aorta (Ao). The left atrium (LA) and left ventricle (LV) are labeled. **B.** Differential clubbing and cyanosis of the toes due to lower extremity perfusion by the deoxygenated blood crossing the PDA. **C.** Angiogram in a dilated main pulmonary artery (MPA) with shunting noted across the PDA to the descending aorta (dAo). The left pulmonary artery (LPA) is labeled. **D.** Direct pressure recordings in the Ao and PA demonstrating suprasystemic PA systolic pressure.

fibrosis commonly lead to death within the first year, although up to 20% of patients survive to adolescence and beyond without surgical correction. The diagnosis is supported by the ECG findings of an anterolateral myocardial infarction and left ventricular hypertrophy (LVH). Operative management of adults consists of coronary artery reimplantation, coronary artery bypass with an internal mammary artery graft, or saphenous vein–coronary artery graft.

CONGENITAL AORTIC STENOSIS

Malformations that cause obstruction to LV outflow include congenital valvular aortic stenosis, discrete subaortic stenosis, or supravalvular aortic stenosis. Bicuspid aortic valves are more common in males than in females. The congenital bicuspid aortic valve, which may initially be functionally normal, is one of the most common congenital malformations of the heart and may go undetected in early life. Because bicuspid valves may develop stenosis or regurgitation with time or be the site of infective endocarditis, the lesion may be difficult to distinguish in older adults from acquired rheumatic or degenerative calcific aortic

valve disease. The dynamics of blood flow associated with a congenitally deformed, rigid aortic valve commonly lead to thickening of the cusps and, in later life, to calcification. Hemodynamically significant obstruction causes concentric hypertrophy of the LV wall. The ascending aorta is often dilated, misnamed “poststenotic” dilatation; this is due to histologic abnormalities of the aortic media and may result in aortic dissection. Diagnosis is made by echocardiography, which reveals the morphology of the aortic valve and aortic root and quantitates severity of stenosis or regurgitation. [The clinical manifestations and hemodynamic abnormalities are discussed in Chap. 283.](#)

TREATMENT VALVULAR AORTIC STENOSIS

In patients with diminished cardiac reserve, medical management includes the administration of digoxin and diuretics and sodium restriction while awaiting operation. A dilated aortic root may require beta blockers, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors. Aortic valve replacement is

indicated in adults with critical obstruction, i.e., with an aortic valve area $<0.45 \text{ cm}^2/\text{m}^2$, with symptoms secondary to LV dysfunction or myocardial ischemia, or with hemodynamic evidence of LV dysfunction. In asymptomatic children or adolescents or young adults with critical aortic stenosis without valvular calcification or these features, aortic balloon valvuloplasty is often useful (Chap. 296e). If surgery is contraindicated in older patients because of a complicating medical problem such as malignancy or renal or hepatic failure, balloon valvuloplasty may provide short-term improvement. This procedure may serve as a bridge to aortic valve replacement in patients with severe heart failure. Transcatheter aortic valve replacement is a potential alternative to surgery.

SUBAORTIC STENOSIS The discrete form of subaortic stenosis consists of a membranous diaphragm or fibromuscular ring encircling the LV outflow tract just beneath the base of the aortic valve. The jet impact from the subaortic stenotic jet on the underside of the aortic valve often begets progressive aortic valve fibrosis and valvular regurgitation. Echocardiography demonstrates the anatomy of the subaortic obstruction; Doppler studies show turbulence proximal to the aortic valve and can quantitate the pressure gradient and severity of aortic regurgitation. Treatment consists of complete excision of the membrane or fibromuscular ring.

SUPRAVALVULAR AORTIC STENOSIS This is a localized or diffuse narrowing of the ascending aorta originating just above the level of the coronary arteries at the superior margin of the sinuses of Valsalva. In contrast to other forms of aortic stenosis, the coronary arteries are subjected to elevated systolic pressures from the LV, are often dilated and tortuous, and are susceptible to premature atherosclerosis. The coronary ostia may also become obstructed by the aortic valve leaflets. In most patients, a genetic defect for the anomaly is located in the same chromosomal region as elastin on chromosome 7. Supravalvular aortic stenosis is the most commonly associated cardiac defect in Williams-Beuren syndrome, typically comprising the following: “elfin” facies, low nasal bridge, cheerful demeanor, mental retardation with retained language skills and love of music, supravalvular aortic stenosis, and transient hypercalcemia.

COARCTATION OF THE AORTA

Narrowing or constriction of the lumen of the aorta may occur anywhere along its length but is most common distal to the origin of the left subclavian artery near the insertion of the ligamentum arteriosum. Coarctation occurs in ~7% of patients with CHD, is more common in males than females, and is particularly frequent in patients with gonadal dysgenesis (e.g., Turner’s syndrome). Clinical manifestations depend on the site and extent of obstruction and the presence of associated cardiac anomalies, most commonly a bicuspid aortic valve. Circle of Willis aneurysms may occur in up to 10%.

Most children and young adults with isolated, discrete coarctation are asymptomatic. Headache, epistaxis, chest pressure, and claudication with exercise may occur, and attention is usually directed to the cardiovascular system when a heart murmur or hypertension in the upper extremities and absence, marked diminution, or delayed pulsations in the femoral arteries are detected on physical examination. Enlarged and pulsatile collateral vessels may be palpated in the intercostal spaces anteriorly, in the axillae, or posteriorly in the interscapular area. The upper extremities and thorax may be more developed than the lower extremities. A midsystolic murmur over the left interscapular space may become continuous if the lumen is narrowed sufficiently to result in a high-velocity jet across the lesion throughout the cardiac cycle. Additional systolic and continuous murmurs over the lateral thoracic wall may reflect increased flow through dilated and tortuous collateral vessels. The ECG usually reveals LV hypertrophy. Chest x-ray may show a dilated left subclavian artery high on the left mediastinal border and a dilated ascending aorta. Indentation of the aorta at the site of coarctation and pre- and poststenotic dilatation (the “3” sign) along the left paramediastinal shadow are essentially pathognomonic. Notching of the third to ninth ribs, an important radiographic sign, is due to inferior rib erosion by dilated collateral vessels.

Two-dimensional echocardiography from suprasternal windows identifies the site of coarctation; Doppler quantitates the pressure gradient. Transesophageal echocardiography and MRI or CT allow visualization of the length and severity of the obstruction and associated collateral arteries. In adults, cardiac catheterization is indicated primarily to evaluate the coronary arteries or to perform catheter-based intervention (angioplasty and stent of the coarctation).

The chief hazards of proximal aortic severe hypertension include cerebral aneurysms and hemorrhage, aortic dissection and rupture, premature coronary arteriosclerosis, aortic valve failure, and LV failure; infective endarteritis may occur on the coarctation site or endocarditis may settle on an associated bicuspid aortic valve, which is estimated to be present in 50% of patients.

TREATMENT

COARCTATION OF THE AORTA

Treatment is surgical or involves percutaneous catheter balloon dilatation with stent placement; the details of selection of therapy are beyond this review; however, the use of transcatheter treatment techniques has increased dramatically, and many previously “surgical” cases are treated via percutaneous or hybrid techniques. Late postoperative systemic hypertension in the absence of residual coarctation is related partly to the duration of preoperative hypertension. Follow-up of rest and exercise blood pressures is important; many have systolic hypertension only during exercise, in part due to a diffuse vasculopathy and to noncompliance of the stented or surgically reconstructed region. All operated or stented coarctation patients deserve a high-quality MRI or CT procedure in follow-up.

PULMONARY STENOSIS WITH INTACT VENTRICULAR SEPTUM

Obstruction to RV outflow may be localized to the supravalvular, valvular, or subvalvular levels or occur at a combination of these sites. Multiple sites of narrowing of the peripheral pulmonary arteries are a feature of rubella embryopathy and may occur with both the familial and sporadic forms of supravalvular aortic stenosis. Valvular pulmonic stenosis (PS) is the most common form of isolated RV obstruction.

The severity of the obstructing lesion, rather than the site of narrowing, is the most important determinant of the clinical course. In the presence of a normal cardiac output, a peak systolic pressure gradient $<30 \text{ mmHg}$ indicates mild PS and $>50 \text{ mmHg}$ indicates severe PS; pressures between these limits are considered to indicate moderate stenosis. Patients with mild PS are generally asymptomatic and demonstrate little or no progression in the severity of obstruction with age. In patients with more significant stenosis, the severity may increase with time. Symptoms vary with the degree of obstruction. Fatigue, dyspnea, RV failure, and syncope may limit the activity of older patients, in whom moderate or severe obstruction may prevent an augmentation of cardiac output with exercise. In patients with severe obstruction, the systolic pressure in the RV may exceed that in the LV, because the ventricular septum is intact. RV ejection is prolonged with moderate or severe stenosis, and the sound of pulmonary valve closure is delayed and soft. RV hypertrophy reduces the compliance of that chamber, and a forceful RA contraction is necessary to augment RV filling. A fourth heart sound; prominent a waves in the jugular venous pulse; and, occasionally, presystolic pulsations of the liver reflect vigorous atrial contraction. The clinical diagnosis is supported by a left parasternal lift and harsh systolic crescendo-decrescendo murmur and thrill at the upper left sternal border, typically preceded by a systolic ejection sound if the obstruction is due to a mobile nondysplastic pulmonary valve. The holosystolic murmur of tricuspid regurgitation may accompany severe PS, especially in the presence of congestive heart failure. Cyanosis usually reflects right-to-left shunting through a patent foramen ovale or ASD. In patients with supravalvular or peripheral pulmonary arterial stenosis, the murmur is systolic or continuous and is best heard over the area of narrowing, with radiation to the peripheral lung fields.

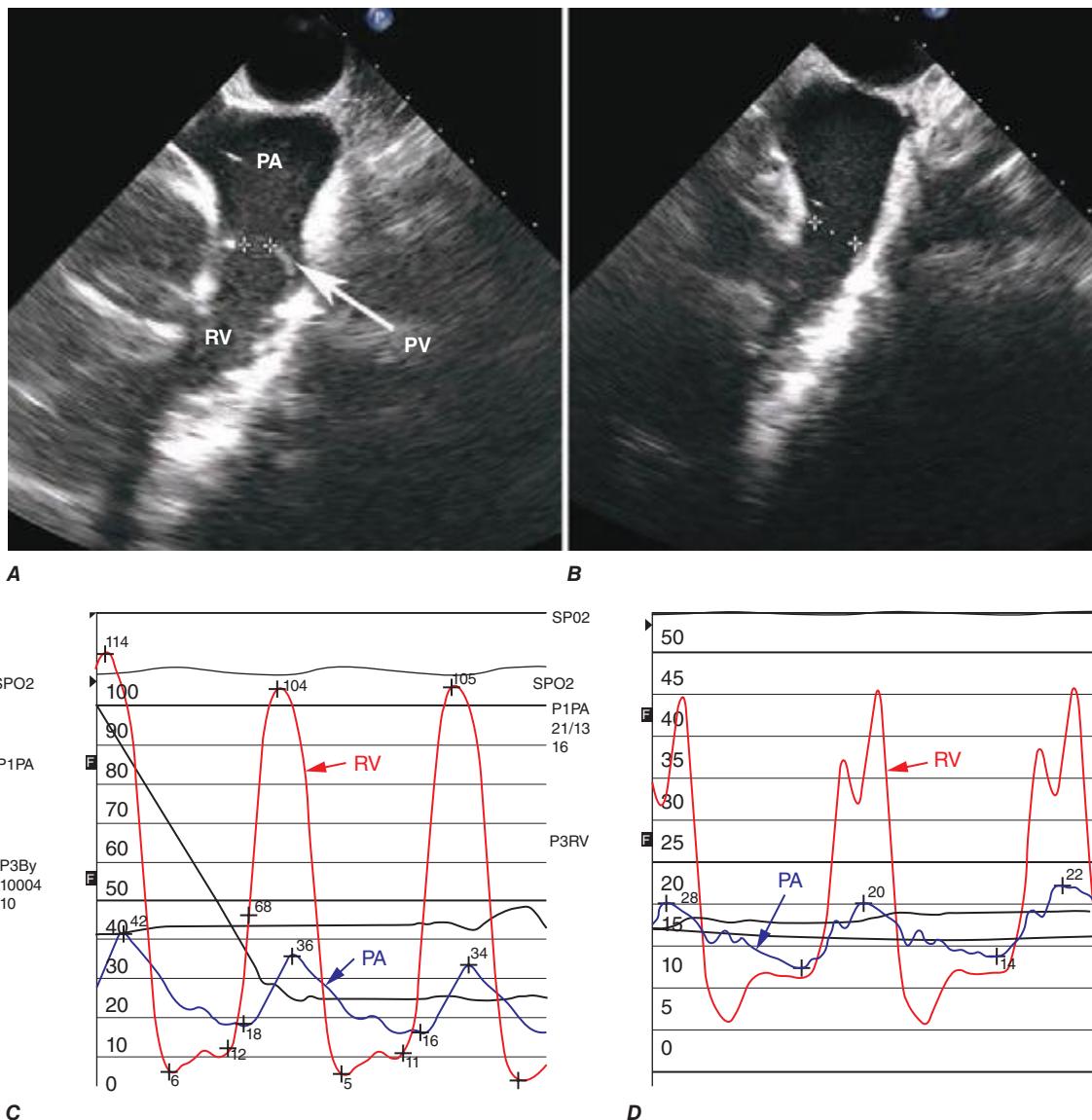


FIGURE 282-4 **A.** Transesophageal echocardiogram of a patient with severe pulmonary stenosis due to a mobile and doming pulmonary valve (PV). The pulmonary artery (PA) and the right ventricle (RV) are labeled. **B.** Following balloon valvuloplasty, the pulmonary valve orifice is larger. **C.** Simultaneous RV and PA pressure tracings before balloon valvuloplasty; the peak-to-peak gradient across the pulmonary valve is ~70 mmHg. **D.** After balloon valvuloplasty, the peak-to-peak gradient is reduced to ~25 mmHg.

In mild cases, the ECG is normal, whereas moderate and severe stenoses are associated with RV hypertrophy. The chest x-ray with mild or moderate PS shows a heart of normal size with normal lung vascularity. In pulmonary valvular stenosis, dilatation of the main and left pulmonary arteries occurs in part due to the direction of the PS jet and in part due to intrinsic tissue weakness. With severe obstruction, RV hypertrophy is generally evident. The pulmonary vascularity may be reduced with severe stenosis, RV failure, and/or a right-to-left shunt at the atrial level. Two- and three-dimensional echocardiography visualizes pulmonary valve morphology; the outflow tract pressure gradient is quantitated by Doppler echocardiography (Fig. 282-4).

TREATMENT PULMONARY STENOSIS

The cardiac catheter technique of balloon valvuloplasty (Chap. 272) is usually effective, and the surgery is rarely necessary. Multiple stenoses of the peripheral pulmonary arteries are effectively treated with transcatheter angioplasty or stenting.

TETRALOGY OF FALLOT

The four components of the tetralogy of Fallot are malaligned VSD, obstruction to RV outflow, aortic override of the VSD, and RV hypertrophy due to the RV's response to aortic pressure via the large VSD.

The severity of RV outflow obstruction determines the clinical presentation. The severity of hypoplasia of the RV outflow tract varies from mild to complete (pulmonary atresia). Pulmonary valve stenosis and supravalvular and peripheral pulmonary arterial obstruction may coexist; rarely, there is unilateral absence of a pulmonary artery (usually the left). A right-sided aortic arch and descending thoracic aorta occur in ~25%.

The relationship between the resistance of blood flow from the ventricles into the aorta and into the pulmonary artery plays a major role in determining the hemodynamic and clinical picture. When the RV outflow obstruction is severe, pulmonary blood flow is reduced markedly, and a large volume of desaturated systemic venous blood shunts right-to-left across the VSD. Severe cyanosis and erythrocytosis occur, and symptoms of systemic hypoxemia are prominent. In many infants and children, the obstruction is mild but progressive.

The ECG shows RV hypertrophy. Chest x-ray shows a normal-sized, boot-shaped heart (*coeur en sabot*) with a prominent RV and a concavity in the region of the pulmonary conus. Pulmonary vascular markings are typically diminished, and the aortic arch and knob may be on the right side. Echocardiography demonstrates the malaligned VSD with the overriding aorta and the site and severity of PS, which may be subpulmonic (fixed or dynamic), at the pulmonary valve or in the main or branch pulmonary arteries. Classic contrast angiography may provide details regarding the RV outflow tract, pulmonary valve and annulus, and caliber of the main branches of the pulmonary artery, as well as about possible associated aortopulmonary collaterals. Coronary arteriography identifies the anatomy and course of the coronary arteries, which may be anomalous. Cardiac MRI and CT complement echocardiography and provide much of the information gathered by angiography as well as additional functional information. MRI is considered the clinical gold standard for quantification of RV volume and function as well as quantification of the pulmonary regurgitation severity.

TREATMENT TETRALOGY OF FALLOT

For a variety of reasons, only a few adults with tetralogy of Fallot have not had some form of previous surgical intervention. Reoperation in adults is most commonly for severe pulmonary regurgitation or pulmonary stenosis. Long-term concerns about ventricular function persist. Ventricular and atrial arrhythmias occur, respectively, in 15% and 25% of adults and may require medical treatment, electrophysiologic study and ablation, defibrillator placement, or transcatheter or surgical intervention, usually including pulmonary valve replacement. Transcatheter pulmonary valve replacement is widely used in patients meeting anatomic criteria. The aortic root has a medial tissue defect; it is commonly enlarged and associated with aortic regurgitation. Endocarditis remains a risk despite surgical repair.

COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

This condition is commonly called *dextro-* or *D-transposition of the great arteries*. The aorta arises rightward anteriorly from the RV, and the pulmonary artery emerges leftward and posteriorly from the LV, which results in two separate parallel circulations; some communication between them must exist after birth to sustain life. Most patients have an interatrial communication, two-thirds have a patent ductus arteriosus, and about one-third have an associated VSD. Transposition is more common in males and accounts for ~10% of cyanotic heart disease. The course is determined by the degree of tissue hypoxemia, the ability of each ventricle to sustain an increased workload in the presence of reduced coronary arterial oxygenation, the nature of the associated cardiovascular anomalies, and the status of the pulmonary vascular bed. Patients who do not undergo surgical palliation generally do not survive to reach adulthood. The long-term outcomes in those that have undergone surgery are in large part determined by the type of surgery performed. By the third decade of life, ~30% of patients with “atrial switch” operations will have developed decreased RV function and progressive tricuspid regurgitation, which may lead to congestive heart failure. Pulmonary vascular obstruction develops by 1–2 years of age in patients with an associated large VSD or large patent ductus arteriosus in the absence of obstruction to LV outflow.

TREATMENT TRANSPOSITION OF THE GREAT ARTERIES

The balloon or blade catheter or surgical creation or enlargement of an interatrial communication in the neonate is the simplest procedure for providing increased intracardiac mixing of systemic and pulmonary venous blood. Systemic pulmonary artery anastomosis may be indicated in the patient with severe obstruction to LV outflow and diminished pulmonary blood flow. Intracardiac repair may be accomplished by rearranging the venous returns

(intraatrial switch, i.e., Mustard or Senning operation) so that the systemic venous blood is directed to the mitral valve and, thence, to the LV and pulmonary artery, while the pulmonary venous blood is diverted through the tricuspid valve and RV to the aorta. The late survival after these repairs is good, but arrhythmias (e.g., atrial flutter) or conduction defects (e.g., sick sinus syndrome) occur in ~50% of such patients by 30 years after the intraatrial switch surgery. Progressive dysfunction of the systemic subaortic RV, tricuspid regurgitation, ventricular arrhythmias, cardiac arrest, and late sudden death are worrisome features. Preferably, this malformation is corrected in infancy by transposing both coronary arteries to the posterior artery and transecting, contraposing, and anastomosing the aorta and pulmonary arteries (arterial-switch operation). For patients with a VSD in whom it is necessary to bypass a severely obstructed LV outflow tract, corrective operation employs an intracardiac ventricular baffle and extracardiac prosthetic conduit to replace the pulmonary artery (Rastelli procedure).

SINGLE VENTRICLE

This is a family of complex lesions with both atrioventricular valves or a common atrioventricular valve opening to a single ventricular chamber. Associated anomalies include abnormal great artery positional relationships, pulmonic valvular or subvalvular stenosis, and subaortic stenosis. Survival to adulthood depends on a relatively normal pulmonary blood flow, yet normal pulmonary resistance and good ventricular function. Modifications of the Fontan approach are generally applied to carefully selected patients with creation of a pathway(s) from the systemic veins to the pulmonary arteries.

TRICUSPID ATRESIA

This malformation is characterized by atresia of the tricuspid valve; an interatrial communication; and, frequently, hypoplasia of the RV and pulmonary artery. The clinical picture is usually dominated by severe cyanosis due to obligatory admixture of systemic and pulmonary venous blood in the LV. The ECG characteristically shows RA enlargement, left-axis deviation, and LV hypertrophy.

Atrial septostomy and palliative operations to increase pulmonary blood flow, often by anastomosis of a systemic artery or vein to a pulmonary artery, may allow survival to the second or third decade. A Fontan atrio pulmonary or total cavopulmonary connection may then allow functional correction in patients with normal or low pulmonary arterial resistance pressure and good LV function. There are a number of important long-term considerations with the Fontan circulation, including the development of arrhythmias, progressive liver dysfunction, thromboembolic complications, and potential long-term need for heart or heart and liver transplantation.

EBSTEIN'S ANOMALY

Characterized by a downward displacement of the tricuspid valve into the RV, due to anomalous attachment of the tricuspid leaflets, the Ebstein tricuspid valve tissue is dysplastic and results in tricuspid regurgitation. The abnormally situated tricuspid orifice produces an “atrialized” portion of the RV lying between the atrioventricular ring and the origin of the valve, which is continuous with the RA chamber. Often, the RV is hypoplastic. Although the clinical manifestations are variable, some patients come to initial attention because of either (1) progressive cyanosis from right-to-left atrial shunting, (2) symptoms due to tricuspid regurgitation and RV dysfunction, or (3) paroxysmal atrial tachyarrhythmias with or without atrioventricular bypass tracts (Wolff-Parkinson-White [WPW] syndrome). Diagnostic findings by two-dimensional echocardiography include the abnormal positional relation between the tricuspid and mitral valves with abnormally increased apical displacement of the septal tricuspid leaflet. Tricuspid regurgitation is quantitated by Doppler examination. Surgical approaches include prosthetic replacement of the tricuspid valve when the leaflets are tethered or repair of the native valve.

The two fundamental anatomic abnormalities in this malformation are transposition of the ascending aorta and pulmonary trunk and inversion of the ventricles. This arrangement results in desaturated systemic venous blood passing from the RA through the mitral valve to the LV and into the pulmonary trunk, whereas oxygenated pulmonary venous blood flows from the left atrium through the tricuspid valve to the RV and into the aorta. Thus, the circulation is corrected functionally. The clinical presentation, course, and prognosis of patients with congenitally corrected transposition vary depending on the nature and severity of any complicating intracardiac anomalies and of development of dysfunction of the systemic subaortic RV. Progressive RV dysfunction and tricuspid regurgitation may also develop in one-third of patients by age 30; Ebstein-type anomalies of the left-side tricuspid atrioventricular valve are common. VSD or PS due to obstruction to outflow from the right-sided subpulmonary (anatomic left) ventricle may coexist. Complete heart block occurs at a rate of 2–10% per decade. The diagnosis of the malformation and associated lesions can be established by comprehensive two-dimensional echocardiography and Doppler examination.

MALPOSITIONS OF THE HEART

Positional anomalies refer to conditions in which the cardiac apex is in the right side of the chest (*dextrocardia*) or at the midline (*mesocardia*), or in which there is a normal location of the heart in the left side of the chest but abnormal position of the viscera (*isolated levocardia*). Knowledge of the position of the abdominal organs and of the branching pattern of the main stem bronchi is important in categorizing these malpositions. When dextrocardia occurs without situs inversus, when the visceral situs is indeterminate, or if isolated levocardia is present, associated, often complex, multiple cardiac anomalies are usually present. In contrast, mirror-image dextrocardia is usually observed with complete situs inversus, which occurs most frequently in individuals whose hearts are otherwise normal.

SURGICALLY MODIFIED CONGENITAL HEART DISEASE

Owing to the enormous strides in cardiovascular surgical techniques that have occurred in the past 70 years, a large number of long-term survivors of palliative or corrective operations in infancy and childhood have reached adulthood. These patients are often challenging because of the diversity of anatomic, hemodynamic, and electrophysiologic residua and sequelae of cardiac operations.

The proper care of the survivor of an operation for CHD requires that the clinician understand the details of the malformation before operation; pay meticulous attention to the details of the operative procedure; and recognize the postoperative residua (conditions left totally or partially uncorrected), the sequelae (conditions caused by surgery), and the complications that may have resulted from the operation. Except for ligation of an uncomplicated patent ductus arteriosus, almost every other surgical repair leaves behind or causes some abnormality of the heart and circulation that may range from trivial to serious. Thus, even with results that are considered clinically to be good to excellent, continued long-term postoperative follow-up is advisable.

Cardiac operations involving the atria, such as closure of ASD, repair of total or partial anomalous pulmonary venous return, or venous switch corrections of complete transposition of the great arteries (the Mustard or Senning operations), may be followed years later by sinus node or atrioventricular node dysfunction and/or by atrial arrhythmias (especially atrial flutter). Intraventricular surgery may also result in electrophysiologic consequences, including complete heart block necessitating pacemaker insertion to avoid sudden death. Valvular problems may arise late after initial cardiac operation. An example is the progressive stenosis of an initially nonobstructive bicuspid aortic valve in the patient who underwent aortic coarctation repair. Such aortic valves may also be the site of infective endocarditis. After repair of the ostium primum ASD, the cleft mitral valve may become progressively regurgitant. Tricuspid regurgitation may also be progressive in the postoperative patient with tetralogy of Fallot

if RV outflow tract obstruction was not relieved adequately at initial surgery. In many patients with surgically modified CHD, inadequate relief of an obstructive lesion, a residual regurgitant lesion, or a residual shunt will cause or hasten the onset of clinical signs and symptoms of myocardial dysfunction. Despite a good hemodynamic repair, many patients with a subaortic RV develop RV decompensation and signs of left heart failure. In many patients, particularly those who were cyanotic for many years before operation, a preexisting compromise in ventricular performance is due to the original underlying malformation.

A final category of postoperative problems involves the use of prosthetic valves, patches, or conduits in the operative repair. The special risks include infective endocarditis, thrombus formation, and premature degeneration and calcification of the prosthetic materials. There are many patients in whom extracardiac conduits are required to correct the circulation functionally and often to carry blood to the lungs from the RA or RV. These conduits may develop intraluminal obstruction, and if they include a prosthetic valve, it may show progressive calcification and thickening. Many such patients face reintervention (interventional cardiac catheterization or surgical reoperation) one or more times in their lives. Such care should be directed to centers specializing in adults with complex congenital cardiovascular malformations. The effect of pregnancy in postoperative patients depends on the outcome of the repair, including the presence and severity of residua, sequelae, or complications. Contraception is an important topic with such patients. Tubal ligation should be considered in those in whom pregnancy is strictly contraindicated.

Endocarditis Prophylaxis Two major predisposing causes of infective endocarditis are a susceptible cardiovascular substrate and a source of bacteremia. The clinical and bacteriologic profile of infective endocarditis in patients with CHD has changed with the advent of intracardiac surgery and of prosthetic devices. Prophylaxis includes both antimicrobial and hygienic measures. Meticulous dental and skin care are required. Routine antimicrobial prophylaxis is recommended for bacteremic dental procedures or instrumentation through an infected site in most patients with operated CHD, particularly if foreign material, such as a prosthetic valve, conduit, or surgically constructed shunt, is in place. In the case of patches, in the absence of a high-pressure patch leak, or transcatheter devices, prophylaxis is usually recommended for 6 months until there is endothelialization. Individuals with unrepaired cyanotic heart disease are also generally recommended to receive prophylaxis (Chap. 155).

283 Aortic Valve Disease

Patrick T. O'Gara, Joseph Loscalzo

GLOBAL BURDEN OF VALVULAR HEART DISEASE

 Primary valvular heart disease ranks well below coronary heart disease, stroke, hypertension, obesity, and diabetes as a major threat to the public health. Nevertheless, it is the source of significant morbidity and mortality rates. Rheumatic fever (Chap. 381) is the dominant cause of valvular heart disease in developing and low-income countries. Its prevalence has been estimated to range from as low as 1 per 100,000 school-age children in Costa Rica to as high as 150 per 100,000 in China. Rheumatic heart disease accounts for 12–65% of hospital admissions related to cardiovascular disease and 2–10% of hospital discharges in some developing countries. Prevalence and mortality rates vary among communities even within the same country as a function of overcrowding and the availability of medical resources and population-wide programs for detection and treatment of group A streptococcal pharyngitis. In economically deprived areas, tropical and subtropical climates (particularly on the Indian subcontinent), Central

America, and the Middle East, rheumatic valvular disease progresses more rapidly than in more-developed nations and frequently causes serious symptoms in patients younger than 20 years of age. This accelerated natural history may be due to repeated infections with more virulent strains of rheumatogenic streptococci. Approximately 15 million to 20 million people live with rheumatic heart disease worldwide, an estimated prevalence characterized by 300,000 new cases and 233,000 case fatalities per year, with the highest mortality rates reported from Southeast Asia (~7.6 per 100,000).

Although there have been recent reports of isolated outbreaks of streptococcal infection in North America, valve disease in high-income countries is dominated by degenerative or inflammatory processes that lead to valve thickening, calcification, and dysfunction. The prevalence of valvular heart disease increases with age for both men and women. Important left-sided valve disease may affect as many as 12–13% of adults older than the age of 75. In the United States, there were 85,000 hospital discharges with valvular heart disease in 2010, and the vast majority of these were related to surgical procedures for heart valve disease (mostly involving the aortic and mitral valves).

The incidence of infective endocarditis ([Chap. 155](#)) has increased with the aging of the population, the more widespread prevalence of vascular grafts and intracardiac devices, the emergence of more virulent multidrug-resistant microorganisms, and the growing epidemic of diabetes. The more restricted use of antibiotic prophylaxis since 2007 has thus far not been associated with an increase in incidence rates. Infective endocarditis has become a relatively more frequent cause of acute valvular regurgitation.

Bicuspid aortic valve disease affects as many as 0.5–1.4% of the general population, with an associated incidence of aortopathy involving root or ascending aortic aneurysm disease or coarctation. An increasing number of childhood survivors of congenital heart disease present later in life with valvular dysfunction. The global burden of valvular heart disease is expected to progress.

As is true for many other chronic health conditions, disparities in access to and quality of care for patients with valvular heart disease have been well documented. Management decisions and outcome differences based on age, gender, race, and geography require educational efforts across all levels of providers.

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in [Chaps. 51e and 267](#); of electrocardiography (ECG) in [Chap. 268](#); of echocardiography and other noninvasive imaging techniques in [Chap. 270e](#); and of cardiac catheterization and angiography in [Chap. 272](#).

AORTIC STENOSIS

Aortic stenosis (AS) occurs in about one-fourth of all patients with chronic valvular heart disease; approximately 80% of adult patients with symptomatic, valvular AS are male.

ETIOLOGY AND PATHOGENESIS

([Table 283-1](#)) AS in adults is due to degenerative calcification of the aortic cusps and occurs most commonly on a substrate of congenital disease (bicuspid aortic valve), chronic (trileaflet) deterioration, or previous rheumatic inflammation. A pathologic study of specimens removed at the time of aortic valve replacement for AS showed that 53% were bicuspid and 4% unicuspid. The process of aortic valve deterioration and calcification is not a passive one, but rather one that shares many features with vascular atherosclerosis, including endothelial dysfunction, lipid accumulation, inflammatory cell activation, cytokine release, and upregulation of several signaling pathways ([Fig. 283-1](#)). Eventually, valvular myofibroblasts differentiate phenotypically into osteoblasts and actively produce bone matrix proteins that allow for the deposition of calcium hydroxyapatite crystals. Genetic polymorphisms involving the vitamin D receptor, the estrogen receptor in postmenopausal women, interleukin 10, and apolipoprotein E4 have been linked to the development of calcific AS, and a strong familial clustering of cases has been reported from western France. Several traditional atherosclerotic risk factors have also been associated with the development and progression of calcific

TABLE 283-1 MAJOR CAUSES OF AORTIC VALVE DISEASE

Valve Lesion	Etiologies
Aortic stenosis	Congenital (bicuspid, unicuspid) Degenerative calcific Rheumatic fever Radiation
Aortic regurgitation	Valvular Congenital (bicuspid) Endocarditis Rheumatic fever Myxomatous (prolapse) Traumatic Syphilis Ankylosing spondylitis Root disease Aortic dissection Cystic medial degeneration Marfan's syndrome Bicuspid aortic valve Nonsyndromic familial aneurysm Aortitis Hypertension

AS, including low-density lipoprotein (LDL) cholesterol, lipoprotein a (Lp[a]), diabetes mellitus, smoking, chronic kidney disease, and the metabolic syndrome. The presence of aortic valve sclerosis (focal thickening and calcification of the leaflets not severe enough to cause obstruction) is associated with an excess risk of cardiovascular death and myocardial infarction (MI) among persons older than age 65. Approximately 30% of persons older than 65 years exhibit aortic valve sclerosis, whereas 2% exhibit frank stenosis.

Rheumatic disease of the aortic leaflets produces commissural fusion, sometimes resulting in a bicuspid-appearing valve. This condition, in turn, makes the leaflets more susceptible to trauma and ultimately leads to fibrosis, calcification, and further narrowing. By the time the obstruction to left ventricular (LV) outflow causes serious clinical disability, the valve is usually a rigid calcified mass, and careful examination may make it difficult or even impossible to determine the etiology of the underlying process. Rheumatic AS is almost always associated with involvement of the mitral valve and with aortic regurgitation. Mediastinal radiation can also result in late scarring, fibrosis, and calcification of the leaflets with AS.

BICUSPID AORTIC VALVE DISEASE

A bicuspid aortic valve (BAV) is the most common congenital heart valve defect and occurs in 0.5–1.4% of the population with a 2–4:1 male-to-female predominance. The inheritance pattern appears to be autosomal dominant with incomplete penetrance, although some have questioned an X-linked component as suggested by the prevalence of BAV disease among patients with Turner's syndrome. The prevalence of BAV disease among first-degree relatives of an affected individual is approximately 10%. A single gene defect to explain the majority of cases has not been identified, although a mutation in the *NOTCH1* gene has been described in some families. Abnormalities in endothelial nitric oxide synthase and *NKX2.5* have been implicated as well. Medial degeneration with ascending aortic aneurysm formation occurs commonly among patients with BAV disease; aortic coarctation is less frequently encountered. Patients with BAV disease have larger aortas than patients with comparable tricuspid aortic valve disease. The aortopathy develops independent of the hemodynamic severity of the valve lesion and is a risk factor for aneurysm formation and/or dissection. A BAV can be a component of more complex congenital heart disease with or without other left heart obstructing lesions, as seen in Shone's complex.

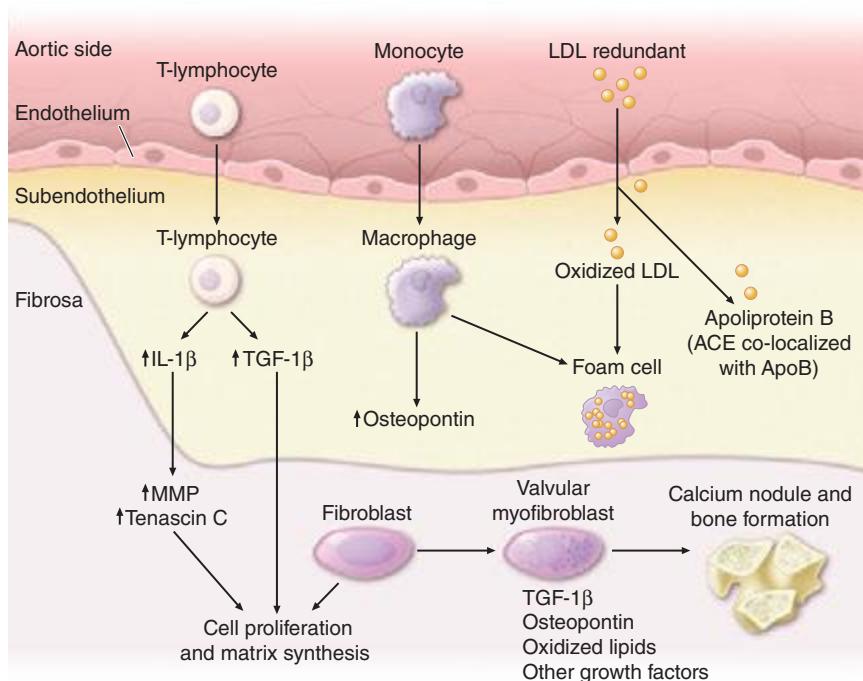


FIGURE 283-1 Pathogenesis of calcific aortic stenosis. Inflammatory cells infiltrate across the endothelial barrier and release cytokines that act on fibroblasts to promote cellular proliferation and matrix remodeling. LDL is oxidatively modified and taken up by macrophage scavengers to become foam cells. Angiotensin-converting enzyme colocalizes with ApoB. A subset of myofibroblasts differentiates into an osteoblast phenotype capable of promoting bone formation. ACE, angiotensin-converting enzyme; ApoB, apolipoprotein B; LDL, low-density lipoprotein; IL, interleukin; MMP, matrix metalloproteinase; TGF, transforming growth factor. (From RV Freeman, CM Otto: Circulation 111:3316, 2005; with permission.)

OTHER FORMS OF OBSTRUCTION TO LEFT VENTRICULAR OUTFLOW

In addition to valvular AS, three other lesions may be responsible for obstruction to LV outflow: *hypertrophic obstructive cardiomyopathy* (Chap. 287), *discrete fibromuscular/membranous subaortic stenosis*, and *supravalvular AS* (Chap. 282). The causes of LV outflow obstruction can be differentiated on the basis of the cardiac examination and Doppler echocardiographic findings.

PATOPHYSIOLOGY

The obstruction to LV outflow produces a systolic pressure gradient between the LV and aorta. When severe obstruction is suddenly produced experimentally, the LV responds by dilation and reduction of stroke volume. However, in some patients, the obstruction may be present at birth and/or increase gradually over the course of many years, and LV contractile performance is maintained by the presence of concentric LV hypertrophy. Initially, this serves as an adaptive mechanism because it reduces toward normal the systolic stress developed by the myocardium, as predicted by the Laplace relation ($S = Pr/h$, where S = systolic wall stress, P = pressure, r = radius, and h = wall thickness). A large transaortic valve pressure gradient may exist for many years without a reduction in cardiac output (CO) or LV dilation; ultimately, however, excessive hypertrophy becomes maladaptive, LV systolic function declines because of afterload mismatch, abnormalities of diastolic function progress, and irreversible myocardial fibrosis develops.

A mean systolic pressure gradient >40 mmHg with a normal CO or an effective aortic orifice area of approximately <1 cm 2 (or approximately <0.6 cm $^2/\text{m}^2$ body surface area in a normal-sized adult)—i.e., less than approximately one-third of the normal orifice area—is generally considered to represent severe obstruction to LV outflow. The elevated LV end-diastolic pressure observed in many patients with severe AS and preserved ejection fraction (EF) signifies the presence of diminished compliance of the hypertrophied LV. Although the CO at rest is within normal limits in most patients with severe AS, it usually fails to rise normally during exercise. Loss of an appropriately timed, vigorous atrial contraction, as occurs in atrial fibrillation (AF) or atrioventricular dissociation, may cause rapid progression of symptoms. Late in the course, contractile function deteriorates because of

afterload excess, the CO and LV-aortic pressure gradient decline, and the mean left atrial (LA), pulmonary artery (PA), and right ventricular (RV) pressures rise. LV performance can be further compromised by superimposed coronary artery disease (CAD). Stroke volume (and thus CO) can also be reduced in patients with significant hypertrophy and a small LV cavity despite a normal EF. Low-flow, low-gradient AS (with either reduced or normal LV systolic function) is both a diagnostic and therapeutic challenge.

The hypertrophied LV causes an increase in myocardial oxygen requirements. In addition, even in the absence of obstructive CAD, coronary blood flow is impaired to the extent that ischemia can be precipitated under conditions of excess demand. Capillary density is reduced relative to wall thickness, compressive forces are increased, and the elevated LV end-diastolic pressure reduces the coronary driving pressure. The subendocardium is especially vulnerable to ischemia by this mechanism.

SYMPTOMS

AS is rarely of clinical importance until the valve orifice has narrowed to approximately 1 cm 2 . Even severe AS may exist for many years without producing any symptoms because of the ability of the hypertrophied LV to generate the elevated intraventricular pressures required to maintain a normal stroke volume. Once symptoms occur, valve replacement is indicated.

Most patients with pure or predominant AS have gradually increasing obstruction over years but do not become symptomatic until the sixth to eighth decades. Adult patients with BAV disease, however, develop significant valve dysfunction and symptoms one to two decades sooner. Exertional dyspnea, angina pectoris, and syncope are the three cardinal symptoms. Often, there is a history of insidious progression of fatigue and dyspnea associated with gradual curtailment of activities and reduced effort tolerance. *Dyspnea* results primarily from elevation of the pulmonary capillary pressure caused by elevations of LV diastolic pressures secondary to impaired relaxation and reduced LV compliance. *Angina pectoris* usually develops somewhat later and reflects an imbalance between the augmented myocardial oxygen requirements and reduced oxygen availability. CAD may or may not

be present, although its coexistence is common among AS patients older than age 65. *Exertional syncope* may result from a decline in arterial pressure caused by vasodilation in the exercising muscles and inadequate vasoconstriction in nonexercising muscles in the face of a fixed CO, or from a sudden fall in CO produced by an arrhythmia.

Because the CO at rest is usually well maintained until late in the course, marked fatigability, weakness, peripheral cyanosis, cachexia, and other clinical manifestations of a low CO are usually not prominent until this stage is reached. Orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema, i.e., symptoms of LV failure, also occur only in the advanced stages of the disease. Severe pulmonary hypertension leading to RV failure and systemic venous hypertension, hepatomegaly, AF, and tricuspid regurgitation (TR) are usually late findings in patients with isolated severe AS.

When AS and mitral stenosis (MS) coexist, the reduction in flow (CO) induced by MS lowers the pressure gradient across the aortic valve and, thereby, masks many of the clinical findings produced by AS. The transaortic pressure gradient can be increased in patients with concomitant aortic regurgitation (AR) due to higher aortic valve flow rates.

PHYSICAL FINDINGS

The rhythm is generally regular until late in the course; at other times, AF should suggest the possibility of associated mitral valve disease. The systemic arterial pressure is usually within normal limits. In the late stages, however, when stroke volume declines, the systolic pressure may fall and the pulse pressure narrow. The carotid arterial pulse rises slowly to a delayed peak (*pulsus parvus et tardus*). A thrill or anacrotic "shudder" may be palpable over the carotid arteries, more commonly the left. In the elderly, the stiffening of the arterial wall may mask this important physical sign. In many patients, the *a* wave in the jugular venous pulse is accentuated. This results from the diminished distensibility of the RV cavity caused by the bulging, hypertrophied interventricular septum.

The LV impulse is sometimes displaced laterally in the later stages of the disease. A double apical impulse (with a palpable S_4) may be recognized, particularly with the patient in the left lateral recumbent position. A systolic thrill may be present at the base of the heart to the right of the sternum when leaning forward or in the suprasternal notch.

Auscultation An early systolic ejection sound is frequently audible in children, adolescents, and young adults with congenital BAV disease. This sound usually disappears when the valve becomes calcified and rigid. As AS increases in severity, LV systole may become prolonged so that the aortic valve closure sound no longer precedes the pulmonic valve closure sound, and the two components may become synchronous, or aortic valve closure may even follow pulmonic valve closure, causing paradoxical splitting of S_2 (Chap. 267). The sound of aortic valve closure can be heard most frequently in patients with AS who have pliable valves, and calcification diminishes the intensity of this sound. Frequently, an S_4 is audible at the apex and reflects the presence of LV hypertrophy and an elevated LV end-diastolic pressure; an S_3 generally occurs late in the course, when the LV dilates and its systolic function becomes severely compromised.

The murmur of AS is characteristically an ejection (mid) systolic murmur that commences shortly after the S_1 , increases in intensity to reach a peak toward the middle of ejection, and ends just before aortic valve closure. It is characteristically low-pitched, rough and rasping in character, and loudest at the base of the heart, most commonly in the second right intercostal space. It is transmitted upward along the carotid arteries. Occasionally it is transmitted downward and to the apex, where it may be confused with the systolic murmur of mitral regurgitation (MR) (Gallavardin effect). In almost all patients with severe obstruction and preserved CO, the murmur is at least grade III/VI. In patients with mild degrees of obstruction or in those with severe stenosis with heart failure and low CO in whom the stroke volume and, therefore, the transvalvular flow rate are reduced, the murmur may be relatively soft and brief.

LABORATORY EXAMINATION

ECG In most patients with severe AS, there is LV hypertrophy. In advanced cases, ST-segment depression and T-wave inversion (LV "strain") in standard leads I and aVL and in the left precordial leads are evident. However, there is no close correlation between the ECG and the hemodynamic severity of obstruction, and the absence of ECG signs of LV hypertrophy does not exclude severe obstruction. Many patients with AS have systemic hypertension, which can also contribute to the development of hypertrophy.

Echocardiogram The key findings on TTE are thickening, calcification, and reduced systolic opening of the valve leaflets and LV hypertrophy. Eccentric closure of the aortic valve cusps is characteristic of congenitally bicuspid valves. TEE imaging can display the obstructed orifice extremely well, but it is not routinely required for accurate characterization of AS. The valve gradient and aortic valve area can be estimated by Doppler measurement of the transaortic velocity. Severe AS is defined by a valve area $<1 \text{ cm}^2$, whereas moderate AS is defined by a valve area of $1\text{--}1.5 \text{ cm}^2$ and mild AS by a valve area of $1.5\text{--}2 \text{ cm}^2$. Aortic valve sclerosis, conversely, is accompanied by a jet velocity of less than 2.5 meters/s (peak gradient $<25 \text{ mmHg}$). LV dilation and reduced systolic shortening reflect impairment of LV function. There is increasing experience with the use of longitudinal strain and strain rate to characterize earlier changes in LV systolic function, well before a decline in EF can be appreciated. Doppler indices of impaired diastolic function are frequently seen.

Echocardiography is useful for identifying coexisting valvular abnormalities; for differentiating valvular AS from other forms of LV outflow obstruction; and for measurement of the aortic root and proximal ascending aortic dimensions. These aortic measurements are particularly important for patients with BAV disease. Dobutamine stress echocardiography is useful for the evaluation of patients with AS and severe LV systolic dysfunction (low-flow, low-gradient, severe AS with reduced EF), in whom the severity of the AS can often be difficult to judge. Patients with severe AS (i.e., valve area $<1 \text{ cm}^2$) with a relatively low mean gradient ($<40 \text{ mmHg}$) despite a normal EF (low-flow, low-gradient, severe AS with normal EF) are often hypertensive, and efforts to control their systemic blood pressure should be optimized before Doppler echocardiography is repeated. The use of dobutamine stress echocardiography in this setting is under investigation. When there is continued uncertainty regarding the severity of AS in patients with reduced CO, quantitative analysis of the amount of aortic valve calcium with chest computed tomography (CT) may be helpful.

Chest X-Ray The chest x-ray may show no or little overall cardiac enlargement for many years. Hypertrophy without dilation may produce some rounding of the cardiac apex in the frontal projection and slight backward displacement in the lateral view. A dilated proximal ascending aorta may be seen along the upper right heart border in the frontal view. Aortic valve calcification may be discernible in the lateral view, but is usually readily apparent on fluoroscopic examination or by echocardiography; the absence of valvular calcification on fluoroscopy in an adult suggests that severe valvular AS is *not* present. In later stages of the disease, as the LV dilates, there is increasing roentgenographic evidence of LV enlargement, pulmonary congestion, and enlargement of the LA, PA, and right heart chambers.

Catheterization Right and left heart catheterization for invasive assessment of AS is performed infrequently but can be useful when there is a discrepancy between the clinical and noninvasive findings. Concern has been raised that attempts to cross the aortic valve for measurement of LV pressures are associated with a risk of cerebral embolization. Catheterization is also useful in three distinct categories of patients: (1) *patients with multivalvular disease*, in whom the role played by each valvular deformity should be defined to aid in the planning of operative treatment; (2) *young, asymptomatic patients with noncalcific congenital AS*, to define the severity of obstruction to LV outflow, because operation or percutaneous aortic balloon valvuloplasty (PABV) may be indicated in these patients if severe AS is

1532 present, even in the absence of symptoms; and (3) *patients in whom it is suspected that the obstruction to LV outflow may not be at the level of the aortic valve but rather at the sub- or supravalvular level.*

Coronary angiography is indicated to screen for CAD in appropriate patients with severe AS who are being considered for surgery. The incidence of significant CAD for which bypass grafting is indicated at the time of aortic valve replacement (AVR) exceeds 50% among adult patients.

NATURAL HISTORY

Death in patients with severe AS occurs most commonly in the seventh and eighth decades. Based on data obtained at postmortem examination in patients before surgical treatment became widely available, the average time to death after the onset of various symptoms was as follows: angina pectoris, 3 years; syncope, 3 years; dyspnea, 2 years; congestive heart failure, 1.5–2 years. Moreover, in >80% of patients who died with AS, symptoms had existed for <4 years. Among adults dying with valvular AS, sudden death, which presumably resulted from an arrhythmia, occurred in 10–20%; however, most sudden deaths occurred in patients who had previously been symptomatic. Sudden death as the first manifestation of severe AS is very uncommon (<1% per year) in asymptomatic adult patients. Calcific AS is a progressive disease, with an annual reduction in valve area averaging 0.1 cm² and annual increases in the peak jet velocity and mean valve gradient averaging 0.3 meters/s and 7 mmHg, respectively (Table 283-2).

TREATMENT AORTIC STENOSIS (FIG. 283-2)

MEDICAL TREATMENT

In patients with severe AS (valve area <1 cm²), strenuous physical activity and competitive sports should be avoided, even in the asymptomatic stage. Care must be taken to avoid dehydration and hypovolemia to protect against a significant reduction in CO. Medications used for the treatment of hypertension or CAD, including beta blockers and angiotensin-converting enzyme (ACE) inhibitors, are generally safe for asymptomatic patients with preserved LV systolic function. Nitroglycerin is helpful in relieving angina pectoris in patients with CAD. Retrospective studies have shown that patients with degenerative calcific AS who receive HMG-CoA reductase inhibitors ("statins") exhibit slower progression of leaflet calcification and aortic valve area reduction than those who do not. However, randomized prospective studies with either high-dose atorvastatin or combination simvastatin/ezetimibe have failed to show a measurable effect on valve-related outcomes. The use of statin medications should continue to be driven by considerations regarding primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events. ACE inhibitors have not been studied prospectively for AS-related outcomes. The need for endocarditis prophylaxis is restricted to AS patients with a prior history of endocarditis.

SURGICAL TREATMENT

Asymptomatic patients with calcific AS and severe obstruction should be followed carefully for the development of symptoms and by serial echocardiograms for evidence of deteriorating LV function. Operation is indicated in patients with severe AS (valve

area <1 cm² or 0.6 cm²/m² body surface area) who are symptomatic, those who exhibit LV systolic dysfunction (EF <50%), and those with BAV disease and an aneurysmal root or ascending aorta (maximal dimension >5.5 cm). Operation for aneurysm disease is recommended at smaller aortic diameters (4.5–5.0 cm) for patients with a family history of an aortic catastrophe and for patients who exhibit rapid aneurysm growth (>0.5 cm/year). Patients with asymptomatic moderate or severe AS who are referred for coronary artery bypass grafting surgery should also have AVR. In patients without heart failure, the operative risk of AVR (including patients with AS or AR) is approximately 2% (Table 283-2) but increases as a function of age and the need for concomitant aortic surgery or coronary revascularization with bypass grafting. The indications for AVR in the asymptomatic patient have been the subject of intense debate over the past 5 years, as surgical outcomes in selected patients have continued to improve. Relative indications for which surgery can be considered include an abnormal response to treadmill exercise; rapid progression of AS, especially when urgent access to medical care might be compromised; very severe AS, defined by an aortic valve jet velocity >5 meters/s or mean gradient >60 mmHg and low operative risk; and excessive LV hypertrophy in the absence of systemic hypertension. Exercise testing can be safely performed in the asymptomatic patient, as many as one-third of whom will show signs of functional impairment.

Operation should be carried out promptly after symptom onset. In patients with low-flow, low-gradient severe AS with reduced LVEF, the perioperative mortality risk is high (15–20%), and evidence of myocardial disease may persist even when the operation is technically successful. Long-term postoperative survival correlates with preoperative LV function. Nonetheless, in view of the even worse prognosis of such patients when they are treated medically, there is usually little choice but to advise valve replacement, especially in patients in whom contractile reserve can be demonstrated bydobutamine stress echocardiography (defined by a ≥20% increase in stroke volume after dobutamine challenge). Patients in this high surgical risk group may benefit from transcatheter aortic valve replacement (TAVR, see below). The treatment of patients with low-flow, low-gradient severe AS with normal LVEF is also difficult. Outcomes appear to be better with surgery compared with conservative medical care for symptomatic patients with this type of "paradoxical" low-flow AS, but more research is needed to guide therapeutic decision-making. In patients in whom severe AS and CAD coexist, relief of the AS and revascularization may sometimes result in striking clinical and hemodynamic improvement (Table 283-2).

Because many patients with calcific AS are elderly, particular attention must be directed to the adequacy of hepatic, renal, and pulmonary function before AVR is recommended. Age alone is not a contraindication to AVR for AS. The perioperative mortality rate depends to a substantial extent on the patient's preoperative clinical and hemodynamic state. Treatment decisions for AS patients who are not at low operative risk should be made by a multidisciplinary heart team with representation from general cardiology, interventional cardiology, imaging, cardiac surgery, and other allied specialties as needed, including geriatrics. The 10-year survival rate of older adult patients with AVR is approximately 60%. Approximately 30% of bioprosthetic valves evidence primary valve failure in 10 years, requiring re-replacement, and an approximately equal percentage of patients with mechanical prostheses develop significant hemorrhagic complications as a consequence of treatment with vitamin K antagonists. Homograft AVR is usually reserved for patients with aortic valve endocarditis.

The Ross procedure involves replacement of the diseased aortic valve with the autologous pulmonic valve and implantation of a homograft in the native pulmonic position. Its use has declined considerably in the United States because of the technical complexity of the procedure and the incidence of late postoperative aortic root dilation and autograft failure with AR. There is also a low incidence of pulmonary homograft stenosis.

TABLE 283-2 MORTALITY RATES AFTER AORTIC VALVE SURGERY*

Operation	Number	Unadjusted Operative Mortality (%)
AVR (isolated)	14,795	2.3
AVR + CAB	9158	4.2
AVR + MVR	876	8.8

*Data are for the first two quarters of calendar year 2013, during which 1004 sites reported a total of 135,666 procedures. Data are available from the Society of Thoracic Surgeons at http://www.sts.org/sites/default/files/documents/2013_3rdHarvestExecutiveSummary.pdf.

Abbreviations: AVR, aortic valve replacement; CAB, coronary artery bypass; MVR, mitral valve replacement.

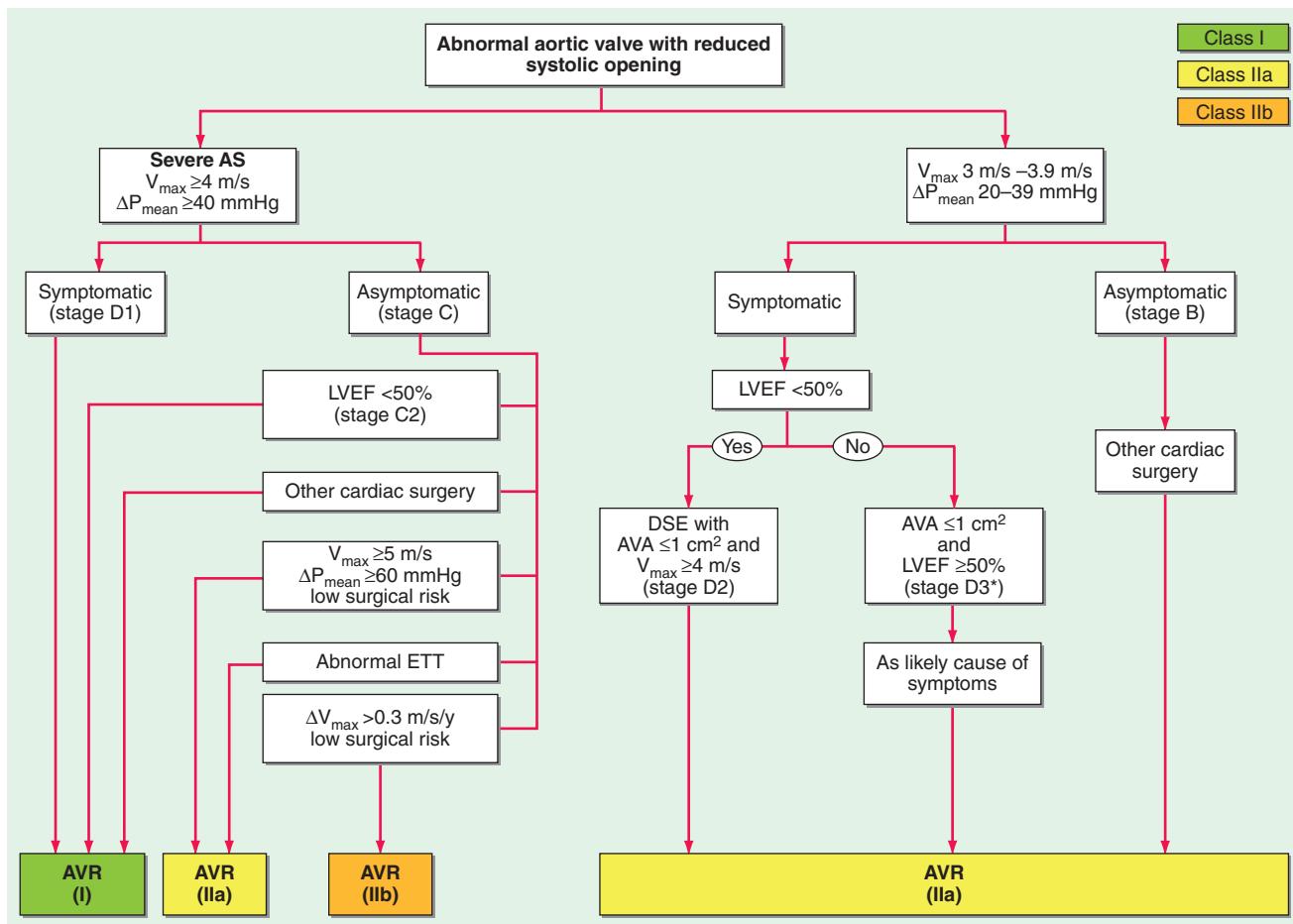


FIGURE 283-2 Management strategy for patients with aortic stenosis. Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Patients who do not meet criteria for intervention should be monitored periodically with clinical and echocardiographic follow-up. The class designations refer to the American College of Cardiology/American Heart Association methodology for treatment recommendations. Class I recommendations should be performed or are indicated; Class IIa recommendations are considered reasonable to perform; Class IIb recommendations may be considered. The stages refer to the stages of progression of the disease. At disease stage A, risk factors are present for the development of valve dysfunction; stage B refers to progressive, mild-moderate, asymptomatic valve disease; stage C disease is severe in nature but clinically asymptomatic; stage C1 characterizes asymptomatic patients with severe valve disease but compensated ventricular function; stage C2 refers to asymptomatic, severe disease with ventricular decompensation; stage D refers to severe, symptomatic valve disease. With aortic stenosis, stage D1 refers to symptomatic patients with severe aortic stenosis and a high valve gradient (>40 mmHg mean gradient); stage D2 comprises patients with symptomatic, severe, low-flow, low-gradient aortic stenosis and low left ventricular ejection fraction; and stage D3 characterizes patients with symptomatic, severe, low-flow, low-gradient severe aortic stenosis and preserved left ventricular ejection fraction (paradoxical, low-flow, low-gradient severe aortic stenosis). AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement by either surgical or transcatheter approach; BP, blood pressure; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; ΔP_{mean}, mean pressure gradient; and V_{max}, maximum velocity. (Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. *J Am Coll Cardiol* doi: 10.1016/j.jacc.2014.02.536, 2014, with permission.)

PERCUTANEOUS AORTIC BALLOON VALVULOPLASTY (PABV)

This procedure is preferable to operation in many children and young adults with congenital, noncalcific AS (Chap. 282). It is not commonly used as definitive therapy in adults with severe calcific AS because of a very high restenosis rate (80% within 1 year) and the risk of procedural complications, but on occasion, it has been used successfully as a “bridge to operation” in patients with severe LV dysfunction and shock who are too ill to tolerate surgery. It is performed routinely as part of the TAVR procedure (see below).

TRANSCATHETER AORTIC VALVE REPLACEMENT

TAVR for treatment of AS has been performed in more than 50,000 prohibitive- or high-surgical-risk adult patients worldwide using one of two available systems, a balloon-expandable valve and a self-expanding valve, both of which incorporate a pericardial prosthesis (Fig. 283-3). More than 250 U.S. centers now offer this procedure.

TAVR is most frequently performed via the transfemoral route, although trans-LV apical, subclavian, carotid, and ascending aortic routes have been used. Aortic balloon valvuloplasty under rapid RV pacing is performed as a first step to create an orifice of sufficient size for the prosthesis. Procedural success rates exceed 90%. Among elderly patients with severe AS who are considered inoperable (i.e., prohibitive surgical risk), 1- and 2-year survival rates are significantly higher with TAVR compared with medical therapy (including PABV) (Fig. 283-4). One- and 2-year survival rates are essentially equal for high-surgical-risk patients treated with TAVR or surgical AVR (SAVR) (Fig. 283-5). TAVR is associated with an early hazard for stroke and a higher incidence of postprocedural, paravalvular AR, a risk factor for mortality over the next 2 years. Postprocedural heart block requiring permanent pacemaker therapy is observed significantly more frequently with the self-expanding valve. Valve performance characteristics are excellent. Overall outcomes with this



FIGURE 283-3 Balloon-expandable (**A**) and self-expanding (**B**) valves for transcatheter aortic valve replacement (TAVR). **B**, inflated balloon; **N**, nose cone; **V**, valve. (Part **A**, courtesy of Edwards Lifesciences, Irvine, CA; with permission. NovaFlex+ is a trademark of Edwards Lifesciences Corporation. Part **B**, © Medtronic, Inc. 2015. Medtronic CoreValve Transcatheter Aortic Valve. CoreValve is a registered trademark of Medtronic, Inc.)

transformative technology have been very favorable and have allowed the extension of AVR to groups of patients previously considered at high or prohibitive risk for conventional surgery. Nevertheless, some patients are not candidates for this procedure because their comorbidity profile, including an assessment of frailty, would make its undertaking inappropriate. The heart team is specifically charged with making challenging decisions of this nature. The use of these devices for the treatment of patients at intermediate operative risk and for those with structural deterioration of bioprosthetic aortic and mitral valves ("valve-in-valve"), as an alternative to reoperative valve replacement, is under active study.

AORTIC REGURGITATION

ETIOLOGY

(Table 283-1) AR may be caused by primary valve disease or by primary aortic root disease.

Primary Valve Disease Rheumatic disease results in thickening, deformity, and shortening of the individual aortic valve cusps, changes that prevent their proper opening during systole and closure during diastole. A rheumatic origin is much less common in patients with isolated AR who do not have associated rheumatic mitral valve disease. Patients with congenital BAV disease may develop predominant AR,

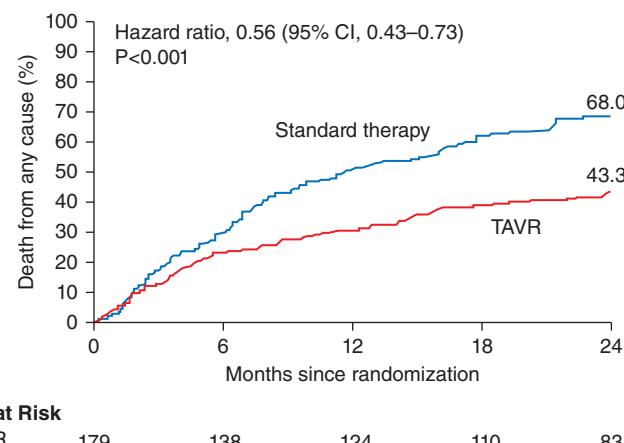


FIGURE 283-4 Twenty-four-month outcomes following transcatheter aortic valve replacement (TAVR) for inoperable patients in the PARTNER I trial (cohort B). CI, confidence interval. (Adapted from RR Makkar et al: *N Engl J Med* 366:1696, 2012; with permission.)

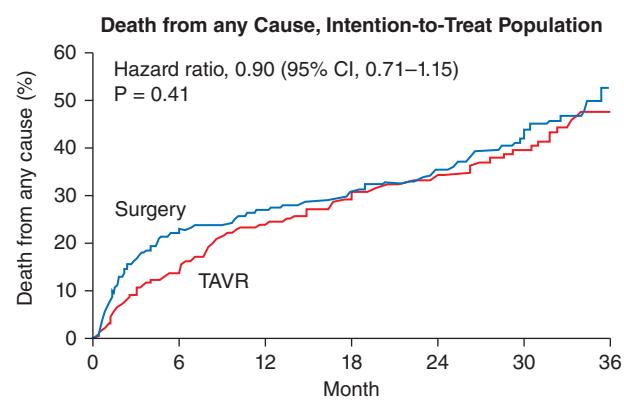


FIGURE 283-5 Thirty-six-month outcomes following transcatheter aortic valve replacement (TAVR) for high-surgical-risk patients (cohort A) in the PARTNER I trial. CI, confidence interval. (Adapted from SK Kodali et al: *New Engl J Med* 366:1686, 2012; with permission.)

and approximately 20% of patients will require aortic valve surgery between 10 and 40 years of age. Congenital fenestrations of the aortic valve occasionally produce mild AR. Membranous subaortic stenosis often leads to thickening and scarring of the aortic valve leaflets with secondary AR. Prolapse of an aortic cusp, resulting in progressive chronic AR, occurs in approximately 15% of patients with ventricular septal defect (*Chap. 282*) but may also occur as an isolated phenomenon or as a consequence of myxomatous degeneration sometimes associated with mitral and/or tricuspid valve involvement.

AR may result from infective endocarditis, which can develop on a valve previously affected by rheumatic disease, a congenitally deformed valve, or on a normal aortic valve, and may lead to perforation or erosion of one or more leaflets. The aortic valve leaflets may become scarred and retracted during the course of syphilis or ankylosing spondylitis and contribute further to the AR that derives primarily from the associated root disease. Although traumatic rupture or avulsion of an aortic cusp is an uncommon cause of acute AR, it represents the most frequent serious lesion in patients surviving nonpenetrating cardiac injuries. The coexistence of hemodynamically significant AS with AR usually excludes all the rarer forms of AR because it occurs almost exclusively in patients with rheumatic or congenital AR. In patients with AR due to primary valvular disease, dilation of the aortic annulus may occur secondarily and lead to worsening regurgitation.

Primary Aortic Root Disease AR also may be due entirely to marked aortic annular dilation, i.e., aortic root disease, without primary involvement of the valve leaflets; widening of the aortic annulus and separation of the aortic leaflets are responsible for the AR (*Chap. 301*). Medial degeneration of the ascending aorta, which may or may not be associated with other manifestations of Marfan's syndrome; idiopathic dilation of the aorta; annuloaortic ectasia; osteogenesis imperfecta; and severe, chronic hypertension may all widen the aortic annulus and lead to progressive AR. Occasionally AR is caused by retrograde dissection of the aorta involving the aortic annulus. Syphilis and ankylosing spondylitis, both of which may affect the aortic leaflets, may also be associated with cellular infiltration and scarring of the media of the thoracic aorta, leading to aortic dilation, aneurysm formation, and severe regurgitation. In syphilis of the aorta (*Chap. 206*), now a very rare condition, the involvement of the intima may narrow the coronary ostia, which in turn may be responsible for myocardial ischemia.

PATOPHYSIOLOGY

The total stroke volume ejected by the LV (i.e., the sum of the effective forward stroke volume and the volume of blood that regurgitates back into the LV) is increased in patients with AR. In patients with severe AR, the volume of regurgitant flow may equal the effective forward stroke volume. In contrast to MR, in which a portion of the LV stroke volume is delivered into the low-pressure LA, in AR the entire LV stroke volume is ejected into a high-pressure zone, the aorta. An increase in the LV end-diastolic volume (increased preload) constitutes the major hemodynamic compensation for AR. The dilation and eccentric hypertrophy of the LV allow this chamber to eject a larger stroke volume without requiring any increase in the relative shortening of each myofibril. Therefore, severe AR may occur with a normal effective forward stroke volume and a normal LVEF (total [forward plus regurgitant] stroke volume/end-diastolic volume), together with an elevated LV end-diastolic pressure and volume. However, through the operation of Laplace's law, LV dilation increases the LV systolic tension required to develop any given level of systolic pressure. Chronic AR is, thus, a state in which LV preload and afterload are both increased. Ultimately, these adaptive measures fail. As LV function deteriorates, the end-diastolic volume rises further and the forward stroke volume and EF decline. Deterioration of LV function often precedes the development of symptoms. Considerable thickening of the LV wall also occurs with chronic AR, and at autopsy, the hearts of these patients may be among the largest encountered, sometimes weighing >1000 g.

The reverse pressure gradient from aorta to LV, which drives the AR flow, falls progressively during diastole, accounting for the decrescendo

nature of the diastolic murmur. Equilibration between aortic and LV pressures may occur toward the end of diastole in patients with chronic severe AR, particularly when the heart rate is slow. In patients with acute severe AR, the LV is unprepared for the regurgitant volume load. LV compliance is normal or reduced, and LV diastolic pressures rise rapidly, occasionally to levels >40 mmHg. The LV pressure may exceed the LA pressure toward the end of diastole, and this reversed pressure gradient closes the mitral valve prematurely.

In patients with chronic severe AR, the effective forward CO usually is normal or only slightly reduced at rest, but often it fails to rise normally during exertion. An early sign of LV dysfunction is a reduction in the EF. In advanced stages, there may be considerable elevation of the LA, PA wedge, PA, and RV pressures and lowering of the forward CO at rest.

Myocardial ischemia may occur in patients with AR because myocardial oxygen requirements are elevated by LV dilation, hypertrophy, and elevated LV systolic tension, and coronary blood flow may be compromised. A large fraction of coronary blood flow occurs during diastole, when arterial pressure is low, thereby reducing coronary perfusion or driving pressure. This combination of increased oxygen demand and reduced supply may cause myocardial ischemia, particularly of the subendocardium, even in the absence of epicardial CAD.

HISTORY

Approximately three-fourths of patients with pure or predominant valvular AR are men; women predominate among patients with primary valvular AR who have associated rheumatic mitral valve disease. A history compatible with infective endocarditis may sometimes be elicited from patients with rheumatic or congenital involvement of the aortic valve, and the infection often precipitates or seriously aggravates preexisting symptoms.

In patients with *acute severe AR*, as may occur in infective endocarditis, aortic dissection, or trauma, the LV cannot dilate sufficiently to maintain stroke volume, and LV diastolic pressure rises rapidly with associated marked elevations of LA and PA wedge pressures. Pulmonary edema and/or cardiogenic shock may develop rapidly.

Chronic severe AR may have a long latent period, and patients may remain relatively asymptomatic for as long as 10–15 years. However, uncomfortable awareness of the heartbeat, especially on lying down, may be an early complaint. Sinus tachycardia, during exertion or with emotion, or premature ventricular contractions may produce particularly uncomfortable palpitations as well as head pounding. These complaints may persist for many years before the development of exertional dyspnea, usually the first symptom of diminished cardiac reserve. The dyspnea is followed by orthopnea, paroxysmal nocturnal dyspnea, and excessive diaphoresis. Anginal chest pain even in the absence of CAD may occur in patients with severe AR, even in younger patients. Anginal pain may develop at rest as well as during exertion. Nocturnal angina may be a particularly troublesome symptom, and it may be accompanied by marked diaphoresis. The anginal episodes can be prolonged and often do not respond satisfactorily to sublingual nitroglycerin. Systemic fluid accumulation, including congestive hepatomegaly and ankle edema, may develop late in the course of the disease.

PHYSICAL FINDINGS

In chronic severe AR, the jarring of the entire body and the bobbing motion of the head with each systole can be appreciated, and the abrupt distention and collapse of the larger arteries are easily visible. The examination should be directed toward the detection of conditions predisposing to AR, such as bicuspid valve, endocarditis, Marfan's syndrome, and ankylosing spondylitis.

Arterial Pulse A rapidly rising "water-hammer" pulse, which collapses suddenly as arterial pressure falls rapidly during late systole and diastole (Corrigan's pulse), and capillary pulsations, an alternate flushing and paling of the skin at the root of the nail while pressure is applied to the tip of the nail (Quincke's pulse), are characteristic

of chronic severe AR. A booming “pistol-shot” sound can be heard over the femoral arteries (Traube’s sign), and a to-and-fro murmur (Duroziez’s sign) is audible if the femoral artery is lightly compressed with a stethoscope.

The arterial pulse pressure is widened as a result of both systolic hypertension and a lowering of the diastolic pressure. The measurement of arterial diastolic pressure with a sphygmomanometer may be complicated by the fact that systolic sounds are frequently heard with the cuff completely deflated. However, the level of cuff pressure at the time of muffling of the Korotkoff sounds (phase IV) generally corresponds fairly closely to the true intraarterial diastolic pressure. As the disease progresses and the LV end-diastolic pressure rises, the arterial diastolic pressure may actually rise as well, because the aortic diastolic pressure cannot fall below the LV end-diastolic pressure. For the same reason, acute severe AR may also be accompanied by only a slight widening of the pulse pressure. Such patients are invariably tachycardic as the heart rate increases in an attempt to preserve the CO.

Palpation In patients with chronic severe AR, the LV impulse is heaving and displaced laterally and inferiorly. The systolic expansion and diastolic retraction of the apex are prominent. A diastolic thrill may be palpable along the left sternal border in thin-chested individuals, and a prominent systolic thrill may be palpable in the suprasternal notch and transmitted upward along the carotid arteries. This systolic thrill and the accompanying murmur do not necessarily signify the coexistence of AS. In some patients with AR or with combined AS and AR, the carotid arterial pulse may be bisferiens, i.e., with two systolic waves separated by a trough (see Fig. 267-2D).

Auscultation In patients with severe AR, the aortic valve closure sound (A_2) is usually absent. A systolic ejection sound is audible in patients with BAV disease, and occasionally an S_4 also may be heard. The murmur of chronic AR is typically a high-pitched, blowing, decrescendo diastolic murmur, heard best in the third intercostal space along the left sternal border (see Fig. 267-5B). In patients with mild AR, this murmur is brief, but as the severity increases, it generally becomes louder and longer, indeed holodiastolic. When the murmur is soft, it can be heard best with the diaphragm of the stethoscope and with the patient sitting up, leaning forward, and with the breath held in forced expiration. In patients in whom the AR is caused by primary valvular disease, the diastolic murmur is usually louder along the left than the right sternal border. However, when the murmur is heard best along the right sternal border, it suggests that the AR is caused by aneurysmal dilation of the aortic root. “Cooing” or musical diastolic murmurs suggest eversion of an aortic cusp vibrating in the regurgitant stream.

A mid-systolic ejection murmur is frequently audible in isolated AR. It is generally heard best at the base of the heart and is transmitted along the carotid arteries. This murmur may be quite loud without signifying aortic obstruction. A third murmur sometimes heard in patients with severe AR is the *Austin Flint murmur*, a soft, low-pitched, rumbling mid-to-late diastolic murmur. It is probably produced by the diastolic displacement of the anterior leaflet of the mitral valve by the AR stream and is not associated with hemodynamically significant mitral obstruction. The auscultatory features of AR are intensified by strenuous and sustained handgrip, which augments systemic vascular resistance.

In acute severe AR, the elevation of LV end-diastolic pressure may lead to early closure of the mitral valve, a soft S_1 , a pulse pressure that is not particularly wide, and a soft, short, early diastolic murmur of AR.

LABORATORY EXAMINATION

ECG In patients with chronic severe AR, the ECG signs of LV hypertrophy become manifest (Chap. 268). In addition, these patients frequently exhibit ST-segment depression and T-wave inversion in leads I, aVL, V_5 , and V_6 (“LV strain”). Left-axis deviation and/or QRS prolongation denote diffuse myocardial disease, generally associated with patchy fibrosis, and usually signify a poor prognosis.

Echocardiogram LV size is increased in chronic AR and systolic function is normal or even supernormal until myocardial contractility declines, as signaled by a decrease in EF or increase in the end-systolic dimension. A rapid, high-frequency diastolic fluttering of the anterior mitral leaflet produced by the impact of the regurgitant jet is a characteristic finding. The echocardiogram is also useful in determining the cause of AR, by detecting dilation of the aortic annulus and root, aortic dissection (see Fig. 270e-5), or primary leaflet pathology. With severe AR, the central jet width assessed by color flow Doppler imaging exceeds 65% of the LV outflow tract, the regurgitant volume is ≥ 60 mL/beat, the regurgitant fraction is $\geq 50\%$, and there is diastolic flow reversal in the proximal descending thoracic aorta. The continuous-wave Doppler profile of the AR jet shows a rapid deceleration time in patients with acute severe AR, due to the rapid increase in LV diastolic pressure. Surveillance transthoracic echocardiography forms the cornerstone of longitudinal follow-up and allows for the early detection of changes in LV size and/or function. For patients in whom transthoracic echocardiography (TTE) is limited by poor acoustical windows or inadequate semiquantitative assessment of LV function or the severity of the regurgitation, cardiac magnetic resonance imaging (MRI) can be performed. This modality also allows for accurate assessment of aortic size and contour. Transesophageal echocardiography (TEE) can also provide detailed anatomic assessment of the valve, root, and portions of the aorta.

Chest X-Ray In chronic severe AR, the apex is displaced downward and to the left in the frontal projection. In the left anterior oblique and lateral projections, the LV is displaced posteriorly and encroaches on the spine. When AR is caused by primary disease of the aortic root, aneurysmal dilation of the aorta may be noted, and the aorta may fill the retrosternal space in the lateral view. Echocardiography, cardiac MRI, and chest CT angiography are more sensitive than the chest x-ray for the detection of root and ascending aortic enlargement.

Cardiac Catheterization and Angiography When needed, right and left heart catheterization with contrast aortography can provide confirmation of the magnitude of regurgitation and the status of LV function. Coronary angiography is performed routinely in appropriate patients prior to surgery.

TREATMENT AORTIC REGURGITATION

ACUTE AORTIC REGURGITATION (FIG. 283-6)

Patients with acute severe AR may respond to intravenous diuretics and vasodilators (such as sodium nitroprusside), but stabilization is usually short-lived and operation is indicated urgently. Intraaortic balloon counterpulsation is contraindicated. Beta blockers are also best avoided so as not to reduce the CO further or slow the heart rate, thus allowing more time for diastolic filling of the LV. Surgery is the treatment of choice and is usually necessary within 24 h of diagnosis.

CHRONIC AORTIC REGURGITATION

Early symptoms of dyspnea and effort intolerance respond to treatment with diuretics; vasodilators (ACE inhibitors, dihydropyridine calcium channel blockers, or hydralazine) may be useful as well. Surgery can then be performed in a more controlled setting. The use of vasodilators to extend the compensated phase of chronic severe AR before the onset of symptoms or the development of LV dysfunction is more controversial and less well established. Systolic blood pressure should be controlled (goal <140 mmHg) in patients with chronic AR, and vasodilators are an excellent first choice as antihypertensive agents. It is often difficult to achieve adequate control because of the increased stroke volume that accompanies severe AR. Cardiac arrhythmias and systemic infections are poorly tolerated in patients with severe AR and must be treated promptly and vigorously. Although nitroglycerin and long-acting nitrates are not as helpful in relieving anginal pain as they are in patients with ischemic heart disease, they are worth a trial. Patients with

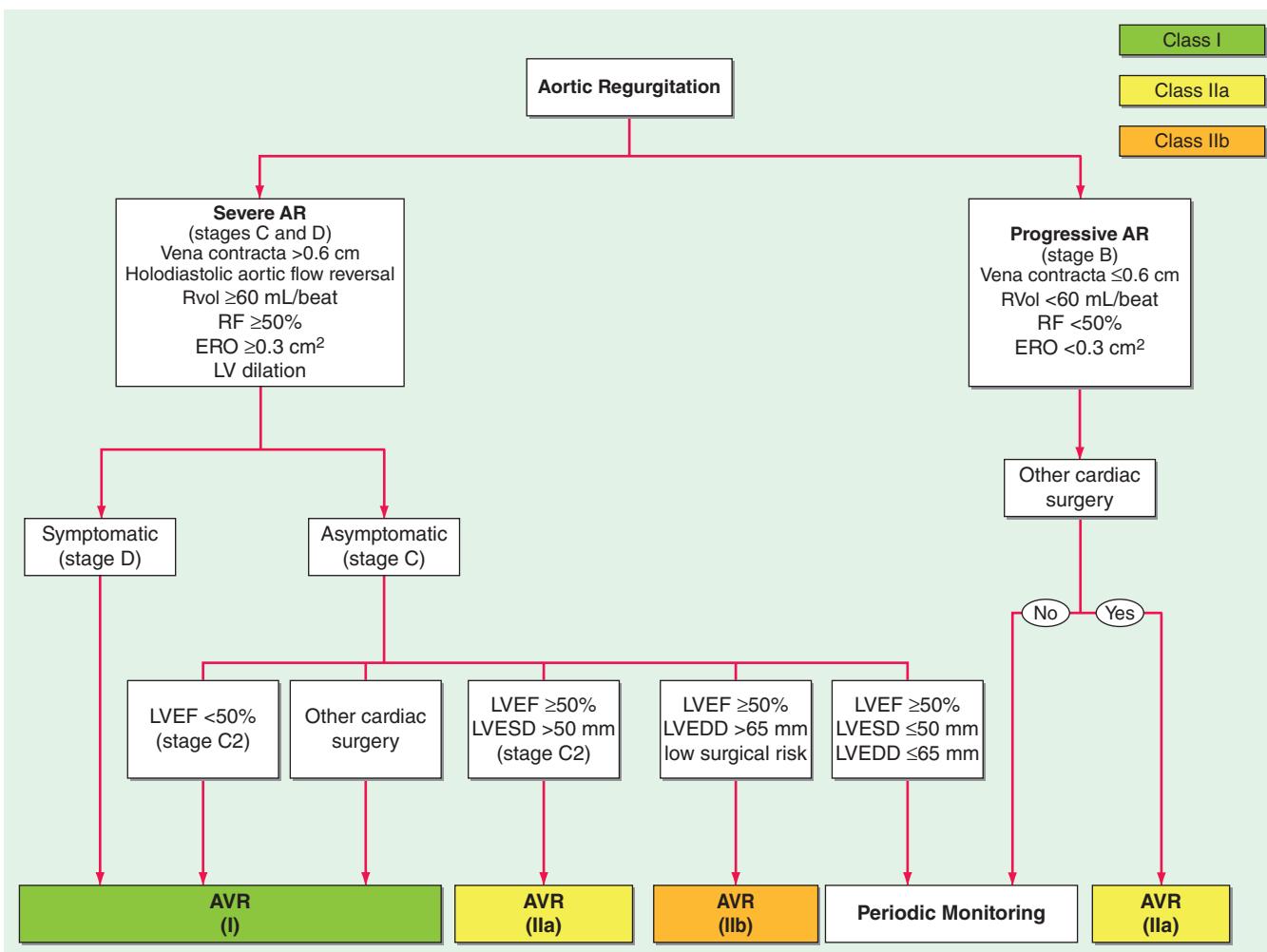


FIGURE 283-6 Management of patients with aortic regurgitation. See legend for Fig. 283-2 for explanation of treatment recommendations (Class I, IIa, and IIb) and disease stages (B, C1, C2, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Patients who do not meet criteria for intervention should be monitored periodically with clinical and echocardiographic follow-up. AR, aortic regurgitation; AVR, aortic valve replacement (valve repair may be appropriate in selected patients); ERO, effective regurgitant orifice; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume. (Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. *J Am Coll Cardiol* doi: 10.1016/j.jacc.2014.02.536, 2014, with permission.)

syphilitic aortitis should receive a full course of penicillin therapy ([Chap. 206](#)). Beta blockers and the angiotensin receptor blocker losartan may be useful to retard the rate of aortic root enlargement in young patients with Marfan's syndrome and aortic root dilation. Early reports of the efficacy of losartan in patients with Marfan's syndrome have led to its use in other populations of patients including those with BAV disease and aortopathy. The use of beta blockers in patients with valvular AR was previously felt to be relatively contraindicated due to concerns that the resulting slowing of the heart rate would allow more time for diastolic regurgitation. More recent observational reports, however, suggest that beta blockers may provide functional benefit in patients with chronic AR. Beta blockers can sometimes provide incremental blood pressure lowering in patients with chronic AR and hypertension. Patients with severe AR, particularly those with an associated aortopathy, should avoid isometric exercises.

SURGICAL TREATMENT

In deciding on the advisability and proper timing of surgical treatment, two points should be kept in mind: (1) patients with chronic severe AR usually do not become symptomatic until

after the development of myocardial dysfunction; and (2) when delayed too long (defined as >1 year from onset of symptoms or LV dysfunction), surgical treatment often does not restore normal LV function. Therefore, in patients with chronic severe AR, careful clinical follow-up and noninvasive testing with echocardiography at approximately 6- to 12-month intervals are necessary if operation is to be undertaken at the optimal time, i.e., *after* the onset of LV dysfunction but *prior* to the development of severe symptoms. Exercise testing may be helpful to assess effort tolerance more objectively. Operation can be deferred as long as the patient both remains asymptomatic and retains normal LV function without severe chamber dilation.

AVR is indicated for the treatment of severe AR in symptomatic patients irrespective of LV function. In general, the operation should be carried out in asymptomatic patients with severe AR and progressive LV dysfunction defined by an LVEF <50%, an LV end-systolic dimension >50 mm, or an LV diastolic dimension >65 mm. Smaller dimensions may be appropriate thresholds in individuals of smaller stature. Patients with severe AR without indications for operation should be followed by clinical and echocardiographic examination every 6–12 months.

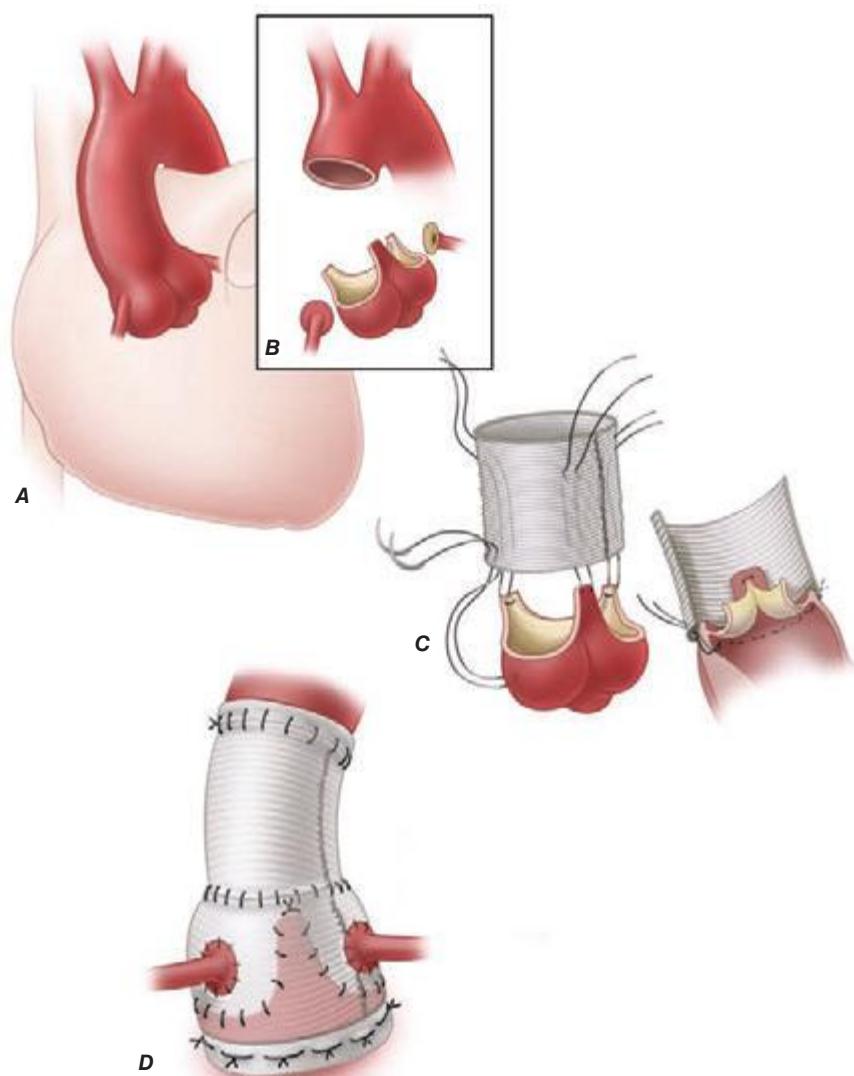


FIGURE 283-7 Valve-sparing aortic root reconstruction (David procedure). (From P Steltzer et al [eds]: *Valvular Heart Disease: A Companion to Braunwald's Heart Disease*, 3rd ed, Fig 12-27, p. 200.)

Surgical options for management of aortic valve and root disease have expanded considerably over the past decade. AVR with a suitable mechanical or tissue prosthesis is generally necessary in patients with rheumatic AR and in many patients with other forms of regurgitation. Rarely, when a leaflet has been perforated during infective endocarditis or torn from its attachments to the aortic annulus by thoracic trauma, primary surgical repair may be possible. When AR is due to aneurysmal dilation of the root or proximal ascending aorta rather than to primary valve involvement, it may be possible to reduce or eliminate the regurgitation by narrowing the annulus or by excising a portion of the aortic root without replacing the valve. Elective, valve-sparing aortic root reconstruction generally involves reimplantation of the valve in a contoured graft with reattachment of the coronary artery buttons into the side of the graft and is best undertaken in specialized surgical centers (Fig. 283-7). Resuspension of the native aortic valve leaflets is possible in approximately 50% of patients with acute AR in the setting of type A aortic dissection. In other conditions, however, regurgitation can be effectively eliminated only by replacing the aortic valve, the dilated or aneurysmal

ascending aorta responsible for the regurgitation, and implanting a composite valve-graft conduit. This formidable procedure entails a higher risk than isolated AVR.

As in patients with other valvular abnormalities, both the operative risk and the late mortality rate are largely dependent on the stage of the disease and myocardial function at the time of operation. The overall operative mortality rate for isolated AVR (performed for either or both AS or AR) is approximately 2% (Table 283-2). However, patients with AR, marked cardiac enlargement, and prolonged LV dysfunction experience an operative mortality rate of approximately 10% and a late mortality rate of approximately 5% per year due to LV failure despite a technically satisfactory operation. Nonetheless, because of the very poor prognosis with medical management, even patients with LV systolic failure should be considered for operation.

Patients with acute severe AR require prompt surgical treatment, which may be lifesaving.

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in [Chaps. 51e and 267](#); of electrocardiography (ECG) in [Chap. 268](#); of echocardiography and other noninvasive imaging techniques in [Chap. 270e](#); and of cardiac catheterization and angiography in [Chap. 272](#).

MITRAL STENOSIS

ETIOLOGY AND PATHOLOGY

Rheumatic fever is the leading cause of mitral stenosis (MS) ([Table 284-1](#)). Other less common etiologies of obstruction to left ventricular inflow include congenital mitral valve stenosis, cor triatriatum, mitral annular calcification with extension onto the leaflets, systemic lupus erythematosus, rheumatoid arthritis, left atrial myxoma, and infective endocarditis with large vegetations. Pure or predominant MS occurs in approximately 40% of all patients with rheumatic heart disease and a history of rheumatic fever ([Chap. 381](#)). In other patients with rheumatic heart disease, lesser degrees of MS may accompany mitral regurgitation (MR) and aortic valve disease. With reductions in the incidence of acute rheumatic fever, particularly in temperate climates and developed countries, the incidence of MS has declined considerably over the past several decades. However, it remains a major problem in developing nations, especially in tropical and semi-tropical climates.

In rheumatic MS, chronic inflammation leads to diffuse thickening of the valve leaflets with formation of fibrous tissue and/or calcific deposits. The mitral commissures fuse, the chordae tendineae fuse and shorten, the valvular cusps become rigid, and these changes, in turn, lead to narrowing at the apex of the funnel-shaped ("fish-mouth") valve. Although the initial insult to the mitral valve is rheumatic, later changes may be exacerbated by a nonspecific process resulting from trauma to the valve due to altered flow patterns. Calcification of the

stenotic mitral valve immobilizes the leaflets and narrows the orifice further. Thrombus formation and arterial embolization may arise from the calcific valve itself, but in patients with atrial fibrillation (AF), thrombi arise more frequently from the dilated left atrium (LA), particularly from within the LA appendage.

PATHOPHYSIOLOGY

In normal adults, the area of the mitral valve orifice is 4–6 cm². In the presence of significant obstruction, i.e., when the orifice area is reduced to <~2 cm², blood can flow from the LA to the left ventricle (LV) only if propelled by an abnormally elevated left atrioventricular pressure gradient, the hemodynamic hallmark of MS. When the mitral valve opening is reduced to <1.5 cm², referred to as "severe" MS, an LA pressure of ~25 mmHg is required to maintain a normal cardiac output (CO). The elevated pulmonary venous and pulmonary arterial (PA) wedge pressures reduce pulmonary compliance, contributing to exertional dyspnea. The first bouts of dyspnea are usually precipitated by clinical events that increase the rate of blood flow across the mitral orifice, resulting in further elevation of the LA pressure (see below).

To assess the severity of obstruction hemodynamically, both the transvalvular pressure gradient and the flow rate must be measured ([Chap. 272](#)). The latter depends not only on the CO but on the heart rate, as well. An increase in heart rate shortens diastole proportionately more than systole and diminishes the time available for flow across the mitral valve. Therefore, at any given level of CO, tachycardia, including that associated with rapid AF, augments the transvalvular pressure gradient and elevates further the LA pressure. Similar considerations apply to the pathophysiology of tricuspid stenosis.

The LV diastolic pressure and ejection fraction (EF) are normal in isolated MS. In MS and sinus rhythm, the elevated LA and PA wedge pressures exhibit a prominent atrial contraction pattern (*a* wave) and a gradual pressure decline after the *v* wave and mitral valve opening (*y* descent). In severe MS and whenever pulmonary vascular resistance is significantly increased, the PA pressure (PAP) is elevated at rest and rises further during exercise, often causing secondary elevations of right ventricular (RV) end-diastolic pressure and volume.

Cardiac Output In patients with severe MS (mitral valve orifice 1–1.5 cm²), the CO is normal or almost so at rest, but rises subnormally during exertion. In patients with very severe MS (valve area <1 cm²), particularly those in whom pulmonary vascular resistance is markedly elevated, the CO is subnormal at rest and may fail to rise or may even decline during activity.

Pulmonary Hypertension The clinical and hemodynamic features of MS are influenced importantly by the level of the PAP. Pulmonary hypertension results from: (1) passive backward transmission of the elevated LA pressure; (2) pulmonary arteriolar constriction (the so-called "second stenosis"), which presumably is triggered by LA and pulmonary venous hypertension (reactive pulmonary hypertension); (3) interstitial edema in the walls of the small pulmonary vessels; and (4) at end stage, organic obliterative changes in the pulmonary vascular bed. Severe pulmonary hypertension results in RV enlargement, secondary tricuspid regurgitation (TR), and pulmonic regurgitation (PR), as well as right-sided heart failure.

SYMPTOMS

In temperate climates, the latent period between the initial attack of rheumatic carditis (in the increasingly rare circumstances in which a history of one can be elicited) and the development of symptoms due to MS is generally about two decades; most patients begin to experience disability in the fourth decade of life. Studies carried out before the development of mitral valvotomy revealed that once a patient with MS became seriously symptomatic, the disease progressed inexorably to death within 2–5 years.

In patients whose mitral orifices are large enough to accommodate a normal blood flow with only mild elevations of LA pressure, marked elevations of this pressure leading to dyspnea and cough may be precipitated by sudden changes in the heart rate, volume status, or CO, as, for example, with severe exertion, excitement, fever, severe anemia, paroxysmal AF

TABLE 284-1 MAJOR CAUSES OF MITRAL VALVE DISEASE

Valve Lesion	Etiologies
Mitral stenosis	Rheumatic fever Congenital Severe mitral annular calcification SLE, RA
Mitral regurgitation	Acute Endocarditis Papillary muscle rupture (post-MI) Trauma Chordal rupture/leaflet flail (MVP, IE) Chronic Myxomatous (MVP) Rheumatic fever Endocarditis (healed) Mitral annular calcification Congenital (cleft, AV canal) HOCM with SAM Ischemic (LV remodeling) Dilated cardiomyopathy Radiation

Abbreviations: AV, atrioventricular; IE, infective endocarditis; HOCM, hypertrophic obstructive cardiomyopathy; LV, left ventricular; MI, myocardial infarction; MVP, mitral valve prolapse; RA, rheumatoid arthritis; SAM, systolic anterior motion; SLE, systemic lupus erythematosus.

and other tachycardias, sexual intercourse, pregnancy, and thyrotoxicosis. As MS progresses, lesser degrees of stress precipitate dyspnea, the patient becomes limited in daily activities, and orthopnea and paroxysmal nocturnal dyspnea develop. The development of persistent AF often marks a turning point in the patient's course and is generally associated with acceleration of the rate at which symptoms progress. *Hemoptysis* (**Chap. 48**) results from rupture of pulmonary-bronchial venous connections secondary to pulmonary venous hypertension. It occurs most frequently in patients who have elevated LA pressures without markedly elevated pulmonary vascular resistances and is rarely fatal. *Recurrent pulmonary emboli* (**Chap. 300**), sometimes with infarction, are an important cause of morbidity and mortality late in the course of MS. *Pulmonary infections*, i.e., bronchitis, bronchopneumonia, and lobar pneumonia, commonly complicate untreated MS, especially during the winter months.

Pulmonary Changes In addition to the aforementioned changes in the pulmonary vascular bed, fibrous thickening of the walls of the alveoli and pulmonary capillaries occurs commonly in MS. The vital capacity, total lung capacity, maximal breathing capacity, and oxygen uptake per unit of ventilation are reduced (**Chap. 306e**). Pulmonary compliance falls further as pulmonary capillary pressure rises during exercise.

Thrombi and Emboli *Thrombi* may form in the left atria, particularly within the enlarged atrial appendages of patients with MS. Systemic embolization, the incidence of which is 10–20%, occurs more frequently in patients with AF, in patients >65 years of age, and in those with a reduced CO. However, systemic embolization may be the presenting feature in otherwise asymptomatic patients with only mild MS.

PHYSICAL FINDINGS

(See also Chaps. 51e and 267)

Inspection and Palpation In patients with severe MS, there may be a malar flush with pinched and blue facies. In patients with sinus rhythm and severe pulmonary hypertension or associated tricuspid stenosis (TS), the jugular venous pulse reveals prominent *a* waves due to vigorous right atrial systole. The systemic arterial pressure is usually normal or slightly low. An RV tap along the left sternal border signifies an enlarged RV. A diastolic thrill may rarely be present at the cardiac apex, with the patient in the left lateral recumbent position.

Auscultation The first heart sound (S_1) is usually accentuated in the early stages of the disease and slightly delayed. The pulmonic component of the second heart sound (P_2) also is often accentuated with elevated PA pressures, and the two components of the second heart sound (S_2) are closely split. The opening snap (OS) of the mitral valve is most readily audible in expiration at, or just medial to, the cardiac apex. This sound generally follows the sound of aortic valve closure (A_2) by 0.05–0.12 s. The time interval between A_2 and OS varies inversely with the severity of the MS. The OS is followed by a low-pitched, rumbling, diastolic murmur, heard best at the apex with the patient in the left lateral recumbent position (**see Fig. 267-5**); it is accentuated by mild exercise (e.g., a few rapid sit-ups) carried out just before auscultation. In general, the duration of this murmur correlates with the severity of the stenosis in patients with preserved CO. In patients with sinus rhythm, the murmur often reappears or becomes louder during atrial systole (presystolic accentuation). Soft, grade I or II/VI systolic murmurs are commonly heard at the apex or along the left sternal border in patients with pure MS and do not necessarily signify the presence of MR. Hepatomegaly, ankle edema, ascites, and pleural effusion, particularly in the right pleural cavity, may occur in patients with MS and RV failure.

Associated Lesions With severe pulmonary hypertension, a pansystolic murmur produced by functional TR may be audible along the left sternal border. This murmur is usually louder during inspiration and diminishes during forced expiration (Carvallo's sign). When the CO is markedly reduced in MS, the typical auscultatory findings, including the diastolic rumbling murmur, may not be detectable (silent MS), but they may reappear as compensation is restored. The *Graham Steell murmur* of PR, a high-pitched, diastolic, decrescendo blowing murmur along the left sternal border, results from dilation of the pulmonary

valve ring and occurs in patients with mitral valve disease and severe pulmonary hypertension. This murmur may be indistinguishable from the more common murmur produced by aortic regurgitation (AR), although it may increase in intensity with inspiration and is accompanied by a loud and often palpable P_2 .

LABORATORY EXAMINATION

ECG In MS and sinus rhythm, the P wave usually suggests LA enlargement (**see Fig. 268-8**). It may become tall and peaked in lead II and upright in lead V₁ when severe pulmonary hypertension or TS complicates MS and right atrial (RA) enlargement occurs. The QRS complex is usually normal. However, with severe pulmonary hypertension, right axis deviation and RV hypertrophy are often present.

Echocardiogram (**See also Chap. 270e**) Transthoracic echocardiography (TTE) with color flow and spectral Doppler imaging provides critical information, including measurements of mitral inflow velocity during early (E wave) and late (A wave in patients in sinus rhythm) diastolic filling, estimates of the transvalvular peak and mean gradients and of the mitral orifice area, the presence and severity of any associated MR, the extent of leaflet calcification and restriction, the degree of distortion of the subvalvular apparatus, and the anatomic suitability for percutaneous mitral balloon valvotomy (percutaneous mitral balloon valvuloplasty [PMBV]; **see below**). In addition, TTE provides an assessment of LV and RV function, chamber sizes, an estimation of the PAP based on the tricuspid regurgitant jet velocity, and an indication of the presence and severity of any associated valvular lesions, such as aortic stenosis and/or regurgitation. Transesophageal echocardiography (TEE) provides superior images and should be used when TTE is inadequate for guiding management decisions. TEE is especially indicated to exclude the presence of LA thrombus prior to PMBV. The performance of TTE with exercise to evaluate the mean mitral diastolic gradient and PA pressures can be very helpful in the evaluation of patients with MS when there is a discrepancy between the clinical findings and the resting hemodynamics.

Chest X-Ray The earliest changes are straightening of the upper left border of the cardiac silhouette, prominence of the main PAs, dilation of the upper lobe pulmonary veins, and posterior displacement of the esophagus by an enlarged LA. Kerley B lines are fine, dense, opaque, horizontal lines that are most prominent in the lower and mid-lung fields and that result from distention of interlobular septae and lymphatics with edema when the resting mean LA pressure exceeds approximately 20 mmHg.

DIFFERENTIAL DIAGNOSIS

Like MS, significant MR may also be associated with a prominent diastolic murmur at the apex due to increased antegrade transmural flow, but in patients with isolated MR, this diastolic murmur commences slightly later than in patients with MS, and there is often clear-cut evidence of LV enlargement. An OS and increased P_2 are absent, and S_1 is soft or absent. An apical pansystolic murmur of at least grade III/VI intensity as well as an S_3 suggest significant MR. Similarly, the apical mid-diastolic murmur associated with severe AR (*Austin Flint murmur*) may be mistaken for MS but can be differentiated from it because it is not intensified in presystole and becomes softer with administration of amyl nitrite or other arterial vasodilators. TS, which occurs rarely in the absence of MS, may mask many of the clinical features of MS or be clinically silent; when present, the diastolic murmur of TS increases with inspiration and the *y* descent in the jugular venous pulse is delayed.

Atrial septal defect (**Chap. 282**) may be mistaken for MS; in both conditions, there is often clinical, ECG, and chest x-ray evidence of RV enlargement and accentuation of pulmonary vascularity. However, the absence of LA enlargement and of Kerley B lines and the demonstration of fixed splitting of S_2 with a grade II or III mid-systolic murmur at the mid to upper left sternal border all favor atrial septal defect over MS. Atrial septal defects with large left-to-right shunts may result in functional TS because of the enhanced diastolic flow.

Left atrial myxoma (Chap. 289e) may obstruct LA emptying, causing dyspnea, a diastolic murmur, and hemodynamic changes resembling those of MS. However, patients with an LA myxoma often have features suggestive of a systemic disease, such as weight loss, fever, anemia, systemic emboli, and elevated serum IgG and interleukin 6 (IL-6) concentrations. The auscultatory findings may change markedly with body position. The diagnosis can be established by the demonstration of a characteristic echo-producing mass in the LA with TTE.

CARDIAC CATHETERIZATION

Left and right heart catheterization can be useful when there is a discrepancy between the clinical and noninvasive findings, including those from TEE and exercise echocardiographic testing as appropriate. Catheterization is helpful in assessing associated lesions, such as aortic stenosis (AS) and AR. Catheterization and coronary angiography are not usually necessary to aid in decision-making about surgery in patients younger than 65 years of age with typical findings of severe mitral obstruction on physical examination and TTE. In men older than 40 years of age, women older than 45 years of age, and younger patients with coronary risk factors, especially those with positive noninvasive stress tests for myocardial ischemia, coronary angiography is advisable preoperatively to identify patients with critical coronary obstructions that should be bypassed at the time of operation. Computed tomographic coronary angiography (CTCA) (Chap. 270e) is now often used to screen preoperatively for the

presence of coronary artery disease (CAD) in patients with valvular heart disease and low pretest likelihood of CAD. Catheterization and left ventriculography may be useful in patients who have undergone PMBV or previous mitral valve surgery for MS, and who have redeveloped limiting symptoms, especially if questions regarding the severity of the valve lesion(s) remain after noninvasive study.

TREATMENT MITRAL STENOSIS

(Fig. 284-1) Penicillin prophylaxis of group A β -hemolytic streptococcal infections (Chap. 381) for secondary prevention of rheumatic fever is important for at-risk patients with rheumatic MS. Recommendations for infective endocarditis prophylaxis are similar to those for other valve lesions and are restricted to patients at high risk for complications from infection, including patients with a history of endocarditis. In symptomatic patients, some improvement usually occurs with restriction of sodium intake and small doses of oral diuretics. Beta blockers, nondihydropyridine calcium channel blockers (e.g., verapamil or diltiazem), and digitalis glycosides are useful in slowing the ventricular rate of patients with AF. Warfarin therapy targeted to an international normalized ratio (INR) of 2–3 should be administered indefinitely to patients with MS who have AF or a history of thromboembolism. The routine use of warfarin in patients in sinus rhythm with LA enlargement (maximal dimension

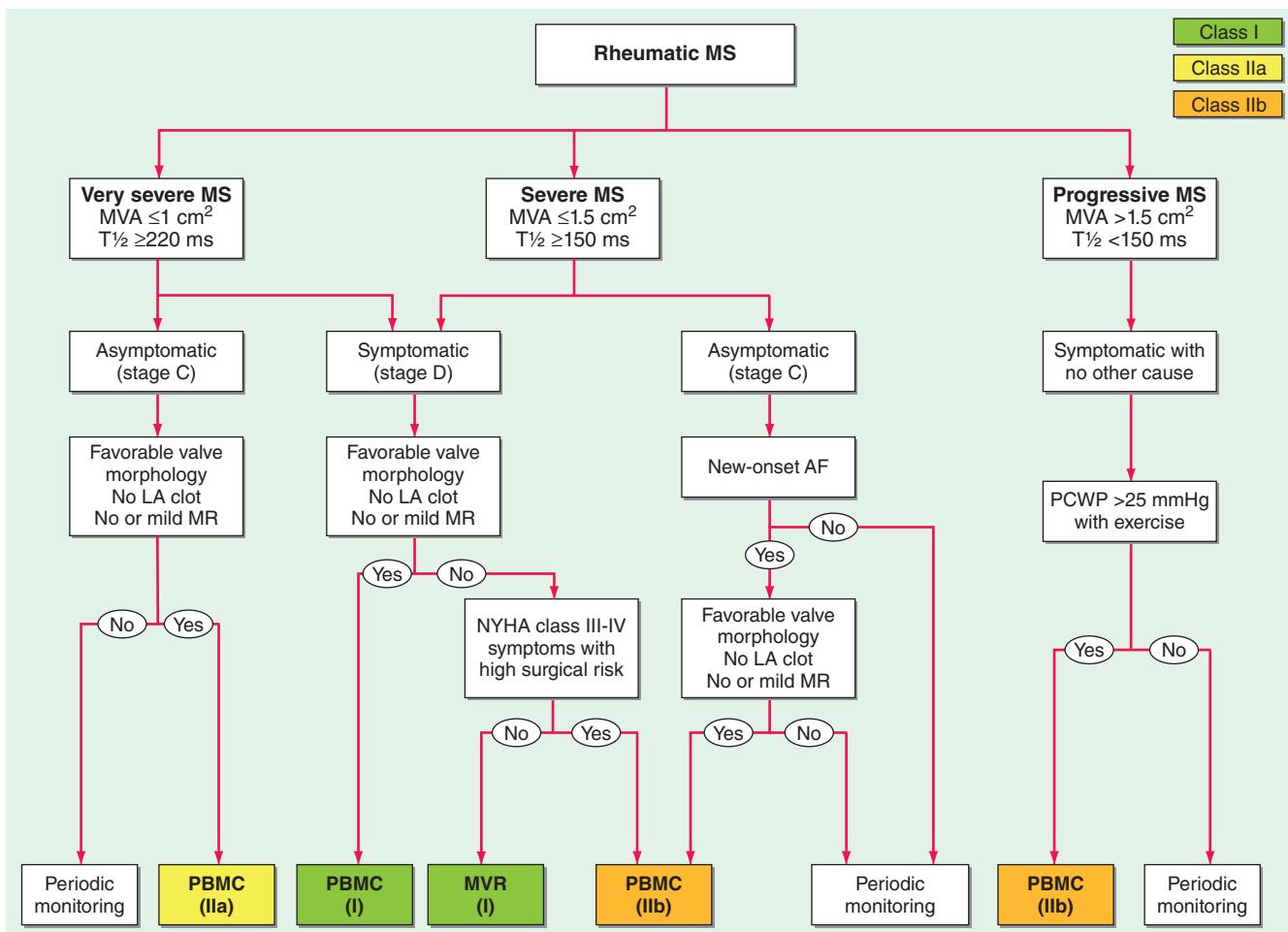


FIGURE 284-1 Management of rheumatic mitral stenosis. See legend for Fig. 283-2 for explanation of treatment recommendations (class I, IIa, IIb) and disease stages (C, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. AF, atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; and T½, pressure half-time. (Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol doi: 10.1016/j.jacc.2014.02.536, 2014, with permission.)

1542 >5.5 cm) with or without spontaneous echo contrast is more controversial. The novel oral anticoagulants are not approved for use in patients with significant valvular heart disease.

If AF is of relatively recent onset in a patient whose MS is not severe enough to warrant PMBV or surgical commissurotomy, reversion to sinus rhythm pharmacologically or by means of electrical countershock is indicated. Usually, cardioversion should be undertaken after the patient has had at least 3 consecutive weeks of anticoagulant treatment to a therapeutic INR. If cardioversion is indicated more urgently, then intravenous heparin should be provided and TEE performed to exclude the presence of LA thrombus before the procedure. Conversion to sinus rhythm is rarely successful or sustained in patients with severe MS, particularly those in whom the LA is especially enlarged or in whom AF has been present for more than 1 year.

PART 10

Disorders of the Cardiovascular System

MITRAL VALVOTOMY

Unless there is a contraindication, mitral valvotomy is indicated in symptomatic (New York Heart Association [NYHA] Functional Class II–IV) patients with isolated severe MS, whose effective orifice (valve area) is <~1 cm²/m² body surface area, or <1.5 cm² in normal-sized adults. Mitral valvotomy can be carried out by two techniques: PMBV and surgical valvotomy. In PMBV (Figs. 284-2 and 284-3), a catheter is directed into the LA after transseptal puncture, and a single balloon is directed across the valve and inflated in the valvular orifice. Ideal patients have relatively pliable leaflets with little or no commissural calcium. In addition, the subvalvular structures should not be significantly scarred or thickened, and there should be no LA thrombus. The short- and long-term results of this procedure in appropriate patients are similar to those of surgical valvotomy, but with less morbidity and a lower periprocedural mortality rate. Event-free

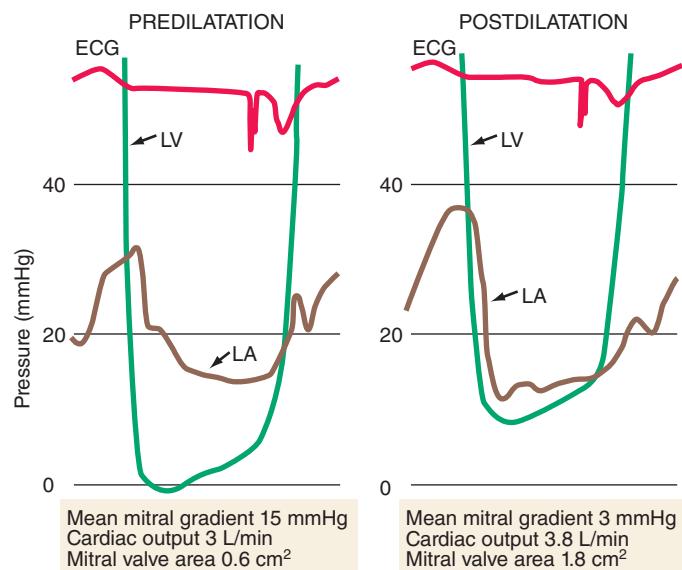


FIGURE 284-3 Simultaneous left atrial (LA) and left ventricular (LV) pressure before and after percutaneous mitral balloon valvuloplasty (PMBV) in a patient with severe mitral stenosis. ECG, electrocardiogram. (Courtesy of Raymond G. McKay, MD; with permission.)

survival in younger (<45 years) patients with pliable valves is excellent, with rates as high as 80–90% over 3–7 years. Therefore, PMBV has become the procedure of choice for such patients when it can be performed by a skilled operator in a high-volume center.

TTE is helpful in identifying patients for the percutaneous procedure, and TEE is performed routinely to exclude LA thrombus and to assess the degree of MR at the time of the scheduled procedure. An “echo score” has been developed to help guide decision-making. The score accounts for the degree of leaflet thickening, calcification, and mobility, and for the extent of subvalvular thickening. A lower score predicts a higher likelihood of successful PMBV.

In patients in whom PMBV is not possible or unsuccessful, or in many patients with restenosis after previous surgery, an “open” valvotomy using cardiopulmonary bypass is necessary. In addition to opening the valve commissures, it is important to loosen any subvalvular fusion of papillary muscles and chordae tendineae; to remove large deposits of calcium, thereby improving valvular function; and to remove atrial thrombi. The perioperative mortality rate is ~2%.

Successful valvotomy is defined by a 50% reduction in the mean mitral valve gradient and a doubling of the mitral valve area. Successful valvotomy, whether balloon or surgical, usually results in striking symptomatic and hemodynamic improvement and prolongs survival. However, there is no evidence that the procedure improves the prognosis of patients with slight or no functional impairment. Therefore, unless recurrent systemic embolization or severe pulmonary hypertension has occurred (PA systolic pressures >50 mmHg at rest or >60 mmHg with exercise), valvotomy is *not* recommended for patients who are entirely asymptomatic and/or who have mild or moderate stenosis (mitral valve area >1.5 cm²). When there is little symptomatic improvement after valvotomy, it is likely that the procedure was ineffective, that it induced MR, or that associated valvular or myocardial disease was present. About half of all patients undergoing surgical mitral valvotomy require reoperation by 10 years. In the pregnant patient with MS, valvotomy should be carried out if pulmonary congestion occurs despite intensive medical treatment. PMBV is the preferred strategy in this setting and is performed with TEE and no or minimal x-ray exposure.

Mitral valve replacement (MVR) is necessary in patients with MS and significant associated MR, those in whom the valve has been severely distorted by previous transcatheter or operative

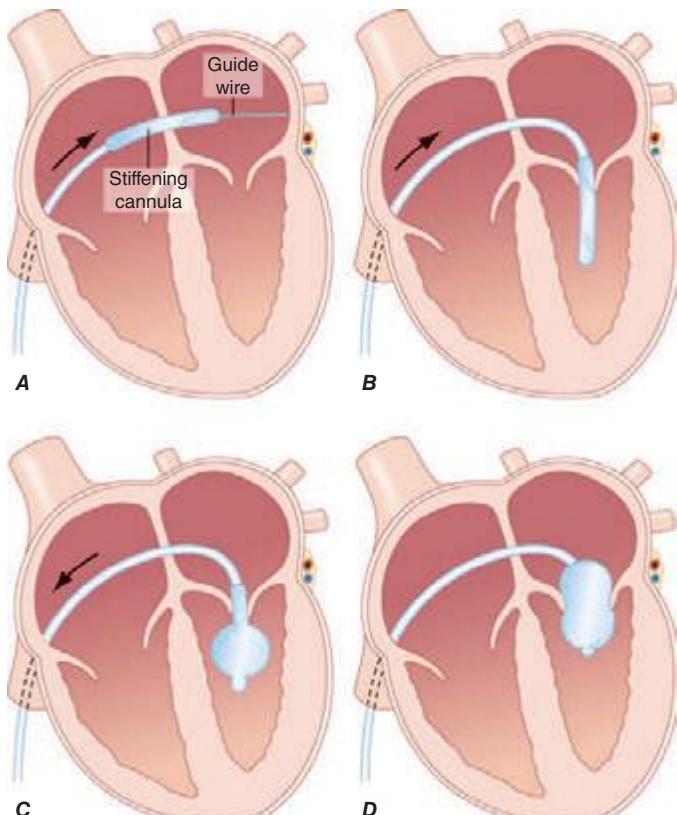


FIGURE 284-2 Inoue balloon technique for percutaneous mitral balloon valvotomy. **A.** After transseptal puncture, the deflated balloon catheter is advanced across the interatrial septum, then across the mitral valve and into the left ventricle. **B–D.** The balloon is inflated stepwise within the mitral orifice.

TABLE 284-2 MORTALITY RATES AFTER MITRAL VALVE SURGERY^a

Operation	Number	Unadjusted Operative Mortality (%)
MVR (isolated)	3154	5.2
MVR + CAB	1184	10.0
MVRp	4215	1.0
MVRp + CAB	2330	4.8

^aData are for the first two quarters of calendar year 2013, during which 1004 sites reported a total of 135,666 procedures. Data are available from the Society of Thoracic Surgeons at http://www.sts.org/sites/default/files/documents/2013_3rdHarvestExecutiveSummary.pdf.

Abbreviations: CAB, coronary artery bypass; MVR, mitral valve replacement; MVRp, mitral valve repair.

manipulation, or those in whom the surgeon does not find it possible to improve valve function significantly with valvotomy. MVR is now routinely performed with preservation of the chordal attachments to optimize LV functional recovery. Perioperative mortality rates with MVR vary with age, LV function, the presence of CAD, and associated comorbidities. They average 5% overall but are lower in young patients and may be twice as high in patients >65 years of age with significant comorbidities (Table 284-2). Because there are also long-term complications of valve replacement, patients in whom preoperative evaluation suggests the possibility that MVR may be required should be operated on only if they have severe MS—i.e., an orifice area $\leq 1.5 \text{ cm}^2$ —and are in NYHA Class III, i.e., symptomatic with ordinary activity despite optimal medical therapy. The overall 10-year survival of surgical survivors is ~70%. Long-term prognosis is worse in patients >65 years of age and those with marked disability and marked depression of the CO preoperatively. Pulmonary hypertension and RV dysfunction are additional risk factors for poor outcome.

MITRAL REGURGITATION

ETIOLOGY

MR may result from an abnormality or disease process that affects any one or more of the five functional components of the mitral valve apparatus (leaflets, annulus, chordae tendineae, papillary muscles, and subjacent myocardium) (Table 284-1). Acute MR can occur in the setting of acute myocardial infarction (MI) with papillary muscle rupture (Chap. 295), following blunt chest wall trauma, or during the course of infective endocarditis. With acute MI, the posteromedial papillary muscle is involved much more frequently than the anterolateral papillary muscle because of its singular blood supply. Transient, acute MR can occur during periods of active ischemia and bouts of angina pectoris. Rupture of chordae tendineae can result in “acute-on-chronic MR” in patients with myxomatous degeneration of the valve apparatus.

Chronic MR can result from rheumatic disease, mitral valve prolapse (MVP), extensive mitral annular calcification, congenital valve defects, hypertrophic obstructive cardiomyopathy (HOCM), and dilated cardiomyopathy (Chap. 287). Distinction also should be drawn between primary (degenerative, organic) MR, in which the leaflets and/or chordae tendineae are primarily responsible for abnormal valve function, and functional (secondary) MR, in which the leaflets and chordae tendineae are structurally normal but the regurgitation is caused by annular enlargement, papillary muscle displacement, leaflet tethering, or their combination. The rheumatic process produces rigidity, deformity, and retraction of the valve cusps and commissural fusion, as well as shortening, contraction, and fusion of the chordae tendineae. The MR associated with both MVP and HOCM is usually dynamic in nature. MR in HOCM occurs as a consequence of anterior papillary muscle displacement and systolic anterior motion of the anterior mitral valve leaflet into the narrowed LV outflow tract. Annular calcification is especially prevalent among patients with advanced renal disease and is commonly observed in women >65 years of age with hypertension and diabetes. MR may occur as a congenital

anomaly (Chap. 282), most commonly as a defect of the endocardial cushions (atrioventricular cushion defects). A cleft anterior mitral valve leaflet accompanies primum atrial septal defect. Chronic MR is frequently secondary to ischemia and may occur as a consequence of ventricular remodeling, papillary muscle displacement, and leaflet tethering, or with fibrosis of a papillary muscle, in patients with healed MI(s) and ischemic cardiomyopathy. Similar mechanisms of annular dilation and ventricular remodeling contribute to the MR that occurs among patients with nonischemic forms of dilated cardiomyopathy once the LV end-diastolic dimension reaches 6 cm.

Irrespective of cause, chronic severe MR is often progressive, because enlargement of the LA places tension on the posterior mitral leaflet, pulling it away from the mitral orifice and thereby aggravating the valvular dysfunction. Similarly, LV dilation increases the regurgitation, which, in turn, enlarges the LA and LV further, resulting in a vicious circle; hence the aphorism, “mitral regurgitation begets mitral regurgitation.”

PATOPHYSIOLOGY

The resistance to LV emptying (LV afterload) is reduced in patients with MR. As a consequence, the LV is decompressed into the LA during ejection, and with the reduction in LV size during systole, there is a rapid decline in LV tension. The initial compensation to MR is more complete LV emptying. However, LV volume increases progressively with time as the severity of the regurgitation increases and as LV contractile function deteriorates. This increase in LV volume is often accompanied by a reduced forward CO. LV compliance is often increased, and thus, LV diastolic pressure does not increase until late in the course. The regurgitant volume varies directly with the LV systolic pressure and the size of the regurgitant orifice; the latter, in turn, is influenced by the extent of LV and mitral annular dilation. Because EF rises in severe MR in the presence of normal LV function, even a modest reduction in this parameter (<60%) reflects significant dysfunction.

During early diastole, as the distended LA empties, there is a particularly rapid γ descent in the absence of accompanying MS. A brief, early diastolic LA-LV pressure gradient (often generating a rapid filling sound [S_1] and mid-diastolic murmur masquerading as MS) may occur in patients with pure, severe MR as a result of the very rapid flow of blood across a normal-sized mitral orifice.

Semiquantitative estimates of LV ejection fraction (LVEF), CO, PA systolic pressure, regurgitant volume, regurgitant fraction (RF), and the effective regurgitant orifice area can be obtained during a careful Doppler echocardiographic examination. These measurements can also be obtained accurately with cardiac magnetic resonance (CMR) imaging, although this technology is not widely available. Left and right heart catheterization with contrast ventriculography is used less frequently. Severe, nonischemic MR is defined by a regurgitant volume $\geq 60 \text{ mL/beat}$, RF $\geq 50\%$, and effective regurgitant orifice area $\geq 0.40 \text{ cm}^2$. Severe ischemic MR, however, is usually associated with an effective regurgitant orifice area of $>0.2 \text{ cm}^2$. In the latter instance, lesser degrees of MR carry relatively greater prognostic weight.

LA Compliance In acute severe MR, the regurgitant volume is delivered into a normal-sized LA having normal or reduced compliance. As a result, LA pressures rise markedly for any increase in LA volume. The γ wave in the LA pressure pulse is usually prominent, LA and pulmonary venous pressures are markedly elevated, and pulmonary edema is common. Because of the rapid rise in LA pressures during ventricular systole, the murmur of acute MR is early in timing and decrescendo in configuration ending well before S_2 , as a reflection of the progressive diminution in the LV-LA pressure gradient. LV systolic function in acute MR may be normal, hyperdynamic, or reduced, depending on the clinical context.

Patients with chronic severe MR, on the other hand, develop marked LA enlargement and *increased* LA compliance with little if any increase in LA and pulmonary venous pressures for any increase in LA volume. The LA γ wave is relatively less prominent. The murmur of chronic MR is classically holosystolic in timing and plateau in configuration, as a reflection of the near-constant LV-LA pressure gradient. These patients usually complain of severe fatigue and exhaustion secondary

to a low forward CO, whereas symptoms resulting from pulmonary congestion are less prominent initially; AF is almost invariably present once the LA dilates significantly.

SYMPTOMS

Patients with chronic mild-to-moderate, isolated MR are usually asymptomatic. This form of LV volume overload is well tolerated. Fatigue, exertional dyspnea, and orthopnea are the most prominent complaints in patients with chronic severe MR. Palpitations are common and may signify the onset of AF. Right-sided heart failure, with painful hepatic congestion, ankle edema, distended neck veins, ascites, and secondary TR, occurs in patients with MR who have associated pulmonary vascular disease and pulmonary hypertension. Acute pulmonary edema is common in patients with acute severe MR.

PHYSICAL FINDINGS

In patients with chronic severe MR, the arterial pressure is usually normal, although the carotid arterial pulse may show a sharp, low-volume upstroke owing to the reduced forward CO. A systolic thrill is often palpable at the cardiac apex, the LV is hyperdynamic with a brisk systolic impulse and a palpable rapid-filling wave (S_3), and the apex beat is often displaced laterally.

In patients with acute severe MR, the arterial pressure may be reduced with a narrow pulse pressure, the jugular venous pressure and wave forms may be normal or increased and exaggerated, the apical impulse is not displaced, and signs of pulmonary congestion are prominent.

Auscultation S_1 is generally absent, soft, or buried in the holosystolic murmur of chronic, severe MR. In patients with severe MR, the aortic valve may close prematurely, resulting in wide but physiologic splitting of S_2 . A low-pitched S_3 occurring 0.12–0.17 s after the aortic valve closure sound, i.e., at the completion of the rapid-filling phase of the LV, is believed to be caused by the sudden tensing of the papillary muscles, chordae tendineae, and valve leaflets. It may be followed by a short, rumbling, mid-diastolic murmur, even in the absence of structural MS. A fourth heart sound is often audible in patients with *acute* severe MR who are in sinus rhythm. A presystolic murmur is not ordinarily heard with isolated MR.

A systolic murmur of at least grade III/VI intensity is the most characteristic auscultatory finding in chronic severe MR. It is usually holosystolic (see Fig. 267-5A), but as previously noted, it is decrescendo and ceases in mid to late systole in patients with acute severe MR. The systolic murmur of chronic MR is usually most prominent at the apex and radiates to the axilla. However, in patients with ruptured chordae tendineae or primary involvement of the posterior mitral leaflet with prolapse or flail, the regurgitant jet is eccentric, directed anteriorly, and strikes the LA wall adjacent to the aortic root. In this situation, the systolic murmur is transmitted to the base of the heart and, therefore, may be confused with the murmur of AS. In patients with ruptured chordae tendineae, the systolic murmur may have a cooing or “seagull” quality, whereas a flail leaflet may produce a murmur with a musical quality. The systolic murmur of chronic MR not due to MVP is intensified by isometric exercise (handgrip) but is reduced during the strain phase of the Valsalva maneuver because of the associated decrease in LV preload.

LABORATORY EXAMINATION

ECG In patients with sinus rhythm, there is evidence of LA enlargement, but RA enlargement also may be present when pulmonary hypertension is significant and affects RV function. Chronic severe MR is frequently associated with AF. In many patients, there is no clear-cut ECG evidence of enlargement of either ventricle. In others, the signs of eccentric LV hypertrophy are present.

Echocardiogram TTE is indicated to assess the mechanism of the MR and its hemodynamic severity. LV function can be assessed from LV end-diastolic and end-systolic volumes and EF. Observations can be made regarding leaflet structure and function, chordal integrity, LA and LV size, annular calcification, and regional and global LV systolic function. Doppler imaging should demonstrate the width or

area of the color flow MR jet within the LA, the duration and intensity of the continuous wave Doppler signal, the pulmonary venous flow contour, the early peak mitral inflow velocity, and quantitative measures of regurgitant volume, RF, and effective regurgitant orifice area. In addition, the PAPs can be estimated from the TR jet velocity. TTE is also indicated to follow the course of patients with chronic MR and to provide rapid assessment for any clinical change. The echocardiogram in patients with MVP is described in the next section. TEE provides greater anatomic detail than TTE (see Fig. 270e-5). Exercise testing with TTE can be useful to assess exercise capacity as well as any dynamic change in MR severity, PA systolic pressures, and biventricular function, for patients in whom there is a discrepancy between clinical findings and the results of functional testing performed at rest.

Chest X-Ray The LA and LV are the dominant chambers in chronic MR. Late in the course of the disease, the LA may be massively enlarged and forms the right border of the cardiac silhouette. Pulmonary venous congestion, interstitial edema, and Kerley B lines are sometimes noted. Marked calcification of the mitral leaflets occurs commonly in patients with long-standing, combined rheumatic MR and MS. Calcification of the mitral annulus may be visualized, particularly on the lateral view of the chest. Patients with acute severe MR may have asymmetric pulmonary edema if the regurgitant jet is directed predominantly to the orifice of an upper lobe pulmonary vein.

TREATMENT

MITRAL REGURGITATION

MEDICAL TREATMENT (FIG. 284-4)

The management of chronic severe MR depends to some degree on its cause. Warfarin should be provided once AF intervenes with a target INR of 2–3. Novel oral anticoagulants are not approved for this indication. Cardioversion should be considered depending on the clinical context and LA size. In contrast to the acute setting, there are no large, long-term prospective studies to substantiate the use of vasodilators for the treatment of chronic, isolated severe MR with preserved LV systolic function *in the absence of systemic hypertension*. The severity of MR in the setting of an ischemic or nonischemic dilated cardiomyopathy may diminish with aggressive guideline-directed treatment of heart failure including the use of diuretics, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, digitalis, and biventricular pacing (cardiac resynchronization therapy [CRT]) when otherwise indicated. Asymptomatic patients with severe MR in sinus rhythm with normal LV size and systolic function should avoid isometric forms of exercise.

Patients with acute severe MR require urgent stabilization and preparation for surgery. Diuretics, intravenous vasodilators (particularly sodium nitroprusside), and even intraaortic balloon counterpulsation may be needed for patients with post-MI papillary muscle rupture or other forms of acute severe MR.

SURGICAL TREATMENT

In the selection of patients with chronic, nonischemic, primary or organic, severe MR for surgical treatment, the often slowly progressive nature of the condition must be balanced against the immediate and long-term risks associated with operation. These risks are significantly lower for primary valve repair than for valve replacement (Table 287-2). Repair usually consists of valve reconstruction using a variety of valvuloplasty techniques and insertion of an annuloplasty ring. Repair spares the patient the long-term adverse consequences of valve replacement, including thromboembolic and hemorrhagic complications in the case of mechanical prostheses and late valve failure necessitating repeat valve replacement in the case of bioprostheses. In addition, by preserving the integrity of the papillary muscles, subvalvular apparatus, and chordae tendineae, mitral repair and valvuloplasty maintain LV function to a relatively greater degree.

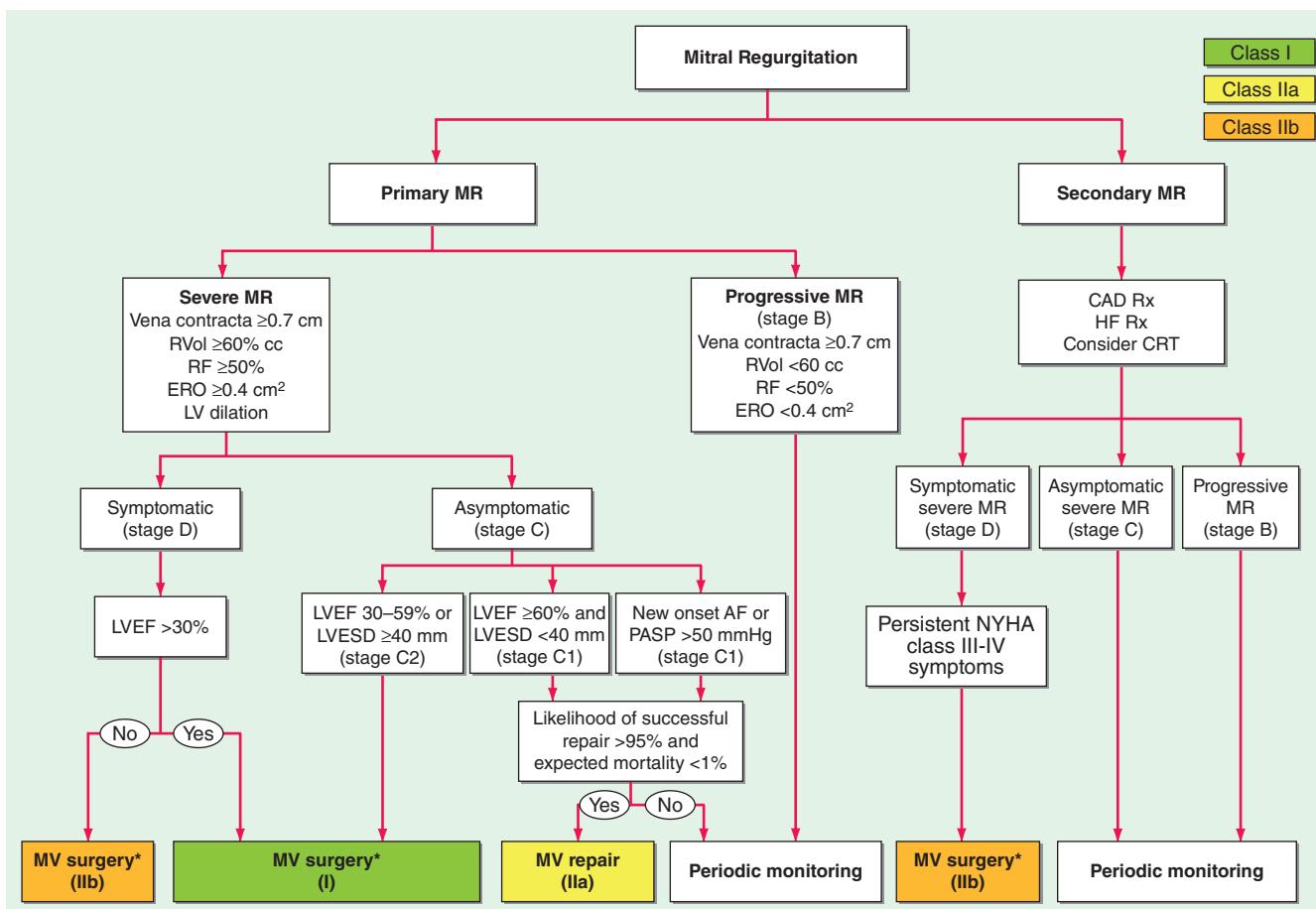


FIGURE 284-4 Management of mitral regurgitation. See legend for Fig. 283-2 for explanation of treatment recommendations (class I, IIa, IIb) and disease stages (B, C1, C2, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. AF, atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy. *Mitral valve repair preferred over MVR when possible. (Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. *J Am Coll Cardiol* doi: 10.1016/j.jacc.2014.02.536, 2014, with permission.)

Surgery for chronic nonischemic severe MR is indicated once symptoms occur, especially if valve repair is feasible (Fig. 284-4). Other indications for early consideration of mitral valve repair include recent-onset AF and pulmonary hypertension defined as a systolic PA pressure ≥ 50 mmHg at rest or ≥ 60 mmHg with exercise. Surgical treatment of chronic nonischemic severe MR is indicated for asymptomatic patients when LV dysfunction is progressive with the LVEF falling below 60% and/or end-systolic dimension increasing beyond 40 mm. These aggressive recommendations for surgery are predicated on the outstanding results achieved with mitral valve repair particularly when applied to patients with myxomatous disease such as that associated with prolapse or flail leaflet. Indeed primary valvuloplasty repair of patients younger than 75 years with normal LV systolic function and no CAD can now be performed by experienced surgeons with $<1\%$ perioperative mortality risk. The risk of stroke, however, is also approximately 1%. Repair is feasible in up to 95% of patients with myxomatous disease operated on by a high-volume surgeon in a referral center of excellence. Long-term durability is excellent; the incidence of reoperative surgery for failed primary repair is $\sim 1\%$ per year for the first 10 years after surgery. For patients with AF, left or batrial maze surgery, or radiofrequency, isolation of the pulmonary veins is often performed to reduce the risk of recurrent postoperative AF.

The surgical management of patients with functional, ischemic MR is more complicated and most often involves simultaneous

coronary artery revascularization. Current surgical practice includes annuloplasty repair with an undersized, rigid ring or chord-sparing valve replacement for patients with moderate or greater degrees of MR. Valve repair for ischemic MR is associated with lower perioperative mortality rates but higher rates of recurrent MR over time. In patients with ischemic MR and significantly impaired LV systolic function ($EF < 30\%$), the risk of surgery is higher, recovery of LV performance is incomplete, and long-term survival is reduced. Referral for surgery must be individualized and made only after aggressive attempts with guideline-directed medical therapy and CRT, when indicated. The routine performance of valve repair in patients with significant MR in the setting of severe, functional, nonischemic dilated cardiomyopathy has not been shown to improve long-term survival compared with optimal medical therapy. Patients with acute severe MR can often be stabilized temporarily with appropriate medical therapy, but surgical correction will be necessary emergently in the case of papillary muscle rupture and within days to weeks in most other settings.

When surgical treatment is contemplated, left and right heart catheterization and left ventriculography may be helpful in confirming the presence of severe MR in patients in whom there is a discrepancy between the clinical and TTE findings that cannot be resolved with TEE or CMR. Coronary angiography identifies patients who require concomitant coronary revascularization.



FIGURE 284-5 Clip used to grasp the free edges of the anterior and posterior leaflets in their midsections during transcatheter repair of selected patients with mitral regurgitation. (Courtesy of Abbott Vascular. © 2014 Abbott Laboratories. All rights reserved.)

TRANSCATHETER MITRAL VALVE REPAIR

A transcatheter approach to the treatment of either organic or functional MR may be feasible in selected patients with appropriate anatomy. The proper role of currently available techniques remains under active investigation. One approach involves the deployment of a clip delivered via transseptal puncture that grasps the leading edges of the mitral leaflets in their mid-portion (anterior scallop to posterior scallop or A2-P2; Fig. 284-5). The length and width of the gap between these leading edges dictate patient eligibility. The device is commercially available for the treatment of prohibitive surgical risk patients with severe, degenerative (organic) MR and is undergoing study in the United States for treatment of patients with symptomatic heart failure, reduced LVEF, and severe, functional MR despite guideline-directed medical therapy. A second approach involves the deployment of a device within the coronary sinus that can be adjusted to reduce its circumference, thus secondarily decreasing the circumference of the mitral annulus and the effective orifice area of the valve much like a surgically implanted ring. Variations in the anatomic relationship of the coronary sinus to the mitral annulus and circumflex coronary artery have limited the applicability of this technique. Attempts to reduce the septal-lateral dimension of a dilated annulus using adjustable cords placed across the LV in a subvalvular location have also been investigated.

MITRAL VALVE PROLAPSE

MVP, also variously termed the *systolic click-murmur syndrome*, *Barlow's syndrome*, *floppy-valve syndrome*, and *billowing mitral leaflet syndrome*, is a relatively common but highly variable clinical syndrome resulting from diverse pathologic mechanisms of the mitral valve apparatus. Among these are excessive or redundant mitral leaflet tissue, which is commonly associated with myxomatous degeneration and greatly increased concentrations of certain glycosaminoglycans.

In most patients with MVP, the cause is unknown, but in some, it appears to be genetically determined. A reduction in the production of type III collagen has been incriminated, and electron microscopy has revealed fragmentation of collagen fibrils.

MVP is a frequent finding in patients with heritable disorders of connective tissue, including Marfan's syndrome (Chap. 427), osteogenesis imperfecta, and Ehlers-Danlos syndrome. MVP may be associated with thoracic skeletal deformities similar to but not as severe as those in Marfan's syndrome, such as a high-arched palate and alterations of the chest and thoracic spine, including the so-called straight back syndrome.

In most patients with MVP, myxomatous degeneration is confined to the mitral valve, although the tricuspid and aortic valves may also be affected. The posterior mitral leaflet is usually more affected than the anterior, and the mitral valve annulus is often dilated. In many patients, elongated, redundant, or ruptured chordae tendineae cause or contribute to the regurgitation.

MVP also may occur rarely as a sequel to acute rheumatic fever, in ischemic heart disease, and in various cardiomyopathies, as well as in 20% of patients with ostium secundum atrial septal defect.

MVP may lead to excessive stress on the papillary muscles, which, in turn, leads to dysfunction and ischemia of the papillary muscles and the subjacent ventricular myocardium. Rupture of chordae tendineae and progressive annular dilation and calcification contribute to valvular regurgitation, which then places more stress on the diseased mitral valve apparatus, thereby creating a vicious circle. ECG changes (see below) and ventricular arrhythmias described in some patients with MVP appear to result from regional ventricular dysfunction related to the increased stress placed on the papillary muscles.

CLINICAL FEATURES

MVP is more common in women and occurs most frequently between the ages of 15 and 30 years; the clinical course is most often benign. MVP may also be observed in older (>50 years) patients, often men, in whom MR is often more severe and requires surgical treatment. There is an increased familial incidence for some patients, suggesting an autosomal dominant form of inheritance with incomplete penetrance. MVP varies in its clinical expression, ranging from only a systolic click and murmur with mild prolapse of the posterior leaflet to severe MR due to chordal rupture and leaflet flail. The degree of myxomatous change of the leaflets can also vary widely. In many patients, the condition progresses over years or decades; in others, it worsens rapidly as a result of chordal rupture or endocarditis.

Most patients are asymptomatic and remain so for their entire lives. However, in North America, MVP is now the most common cause of isolated severe MR requiring surgical treatment. Arrhythmias, most commonly ventricular premature contractions and paroxysmal supraventricular and ventricular tachycardia, as well as AF, have been reported and may cause palpitations, light-headedness, and syncope. Sudden death is a very rare complication and occurs most often in patients with severe MR and depressed LV systolic function. There may be an excess risk of sudden death among patients with a flail leaflet. Many patients have chest pain that is difficult to evaluate; it is often substernal, prolonged, and not related to exertion, but may rarely resemble angina pectoris. Transient cerebral ischemic attacks secondary to emboli from the mitral valve due to endothelial disruption have been reported. Infective endocarditis may occur in patients with MR and/or leaflet thickening.

Auscultation A frequent finding is the mid or late (nonejection) systolic click, which occurs 0.14 s or more after S_1 and is thought to be generated by the sudden tensing of slack, elongated chordae tendineae or by the prolapsing mitral leaflet when it reaches its maximal excursion. Systolic clicks may be multiple and may be followed by a high-pitched, mid-late systolic crescendo-decrescendo murmur, which occasionally is "whooping" or "honking" and is heard best at the apex. The click and murmur occur earlier with standing, during the strain phase of the Valsalva maneuver, and with any intervention that decreases LV volume, exaggerating the propensity of mitral leaflet prolapse. Conversely, squatting and isometric exercises, which increase LV volume, diminish MVP; the click-murmur complex is delayed, moves away from S_1 , and may even disappear. Some patients have a mid-systolic click without a murmur; others have a murmur without a click. Still others have both sounds at different times.

LABORATORY EXAMINATION

The ECG most commonly is normal but may show biphasic or inverted T waves in leads II, III, and aVF, and occasionally supraventricular or ventricular premature beats. TTE is particularly effective in identifying the abnormal position and prolapse of the mitral valve leaflets. A useful echocardiographic definition of MVP is systolic displacement (in the

parasternal long axis view) of the mitral valve leaflets by at least 2 mm into the LA superior to the plane of the mitral annulus. Color flow and continuous wave Doppler imaging is helpful to evaluate the associated MR and provide semiquantitative estimates of severity. The jet lesion of MR due to MVP is most often eccentric, and assessment of RF and effective regurgitant orifice area can be difficult. TEE is indicated when more accurate information is required and is performed routinely for intraoperative guidance for valve repair. Invasive left ventriculography is rarely necessary but can also show prolapse of the posterior and sometimes of both mitral valve leaflets.

TREATMENT MITRAL VALVE PROLAPSE

Infective endocarditis prophylaxis is indicated only for patients with a prior history of endocarditis. Beta blockers sometimes relieve chest pain and control palpitations. If the patient is symptomatic from severe MR, mitral valve repair (or rarely, chord-sparing replacement) is indicated (Fig. 284-4). Antiplatelet agents, such as aspirin, should be given to patients with transient ischemic attacks, and if these are not effective, warfarin should be considered. Warfarin is also indicated once AF intervenes.

285 Tricuspid and Pulmonic Valve Disease

Patrick T. O'Gara, Joseph Loscalzo

TRICUSPID STENOSIS

Tricuspid stenosis (TS), which is much less prevalent than mitral stenosis (MS) in North America and Western Europe, is generally rheumatic in origin, and is more common in women than men (**Table 285-1**). It does not occur as an isolated lesion and is usually associated with MS. Hemodynamically significant TS occurs in 5–10% of patients with severe MS; rheumatic TS is commonly associated with some degree of tricuspid regurgitation (TR). Nonrheumatic causes of TS are rare.

PATHOPHYSIOLOGY

A diastolic pressure gradient between the right atrium (RA) and right ventricle (RV) defines TS. It is augmented when the transvalvular blood flow increases during inspiration and declines during expiration. A mean diastolic pressure gradient of 4 mmHg is usually sufficient to elevate the mean RA pressure to levels that result in systemic venous congestion. Unless sodium intake has been restricted and diuretics administered, this venous congestion is associated with hepatomegaly, ascites, and edema, sometimes severe. In patients with sinus rhythm, the RA *a* wave may be extremely tall and may even approach the level of the RV systolic pressure. The *y* descent is prolonged. The cardiac output (CO) at rest is usually depressed, and it fails to rise during exercise. The low CO is responsible for the normal or only slightly elevated left atrial (LA), pulmonary artery (PA), and RV systolic pressures despite the presence of MS. Thus, the presence of TS can mask the hemodynamic and clinical features of any associated MS.

SYMPOMTS

Because the development of MS generally precedes that of TS, many patients initially have symptoms of pulmonary congestion and fatigue. Characteristically, patients with severe TS complain of relatively little dyspnea for the degree of hepatomegaly, ascites, and edema that they have. However, fatigue secondary to a low CO and discomfort due to refractory edema, ascites, and marked hepatomegaly are common in patients with advanced TS and/or TR. In some patients, TS may be

TABLE 285-1 CAUSES OF TRICUSPID AND PULMONIC VALVE DISEASES

Valve Lesion	Etiologies
Tricuspid stenosis	Rheumatic Congenital
Tricuspid regurgitation	Primary (organic) Rheumatic Endocarditis Myxomatous (TVP) Carcinoid Radiation Congenital (Ebstein's) Trauma Papillary muscle injury (post-MI) Secondary (functional) RV and tricuspid annular dilatation due to multiple causes of RV enlargement (e.g., long-standing pulmonary HTN, remodeling post-RV MI) Chronic RV apical pacing
Pulmonic stenosis	Congenital Carcinoid Tumor Endocarditis
Pulmonic regurgitation	Primary valve disease Congenital Postvalvotomy Endocarditis Carcinoid Annular enlargement Pulmonary hypertension Idiopathic dilation Marfan's syndrome

Abbreviations: HTN, hypertension; MI, myocardial infarction; RV, right ventricular; TVP, tricuspid valve prolapse.

suspected for the first time when symptoms of right-sided failure persist after an adequate mitral valvotomy.

PHYSICAL FINDINGS

Because TS usually occurs in the presence of other obvious valvular disease, the diagnosis may be missed unless it is considered. Severe TS is associated with marked hepatic congestion, often resulting in cirrhosis, jaundice, serious malnutrition, anasarca, and ascites. Congestive hepatomegaly and, in cases of severe tricuspid valve disease, splenomegaly are present. The jugular veins are distended, and in patients with sinus rhythm, there may be giant *a* waves. The *v* waves are less conspicuous, and because tricuspid obstruction impedes RA emptying during diastole, there is a slow *y* descent. In patients with sinus rhythm, there may be prominent presystolic pulsations of the enlarged liver as well.

On auscultation, an opening snap (OS) of the tricuspid valve may rarely be heard approximately 0.06 s after pulmonic valve closure. The diastolic murmur of TS has many of the qualities of the diastolic murmur of MS, and because TS almost always occurs in the presence of MS, it may be missed. However, the tricuspid murmur is generally heard best along the left lower sternal border and over the xiphoid process, and is most prominent during presystole in patients with sinus rhythm. The murmur of TS is augmented during inspiration, and it is reduced during expiration and particularly during the strain phase of the Valsalva maneuver, when tricuspid transvalvular flow is reduced.

LABORATORY EXAMINATION

The electrocardiogram (ECG) features of RA enlargement (**see Fig. 268-8**) include tall, peaked P waves in lead II, as well as prominent, upright P waves in lead V₁. The absence of ECG evidence of RV

hypertrophy (RVH) in a patient with right-sided heart failure who is believed to have MS should suggest associated tricuspid valve disease. The chest x-ray in patients with combined TS and MS shows particular prominence of the RA and superior vena cava without much enlargement of the PA and with less evidence of pulmonary vascular congestion than occurs in patients with isolated MS. On echocardiographic examination, the tricuspid valve is usually thickened and domes in diastole; the transvalvular gradient can be estimated by continuous wave Doppler echocardiography. Severe TS is characterized by a valve area $\leq 1 \text{ cm}^2$ or pressure half-time of $\geq 190 \text{ ms}$. The RA and inferior vena cava (IVC) are enlarged. Transthoracic echocardiography (TTE) provides additional information regarding the severity of any associated TR, mitral valve structure and function, left ventricle (LV) and RV size and function, and PA pressure. Cardiac catheterization is not routinely necessary for assessment of TS.

TREATMENT TRICUSPID STENOSIS

Patients with TS generally exhibit marked systemic venous congestion; salt restriction, bed rest, and diuretic therapy are required during the preoperative period. Such a preparatory period may diminish hepatic congestion and thereby improve hepatic function sufficiently so that the risks of operation, particularly bleeding, are diminished. Surgical relief of the TS should be carried out, preferably at the time of surgical mitral valvotomy or mitral valve replacement (MVR) for mitral valve disease, in patients with moderate or severe TS who have mean diastolic pressure gradients exceeding $\sim 4 \text{ mmHg}$ and tricuspid orifice areas $< 1.5\text{--}2 \text{ cm}^2$. TS is almost always accompanied by significant TR. Operative repair may permit substantial improvement of tricuspid valve function. If repair cannot be accomplished, the tricuspid valve may have to be replaced. Meta-analysis has shown no difference in overall survival between mechanical and tissue valve replacement. Mechanical valves in the tricuspid position are more prone to thromboembolic complications than in other positions. Percutaneous tricuspid balloon valvuloplasty for isolated severe TS without significant TR is very rarely performed.

TRICUSPID REGURGITATION

In at least 80% of cases, TR is secondary to marked dilation of the tricuspid annulus from RV enlargement due to PA hypertension (Table 285-1). Functional TR may complicate RV enlargement of any cause, however, including an inferior myocardial infarction (MI) that involves the RV. It is commonly seen in the late stages of heart failure due to rheumatic or congenital heart disease with severe PA hypertension (PA systolic pressure $> 55 \text{ mmHg}$), as well as in ischemic and idiopathic dilated cardiomyopathies. It is reversible in part if PA hypertension can be relieved. Functional TR can also develop from chronic RV apical pacing. Rheumatic fever may produce primary (organic) TR, often associated with TS. Infarction of RV papillary muscles, tricuspid valve prolapse, carcinoid heart disease, endomyocardial fibrosis, radiation, infective endocarditis, and leaflet trauma all may produce TR. Less commonly, TR results from congenitally deformed tricuspid valves, and it occurs with defects of the atrioventricular canal, as well as with Ebstein's malformation of the tricuspid valve (Chap. 282).

PATHOPHYSIOLOGY

The incompetent tricuspid valve allows blood to flow backward from the RV into the RA, the volume of which is dependent on the driving pressure (i.e., RV systolic pressure) and the size of the regurgitant orifice. The severity and physical signs of TR can vary as a function of PA systolic pressure (in the absence of RV outflow tract stenosis), the dimension of the tricuspid valve annulus, the respiratory cycle-dependent changes in RV preload, and RA compliance. RV filling is increased during inspiration. Forward CO is reduced and does not augment with exercise. Significant degrees of TR will lead to RA enlargement and elevation of the RA and jugular venous pressures with prominent *c-v* waves in the pulse tracings. Progressively severe TR

can lead to "ventricularization" of the RA wave form (see Fig. 267-1B). Severe TR is also characterized by RV dilation (RV volume overload) and eventual systolic dysfunction, the rate of which can be accelerated by a concomitant pressure load from PA hypertension or by myocardial fibrosis from previous injury.

SYMPTOMS

Mild or moderate degrees of TR are usually well tolerated in the absence of other hemodynamic disturbances. Because TR most often coexists with left-sided valve lesions, LV dysfunction, and/or PA hypertension, symptoms related to these lesions may dominate the clinical picture. Fatigue and exertional dyspnea owing to reduced forward CO are early symptoms of isolated, severe TR. As the disease progresses and RV function declines, patients may report cervical pulsations, abdominal fullness/bloating, diminished appetite, and muscle wasting, although with progressive weight gain and painful swelling of the lower extremities.

PHYSICAL FINDINGS

The neck veins in patients with severe TR are distended with prominent *c-v* waves and rapid *y* descents (in the absence of TS). TR is more often diagnosed by examination of the neck veins than by auscultation of the heart sounds. Other findings may include marked hepatomegaly with systolic pulsations, ascites, pleural effusions, edema, and a positive hepatojugular reflex. A prominent RV pulsation along the left parasternal region and a blowing holosystolic murmur along the lower left sternal margin, which may be intensified during inspiration (Carvallo's sign) and reduced during expiration or the strain phase of the Valsalva maneuver, are characteristic findings. The murmur of TR may sometimes be confused with that of MR unless attention is paid to its variation during the respiratory cycle and the extent of RV enlargement is appreciated. Atrial fibrillation (AF) is usually present in the chronic phase of the disease.

LABORATORY EXAMINATION

The ECG may show changes characteristic of the lesion responsible for the TR, e.g., an inferior Q-wave MI suggestive of a prior RV MI, RVH, or a bizarre right bundle branch type pattern with preexcitation in patients with Ebstein's anomaly. ECG signs of RA enlargement may be present in patients with sinus rhythm; AF is frequently noted. The chest x-ray may show RA and RV enlargement, depending on the chronicity and severity of TR. TTE is usually definitive with demonstration of RA dilation and RV volume overload and prolapsing, flail, scarred, or displaced/tethered tricuspid leaflets; the diagnosis and assessment of TR can be made by color flow Doppler imaging (see Fig. 270e-8). Severe TR is accompanied by hepatic vein systolic flow reversal. Continuous wave Doppler of the TR velocity profile is useful in estimating PA systolic pressure. Accurate assessment of TR severity, PA pressures, and RV size and systolic function with TTE can be quite challenging in many patients. Real-time three-dimensional echocardiography and cardiac magnetic resonance (CMR) imaging provide alternative imaging modalities, although they are not widely available. In patients with severe TR, the CO is usually markedly reduced, and the RA pressure pulse may exhibit no *x* descent during early systole but a prominent *c-v* wave with a rapid *y* descent. The mean RA and RV end-diastolic pressures are often elevated. Exercise testing can be used to assess functional capacity in patients with asymptomatic severe TR. The prognostic significance of exercise-induced changes in TR severity and RV function has not been well studied.

TREATMENT TRICUSPID REGURGITATION (FIG. 285-1)

Diuretics can be useful for patients with severe TR and signs of right heart failure. An aldosterone antagonist may be particularly helpful because many patients have secondary hyperaldosteronism from marked hepatic congestion. Therapies to reduce elevated PA pressures and/or pulmonary vascular resistance, including those targeted at left-sided heart disease, can also be considered for patients with PA hypertension and severe functional TR. Tricuspid valve surgery is recommended for patients with severe TR who are undergoing

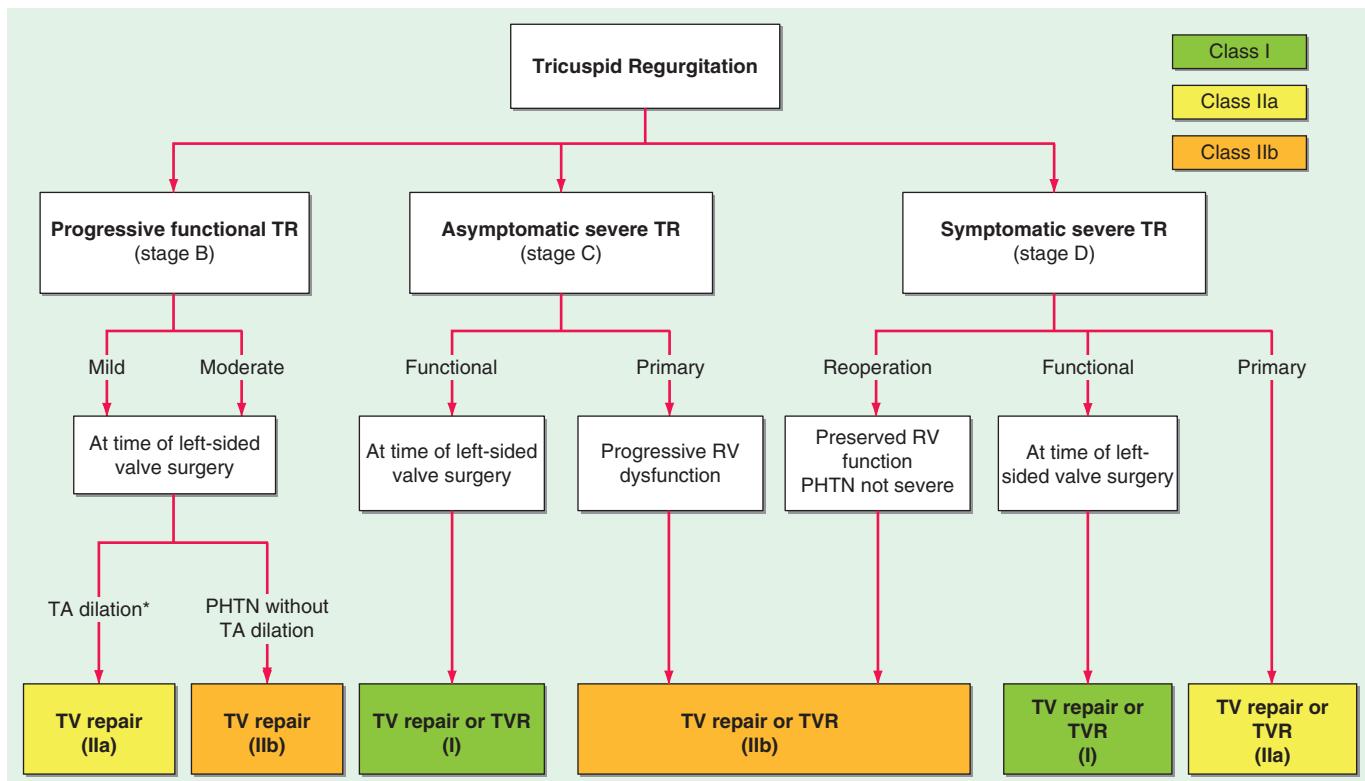


FIGURE 285-1 Management of tricuspid regurgitation. See legend for Fig. 283-2 for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (B, C, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. PHTN, pulmonary hypertension; RV, right ventricular; TA, tricuspid annular; TTE, transthoracic echocardiogram; TR, tricuspid regurgitation; TV, tricuspid valve; TVR, tricuspid valve replacement. *TA dilation is defined by >40 mm on TTE (>21 mm/m²) or >70 mm on direct intraoperative measurement. (Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol doi: 10.1016/j.jacc.2014.02.536, 2014, with permission.)

left-sided valve surgery and is also undertaken frequently for treatment of even moderate TR in patients undergoing left-sided valve surgery who have tricuspid annular dilation (>40 mm), a history of right heart failure, or PA hypertension. Operation most often comprises repair rather than replacement in these settings and has become routine in most major surgical centers. Surgery may also infrequently be required for treatment of severe, primary TR with right heart failure not responsive to standard medical therapy or because of progressively declining RV systolic function. Reported perioperative mortality rates for isolated tricuspid valve surgery (repair and replacement) are high (~8–9%) and likely are influenced by the hazards encountered during reoperation on patients who have undergone previous left-sided valve surgery and have reduced RV function. Indwelling pacemaker or defibrillator leads can also pose technical challenges.

PULMONIC STENOSIS

Pulmonic valve stenosis (PS) is essentially a congenital disorder (Table 285-1). With isolated PS, the valve is typically domed. Dysplastic pulmonic valves are seen as part of the Noonan's syndrome (Chap. 302), which maps to chromosome 12. Much less common etiologies include carcinoid and obstructing tumors or bulky vegetations. The pulmonic valve is only very rarely affected by the rheumatic process.

PATHOPHYSIOLOGY

PS is defined hemodynamically by a systolic pressure gradient between the RV and main PA. RV hypertrophy develops as a consequence of sustained obstruction to RV outflow, and systolic ejection is prolonged. Compared with the ability of the LV to compensate for the pressure overload imposed by aortic stenosis (AS), RV dysfunction from afterload mismatch occurs earlier in the course of PS and at lower peak systolic pressures, because the RV adapts less well to this type of

hemodynamic burden. With normal systolic function and CO, severe PS is defined by a peak systolic gradient across the pulmonic valve of >50 mmHg; moderate PS correlates with a peak gradient of 30–50 mmHg. PS rarely progresses in patients with peak gradients less than 30 mmHg, but may worsen in those with moderate disease due to valve thickening and calcification with age. The RA *a* wave elevates in relation to the higher pressures needed to fill a noncompliant, hypertrophied RV. A prominent RA *v* wave signifies functional TR from RV and annular dilation. The CO is maintained until late in the course of the disease.

SYMPTOMS

Patients with mild or even moderate PS are usually asymptomatic and first come to medical attention because of a heart murmur that leads to echocardiography. With severe PS, patients may report exertional dyspnea or early-onset fatigue. Anginal chest pain from RV oxygen supply-demand mismatch and syncope may occur with very severe forms of obstruction, particularly in the presence of a destabilizing trigger such as atrial fibrillation, fever, infection, or anemia.

PHYSICAL FINDINGS

The murmur of mild or moderate PS is mid-systolic in timing, crescendo-decrescendo in configuration, heard best in the left second interspace, and usually introduced by an ejection sound (click) in younger adults whose valves are still pliable. The ejection sound is the only right-sided acoustic event that decreases in intensity with inspiration. This phenomenon reflects premature opening of the pulmonic valve by the elevated RV end-diastolic (postatrial *a* wave) pressure. The systolic murmur increases in intensity during inspiration. With progressively severe PS, the ejection sound moves closer to the first heart sound and eventually becomes inaudible. A right-sided fourth heart sound may emerge. The systolic murmur peaks later and may persist through the aortic component of the second heart sound (A_2). Pulmonic valve

1550 closure is delayed, and the pulmonic component of the second heart sound (P_2) is reduced or absent. A prominent a wave, indicative of the higher atrial pressure necessary to fill the noncompliant RV, may be seen in the jugular venous pulse. A parasternal or RV lift can be felt with significant pressure overload. Signs of right heart failure, such as hepatomegaly, ascites, and edema, are uncommon but may appear very late in the disease.

LABORATORY EXAMINATION

The ECG will show right axis deviation, RVH, and RA enlargement in adult patients with severe PS. Chest x-ray findings include poststenotic dilation of the main PA in the frontal plane projection and filling of the retrosternal airspace due to RV enlargement on the lateral film. In some patients with RVH, the cardiac apex appears to be lifted off the left hemidiaphragm. The RA may also be enlarged. TTE allows definitive diagnosis and characterization in most cases, with depiction of the valve and assessment of the gradient, RV function, PA pressures (which should be low), and any associated cardiac lesions. TEE may be useful in some patients for improved delineation of the RV outflow tract (RVOT) and assessment of infundibular hypertrophy. Cardiac catheterization is not usually necessary, but if performed, pressures should be obtained from just below and above the pulmonic valve with attention to the possibility that a dynamic component to the gradient may exist. The correlation between Doppler assessment of peak instantaneous gradient and catheterization-measured peak-to-peak gradient is weak. The latter may correlate better with the Doppler mean gradient.

TREATMENT PULMONIC STENOSIS

Diuretics can be used to treat symptoms and signs of right heart failure. Provided there is less than moderate pulmonic regurgitation, pulmonic balloon valvotomy is recommended for symptomatic patients with a domed valve and a peak gradient >50 mmHg (or mean gradient >30 mmHg) and for asymptomatic patients with a peak gradient >60 mmHg (or mean gradient >40 mmHg). Surgery may be required when the valve is dysplastic (as seen in patients with Noonan's syndrome and other disorders). A multidisciplinary heart team is best positioned to make treatment decisions of this nature.

PULMONIC REGURGITATION

Pulmonic regurgitation (PR) may develop as a consequence of primary valve pathology, annular enlargement, or their combination; after surgical treatment of RVOT obstruction in children with such disorders as tetralogy of Fallot; or after pulmonic balloon valvotomy (Table 285-1). Carcinoid usually causes mixed pulmonic valve disease with PR and PS. Long-standing severe PA hypertension from any cause can result in dilation of the pulmonic valve ring and PR.

PATHOPHYSIOLOGY

Severe PR results in RV chamber enlargement and eccentric hypertrophy. As is the case for aortic regurgitation (AR), PR is a state of increased preload and afterload. The reverse pressure gradient from the PA to the RV, which drives the PR, progressively decreases throughout diastole and accounts for the decrescendo nature of the diastolic murmur. As RV diastolic pressure increases, the murmur becomes shorter in duration. The forward CO is preserved during the early stages of the disease, but may not increase normally with exercise and declines over time. A reduction in RV ejection fraction may be an early indicator of hemodynamic compromise. In advanced stages, there is significant enlargement of the RV and RA with marked elevation of the jugular venous pressure.

SYMPTOMS

Mild or moderate degrees of PR do not, by themselves, result in symptoms. Other problems, such as PA hypertension, may dominate the clinical picture. With progressively severe PR and RV dysfunction,

fatigue, exertional dyspnea, abdominal fullness/bloating, and lower extremity swelling may be reported.

PHYSICAL FINDINGS

The physical examination hallmark of PR is a high-pitched, decrescendo diastolic murmur (Graham Steell murmur) heard along the left sternal border that can be difficult to distinguish from the more frequently appreciated murmur of aortic regurgitation. The Graham Steell murmur may become louder with inspiration and is usually associated with a loud and sometimes palpable P_2 and an RV lift, as would be expected in patients with significant PA hypertension of any cause. Survivors of childhood surgery for tetralogy of Fallot or PS/pulmonary atresia may have an RV-PA conduit that is freely regurgitant because it does not contain a valve. PA pressures in these individuals are not elevated and the diastolic murmur can be misleadingly low pitched and of short duration despite significant degrees of PR and RV volume overload.

LABORATORY EXAMINATION

Depending on both the etiology and severity of PR, the ECG may show findings of RVH and RA enlargement. On chest x-ray, the RV and RA may be enlarged. Pulmonic valve morphology and function can be assessed with transthoracic Doppler echocardiography. PA pressures can be estimated from the tricuspid valve systolic jet velocity. CMR provides greater anatomic detail, particularly in patients with repaired congenital heart disease, and more precise assessment of RV volumes. Cardiac catheterization is not routinely necessary but would be performed as part of a planned transcatheter procedure.

TREATMENT PULMONIC REGURGITATION

In patients with functional PR due to PA hypertension and annular dilation, efforts to reduce PA vascular resistance and pressure should be optimized. Such efforts may include pharmacologic/vasodilator and/or surgical/interventional strategies, depending on the cause of the PA hypertension. Diuretics can be used to treat the manifestations of right heart failure. Surgical valve replacement for primary, severe, pulmonic valve disease, such as carcinoid or endocarditis, is rarely undertaken. Transcatheter pulmonic valve replacement has been successfully performed in many patients with severe PR after childhood repair of tetralogy of Fallot or pulmonic valve stenosis or atresia. This procedure was introduced clinically prior to transcatheter aortic valve replacement.

286 Multiple and Mixed Valvular Heart Disease

Patrick T. O'Gara, Joseph Loscalzo

Many acquired and congenital cardiac lesions may result in stenosis and/or regurgitation of one or more heart valves. For example, rheumatic heart disease can involve the mitral (mitral stenosis [MS], mitral regurgitation [MR], or MS and MR), aortic (aortic stenosis [AS], aortic regurgitation [AR], or AS and AR), and/or tricuspid (tricuspid stenosis [TS], tricuspid regurgitation [TR], or TS and TR) valve, alone or in combination. The common association of functional TR with significant mitral valve disease is discussed in [Chap. 285](#). Severe mitral annular calcification can result in regurgitation (due to decreased annular shortening during systole) and mild stenosis (caused by extension of the calcification onto the leaflets resulting in restricted valve opening). Patients with severe AS may develop functional MR that may not improve after isolated aortic valve replacement (AVR). Chordal rupture

has been described infrequently in patients with severe AS. Aortic valve infective endocarditis may secondarily involve the mitral apparatus either by abscess formation and contiguous spread via the inter-valvular fibrosa or by “drop metastases” from the aortic leaflets onto the anterior leaflet of the mitral valve. Mediastinal radiation may result in aortic, mitral, and even tricuspid valve disease, most often with mixed stenosis and regurgitation. Carcinoid heart disease may cause mixed lesions of either or both the tricuspid and pulmonic valves. Ergotamines, and the previously used combination of fenfluramine and phentermine, can rarely result in mixed lesions of the aortic and/or mitral valve. Patients with Marfan’s syndrome may have both AR from aortic root dilation and MR due to mitral valve prolapse (MVP). Myxomatous degeneration causing prolapse of multiple valves (mitral, aortic, tricuspid) can also occur in the absence of an identifiable connective tissue disorder. Bicuspid aortic or pulmonic valve disease can result in mixed stenosis and regurgitation.

PATOPHYSIOLOGY

In patients with multivalvular heart disease, the pathophysiologic derangements associated with the more proximal valve disease can mask the full expression of the attributes of the more distal valve lesion. For example, in patients with rheumatic mitral and aortic valve disease, the reduction in cardiac output (CO) imposed by the mitral valve disease will decrease the magnitude of the hemodynamic derangements related to the severity of the aortic valve lesion (stenotic, regurgitant, or both). Alternatively, the development of atrial fibrillation (AF) during the course of MS can lead to sudden worsening in a patient whose aortic valve disease was not previously felt to be significant. The development of reactive pulmonary vascular disease, sometimes referred to as a “secondary obstructive lesion in series,” can impose an additional challenge in these settings. As CO falls with progressive tricuspid valve disease, the severity of any associated mitral or aortic disease can be underestimated.

One of the most common examples of multivalve disease is that of functional TR in the setting of significant mitral valve disease. Functional TR occurs as a consequence of right ventricular and annular dilation; pulmonary artery (PA) hypertension is often present. The tricuspid leaflets are morphologically normal. Progressive degrees of TR lead to right ventricular volume overload and continued chamber and annular dilation. The TR is usually central in origin; reflux into the right atrium (RA) is expressed as large, systolic *c-v* waves in the RA pressure pulse. The height of the *c-v* wave is dependent on RA compliance and the volume of regurgitant flow. The RA wave form may become “ventricularized” in advanced stages of chronic, severe TR with PA hypertension. CO falls and the severity of the associated mitral valve disease may become more difficult to appreciate. Primary rheumatic tricuspid valve disease may occur with rheumatic mitral disease and cause hemodynamic changes reflective of TR, TS, or their combination. With TS, the *y* descent in the RA pressure pulse is prolonged.

Another example of rheumatic, multivalve disease involves the combination of mitral and aortic valve pathology, frequently characterized by MS and AR. In isolated MS, left ventricular (LV) preload and diastolic pressure are reduced as a function of the severity of inflow obstruction. With concomitant AR, however, LV filling is enhanced and diastolic pressure may rise depending on the compliance characteristics of the chamber. Because the CO falls with progressive degrees of MS, transaortic valve flows will decline, masking the potential severity of the aortic valve lesion (AR, AS, or its combination). As noted above, onset of AF in such patients can be especially deleterious.

Functional MR may complicate the course of some patients with severe AS. The mitral valve leaflets and chordae tendineae are usually normal. Incompetence is related to changes in LV geometry (remodeling) and abnormal systolic tethering of the leaflets in the context of markedly elevated LV systolic pressures. Relief of the excess afterload with surgical or transcatheter AVR often, but not always, results in reduction or elimination of the MR. Persistence of significant MR following AVR is associated with impaired functional outcomes and reduced survival. Identification of patients who would benefit from concomitant treatment of their functional MR at time of AVR is quite

challenging. Most surgeons advocate for repair of moderate-to-severe or severe functional MR at time of surgical AVR.

In patients with mixed AS and AR, assessment of valve stenosis can be influenced by the magnitude of the regurgitant valve flow. Because transvalvular systolic flow velocities are augmented in patients with AR and preserved LV systolic function, the LV-aortic Doppler-derived pressure gradient and the intensity of the systolic murmur will be elevated to values higher than expected for the true systolic valve orifice size as delineated by planimetry. Uncorrected, the Gorlin formula, which relies on forward CO (systolic transvalvular flow) and the mean pressure gradient for calculation of valve area, is not accurate in the setting of mixed aortic valve disease. Similar considerations apply to patients with mixed mitral valve disease. The peak mitral valve Doppler E wave velocity (v_e) is increased in the setting of severe MR because of enhanced early diastolic flow and may not accurately reflect the contribution to left atrial (LA) hypertension from any associated MS. When either AR or MR is the dominant lesion in patients with mixed aortic or mitral valve disease, respectively, the LV is dilated. When AS or MS predominates, LV chamber size will be normal or small. It can sometimes be difficult to ascertain whether stenosis or regurgitation is the dominant lesion in patients with mixed valve disease, although an integrated clinical and noninvasive assessment can usually provide clarification for purposes of patient management and follow-up.

Patients with significant AS, a nondilated LV chamber, and concentric hypertrophy will poorly tolerate the abrupt development of aortic regurgitation, as may occur, for example, with infective endocarditis or after surgical or transcatheter AVR complicated by paravalvular leakage. The noncompliant LV is not prepared to accommodate the sudden volume load, and as a result, LV diastolic pressure rises rapidly and severe heart failure develops. Indeed, paravalvular regurgitation is a significant risk factor for short- to intermediate-term death following transcatheter AVR. Conditions in which the LV may not be able to dilate in response to chronic AR (or MR) include radiation heart disease and, in some patients, the cardiomyopathy associated with obesity and diabetes. Noncompliant ventricles of small chamber size predispose to earlier onset diastolic dysfunction and heart failure in response to any further perturbation in valve function.

SYMPTOMS

Compared with patients with isolated, single-lesion valve disease, patients with multiple or mixed valve disease may develop symptoms at a relatively earlier stage in the natural history of their disease. Symptoms such as exertional dyspnea and fatigue are usually related to elevated filling pressures, reduced CO, or their combination. Palpitations may signify AF and identify mitral valve disease as an important component of the clinical presentation, even when not previously suspected. Chest pain compatible with angina could reflect left or right ventricular oxygen supply/demand mismatch on a substrate of hypertrophy and pressure/volume overload with or without superimposed coronary artery disease. Symptoms related to right heart failure (abdominal fullness/bloating, edema) are late manifestations of advanced disease.

PHYSICAL FINDINGS

Mixed disease of a single valve is most often manifested by systolic and diastolic murmurs, each with the attributes expected for the valve in question. Thus, patients with AS and AR will have characteristic mid-systolic, crescendo-decrescendo and blowing, decrescendo diastolic murmurs at the base of the heart in the second right interspace and along the left sternal edge, respectively. Many patients with significant AR have mid-systolic outflow murmurs even in the absence of valve sclerosis/stenosis, and other findings of AS must be sought. The separate murmurs of AS and AR can occasionally be difficult to distinguish from the continuous murmurs associated with either a patent ductus arteriosus (PDA) or ruptured sinus of Valsalva aneurysm. With mixed aortic valve disease, the systolic murmur should end before, and not envelope or extend through, the second heart sound (S_2). The murmur associated with a PDA is heard best to the left of the upper sternum. The continuous murmur heard with a ruptured sinus of Valsalva

aneurysm is often first appreciated after an episode of acute chest pain. An early ejection click, which usually defines bicuspid aortic valve disease in young adults, is often not present in patients with congenital, mixed AS and AR. As noted above, both the intensity and duration of these separate murmurs can be influenced by a reduction in CO and transvalvular flow due to coexistent mitral valve disease. In patients with isolated MS and MR, expected findings would include a blowing, holosystolic murmur and a mid-diastolic rumble (with or without an opening snap) best heard at the cardiac apex. An irregularly irregular heart rhythm in such patients would likely signify AF. Findings with TS and TR would mimic those of left-sided MS and MR, save for the expected changes in the murmurs with respiration. The murmurs of pulmonic stenosis and regurgitation behave in a fashion directionally similar to AS and AR; dynamic changes during respiration should be noted. **Specific attributes of these cardiac murmurs are reviewed in Chap. 285.**

LABORATORY EXAMINATION

The electrocardiogram (ECG) may show evidence of ventricular hypertrophy and/or atrial enlargement. ECG signs indicative of right-sided cardiac abnormalities in patients with left-sided valve lesions should prompt additional assessment for PA hypertension and/or right-sided valve disease. The presence of AF in patients with aortic valve disease may be a clue to the presence of previously unsuspected mitral valve disease in the appropriate context. The chest x-ray can be reviewed for evidence of cardiac chamber enlargement, valve and/or annular calcification, and any abnormalities in the appearance of the pulmonary vasculature. The latter could include enlargement of the main and proximal pulmonary arteries with PA hypertension and pulmonary venous redistribution/engorgement or Kerley B lines with increasing degrees of LA hypertension. An enlarged azygos vein in the frontal projection indicates RA hypertension. Roentgenographic findings not expected based on a single or mixed valve lesion may reflect other valve disease.

Transthoracic echocardiography (TTE) is the most commonly used imaging modality for the diagnosis and characterization of multiple and/or mixed valvular heart disease and may often demonstrate findings not clinically suspected. Transesophageal echocardiography (TEE) may sometimes be required for more accurate assessment of valve anatomy (specifically, the mitral valve) and when infective endocarditis (IE) is considered responsible for the clinical presentation. TTE findings of particular interest include those related to valve morphology and function, calcification, chamber size, ventricular wall thickness, estimated PA systolic pressure, and the dimensions of the great vessels, including the root and ascending aorta, PA, and inferior vena cava. Exercise testing (with or without echocardiography) can be useful when the degree of functional limitation reported by the patient is not adequately explained by the findings on TTE performed at rest. An integrated assessment of the clinical and TTE findings is needed to help determine the dominant valve lesion(s) and establish an appropriate plan for treatment and follow-up. Natural history is usually influenced to a relatively greater degree by the dominant lesion. Exercise testing (with or without echocardiography) can

Cardiac magnetic resonance (CMR) can be used to provide additional anatomic and physiologic information when echocardiography proves suboptimal, but is less well suited to the evaluation of valve morphology. Cardiac computed tomography (CT) has been used to assess intracardiac structures in patients with complicated IE. Coronary CT angiography provides a noninvasive alternative for the assessment of coronary artery anatomy prior to surgery.

Invasive hemodynamic evaluation with right and left heart catheterization may be required to characterize more completely the individual contributions of each lesion in patients with either multiple or mixed valvular heart disease. Measurement of PA pressures and calculation of pulmonary vascular resistance (PVR) can help inform clinical decision-making in certain patient subsets, such as those with advanced mitral and tricuspid valve disease. Attention to the accurate assessment of CO is essential. Coronary angiography (if indicated) can be performed as part of the procedure. Contrast ventriculography and great vessel angiography are performed infrequently.

Management of patients with multiple or mixed valve disease can be challenging. As noted above, it is helpful to determine the dominant valve lesion and proceed according to the treatment and follow-up recommendations for it ([Chaps. 283 to 285](#)), being mindful of deviations from the expected course because of problems related to another valve disorder. For example, AF that emerges in the course of moderate mitral valve disease may precipitate heart failure in patients with concomitant, severe aortic valve disease.

Medical therapies are limited and include diuretics when indicated for relief of congestion and vitamin K antagonists for anticoagulation to prevent stroke and thromboembolism in patients with AF. The novel oral anticoagulants are not approved for use in the setting of significant valvular heart disease. Blood pressure–lowering medications may be needed to treat systemic hypertension, which may aggravate left-sided regurgitant valve lesions, but should be initiated and titrated carefully. Pulmonary vasodilators to lower PVR are not generally effective in this context.

There is a paucity of evidence to inform practice guidelines for surgical and/or transcatheter valve intervention in patients with multiple or mixed valve disease. When there is a clear, dominant lesion, as for example in a patient with severe AS and mild AR, indications for intervention are straightforward and follow those recommended for patients with AS ([Chap. 283](#)). In other patients, however, there is less clarity, and decisions regarding intervention should be based on several considerations, including those related to lesion severity, ventricular remodeling, functional capacity, and PA pressures. In this regard, it is important to realize that patients with multiple and/or mixed valve disease may develop limiting symptoms or signs of physiologic impairment even with moderate valve lesions.

Concomitant aortic and mitral valve replacement surgery is associated with a significantly higher perioperative mortality risk than replacement of either valve alone ([see Tables 283-2 and 284-2](#)), and operation should be carefully considered. Double valve replacement surgery is usually performed for treatment of severe (unrepairable) valve disease at both locations and for the combination of severe disease at one location with moderate disease at the other, so as to avoid the hazards of reoperation in the intermediate to late term for progressive disease of the unoperated valve. In addition, the presence of a prosthesis in the aortic position significantly restricts surgical exposure of the native mitral valve. The need for double valve replacement may also impact the decision regarding the type of prosthesis (i.e., mechanical vs tissue).

Tricuspid valve repair for moderate or severe functional TR at the time of left-sided valve surgery is now commonplace, particularly if there is dilation of the tricuspid annulus (>40 mm). The addition of tricuspid valve repair, consisting usually of insertion of an annuloplasty ring, adds little time or complexity to the procedure and is well tolerated. Reoperation for repair (or replacement) of progressive TR years after initial surgery for left-sided valve disease, on the other hand, is associated with a relatively high perioperative mortality risk. Repair of moderate or severe functional MR at time of AVR for AS can usually be undertaken with acceptable risk for perioperative death or major complication.

The presence of moderate or severe MR in patients with rheumatic MS is a contraindication to percutaneous mitral balloon valvotomy (PMBV). Likewise, the presence of significant AR in patients with AS disqualifies them from percutaneous aortic balloon valvotomy (PABV). The presence of severe, coexistent AR was an exclusion criterion for enrollment in the initial PARTNER trials of transcatheter AVR (TAVR) in prohibitive- and high-surgical-risk patients with severe, calcific AS. Transcatheter management of both severe AS (with TAVR) and functional MR (with deployment of a MitralClip) has been reported. Further advances in transcatheter treatments for multiple and mixed valve disease are anticipated.

DEFINITION AND CLASSIFICATION

Cardiomyopathy is disease of the heart muscle. It is estimated that cardiomyopathy accounts for 5–10% of the heart failure in the 5–6 million patients carrying that diagnosis in the United States. This term is intended to exclude cardiac dysfunction that results from other structural heart disease, such as coronary artery disease, primary valve disease, or severe hypertension; however, in general usage, the phrase *ischemic cardiomyopathy* is sometimes applied to describe diffuse dysfunction attributed to multivessel coronary artery disease, and *nonischemic cardiomyopathy* to describe cardiomyopathy from other causes. As of 2006, cardiomyopathies are defined as “a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic.”¹

The traditional classification of cardiomyopathies into a triad of dilated, restrictive, and hypertrophic was based initially on autopsy specimens and later on echocardiographic findings. Dilated and hypertrophic cardiomyopathies can be distinguished on the basis of left ventricular wall thickness and cavity dimension; however, restrictive cardiomyopathy can have variably increased wall thickness and chamber dimensions that range from reduced to slightly increased, with prominent atrial enlargement. Restrictive cardiomyopathy is now defined more on the basis of abnormal diastolic function, which is also present but initially less prominent in dilated and hypertrophic cardiomyopathy. Restrictive cardiomyopathy can overlap in presentation, gross morphology, and etiology with both hypertrophic and dilated cardiomyopathies (Table 287-1).

Expanding information renders this classification triad based on phenotype increasingly inadequate to define disease or therapy. Identification of more genetic determinants of cardiomyopathy has suggested a four-way classification scheme of etiology as primary (affecting primarily the heart) and secondary to other systemic disease. The primary causes are then divided into genetic, mixed genetic and acquired, and acquired; however, genetic information is often unavailable at the time of initial presentation, the phenotypic expression of a given mutation varies widely, and genetic predisposition influences the clinical phenotype of acquired cardiomyopathies, as well. Although the proposed genetic classification does not yet guide many current clinical strategies, it will likely become increasingly relevant as classification of disease moves beyond individual organ pathology to more integrated systems approaches.

GENERAL PRESENTATION

For all cardiomyopathies, the early symptoms often relate to exertional intolerance with breathlessness or fatigue, usually from inadequate cardiac reserve during exercise. These symptoms may initially go unnoticed or be attributed to other causes, commonly lung disease or age-dependent exercise limitation. As fluid retention leads to elevation of resting filling pressures, shortness of breath may occur during routine daily activity such as dressing and may manifest as dyspnea or cough when lying down at night. Although often considered the hallmark of congestion, peripheral edema may be absent despite severe fluid retention, particularly in younger patients in whom ascites and abdominal discomfort may dominate. The non-specific term *congestive heart failure* describes only the resulting syndrome of fluid retention, which is common to all three types of cardiomyopathy and also to cardiac structural diseases associated

with elevated filling pressures. All three types of cardiomyopathy can be associated with atrioventricular valve regurgitation, typical and atypical chest pain, atrial and ventricular tachyarrhythmias, and embolic events (Table 287-1). Initial evaluation begins with a detailed clinical history and examination, looking for clues to cardiac, extracardiac, and familial disease (Table 287-2).

GENETIC ETIOLOGIES OF CARDIOMYOPATHY

 Estimates for the prevalence of genetic etiology for cardiomyopathy continue to rise, with increasing attention paid to the family history and the availability of genetic testing. Well-recognized in hypertrophic cardiomyopathy, heritability is also present in at least 30% of dilated cardiomyopathy without other clear etiology. Careful family history should elicit not only known cardiomyopathy and heart failure, but also family members who have had sudden death, often incorrectly attributed to “a massive heart attack,” who have had atrial fibrillation or pacemaker implantation by middle age, or who have muscular dystrophy.

Most familial cardiomyopathies are inherited in an autosomal dominant pattern, with occasional autosomal recessive and X-linked inheritance (Table 287-3). Missense mutations with amino acid substitutions are the most common in cardiomyopathy. Expressed mutant proteins may interfere with function of the normal allele through a dominant negative mechanism. Mutations introducing a premature stop codon (nonsense) or shift in the reading frame (frameshift) may create a truncated or unstable protein the lack of which causes cardiomyopathy (haploinsufficiency). Deletions or duplications of an entire exon or gene are uncommon causes of cardiomyopathy, except for the dystrophinopathies.

Many different genes have been implicated in human cardiomyopathy (locus heterogeneity), and many mutations within those genes have been associated with disease (allelic heterogeneity). Although most identified mutations are “private” to individual families, several specific mutations are found repeatedly, either due to a founder effect or recurrent mutations at a common residue.

Genetic cardiomyopathy is characterized by age dependence and incomplete penetrance. The defining phenotype of cardiomyopathy is rarely present at birth and, in some individuals, may never manifest. Related individuals who carry the same mutation may differ in the severity of cardiomyopathy and associated consequences of rhythm disorders and need for transplantation, indicating the important role of other genetic, epigenetic, and environmental modifiers in disease expression. Sex appears to play a role, as penetrance and clinical severity may be greater in men for most cardiomyopathies. Clinical disease expression is generally more severe in the 3–5% of individuals who harbor two or more mutations linked to cardiomyopathy. However, the clinical course of a patient usually cannot be predicted based on which mutation is present; thus, current therapy is based on the phenotype rather than the genetic defect. Currently, the greatest utility of genetic testing for cardiomyopathy is to inform family evaluations. However, genetic testing occasionally enables the detection of a disease for which specific therapy is indicated, such as the replacements for defective metabolic enzymes in Fabry’s disease and Gaucher disease.

GENES AND PATHWAYS IN CARDIOMYOPATHY

Mutations in sarcomeric genes, encoding the thick and thin myofilament proteins, are the best characterized. While the majority are associated with hypertrophic cardiomyopathy, an increasing number of sarcomeric mutations have now been implicated in dilated cardiomyopathy, and some in left ventricular noncompaction. Few mutations have been identified in excitation-contraction coupling proteins, perhaps because they are too crucial for survival to allow variation. The most commonly recognized genetic causes of dilated cardiomyopathy are structural mutations of the giant protein titin, encoded *TTN*, which maintains sarcomere structure and acts as a key signaling molecule.

As cytoskeletal proteins play crucial roles in the structure, connection, and stability of the myocyte, multiple defects in these proteins can lead to cardiomyopathy, usually with a dilated phenotype (Fig. 287-1). For example, desmin forms intermediate filaments that connect the nuclear and plasma membranes, Z-lines,

¹From BJ Maron et al: Circulation 113:1807, 2006.

	Dilated	Restrictive	Hypertrophic
Ejection fraction (normal >55%)	Usually <30% when symptoms severe	25–50%	>60%
Left ventricular diastolic dimension (normal <55 mm)	≥60 mm	<60 mm (may be decreased)	Often decreased
Left ventricular wall thickness	Normal or decreased	Normal or increased	Markedly increased
Atrial size	Increased, may also be primarily affected	Increased; may be massive	Increased; related to elevated filling pressures
Valvular regurgitation	Related to annular dilation; mitral appears earlier during decompensation; tricuspid regurgitation with right ventricular dysfunction	Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe	Related to valve-septum interaction; mitral regurgitation
Common first symptoms	Exertional intolerance	Exertional intolerance, fluid retention early, may have dominant right-sided symptoms	Exertional intolerance; may have chest pain
Congestive symptoms ^a	Left before right, except right prominent in young adults	Right often dominates	Left-sided congestion at rest may develop late
Arrhythmias	Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some families. Atrial fibrillation.	Ventricular uncommon except in sarcoidosis, conduction block in sarcoidosis and amyloidosis. Atrial fibrillation.	Ventricular tachyarrhythmias; atrial fibrillation

^aLeft-sided symptoms of pulmonary congestion: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea. Right-sided symptoms of systemic venous congestion: hepatic and abdominal distention, discomfort on bending, peripheral edema.

TABLE 287-2 INITIAL EVALUATION OF CARDIOMYOPATHY

Clinical Evaluation

Thorough history and physical examination to identify cardiac and noncardiac disorders^a
 Detailed family history of heart failure, cardiomyopathy, skeletal myopathy, conduction disorders, tachyarrhythmias, and sudden death
 History of alcohol, illicit drugs, chemotherapy or radiation therapy^a
 Assessment of ability to perform routine and desired activities^a
 Assessment of volume status, orthostatic blood pressure, body mass index^a

Laboratory Evaluation

Electrocardiogram^a
 Chest radiograph^a
 Two-dimensional and Doppler echocardiogram^a
 Magnetic resonance imaging for evidence of myocardial inflammation and fibrosis
 Chemistry:
 Serum sodium,^a potassium,^a calcium,^a magnesium^a
 Fasting glucose (glycohemoglobin in diabetes mellitus)
 Creatinine,^a blood urea nitrogen^a
 Albumin,^a total protein,^a liver function tests^a
 Lipid profile
 Thyroid-stimulating hormone^a
 Serum iron, transferrin saturation
 Urinalysis
 Creatine kinase isoforms
 Cardiac troponin levels
 Hematology:
 Hemoglobin/hematocrit^a
 White blood cell count with differential,^a including eosinophils
 Erythrocyte sedimentation rate

Initial Evaluation When Specific Diagnoses Are Suspected

Titers for infection in the setting of clinical suspicion:
 Acute viral (coxsackie, echovirus, influenza)
 Human immunodeficiency virus
 Chagas' (*Trypanosoma cruzi*), Lyme (*Borrelia burgdorferi*), toxoplasmosis
 Catheterization with coronary angiography in patients with angina who are candidates for intervention^a
 Serologies for active rheumatologic disease
 Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications
 Screening for sleep-disordered breathing

^aLevel I recommendations from ACC/AHA Practice Guidelines for Chronic Heart Failure in the Adult.

and the intercalated disks between muscle cells. Desmin mutations impair the transmission of force and signaling for both cardiac and skeletal muscle and may cause combined cardiac and skeletal myopathy.

Sarcolemmal membrane protein defects are associated with dilated cardiomyopathy. The best known is dystrophin, encoded by the X chromosome gene *DMD*, abnormalities of which cause Duchenne's and Becker's muscle dystrophy. (Interestingly, abnormal dystrophin can be acquired when the coxsackie virus cleaves dystrophin during viral myocarditis.) This protein provides a network that supports the sarcolemma and also connects to the sarcomere. The progressive functional defect in both cardiac and skeletal muscle reflects vulnerability to mechanical stress. Dystrophin is associated at the membrane with a complex of other proteins, such as metavinculin, abnormalities of which also cause dilated cardiomyopathy. Defects in the sarcolemmal channel proteins (*channelopathies*) are generally associated with primary arrhythmias, but mutations in *SCN5A*, distinct from those that cause the Brugada or long-QT syndromes, have been implicated in dilated cardiomyopathy with conduction disease.

Nuclear membrane protein defects in cardiac and skeletal muscle occur in either autosomal (lamin A/C) or X-linked (emerin) patterns. These defects are associated with a high prevalence of atrial arrhythmias and conduction system disease, which can occur in some family members without or before detectable cardiomyopathy.

Intercalated disks contribute to intracellular connections, allowing mechanical and electrical coupling between cells and also connections to desmin filaments within the cell. Mutations in proteins of the desmosomal complex compromise attachment of the myocytes, which can become disconnected and die, to be replaced by fat and fibrous tissue. These areas are highly arrhythmogenic and may dilate to form aneurysms. Although more often noted in the right ventricle (arrhythmogenic right ventricular dysplasia), this condition can affect both ventricles and has also been termed "arrhythmogenic cardiomyopathy."

Owing to the conservation of signaling pathways in multiple systems, we may expect to discover more extracardiac manifestations of genetic abnormalities initially considered to manifest exclusively in the heart. In contrast, the monogenic disorders of metabolism that affect the heart are already clearly recognized to affect multiple organ systems. Currently, it is most important to diagnose defective enzymes for which specific enzyme replacement therapy can now ameliorate the course of disease, such as with alpha-galactosidase A deficiency (Fabry's disease). Abnormalities of mitochondrial DNA (maternally transmitted) impair energy production with multiple clinical manifestations, including impaired cognitive function and skeletal myopathy. The phenotypic expression is highly variable depending on the

TABLE 287-3 SELECTED GENETIC DEFECTS ASSOCIATED WITH CARDIOMYOPATHY

	Gene Product	Inheritance	Cardiac Phenotype	Isolated Cardiac Phenotype	Extracardiac Manifestations
Sarcomere	MYH7 (β myosin heavy chain)	AD	HCM, DCM, LVNC	Yes	Skeletal myopathy
	MYBPC3 (myosin binding protein C)	AD	HCM	Yes	
	TNNT2 (cardiac troponin T)	AD	HCM, DCM, LVNC	Yes	
	TNNI3 (cardiac troponin I)	AD, AR	HCM, DCM, RCM	Yes	
	TTN (Titin)	AD	DCM	Yes	
	TPM1 (α -tropomyosin)	AD	HCM, DCM	Yes	
	TNNC1 (cardiac troponin C)	AD	DCM	Yes	
	ACTC (α -actin)	AD	HCM, DCM, (LVNC)	Yes	
	MYL2 (myosin regulatory light chain)	AD	HCM	Yes	Skeletal myopathy
	MYL3 (myosin essential light chain)	AD	HCM	Yes	
Z-disk and Cytoskeleton	DES (Desmin)	AD	DCM, RCM	Yes	Skeletal myopathy
	LDB3 (Cypher-ZASP)	AD	DCM, LVNC	Yes	Skeletal myopathy
	MYOZ2 (Myozinin)	AD	HCM	Yes	
	TCAP (Telethonin)	AD	DCM, HCM	Yes	
	ANKRD1 (CARP)	AD	HCM, (DCM)	Yes	
	CSRP3 (MLP)	AD	DCM, (HCM)	Yes	
	ACTN2 (α -actinin-2)	AD	DCM	Yes	
Nuclear Membrane	CRYAB (α B-crystallin)	AD	DCM	Yes	
	LMNA (Lamin A/C)	AD, AR	CDDC	Yes	Skeletal myopathy
	EMD (Emerin)	X-linked	CDDC	No	Skeletal myopathy, contractures
Excitation-Contraction Coupling	PLN (Phospholamban)	AD	DCM	Yes	
	SCN5A (NAV 1.5)	AD	CDDC	Yes	Note other mutations associated with Brugada syndrome
	RYR2 (cardiac ryanodine receptor)	AD	ARVC	Yes	
Cellular Metabolism	CASQ2 (calsequestrin 2)	AR	ARVC	Yes	
	PRKAG2 (γ -subunit of AMP kinase)	AD	HCM+	Yes	
	LAMP2 (lysosomal associated membrane protein)	X-linked	HCM+	No ^a	Danon's disease: skeletal myopathy, cognitive impairment
	TAZ (Tafazzin)	X-linked	DCM, LVNC	No	Barth's syndrome: skeletal myopathy, cognitive impairment, neutropenia
	FXN (Frataxin)	AR	HCM	No	Friedreich's ataxia: ataxia, diabetes mellitus type 2
Mitochondria	TMEM43 (transmembrane protein 43)	AD	ARVC	Yes	
	GLA (α -galactosidase-A)	X-linked	HCM+	Yes	Fabry's disease: renal failure, angiokeratomas and painful neuropathy
	Mitochondrial DNA	Maternal transmission	DCM, HCM	No	MELAS, MERRF, Kearns-Sayre syndrome, ocular myopathy
Sarcolemmal Membrane	DMD (Dystrophin)	X-linked	DCM	No ^a	Duchenne's and Becker's muscular dystrophy
	DMPK (dystrophica myotonica protein kinase)	AD	DCM	No	Myotonic dystrophy type 1
	SGCD (δ -sarcoglycan)	AD	DCM	Yes	
Desmosome	DSP (Desmoplakin)	AD, AR	ARVC	Yes	Carvajal syndrome (AR), Naxos syndrome (AR), "woolly hair" and hyperkeratosis of palms and soles
	JUP (Plakoglobin)				
Other Examples	DSG2 (Desmoglein 2)	AD	ARVC	Yes	
	DSC2 (Desmocollin 2)				
	PKP2 (Plakophilin 2)				
	RBM20 (RNA binding motif 20)	AD	DCM	Yes	
	PSEN1 (Presenilin-1,2)	AD	DCM	Yes	Dementia
	BAG3 (BCL2-associated athanogene 3)	AD	DCM	Yes	

^aIndicates that isolated cardiac phenotype can occur in women with the X-linked defects.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; CDDC, conduction disease with dilated cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HCM+, HCM with preexcitation; HCMc, HCM with conduction disease; LVNC, left ventricular noncompaction; MELAS, (mitochondrial) myopathy, encephalopathy, lactic acidosis, and strokelike episodes syndrome; MERRF, myoclonic epilepsy with ragged red fibers; RCM, restrictive cardiomyopathy.

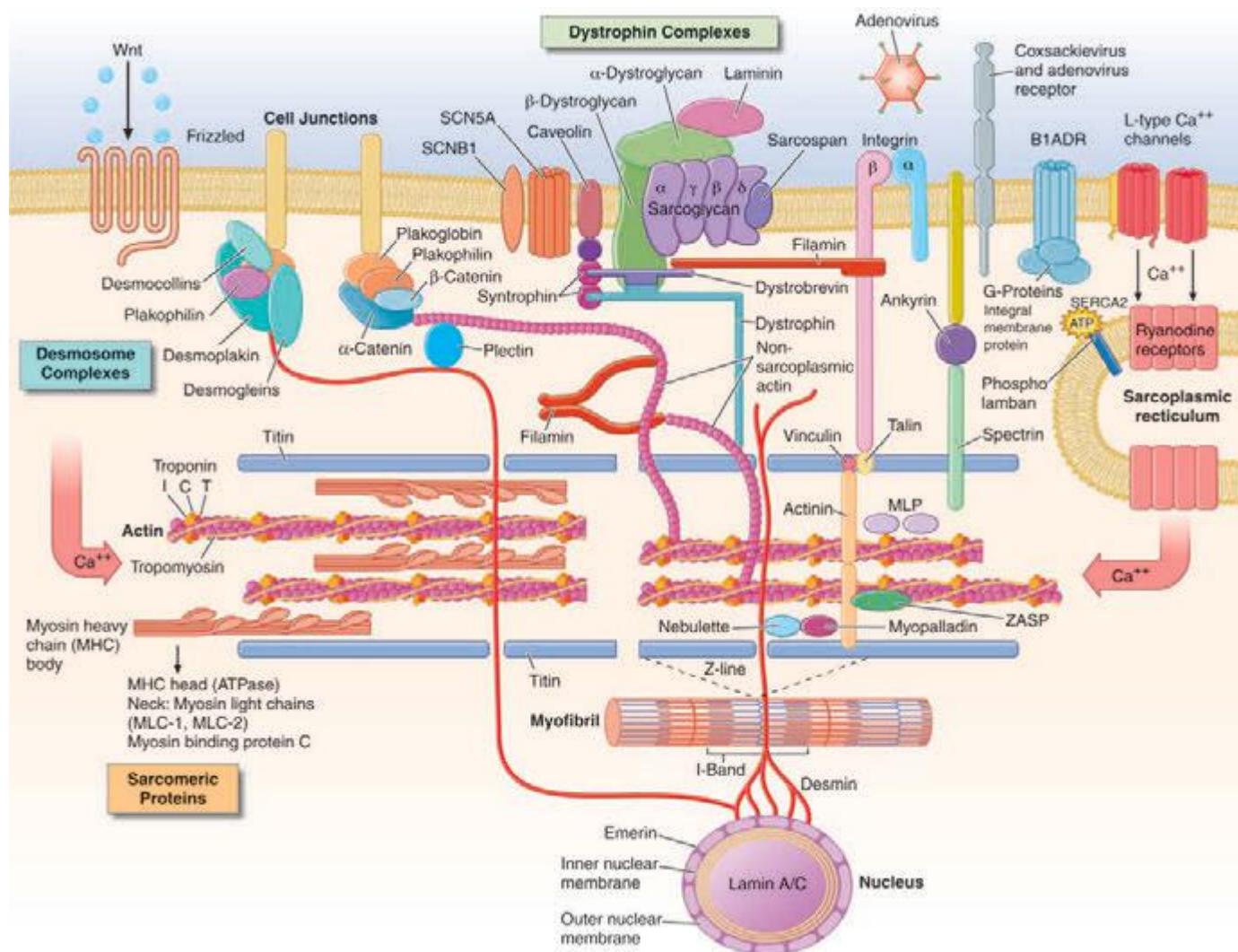


FIGURE 287-1 Drawing of myocyte indicating multiple sites of abnormal gene products associated with cardiomyopathy. Major functional groups include the sarcomeric proteins (actin, myosin, tropomyosin, and the associated regulatory proteins), the dystrophin complex stabilizing and connecting the cell membrane to intracellular structures, the desmosome complexes associated with cell-cell connections and stability, and multiple cytoskeletal proteins that integrate and stabilize the myocyte. ATP, adenosine triphosphate. (Figure adapted from Jeffrey A. Towbin, MD, University of Cincinnati, with permission.)

distribution of the maternal mitochondria during embryonic development. Heritable systemic diseases, such as familial amyloidosis and hemochromatosis, can affect the heart without mutation of genes expressed in the heart.

For any patient with suspected or proven genetic disease, family members should be considered and evaluated in a longitudinal fashion. Screening includes an echocardiogram and electrocardiogram (ECG). The indications and implications for confirmatory specific genetic testing vary depending on the specific mutation. The profound questions raised by families about diseases shared and passed down merit serious and sensitive discussion, ideally provided by a trained genetic counselor.

DILATED CARDIOMYOPATHY

An enlarged left ventricle with decreased systolic function as measured by left ventricular ejection fraction characterizes dilated cardiomyopathy (Figs. 287-2, 287-3, and 287-4). *Systolic failure* is more marked than diastolic dysfunction. Although the syndrome of dilated cardiomyopathy has multiple etiologies (Table 287-4), there appear to be common pathways of secondary response and disease progression. When myocardial injury is acquired, some myocytes may die initially, whereas others survive only to have later programmed cell death (apoptosis), and remaining myocytes hypertrophy in response to

increased wall stress. Local and circulating factors stimulate deleterious secondary responses that contribute to progression of disease. Dynamic remodeling of the interstitial scaffolding affects diastolic function and the amount of ventricular dilation. Mitral regurgitation commonly develops as the valvular apparatus is distorted and is usually substantial by the time heart failure is severe. Many cases that present “acutely” have progressed silently through these stages over months to years. Dilatation and decreased function of the right ventricle may result from the initial injury and occasionally dominate, but more commonly appear later in relation to mechanical interactions with the failing left ventricle and the elevated afterload presented by secondary pulmonary hypertension.

Regardless of the nature and degree of direct cell injury, the resulting functional impairment often includes some contribution from secondary responses that may be modifiable or reversible. Almost half of all patients with new-onset cardiomyopathy demonstrate substantial spontaneous recovery. Even with long-standing disease, some patients have dramatic improvement to near-normal ejection fractions during pharmacologic therapy, particularly notable with the β -adrenergic antagonists coupled with renin-angiotensin system inhibition. For patients in whom left bundle branch block precedes clinical heart failure by many years, cardiac resynchronization pacing may be particularly likely to improve ejection fraction and decrease ventricular size. Interest in the potential for recovery of cardiomyopathy has been



FIGURE 287-2 Dilated cardiomyopathy. This gross specimen of a heart removed at the time of transplantation shows massive left ventricular dilation and moderate right ventricular dilation. Although the left ventricular wall in particular appears thinned, there is significant hypertrophy of this heart, which weighs more than 800 g (upper limit of normal = 360 g). A defibrillator lead is seen traversing the tricuspid valve into the right ventricular apex. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

further stimulated by occasional “recovery” of left ventricular function after prolonged mechanical circulatory support. The diagnosis and therapy for dilated cardiomyopathy are generally dictated by the stage of heart failure (Chap. 279), with specific aspects discussed for relevant etiologies below.

MYOCARDITIS

Myocarditis (inflammation of the heart) can result from multiple causes but is most commonly attributed to infective agents that can injure the myocardium through direct invasion, production of cardio-toxic substances, or chronic inflammation with or without persistent infection. Myocarditis cannot be assumed from a presentation of decreased systolic function in the setting of an acute infection, as any severe infection causing systemic cytokine release can depress cardiac function transiently. Infectious myocarditis has been reported with almost all types of infective agents but is most commonly associated with viruses and the protozoan *Trypanosoma cruzi*.

INFECTIVE MYOCARDITIS

The pathogenesis of viral myocarditis has been extensively studied in murine models. After viruses gain entry through the respiratory or gastrointestinal tract, they can infect organs possessing specific receptors, such as the coxsackie-adenovirus receptor on the heart. Viral infection and replication can cause myocardial injury and lysis. For example, the enteroviral protease 2A facilitates viral replication and infection through degradation of the myocyte protein dystrophin, which is crucial for myocyte stability. Activation of viral receptor proteins can also activate host tyrosine kinases, which modify the cytoskeleton to facilitate further viral entry.

The first host response to infection is the nonspecific innate immune response, heavily dependent on Toll-like receptors that recognize common antigenic patterns. Cytokine release is rapid, followed by triggered activation and expansion of specific T- and B-cell populations. This initial response appears to be crucial, as early immunosuppression

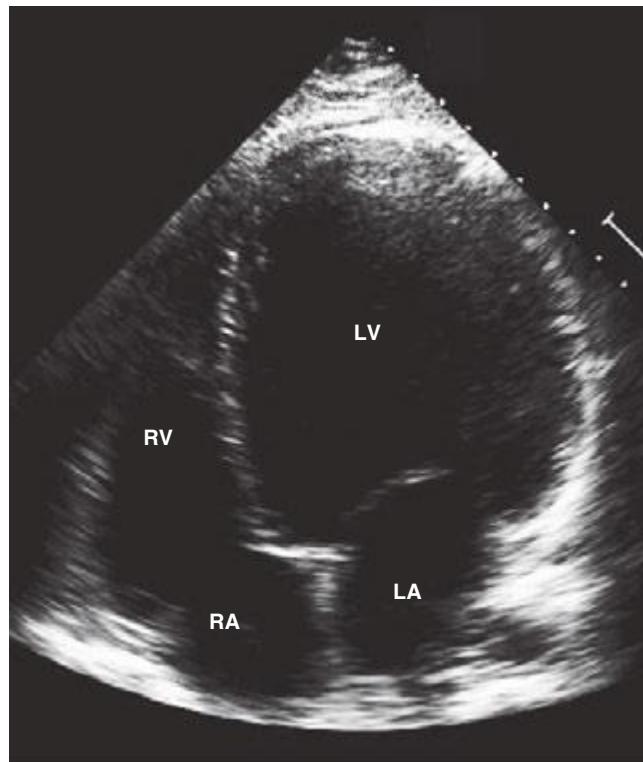


FIGURE 287-3 Dilated cardiomyopathy. This echocardiogram of a young man with dilated cardiomyopathy shows massive global dilation and thinning of the walls of the left ventricle (LV). The left atrium (LA) is also enlarged compared to normal. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. RA, right atrium; RV, right ventricle. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)

in animal models can increase viral replication and worsen cardiac injury. However, successful recovery from viral infection depends not only on the efficacy of the immune response to limit viral infection, but also on timely downregulation to prevent overreaction and autoimmune injury to the host.

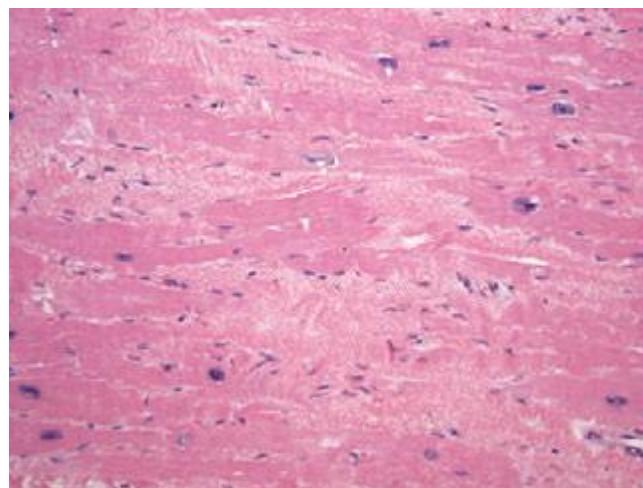


FIGURE 287-4 Dilated cardiomyopathy. Microscopic specimen of a dilated cardiomyopathy showing the nonspecific changes of interstitial fibrosis and myocyte hypertrophy characterized by increased myocyte size and enlarged, irregular nuclei. Hematoxylin and eosin-stained section, 100 \times original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

TABLE 287-4 MAJOR CAUSES OF DILATED CARDIOMYOPATHY (WITH COMMON EXAMPLES)

Inflammatory Myocarditis
Infective
Viral (coxsackie, ^a adenovirus, ^a HIV, hepatitis C)
Parasitic (<i>T. cruzi</i> —Chagas' disease, trypanosomiasis, toxoplasmosis)
Bacterial (diphtheria)
Spirochetal (<i>Borrelia burgdorferi</i> —Lyme disease)
Rickettsial (Q fever)
Fungal (with systemic infection)
Noninfective
Granulomatous inflammatory disease
Sarcoidosis
Giant cell myocarditis
Eosinophilic myocarditis
Polymyositis, dermatomyositis
Collagen vascular disease
Peripartum cardiomyopathy
Transplant rejection
Toxic
Alcohol
Catecholamines: amphetamines, cocaine
Chemotherapeutic agents (anthracyclines, trastuzumab)
Interferon
Other therapeutic agents (hydroxychloroquine, chloroquine)
Drugs of misuse (emetine, anabolic steroids)
Heavy metals: lead, mercury
Occupational exposure: hydrocarbons, arsenicals
Metabolic ^a
Nutritional deficiencies: thiamine, selenium, carnitine
Electrolyte deficiencies: calcium, phosphate, magnesium
Endocrinopathy
Thyroid disease
Pheochromocytoma
Diabetes
Obesity
Hemochromatosis
Inherited Metabolic Pathway Defects ^a
Familial ^a (See Table 287-3)
Skeletal and cardiac myopathy
Dystrophin-related dystrophy (Duchenne's, Becker's)
Mitochondrial myopathies (e.g., Kearns-Sayre syndrome)
Arrhythmogenic ventricular dysplasia
Hemochromatosis
Associated with other systemic diseases
Susceptibility to immune-mediated myocarditis
Overlap with Nondilated Cardiomyopathy
"Minimally dilated cardiomyopathy"
Hemochromatosis ^a
Amyloidosis ^a
Hypertrophic cardiomyopathy ^a ("burned-out")
"Idiopathic" ^a
Miscellaneous (Shared Elements of Above Etiologies)
Arrhythmogenic right ventricular dysplasia (may also affect left ventricle) ^a
Left ventricular noncompaction ^a
Peripartum cardiomyopathy
Tachycardia-related cardiomyopathy
Supraventricular arrhythmias with uncontrolled rate
Very frequent nonsustained ventricular tachycardia or high premature ventricular complex burden
Left bundle branch block (LBBB) has been implicated as a cause of dilated cardiomyopathy appearing late after idiopathic LBBB and responding with near-normal left ventricle size and function after cardiac resynchronization therapy.

^aSome specific cases can be linked now to specific genetic mutation in a familial cardiomyopathy; others with similar phenotypes that appear to be acquired or idiopathic may represent genetic factors not yet identified.

The secondary acquired immune response is more specifically addressed against the viral proteins and can include both T-cell infiltration and antibodies to viral proteins. If unchecked, the acquired immune response can perpetuate secondary cardiac damage. Ongoing cytokine release activates matrix metalloproteinases that can disrupt the collagen and elastin scaffolding of the heart, potentiating ventricular dilation. Stimulation of profibrotic factors leads to pathologic interstitial fibrosis. Some of the antibodies triggered through co-stimulation or molecular mimicry also recognize targets within the host myocyte, such as the β -adrenergic receptor, troponin, and Na^+/K^+ ATPase, but it remains unclear whether these antibodies contribute actively to cardiac dysfunction in humans or merely serve as markers of cardiac injury.

It is not known how long the viruses persist in the human heart, whether late persistence of the viral genome continues to be deleterious, or how often a dormant virus can again become pathogenic. Genomes of common viruses have frequently been detected in patients with clinical diagnoses of myocarditis or dilated cardiomyopathy, but there is little information on how often these are present in patients without cardiac disease (see below). Further information is needed to understand the relative timing and contribution of infection, immune responses, and secondary adaptations in the progression of heart failure after viral myocarditis (Fig. 287-5).

Clinical Presentation of Viral Myocarditis *Acute viral myocarditis* often presents with symptoms and signs of heart failure. Some patients present with chest pain suggestive of pericarditis or acute myocardial infarction. Occasionally, the presentation is dominated by atrial or ventricular tachyarrhythmias, or by pulmonary or systemic emboli from intracardiac thrombi. Electrocardiographic or echocardiographic abnormalities may also be detected incidentally during evaluation for other diagnoses. The typical patient with presumed viral myocarditis is a young to middle-aged adult who develops progressive dyspnea and weakness within a few days to weeks after a viral syndrome that was accompanied by fever and myalgias.

A small number of patients present with fulminant myocarditis, with rapid progression from a severe febrile respiratory syndrome to cardiogenic shock that may involve multiple organ systems, leading to renal failure, hepatic failure, and coagulopathy. These patients are typically young adults who have recently been dismissed from urgent care settings with antibiotics for bronchitis or oseltamivir for viral syndromes, only to return within a few days in rapidly progressive cardiogenic shock. Prompt triage is vital to provide aggressive support with high-dose intravenous catecholamine therapy and sometimes with temporary mechanical circulatory support. Recognition of patients with this fulminant presentation is potentially life-saving as more than half can survive, with marked improvement demonstrable within the first few weeks. The ejection fraction function of these patients often recovers to near-normal, although residual diastolic dysfunction may limit vigorous exercise for some survivors.

Chronic viral myocarditis is often invoked, but rarely proven, as a diagnosis when no other cause of dilated cardiomyopathy can be identified. However, some cases of otherwise unexplained cardiomyopathy will later be recognized to have a genetic basis, or ultimately found to have resulted from excess alcohol consumption or illicit drugs. There are likely many other causes that cannot yet be identified. The prevalence of previous or persistent viral infection as the cause for chronic dilated cardiomyopathy remains highly controversial.

Laboratory evaluation for myocarditis The initial evaluation for suspected myocarditis includes an ECG, an echocardiogram, and serum levels of troponin and creatine phosphokinase fractions. Magnetic resonance imaging is increasingly used for the diagnosis of myocarditis, which is supported by evidence of increased tissue edema and gadolinium enhancement (Fig. 287-6), particularly in the mid-wall (as distinct from usual coronary artery territories).

Endomyocardial biopsy is not often indicated for the initial evaluation of suspected viral myocarditis unless ventricular tachyarrhythmias suggest possible etiologies of sarcoidosis or giant cell myocarditis. The indications and benefit of endomyocardial biopsy for evaluation of myocarditis or new-onset cardiomyopathy remain controversial.

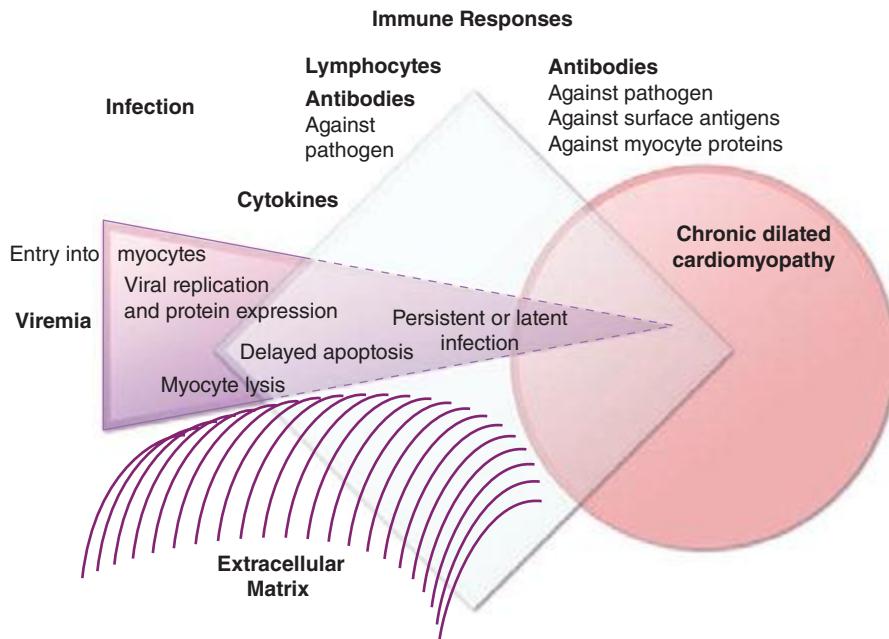


FIGURE 287-5 Schematic diagram demonstrating the possible progression from infection through direct, secondary, and autoimmune responses to dilated cardiomyopathy. Most of the supporting evidence for this sequence is derived from animal models. It is not known to what degree persistent infection and/or ongoing immune responses contribute to ongoing myocardial injury in the chronic phase.

The Dallas Criteria for myocarditis on endomyocardial biopsy include lymphocytic infiltrate with evidence of myocyte necrosis (Fig. 287-7) and are negative in 80–90% of patients with clinical myocarditis. Negative Dallas Criteria can reflect sampling error or early resolution of lymphocytic infiltrates, but also the insensitivity of the test when inflammation results from cytokines and antibody-mediated injury. Routine histologic examination of endomyocardial biopsy rarely reveals a specific infective etiology, such as toxoplasmosis or *Cytomegalovirus*. Immunohistochemistry of myocardial biopsy samples is commonly used to identify active lymphocyte subtypes and may also detect upregulation of HLA antigens and the presence of complement components attributed to inflammation, but the specificity and significance of these findings are uncertain.

An increase in circulating viral titers between acute and convalescent blood samples supports a diagnosis of acute viral myocarditis with potential spontaneous improvement. There is no established role for

measuring circulating anti-heart antibodies, which may be the result rather than a cause, of myocardial injury and have been found also in patients with coronary artery disease and genetic cardiomyopathy.

Patients with recent or ongoing viral syndromes can be classified into three levels of diagnosis:

- Possible subclinical acute myocarditis is diagnosed when a patient has a typical viral syndrome but *no* cardiac symptoms, with one or more of the following:
 - Elevated biomarkers of cardiac injury (troponin or CK-MB)
 - ECG findings suggestive of acute injury
 - Reduced left ventricular ejection fraction or regional wall motion
 - Abnormality on cardiac imaging, usually echocardiography

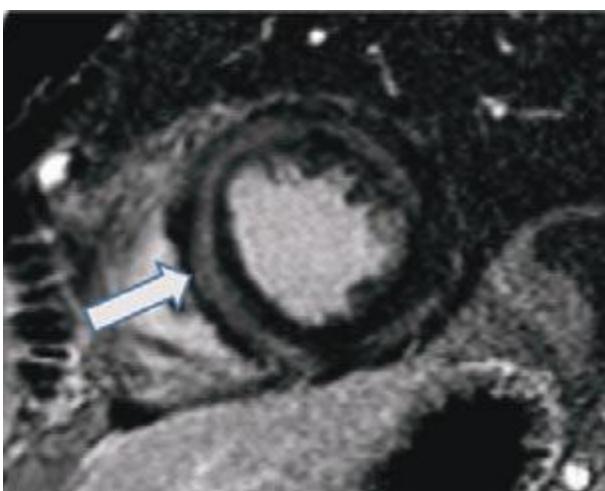


FIGURE 287-6 Magnetic resonance image of myocarditis showing the typical mid-wall location (arrow) for late gadolinium enhancement from cardiac inflammation and scarring. (Image courtesy of Ron Blankstein, MD, and Marcelo Di Carli, MD, Division of Nuclear Medicine, Brigham and Women's Hospital, Boston.)

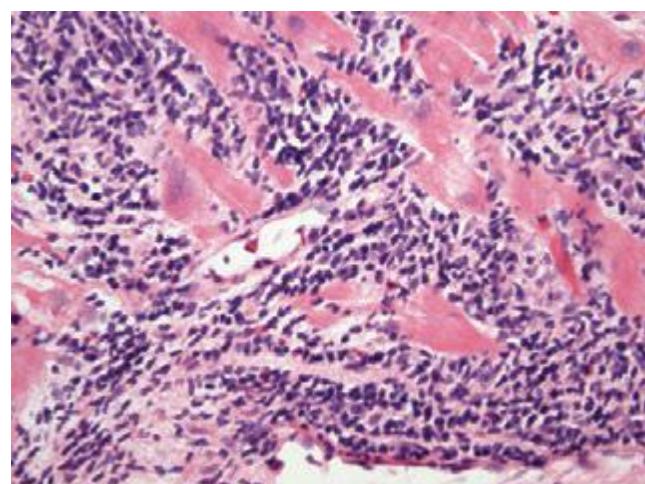


FIGURE 287-7 Acute myocarditis. Microscopic image of an endomyocardial biopsy showing massive infiltration with mononuclear cells and occasional eosinophils associated with clear myocyte damage. The myocyte nuclei are enlarged and reactive. Such extensive involvement of the myocardium would lead to extensive replacement fibrosis even if the inflammatory response could be suppressed. Hematoxylin and eosin-stained section, 200× original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

- 1560** 2. Probable acute myocarditis is diagnosed when the above criteria are met and accompanied also by cardiac symptoms, such as shortness of breath or chest pain, which can result from pericarditis or myocarditis. When clinical findings of pericarditis (pleuritic chest pain, ECG abnormalities, pericardial rub or effusion) are accompanied by elevated troponin or CK-MB or abnormal cardiac wall motion, the terms perimyocarditis or myopericarditis are sometimes used.
3. Definite myocarditis is diagnosed when there is histologic or immunohistologic evidence of inflammation on endomyocardial biopsy (see below) and does *not* require any other laboratory or clinical criteria.

PART 10

Disorders of the Cardiovascular System

SPECIFIC VIRUSES IMPLICATED IN MYOCARDITIS

In humans, viruses are often suspected but rarely proven to be the direct cause of clinical myocarditis. First implicated was the picornavirus family of RNA viruses, principally the enteroviruses, coxsackie virus, echovirus, and poliovirus. Influenza, another RNA virus, is implicated with varying frequency every winter and spring as epitopes change. Of the DNA viruses, adenovirus, vaccinia (smallpox vaccine), and the herpesviruses (varicella zoster, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 [HHV6]) are well-recognized to cause myocarditis but also occur commonly in the healthy population. Polymerase chain reaction (PCR) detects viral genomes in the majority of patients with dilated cardiomyopathy, but also in normal “control” hearts. Most often detected are parvovirus B19 and HHV6, which may affect the cardiovascular system, in part, through infection of vascular endothelial cells. However, their contribution to chronic cardiomyopathy is uncertain, as serologic evidence of exposure is present in many children and most adults.

Human immunodeficiency virus (HIV) was associated with an incidence of dilated cardiomyopathy of 1–2%; however, with the advent of highly active antiretroviral therapy (HAART), HIV has been associated with a significantly lower incidence of cardiac disease. Cardiomyopathy in HIV may result from cardiac involvement with other associated viruses, such as cytomegalovirus and hepatitis C, as well as by HIV directly. Antiviral drugs to treat chronic HIV can cause cardiomyopathy, both directly and through drug hypersensitivity. The clinical picture may be complicated by pericardial effusions and pulmonary hypertension. There is a high frequency of lymphocytic myocarditis found at autopsy, and viral particles have been demonstrated in the myocardium in some cases, consistent with direct causation.

Hepatitis C has been repeatedly implicated in cardiomyopathy, particularly in Germany and Asia. Cardiac dysfunction may improve after interferon therapy. As this cytokine itself often depresses cardiac function transiently, careful coordination of administration and ongoing clinical evaluation are critical. Involvement of the heart with hepatitis B is uncommon, but can be seen when associated with systemic vasculitis (polyarteritis nodosa).

Additional viruses implicated specifically in myocarditis include *mumps*, *respiratory syncytial virus*, the *arboviruses* (*dengue fever and yellow fever*), and *arenaviruses* (*Lassa fever*). However, for any serious infection, the systemic inflammatory response can cause nonspecific depression of cardiac function, which is generally reversible if the patient survives.

THERAPY

There is currently no specific therapy recommended during any stage of viral myocarditis. During acute infection, therapy with anti-inflammatory or immunosuppressive medications is avoided, as their use has been shown to increase viral replication and myocardial injury in animal models. Therapy with specific antiviral agents (such as oseltamivir) has not been studied in relation to cardiac involvement. There is ongoing investigation into the impact of antiviral therapy to treat chronic viral persistence identified from endomyocardial biopsy. Large trials of immunosuppressive therapy for Dallas Criteria-positive myocarditis have been negative. There are some initial encouraging results and ongoing investigations with immunosuppressive therapy for immune-mediated myocarditis defined by immunohistologic criteria on biopsy or circulating anti-heart antibodies in the absence

of myocardial viral genomes. However, neither antiviral nor anti-inflammatory therapies are currently recommended. Until we have a better understanding of the different phases of viral myocarditis and its sequelae and the effects of timed or targeted therapies, treatment will continue to be directed to the clinical cardiovascular stage of the disease, for dilated cardiomyopathy in general.

Parasitic Myocarditis *Chagas' disease* is the third most common parasitic infection in the world and the most common infective cause of cardiomyopathy. The protozoan *T. cruzi* is transmitted by the bite of the reduviid bug, endemic in the rural areas of South and Central America. Transmission can also occur through blood transfusion, organ donation, from mother to fetus, and occasionally orally. While programs to eradicate the insect vector have decreased the prevalence from about 16 million to less than 10 million in South America, cases are increasingly recognized in Western developed countries. Approximately 100,000 affected individuals are currently living in the United States, most of whom contracted the disease in endemic areas.

Multiple pathogenic mechanisms are implicated. The parasite itself can cause myocyte lysis and primary neuronal damage, and specific immune responses may recognize the parasites or related antigens and lead to chronic immune activation in the absence of detectable parasites. Molecular techniques have revealed persistent parasite DNA fragments in infected individuals. Further evidence for persistent infection is the eruption of parasitic skin lesions during immunosuppression after cardiac transplantation. As with viral myocarditis, the relative roles of persistent infection and of secondary autoimmune injury have not been resolved (Fig. 287-5). An additional factor in the progression of Chagas' disease is the autonomic dysfunction and microvascular damage that may contribute to cardiac and gastrointestinal disease.

The acute phase of Chagas' disease with parasitemia is usually unrecognized, but in fewer than 5% of cases, it presents clinically within a few weeks of infection, with nonspecific symptoms or occasionally with acute myocarditis and meningoencephalitis. In the absence of antiparasitic therapy, the silent stage progresses slowly over 10–30 years in almost half of patients to manifest in the cardiac and gastrointestinal systems in the chronic stages. Features typical of Chagas' disease are conduction system abnormalities, particularly sinus node and atrioventricular (AV) node dysfunction and right bundle branch block. Atrial fibrillation and ventricular tachyarrhythmias also occur. Small ventricular aneurysms are common, particularly at the ventricular apex. These dilated ventricles are particularly thrombotic, giving rise to pulmonary and systemic emboli. Xenodiagnosis, detection of the parasite itself, is rarely performed. The serologic tests for specific IgG antibodies against the trypanosome lack sufficient specificity and sensitivity, thereby requiring two separate positive tests required to make a diagnosis.

Treatment of the advanced stages focuses on clinical manifestations of the disease and includes heart failure medications, pacemaker-defibrillators, and anticoagulation. Increasing attention is directed to antiparasitic therapy even in chronic disease without obvious active infection. The most common effective antiparasitic therapies are benznidazole and nifurtimox, both associated with multiple severe reactions, including dermatitis, gastrointestinal distress, and neuropathy. Survival is less than 30% at 5 years after the onset of overt clinical heart failure. Patients without major extracardiac disease have occasionally undergone transplantation, after which they may require lifelong therapy to suppress reactivation of infection.

African trypanosomiasis infection results from the tsetse fly bite and can occur in travelers exposed during trips to Africa. The West African form is caused by *Trypanosoma brucei gambiense* and progresses silently over years. The East African form caused by *T. brucei rhodesiense* can progress rapidly through perivasicular infiltration to myocarditis and heart failure, with frequent arrhythmias. The diagnosis is made by identification of trypanosomes in blood, lymph nodes, or other affected sites. Antiparasitic therapy has limited efficacy and is determined by the specific type and the stage of infection (hemolytic or neurologic).

Toxoplasmosis is contracted through undercooked infected beef or pork, transmission from feline feces, organ transplantation, transfusion, or maternal-fetal transmission. Immunocompromised hosts are most likely to experience reactivation of latent infection from cysts. The cysts have been found in up to 40% of autopsies of patients dying from HIV infection. Toxoplasmosis may present with encephalitis or chorioretinitis and, in the heart, can cause myocarditis, pericardial effusion, constrictive pericarditis, and heart failure. The diagnosis in an immunocompetent patient is made when the IgM is positive and the IgG becomes positive later. Active toxoplasmosis may be suspected in an immunocompromised patient with myocarditis and a positive IgG titer for toxoplasmosis, particularly when avidity testing identifies high specificity of the antibody. Fortuitous sampling occasionally reveals the cysts in the myocardium. Combination therapy can include pyrimethamine and sulfadiazine or clindamycin.

Trichinellosis is caused by *Trichinella spiralis* larva ingested with undercooked meat. Larvae migrating into skeletal muscles cause myalgias, weakness, and fever. Periorbital and facial edema and conjunctival and retinal hemorrhage may also be seen. Although the larva may occasionally invade the myocardium, clinical heart failure is rare and, when observed, attributed to the eosinophilic inflammatory response. The diagnosis is made from the specific serum antibody and is further supported by the presence of eosinophilia. Treatment includes anti-helminthic drugs (albendazole, mebendazole) and glucocorticoids if inflammation is severe.

Cardiac involvement with *Echinococcus* is rare, but cysts can form and rupture in the myocardium and pericardium.

Bacterial Infections Most bacterial infections can involve the heart occasionally through direct invasion and abscess formation, but do so rarely. More commonly, systemic inflammatory responses depress contractility in severe infection and sepsis. *Diphtheria* specifically affects the heart in almost one-half of cases, and cardiac involvement is the most common cause of death in patients with this infection. The prevalence of vaccines has shifted the incidence of diphtheria from children worldwide to countries without routine immunization and to older populations who have lost their immunity. The bacillus releases a toxin that impairs protein synthesis and may particularly affect the conduction system. The specific antitoxin should be administered as soon as possible, with higher priority than antibiotic therapy. Other systemic bacterial infections that can involve the heart include *brucellosis*, *chlamydophila*, *legionella*, *meningococcus*, *mycoplasma*, *psittacosis*, and *salmonellosis*, for which specific treatment is directed at the systemic infection.

Clostridial infections cause myocardial damage from the released toxin. Gas bubbles can be detected in the myocardium, and occasionally abscesses can form in the myocardium and pericardium. *Streptococcal infection* with β-hemolytic streptococci is most commonly associated with acute rheumatic fever and is characterized by inflammation and fibrosis of cardiac valves and systemic connective tissue, but it can also lead to a myocarditis with focal or diffuse infiltrates of mononuclear cells.

Tuberculosis can involve the myocardium directly as well as through tuberculous pericarditis, but rarely does so when the disease is treated with antibiotics. *Whipple's disease* is caused by *Tropheryma whipplei*. The usual manifestations are in the gastrointestinal tract, but pericarditis, coronary arteritis, valvular lesions, and occasionally clinical heart failure may also occur. Multidrug antituberculous regimens are effective, but the disease tends to relapse even with appropriate treatment.

Other Infections *Spirochetal myocarditis* has been diagnosed from myocardial biopsies containing *Borrelia burgdorferi* that causes *Lyme disease*. Lyme carditis most often presents with arthritis and conduction system disease that resolves within 1–2 weeks of antibiotic treatment, only rarely implicated in chronic heart failure.

Fungal myocarditis can occur due to hematogenous or direct spread of infection from other sites, as has been described for aspergillosis, actinomycosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, and mucormycosis. However, cardiac involvement is rarely the dominant clinical feature of these infections.

The *rickettsial infections*, *Q fever*, *Rocky Mountain spotted fever*, and *scrub typhus* are frequently accompanied by ECG changes, but most clinical manifestations relate to systemic vascular involvement.

NONINFECTIVE MYOCARDITIS

Myocardial inflammation can occur without apparent preceding infection. The paradigm of noninfective inflammatory myocarditis is cardiac transplant rejection, from which we have learned that myocardial depression can develop and reverse quickly, that noncellular mediators such as antibodies and cytokines play a major role in addition to lymphocytes, and that myocardial antigens are exposed by prior physical injury and viral infection.

The most commonly diagnosed noninfective inflammation is granulomatous myocarditis, including both sarcoidosis and giant cell myocarditis. Sarcoidosis, as discussed in Chap. 390, is a multisystem disease most commonly affecting the lungs. Although classically presenting with higher prevalence in young African-American men, the epidemiology appears to be changing, with increasing recognition of sarcoidosis in Caucasian patients in nonurban areas. Patients with pulmonary sarcoid are at high risk for cardiac involvement, but cardiac sarcoidosis also occurs without clinical lung disease. Regional clustering of the disease supports the suspicion that the granulomatous reaction is triggered by an infectious or environmental allergen not yet identified.

The sites and density of cardiac granulomata, the time course, and the degree of extracardiac involvement are remarkably variable. Patients may present with rapid-onset heart failure and ventricular tachyarrhythmias, conduction block, chest pain syndromes, or minor cardiac findings in the setting of ocular involvement, an infiltrative skin rash, or a nonspecific febrile illness. They may also present less acutely after months to years of fluctuating cardiac symptoms. When ventricular tachycardia or conduction block dominates the initial presentation of heart failure without coronary artery disease, suspicion should be high for these granulomatous myocarditides.

Depending on the time course, the ventricles may appear restrictive or dilated. There is often right ventricular predominance of both dilation and ventricular arrhythmias, sometimes initially attributed to arrhythmogenic right ventricular dysplasia. Small ventricular aneurysms are common. Computed tomography of the chest often reveals pulmonary lymphadenopathy even in the absence of clinical lung disease. Metabolic imaging (positron emission tomography (PET)) of the whole chest can highlight active sarcoid lesions that are avid for glucose. Magnetic resonance imaging (MRI) of the heart can identify areas likely to be inflammatory. To rule out chronic infections, such as tuberculosis or histoplasmosis as the cause of adenopathy, the diagnosis usually requires pathologic confirmation. Biopsy of enlarged mediastinal nodes may provide the highest yield. The scattered granulomata of sarcoidosis can easily be missed on cardiac biopsy (Fig. 287-8).

Immunosuppressive treatment for sarcoidosis is initiated with high-dose glucocorticoids, which are often more effective for arrhythmias than for the heart failure. Patients with sarcoid lesions that persist or recur during tapering of corticosteroids are considered candidates for other immunosuppressive therapies, frequently with agents also used for cardiac transplantation. Pacemakers and implantable defibrillators are generally indicated to prevent life-threatening heart block or ventricular tachycardia, respectively. Because the inflammation often resolves into extensive fibrosis that impairs cardiac function and provides pathways for reentrant arrhythmias, the prognosis for improvement is best when the granulomata are not extensive and the ejection fraction is not severely reduced.

Giant cell myocarditis is less common than sarcoidosis, but accounts for 10–20% of biopsy-positive cases of myocarditis. Giant cell myocarditis typically presents with rapidly progressive heart failure and tachyarrhythmias. Diffuse granulomatous lesions are surrounded by extensive inflammatory infiltrate unlikely to be missed on endomyocardial biopsy, often with extensive eosinophilic infiltration. Associated conditions are thymomas, thyroiditis, pernicious anemia, other autoimmune diseases, and occasionally recent infections. Glucocorticoid therapy is less effective than for sarcoidosis and is

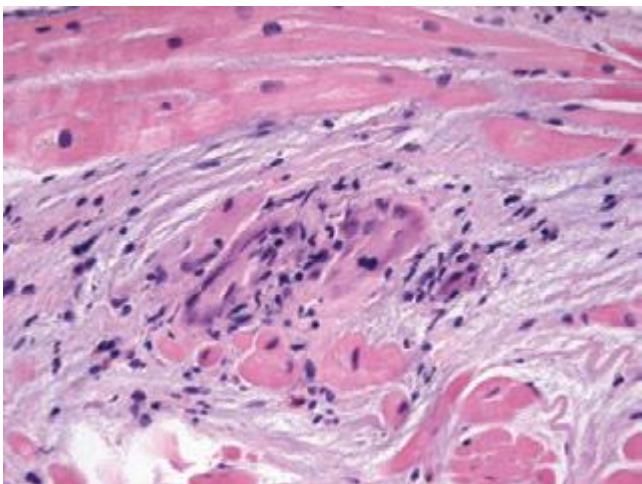


FIGURE 287-8 Sarcoidosis. Microscopic image of an endomyocardial biopsy showing a noncaseating granuloma and associated interstitial fibrosis typical of sarcoidosis. No microorganisms were present on special stains, and no foreign material was identified. Hematoxylin and eosin-stained section, 200x original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

sometimes combined with other immunosuppressive agents. The course is generally of rapid deterioration requiring urgent transplantation. Although the severity of presentation and myocardial histology are more fulminant than with sarcoidosis, the occasional finding of giant cell myocarditis after sarcoidosis suggests that they may in some cases represent different stages of the same disease spectrum.

Eosinophilic myocarditis can be an important manifestation of the hypereosinophilic syndrome, which in Western countries is often idiopathic, although in Mediterranean and African countries, it is likely a consequence of antecedent infection. It may also be seen with systemic eosinophilic syndromes such as Churg-Strauss syndrome or malignancies. *Hypersensitivity myocarditis* is often an unexpected diagnosis, made when the biopsy reveals infiltration with lymphocytes and mononuclear cells with a high proportion of eosinophils. Most commonly, the reaction is attributed to antibiotics, particularly those taken chronically, but thiazides, anticonvulsants, indomethacin, and methyldopa have also been implicated. Occasional associations with the smallpox vaccine have been reported. Although the circulating eosinophil count may be slightly elevated in hypersensitivity myocarditis, it does not reach the high levels of the hypereosinophilic syndrome. High-dose glucocorticoids and discontinuation of the trigger agent can be curative for hypersensitivity myocarditis.

Myocarditis is often associated with systemic inflammatory diseases, such as polymyositis and *dermatomyositis*, which affect skeletal and cardiac muscle. Although noninfective inflammatory myocarditis is sometimes included in the differential diagnosis of cardiac findings in patients with connective tissue disease such as systemic lupus erythematosus, pericarditis, vasculitis, pulmonary hypertension, and accelerated coronary artery disease are more common cardiac manifestations of connective tissue disease.

Peripartum cardiomyopathy (PPCM) develops during the last trimester or within the first 6 months after pregnancy, with a frequency between 1:2000 and 1:15,000 deliveries. Risk factors are increased maternal age, increased parity, twin pregnancy, malnutrition, use of tocolytic therapy for premature labor, and preeclampsia or toxemia of pregnancy. Heart failure early after delivery was previously common in Nigeria, when the custom for new mothers included salt ingestion while reclining on a warm bed, which likely impaired mobilization of the excess circulating volume after delivery. In the Western world, lymphocytic myocarditis has sometimes been found on myocardial biopsy. This inflammation has been hypothesized to reflect increased susceptibility to viral myocarditis or an autoimmune myocarditis due

to cross-reactivity of anti-uterine antibodies against cardiac muscle. Another proposed mechanism invokes an abnormal prolactin cleavage fragment, which is induced by oxidative stress and may trigger myocardial apoptosis; this observation has led to preliminary investigation of bromocriptine as possible therapy.

Very recently, PPCM has been found to be associated with increased antiangiogenic signaling, a process that is exacerbated by preeclampsia. In animal models of this disease, proangiogenic therapies have proven curative.

As the increased circulatory demand of pregnancy can aggravate other cardiac disease that was clinically unrecognized, it is crucial to the diagnosis of PPCM that there be no evidence for a preexisting cardiac disorder. By contrast, heart failure presenting earlier in pregnancy has been termed pregnancy-associated cardiomyopathy (PACM). Both PPCM and PACM have been found in some families with other presentations of dilated cardiomyopathy, in some cases with known sarcomeric protein mutations. Pregnancy may, thus, represent an environmental trigger for accelerated phenotypic expression of genetic cardiomyopathy.

TOXIC CARDIOMYOPATHY

Cardiotoxicity has been reported with multiple environmental and pharmacologic agents. Often these associations are seen only with very high levels of exposure or acute overdoses, in which acute electrocardiographic and hemodynamic abnormalities may reflect both direct drug effect and systemic toxicity.

Alcohol is the most common toxin implicated in chronic dilated cardiomyopathy. Excess consumption may contribute to more than 10% of cases of heart failure, including exacerbation of cases with other primary etiologies such as valvular disease or previous infarction. Toxicity is attributed both to alcohol and to its primary metabolite, acetaldehyde. Polymorphisms of the genes encoding alcohol dehydrogenase and the angiotensin-converting enzyme increase the likelihood of alcoholic cardiomyopathy in an individual with excess consumption. Superimposed vitamin deficiencies and toxic alcohol additives are rarely implicated. The alcohol consumption necessary to produce cardiomyopathy in an otherwise normal heart has been estimated to be five to six drinks (about 4 ounces of pure ethanol) daily for 5–10 years, but frequent binge drinking may also be sufficient. Many patients with alcoholic cardiomyopathy are fully functional in their daily lives without apparent stigmata of alcoholism. The cardiac impairment in severe alcoholic cardiomyopathy is the sum of both permanent damage and a substantial component that is reversible after cessation of alcohol consumption. Atrial fibrillation occurs commonly both early in the disease ("holiday heart") and in advanced stages. Medical therapy includes neurohormonal antagonists and diuretics as needed for fluid management. Withdrawal should be supervised to avoid exacerbations of heart failure or arrhythmias, and ongoing support arranged. Even with severe disease, marked improvement can occur within 3–6 months of abstinence. Implantable defibrillators are generally deferred until an adequate period of abstinence, after which they may not be necessary if the ejection fraction has improved. With continued consumption, the prognosis is grim.

Cocaine, amphetamines, and related catecholaminergic stimulants can produce chronic cardiomyopathy as well as acute ischemia and tachyarrhythmias. Pathology reveals microinfarcts consistent with small vessel ischemia, similar to those seen with pheochromocytoma.

Chemotherapy agents are the most common drugs implicated in toxic cardiomyopathy. Judicious use of these drugs requires balancing the risks of the malignancy and the risks of cardiotoxicity, as many cancers have a chronic course with better prognosis than heart failure.

Anthracyclines cause characteristic histologic changes of vacuolar degeneration and myofibrillar loss. Generation of reactive oxygen species involving heme compounds is currently the favored explanation for myocyte injury and fibrosis. Disruption of the large titin protein may contribute to loss of sarcomere organization. Risk for cardiotoxicity increases with higher doses, preexisting cardiac disease, and concomitant chest irradiation. There are three different presentations of anthracycline-induced cardiomyopathy. (1) Heart failure can develop acutely during administration of a single dose, but may clinically resolve

in a few weeks. (2) Early-onset doxorubicin cardiotoxicity develops in about 3% of patients during or shortly after a chronic course, relating closely to total dose. It may be rapidly progressive, but may also resolve to good, but not normal, ventricular function. (3) The chronic presentation differs according to whether therapy was given before or after puberty. Patients who received doxorubicin while still growing may have impaired development of the heart, which leads to clinical heart failure by the time the patient reaches the early twenties. Late after adult exposure, patients may develop the gradual onset of symptoms or an acute onset precipitated by a reversible second insult, such as influenza or atrial fibrillation. Doxorubicin cardiotoxicity leads to a relatively nondilated ventricle, perhaps due to the accompanying fibrosis. Thus, the stroke volume may be severely reduced with an ejection fraction of 30–40%, which would be well tolerated in a patient with a larger ventricle typical of other cardiomyopathies with systolic dysfunction. Therapy includes angiotensin-converting enzyme inhibitors and β -adrenergic blocking agents used for other causes of heart failure, with careful suppression of “inappropriate” sinus tachycardia, and attention to postural hypotension that can occur in these patients. Once thought to have an inexorable downward course, some patients with doxorubicin cardiotoxicity improve under careful management to near-normal clinical function for many years.

Trastuzumab (Herceptin) is a monoclonal antibody that interferes with cell surface receptors crucial for some tumor growth and for cardiac adaptation. The incidence of cardiotoxicity is lower than for anthracyclines but enhanced by coadministration with them. Although considered to be more often reversible, trastuzumab cardiotoxicity does not always resolve, and some patients progress to clinical heart failure and death. As with anthracycline cardiotoxicity, therapy is as usual for heart failure, but it is not clear whether the spontaneous rate of improvement is enhanced by neurohormonal antagonists.

Cardiotoxicity with *cyclophosphamide* and *ifosfamide* generally occurs acutely and with very high doses. 5-Fluorouracil, cisplatin, and some other alkylating agents can cause recurrent coronary spasm that occasionally leads to depressed contractility. Acute administration of *interferon- α* can cause hypotension and arrhythmias. Clinical heart failure occurring during repeated chronic administration usually resolves after discontinuation.

Many small-molecule *tyrosine kinase inhibitors* are under development for different malignancies. Although these agents are “targeted” at specific tumor receptors or pathways, the biologic conservation of signaling pathways can cause these inhibitors to have “off-target” effects that include the heart and vasculature. Recognition of cardiotoxicity during therapy with these agents is complicated because they occasionally cause peripheral fluid accumulation (ankle edema, periorbital swelling, pleural effusions) due to local factors rather than elevated central venous pressures. Therapeutic approaches include withdrawal of the tyrosine kinase inhibitor (when possible) and substitution with a congener (when available), as well as conventional treatment for heart failure. Prophylactic treatment with beta blockers and angiotensin-converting enzyme inhibitors prior to and during chemotherapy is a topic of ongoing investigation.

Other therapeutic drugs that can cause cardiotoxicity during chronic use include hydroxychloroquine, chloroquine, emetine, and antiretroviral therapies.

Toxic exposures can cause arrhythmias or respiratory injury acutely during accidents. Chronic exposures implicated in cardiotoxicity include hydrocarbons, fluorocarbons, arsenicals, lead, and mercury.

METABOLIC CAUSES OF CARDIOMYOPATHY

Endocrine disorders affect multiple organ systems, including the heart. *Hyperthyroidism* and *hypothyroidism* do not often cause clinical heart failure in an otherwise normal heart, but commonly exacerbate heart failure. Clinical signs of thyroid disease may be masked, so tests of thyroid function are part of the routine evaluation of cardiomyopathy. Hyperthyroidism should always be considered with new-onset atrial fibrillation or ventricular tachycardia or atrial fibrillation in which the rapid ventricular response is difficult to control. The most common current reason for thyroid abnormalities in the cardiac

population is the treatment of tachyarrhythmias with amiodarone, a drug with substantial iodine content. Hypothyroidism should be treated with very slow escalation of thyroid supplements to avoid exacerbating tachyarrhythmias and heart failure. Hyperthyroidism and heart failure are a dangerous combination that merits very close supervision, often hospitalization, during titration of antithyroid medications, during which decompensation of heart failure may occur precipitously and fatally.

Pheochromocytoma is rare, but should be considered when a patient has heart failure and very labile blood pressure and heart rate, sometimes with episodic palpitations ([Chap. 407](#)). Patients with pheochromocytoma often have postural hypotension. In addition to α -adrenergic receptor antagonists, definitive therapy requires surgical extirpation. Very high renin states, such as those caused by renal artery stenosis, can lead to modest depression in ejection fraction with little or no ventricular dilation and markedly labile symptoms with flash pulmonary edema, related to sudden shifts in vascular tone and intravascular volume.

Controversies remain regarding whether *diabetes* and *obesity* are sufficient to cause cardiomyopathy. Most heart failure in diabetes results from epicardial coronary disease, with further increase in coronary artery risk due to accompanying hypertension and renal dysfunction. Cardiomyopathy may result in part from insulin resistance and increased advanced-glycosylation end products, which impair both systolic and diastolic function. However, much of the dysfunction can be attributed to scattered focal ischemia resulting from distal coronary artery tapering and limited microvascular perfusion even without proximal focal stenoses. Diabetes is a typical factor in heart failure with “preserved” ejection fraction, along with hypertension, advanced age, and female gender.

The existence of a cardiomyopathy due to *obesity* is generally accepted. In addition to cardiac involvement from associated diabetes, hypertension, and vascular inflammation of the metabolic syndrome, obesity alone is associated with impaired excretion of excess volume load, which, over time, can lead to increased wall stress and secondary adaptive neurohumoral responses. Fluid retention may be aggravated by large fluid intake and the rapid clearance of natriuretic peptides by adipose tissue. In the absence of another obvious cause of cardiomyopathy in an obese patient with systolic dysfunction without marked ventricular dilation, effective weight reduction is often associated with major improvement in ejection fraction and clinical function. Improvement in cardiac function has been described after successful bariatric surgery, although all major surgical therapy poses increased risk for patients with heart failure. Postoperative malabsorption and nutritional deficiencies, such as calcium and phosphate deficiencies, may be particularly deleterious for patients with cardiomyopathy.

Nutritional deficiencies can occasionally cause dilated cardiomyopathy but are not commonly implicated in developed Western countries. *Beri-beri heart disease* due to thiamine deficiency can result from poor nutrition in undernourished populations and in patients deriving most of their calories from alcohol, and has been reported in teenagers subsisting only on highly processed foods. This disease is initially a vasodilated state with very high output heart failure that can later progress to a low output state; thiamine repletion can lead to prompt recovery of cardiovascular function. Abnormalities in *carnitine* metabolism can cause dilated or restrictive cardiomyopathies, usually in children. Deficiency of trace elements such as *selenium* can cause cardiomyopathy (Keshan’s disease).

Calcium is essential for excitation-contraction coupling. Chronic deficiencies of calcium, such as can occur with hypoparathyroidism (particularly postsurgical) or intestinal dysfunction (from diarrheal syndromes and following extensive resection), can cause severe chronic heart failure that responds over days or weeks to vigorous calcium repletion. *Phosphate* is a component of high-energy compounds needed for efficient energy transfer and multiple signaling pathways. *Hypophosphatemia* can develop during starvation and early refeeding following a prolonged fast, and occasionally during hyperalimentation. *Magnesium* is a cofactor for thiamine-dependent reactions and for the sodium-potassium adenosine triphosphatase (ATPase), but

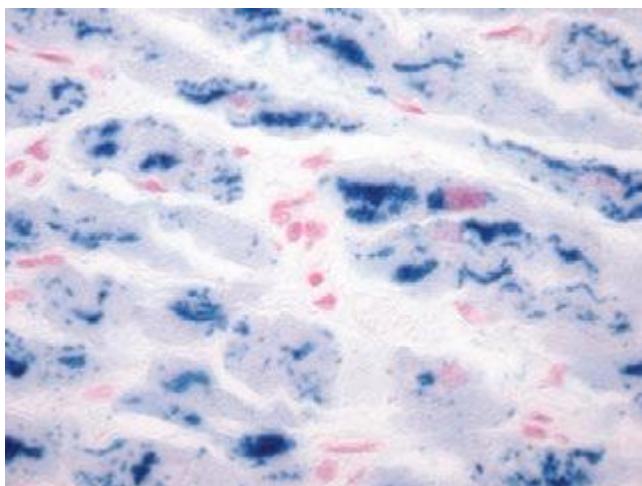


FIGURE 287-9 Hemochromatosis. Microscopic image of an endomyocardial biopsy showing extensive iron deposition within the cardiac myocytes with the Prussian blue stain (400x original magnification). (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

hypomagnesemia rarely becomes sufficiently profound to cause clinical cardiomyopathy.

Hemochromatosis is variably classified as a metabolic or storage disease (Chap. 428). It is included among the causes of restrictive cardiomyopathy, but the clinical presentation is often that of a dilated cardiomyopathy. The autosomal recessive form is related to the *HFE* gene. With up to 10% of the population heterozygous for one mutation, the clinical prevalence might be as high as 1 in 500. The lower observed rates highlight the limited penetrance of the disease, suggesting the role of additional genetic and environmental factors for clinical expression. Hemochromatosis can also be acquired from iron overload due to hemolytic anemia and transfusions. Excess iron is deposited in the perinuclear compartment of cardiomyocytes, with resulting disruption of intracellular architecture and mitochondrial function. Diagnosis is easily made from measurement of serum iron and transferrin saturation, with a threshold of >60% for men and >45–50% for women. MRI can help to quantitate iron stores in the liver and heart, and endomyocardial biopsy tissue can be stained for iron (Fig. 287-9), which is particularly important if the patient has another cause for cardiomyopathy. If diagnosed early, hemochromatosis can often be managed by repeated phlebotomy to remove iron. For more severe iron overload, iron chelation therapy with desferrioxamine (deferoxamine) or deferasirox can help to improve cardiac function if myocyte loss and replacement fibrosis are not too severe.

Inborn disorders of metabolism occasionally present with dilated cardiomyopathy, although they are most often associated with restrictive cardiomyopathy (Table 287-4).

FAMILIAL DILATED CARDIOMYOPATHY

The genetic basis for cardiomyopathy is discussed in the section, “Genetic Etiologies of Cardiomyopathy.” The recognized frequency of familial involvement in dilated cardiomyopathy has increased to over 30%. Mutations in *TTN*, encoding the giant sarcomeric protein titin, are the most common cause of dilated cardiomyopathy, accounting for up to 25% of familial disease. On average, men with *TTN* mutations develop cardiomyopathy a decade before women, without distinctive clinical features. Mutations in thick and thin filament genes account for ~8% of dilated cardiomyopathy and may manifest in early childhood.

The most recognizable familial cardiomyopathy syndromes with extra-cardiac manifestations are the *muscular dystrophies*. Both Duchenne’s and the milder Becker’s dystrophy result from abnormalities in the X-linked dystrophin gene of the sarcolemmal membrane. Skeletal myopathy is present in multiple other genetic cardiomyopathies (Table 287-3), some of which are associated with creatine kinase elevations.

Families with a history of atrial arrhythmias, conduction system disease, and cardiomyopathy may have abnormalities of the nuclear membrane lamin proteins. While all dilated cardiomyopathies carry a risk of sudden death, a family history of cardiomyopathy with sudden death raises suspicion for a particularly arrhythmogenic mutation; affected family members may be considered for implantable defibrillators even before meeting the reduced ejection fraction threshold for primary prevention of sudden death.

A prominent family history of sudden death or ventricular tachycardia before clinical cardiomyopathy suggests genetic defects in the desmosomal proteins (Fig. 287-10). Originally described as affecting the right ventricle (arrhythmogenic right ventricular dysplasia [ARVD]), this disorder (arrhythmogenic ventricular dysplasia) can affect either or both ventricles. Patients often present first with ventricular tachycardia. Genetic defects in proteins of the desmosomal complex disrupt myocyte junctions and adhesions, leading to replacement of myocardium by deposits of fat. Thin ventricular walls may be recognized on echocardiography but are better visualized on MRI. Because desmosomes are also important for elasticity of hair and skin, some of the defective desmosomal proteins are associated with striking “woolly hair” and thickened skin on the palms and soles. Implantable defibrillators are usually indicated to prevent sudden death. There is variable progression to right, left, or biventricular failure.

Left ventricular noncompaction is a condition of unknown prevalence that is increasingly revealed with the refinement of imaging techniques. The diagnostic criteria include the presence of multiple trabeculations in the left ventricle distal to the papillary muscles, creating a “spongy” appearance of the apex. Noncompaction has been associated with multiple genetic variants in the sarcomeric and other genes, such as *TAZ* (encoding tafazzin). The diagnosis may be made incidentally or in patients previously diagnosed with cardiomyopathy, in whom the criteria for noncompaction may appear and resolve with changing left ventricular size and function. The three cardinal clinical features are ventricular arrhythmias, embolic events, and heart failure. Treatment generally includes anticoagulation and early consideration for an implantable defibrillator, in addition to neurohormonal antagonists as indicated by stage of disease.

Some families inherit a susceptibility to viral-induced myocarditis. This propensity may relate to abnormalities in cell surface receptors, such as the coxsackie-adenovirus receptor, that bind viral proteins.

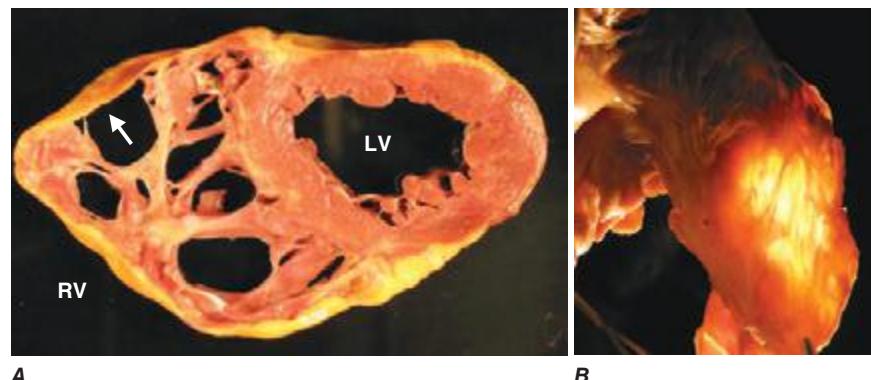


FIGURE 287-10 Arrhythmogenic right ventricular dysplasia. **A.** Cross-sectional slice of a pathology specimen removed at transplantation, showing severe dysplasia of the right ventricle (RV) with extensive fatty replacement of right ventricular myocardium. **B.** The remarkably thin right ventricular free wall is revealed by transillumination. LV, left ventricle. (Images courtesy of Gayle Winters, MD, and Richard Mitchell, MD, PhD, Division of Pathology, Brigham and Women's Hospital, Boston.)

Some may have partial homology with viral proteins such that an autoimmune response is triggered against the myocardium.

Prognosis and therapy of familial dilated cardiomyopathy are dictated primarily by the stage of clinical disease and the risk for sudden death. In some cases, the familial etiology facilitates prognostic decisions, particularly regarding the likelihood of recovery after a new diagnosis, which is unlikely for familial disease. The rate of progression of disease, once manifest, is, to some extent, heritable, although marked variation can be seen. However, there have been cases of remarkable clinical remission after acute presentation, likely after a reversible additional insult, such as prolonged tachycardia or infective myocarditis.

TAKOTSUBO CARDIOMYOPATHY

The apical ballooning syndrome, or stress-induced cardiomyopathy, occurs typically in older women after sudden intense emotional or physical stress. The ventricle shows global ventricular dilation with basal contraction, forming the shape of the narrow-necked jar (*takotsubo*) used in Japan to trap octopi. Originally described in Japan, it is increasingly recognized elsewhere during emergency cardiac catheterization and intensive care unit admissions for noncardiac conditions. Presentations include pulmonary edema, hypotension, and chest pain with ECG changes mimicking an acute infarction. The left ventricular dysfunction extends beyond a specific coronary artery distribution and generally resolves within days to weeks. Animal models and ventricular biopsies suggest that this acute cardiomyopathy may result from intense sympathetic activation with heterogeneity of myocardial autonomic innervation, diffuse microvascular spasm, and/or direct catecholamine toxicity. Coronary angiography may be required to rule out acute coronary occlusion. No therapies have been proven beneficial, but reasonable strategies include nitrates for pulmonary edema, intraaortic balloon pump if needed for low output, combined alpha and beta blockers rather than selective beta blockade if hemodynamically stable, and magnesium for arrhythmias related to QT prolongation. Anticoagulation is generally withheld due to the occasional occurrence of ventricular rupture. While the prognosis is generally good, recurrences have been described in up to 10% of patients.

IDIOPATHIC DILATED CARDIOMYOPATHY

Idiopathic dilated cardiomyopathy is a diagnosis of exclusion, when all other known factors have been excluded. Approximately two-thirds of dilated cardiomyopathies are still labeled as idiopathic; however, a substantial proportion of these may reflect unrecognized genetic disease. Continued reconsideration of etiology during chronic heart failure management often reveals specific causes later in a patient's course.

OVERLAPPING TYPES OF CARDIOMYOPATHY

The limitations of our phenotypic classification are revealed through the multiple overlaps between the etiologies and presentations of the three types. Cardiomyopathy with reduced systolic function but without severe dilation can represent early dilated cardiomyopathy, "minimally dilated cardiomyopathy," or restrictive diseases without marked increases in ventricular wall thickness. For example, sarcoidosis and hemochromatosis can present as dilated or restrictive disease. Early stages of amyloidosis are often mistaken for hypertrophic cardiomyopathy. Progression of hypertrophic cardiomyopathy into a "burned-out" phase occurs occasionally, with decreased contractility and modest ventricular dilation. Overlaps are particularly common with the inherited metabolic disorders, which can present as any of the three major phenotypes (Fig. 287-4).

DISORDERS OF METABOLIC PATHWAYS

Multiple genetic disorders of metabolic pathways can cause myocardial disease, due to infiltration of abnormal products or cells containing them between the myocytes, and storage disease, due to their accumulation within cells (see **HPIM 18e**, Table 238-4, and 287-5). The restrictive phenotype is most common, but mildly dilated cardiomyopathy may occur. Hypertrophic cardiomyopathy may be mimicked by the myocardium thickened with these abnormal products causing "pseudo-hypertrophy." Most of these diseases are diagnosed during childhood.

TABLE 287-5 CAUSES OF RESTRICTIVE CARDIOMYOPATHIES

Infiltrative (Between Myocytes)

Amyloidosis

Primary (light chain amyloid)

Familial (abnormal transthyretin)^a

Senile (normal transthyretin or atrial peptides)

Inherited metabolic defects^a

Storage (Within Myocytes)

Hemochromatosis (iron)^a

Inherited metabolic defects^a

Fabry's disease

Glycogen storage disease (II, III)

Fibrotic

Radiation

Scleroderma

Endomyocardial

Possibly related fibrotic diseases

Tropical endomyocardial fibrosis

Hypereosinophilic syndrome (Löffler's endocarditis)

Carcinoid syndrome

Radiation

Drugs: e.g., serotonin, ergotamine

Overlap with Other Cardiomyopathies

Hypertrophic cardiomyopathy/"pseudohypertrophic"^a

"Minimally dilated" cardiomyopathy

Early-stage dilated cardiomyopathy

Partial recovery from dilated cardiomyopathy

Sarcoidosis

Idiopathic^a

^aCan be familial.

Fabry's disease results from a deficiency of the lysosomal enzyme alpha-galactosidase A caused by one of more than 160 mutations. This disorder of glycosphingolipid metabolism is an X-linked recessive disorder that may also cause clinical disease in female carriers. Glycolipid accumulation may be limited to the cardiac tissues or may also involve the skin and kidney. Electron microscopy of endomyocardial biopsy tissue shows diagnostic vesicles containing concentric lamellar figures (Fig. 287-11). Diagnosis is crucial because enzyme replacement can reduce abnormal deposits and improve cardiac and clinical function. The magnitude of clinical impact has not been well-established for this therapy, which requires frequent infusions of the enzyme at a cost of over \$100,000 a year. Enzyme replacement can also improve the course of Gaucher's disease, in which cerebroside-rich cells accumulate in multiple organs due to a deficiency of beta-glucuronidase. Cerebroside-rich cells infiltrate the heart, which can also lead to a hemorrhagic pericardial effusion and valvular disease.

Glycogen storage diseases lead to accumulation of lysosomal storage products and intracellular glycogen accumulation, particularly with *glycogen storage disease type III*, due to a defective debranching enzyme. There are more than 10 types of *mucopolysaccharidoses*, in which autosomal dominant or X-linked deficiencies of lysosomal enzymes lead to the accumulation of glycosaminoglycans in the skeleton, nervous system, and occasionally the heart. With characteristic facies, short stature, and frequent cognitive impairment, most individuals are diagnosed early in childhood and die before adulthood.

Carnitine is an essential cofactor in long-chain fatty acid metabolism. Multiple defects have been described that lead to carnitine deficiency, causing intracellular lipid inclusions and restrictive or dilated cardiomyopathy, often presenting in children. Fatty acid oxidation requires many metabolic steps with specific enzymes that can be deficient, with complex interactions with carnitine. Depending on the defect, cardiac and skeletal myopathy can be ameliorated with replacement of fatty acid intermediates and carnitine.

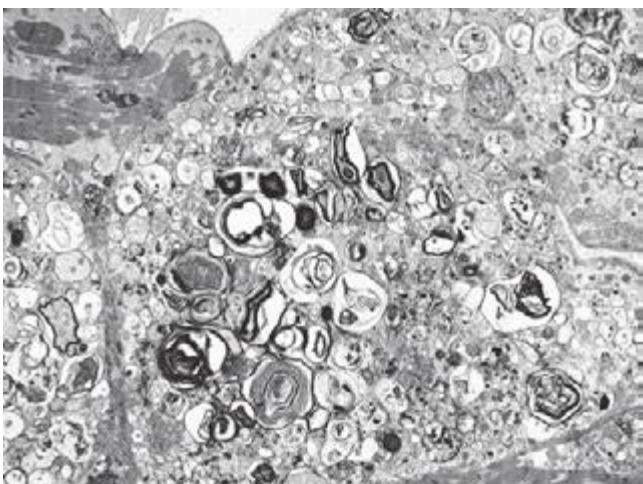


FIGURE 287-11 **Fabry's disease.** Transmission electron micrograph of a right ventricular endomyocardial biopsy specimen at high magnification showing the characteristic concentric lamellar inclusions of glycosphingolipids accumulating as a result of deficiency of the lysosomal enzyme alpha-galactosidase A. Image taken at 15,000 \times original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

Two monogenic metabolic cardiomyopathies have recently been described as causes of increased ventricular wall thickness without an increase of muscle subunits or an increase in contractility. Mutations in the gamma-2 regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase important for glucose metabolism (*PRKAG2*) have been associated with a high prevalence of conduction abnormalities, such as AV block and ventricular preexcitation (Wolff-Parkinson-White syndrome). Several defects have been reported in an X-linked lysosome-associated membrane protein (*LAMP2*). This defect can be maternally transmitted or sporadic and has occasionally been isolated to the heart, although it often leads to a syndrome of skeletal myopathy, mental retardation, and hepatic dysfunction referred to as *Danon's disease*. Extreme left ventricular hypertrophy appears early, often in childhood, and can progress rapidly to end-stage heart failure with low ejection fraction. Electron microscopy of these metabolic disorders shows that the myocytes are enlarged by multiple intracellular vacuoles of metabolic by-products.

RESTRICTIVE CARDIOMYOPATHY

The least common of the physiologic triad of cardiomyopathies is restrictive cardiomyopathy, which is dominated by abnormal diastolic function, often with mildly decreased contractility and ejection fraction (usually >30–50%). Both atria are enlarged, sometimes massively. Modest left ventricular dilation can be present, usually with an end-diastolic dimension <6 cm. End-diastolic pressures are elevated in both ventricles, with preservation of cardiac output until late in the disease. Subtle exercise intolerance is usually the first symptom but is often not recognized until after clinical presentation with congestive symptoms. The restrictive diseases often present with relatively more right-sided symptoms, such as edema, abdominal discomfort, and ascites, although filling pressures are elevated in both ventricles. The cardiac impulse is less displaced than in dilated cardiomyopathy and less dynamic than in hypertrophic cardiomyopathy. A fourth heart sound is more common than a third heart sound in sinus rhythm, but atrial fibrillation is common. Jugular venous pressures often show rapid Y descents and may increase during inspiration (positive Kussmaul's sign). Most restrictive cardiomyopathies are due to infiltration of abnormal substances between myocytes, storage of abnormal metabolic products within myocytes, or fibrotic injury (Table 287-5). The differential diagnosis should include constrictive pericardial disease, which may also be dominated by right-sided heart failure.

INFILTRATIVE DISEASE

Amyloidosis is the major cause of restrictive cardiomyopathy (Figs. 287-12, 287-13, and 287-14). Several proteins can self-assemble to form the beta-sheets of amyloid proteins, which deposit with different consequences depending on the type of protein. The systemic amyloidoses are discussed in Chap. 137. In addition to cardiac infiltration, neurologic involvement occurs commonly with primary amyloidosis (immunoglobulin light chains) and with familial amyloidosis (genetic abnormalities of transthyretin). There are over 100 identified mutations in transthyretin on chromosome 13, among which the V122I transthyretin mutation has been identified in about 4% of African Americans and in 10% of African Americans with heart failure and may contribute importantly to heart failure in general in the elderly African-American population. Organ dysfunction was previously attributed solely to physical disruption from the infiltrating amyloid fibrils, but newer information suggests additional direct toxicity from the immunoglobulin light chain and abnormal transthyretin protein aggregates themselves. In senile amyloidosis, there is abnormal accumulation of normal transthyretin or natriuretic peptide folding, detected in 10% of people over 80 years and half of those over 90 years but often without apparent clinical disease. Men show a greater burden of amyloid deposition and 20-fold greater likelihood of clinical disease with senile amyloidosis. The aging of the population will soon render senile amyloidosis the most common of the amyloidoses.

Cardiac amyloid is classically suspected from thickened ventricular walls with an ECG that shows low voltage. However, low voltage is not always present and is less common in familial or senile amyloidosis than in primary AL amyloidosis. A characteristic refractile brightness in the septum on echocardiography is suggestive of the diagnosis, but neither sensitive nor specific. Both atria are dilated, often dramatically, and diastolic dysfunction may be more obvious than in left ventricular hypertrophy from other causes. Amyloid infiltration can also be detected with gadolinium enhancement in MRI.



FIGURE 287-12 **Restrictive cardiomyopathy—amyloidosis.** Gross specimen of a heart with amyloidosis. The heart is firm and rubbery with a waxy cut surface. The atria are markedly dilated, and the left atrial endocardium, normally smooth, has yellow-brown amyloid deposits that give texture to the surface. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

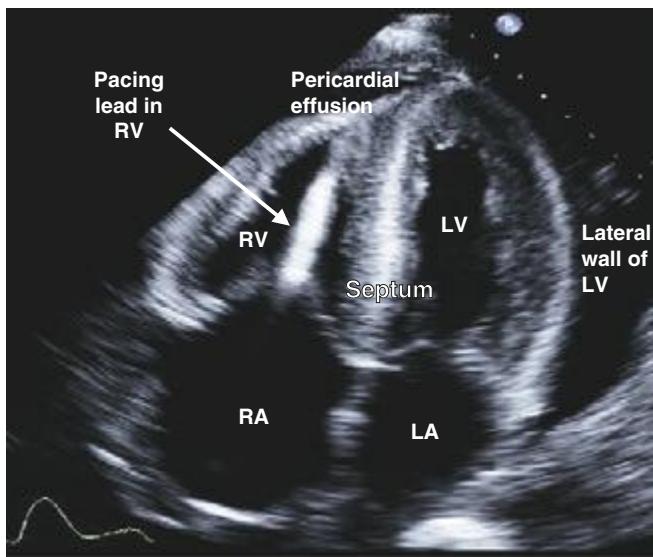


FIGURE 287-13 Restrictive cardiomyopathy—amyloidosis.

Echocardiogram showing thickened walls of both ventricles without major chamber dilation. The atria are markedly dilated, consistent with chronically elevated ventricular filling pressures. In this example, there is a characteristic hyperrefractile “glittering” of the myocardium typical of amyloid infiltration, which is often absent (especially with more recent echocardiographic systems of better resolution). The mitral and tricuspid valves are thickened. A pacing lead is visible in the right ventricle (RV), and a pericardial effusion is evident. Note that the echocardiographic and pathologic images are vertically opposite, such that the left ventricle (LV) is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. LA, left atrium; RA, right atrium. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)

The diagnosis of primary or familial amyloidosis can sometimes be made from biopsies of an abdominal fat pad or the rectum, but cardiac amyloidosis is most reliably identified from a biopsy of the heart, in which amyloid fibrils infiltrate the myocardium diffusely, particularly around the conduction system and coronary vessels (Fig. 287-14). Diagnosis of the type of amyloid protein requires immunohistochemistry of biopsied tissue rather than serum or urine electrophoresis, which can lead to incorrect classification.

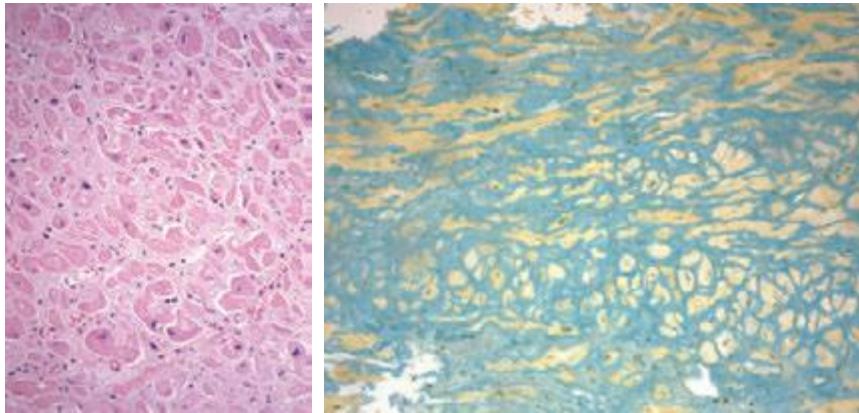


FIGURE 287-14 Amyloidosis—microscopic images of amyloid involving the myocardium. The left panel (hematoxylin and eosin stain) shows glassy, grey-pink amorphous material infiltrating between cardiomyocytes, which stain a darker pink. The right panel shows a sulfated blue stain that highlights the amyloid green and stains the cardiac myocytes yellow. (The Congo red stain can also be used to highlight amyloid; under polarized light, amyloid will have an apple-green birefringence when stained with Congo red.) Images at 100x original magnification. (Image courtesy of Robert Padra, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

Therapy for all types of amyloid is predominantly for symptoms of fluid retention, which often requires high doses of loop diuretics. Digoxin bound to the amyloid fibrils can reach toxic levels, and should therefore be used only in very low doses, if at all. There is no evidence regarding use of neurohormonal antagonists in amyloid heart disease, where the possible theoretical benefit has to be balanced against the possibility of aggravating postural hypotension and diminishing the crucial heart rate reserve. The risk of intracardiac thrombi may warrant chronic anticoagulation.

The prognosis is worst for primary amyloid, with a median survival of 6–12 months after symptoms of heart failure. If present, multiple myeloma is treated with chemotherapy, the extent of which is often limited by the potential of worsening cardiac dysfunction. Immunoglobulin-associated amyloid has occasionally been treated with sequential heart transplantation and delayed bone marrow transplant, with frequent recurrence of amyloid in the transplanted heart. Abnormal transthyretin-associated cardiac amyloid has a somewhat better prognosis and can be treated in selected patients with heart and liver transplantation. Senile cardiac amyloid has the slowest progression and best overall prognosis.

FIBROTIC RESTRICTIVE CARDIOMYOPATHY

Progressive fibrosis can cause restrictive myocardial disease without ventricular dilation. Thoracic radiation, common for breast and lung cancer or mediastinal lymphoma, can produce early or late restrictive cardiomyopathy. Patients with *radiation cardiomyopathy* may present with a possible diagnosis of constrictive pericarditis, as the two conditions often coexist. Careful hemodynamic evaluation and, often, endomyocardial biopsy should be performed if considering pericardial stripping surgery, which is unlikely to be successful in the presence of underlying restrictive cardiomyopathy.

Scleroderma causes small vessel spasm and ischemia that can lead to a small, stiff heart with reduced ejection fraction without dilation. The pulmonary hypertension associated with scleroderma may lead to more clinical right heart failure because of concomitant fibrotic disease of the right ventricle. Doxorubicin causes direct myocyte injury usually leading to dilated cardiomyopathy, but the limited degree of dilation may result from increased fibrosis, which restricts remodeling.

ENDOMYOCARDIAL DISEASE

The physiologic picture of elevated filling pressures with atrial enlargement and preserved ventricular contractility with normal or reduced ventricular volumes can result from extensive fibrosis of the endocardium, without transmural myocardial disease. For patients who have not

lived in the equatorial regions, this picture is rare, and when seen is often associated with a history of chronic hypereosinophilic syndrome (*Löffler's endocarditis*), which is more common in men than women. In this disease, persistent hypereosinophilia of >1500 eos/mm 3 for at least 6 months can cause an acute phase of eosinophilic injury in the endocardium (see earlier discussion of eosinophilic myocarditis), with systemic illness and injury to other organs. There is usually no obvious cause, but the hypereosinophilia can occasionally be explained by allergic, parasitic, or malignant disease. It is postulated to be followed by a period in which cardiac inflammation is replaced by evidence of fibrosis with superimposed thrombosis. In severe disease, the dense fibrotic layer can obliterate the ventricular apices and extend to thicken and tether the AV valve leaflets. The clinical disease may present with heart failure, embolic events, and atrial arrhythmias. While plausible, the sequence of transition from eosinophilic myocarditis or *Löffler's endocarditis* to endomyocardial fibrosis has not been clearly demonstrated.

In tropical countries, up to one-quarter of heart failure may be due to *endomyocardial fibrosis*,

1568 affecting either or both ventricles. This condition shares with the previous condition the partial obliteration of the ventricular apex with fibrosis extending into the valvular inflow tract and leaflets; however, it is not clear that the etiologies are the same for all cases. Pericardial effusions frequently accompany endomyocardial fibrosis but are not common in Löffler's endocarditis. For endomyocardial fibrosis, there is no gender difference, but a higher prevalence in African-American populations. While tropical endomyocardial fibrosis could represent the end-stage of previous hypereosinophilic disease triggered by endemic parasites, neither prior parasitic infection nor hypereosinophilia is usually documented. Geographic nutritional deficiencies have also been proposed as an etiology.

Medical treatment focuses on glucocorticoids and chemotherapy to suppress hypereosinophilia when present. Fluid retention may become increasingly resistant to diuretic therapy. Anticoagulation is recommended. Atrial fibrillation is associated with worse symptoms and prognosis, but may be difficult to suppress. Surgical resection of the apices and replacement of the fibrotic valves can improve symptoms, but surgical morbidity and mortality and later recurrence rates are high.

The serotonin secreted by *carcinoid* tumors can produce fibrous plaques in the endocardium and right-sided cardiac valves, occasionally affecting left-sided valves, as well. Valvular lesions may be stenotic or regurgitant. Systemic symptoms include flushing and diarrhea. Liver disease from hepatic metastases may play a role by limiting hepatic function and thereby allowing more serotonin to reach the venous circulation.

PART 10

Disorders of the Cardiovascular System

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is defined as left ventricular hypertrophy that develops in the absence of causative hemodynamic factors, such as hypertension, aortic valve disease, or systemic infiltrative or storage diseases (Figs. 287-15 and 287-16). It has previously been termed *hypertrophic obstructive cardiomyopathy* (HOCM), *asymmetric septal hypertrophy* (ASH), and *idiopathic hypertrophic subaortic stenosis* (IHSS). However, the accepted terminology is now hypertrophic

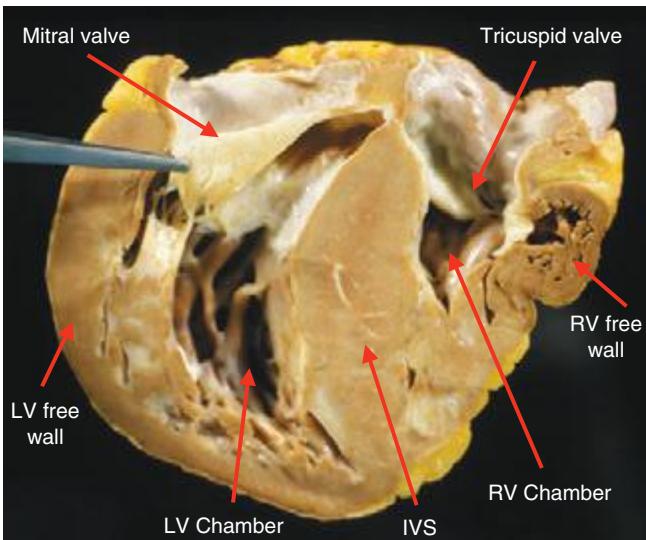


FIGURE 287-15 Hypertrophic cardiomyopathy. Gross specimen of a heart with hypertrophic cardiomyopathy removed at the time of transplantation, showing asymmetric septal hypertrophy (septum much thicker than left ventricular free wall) with the septum bulging into the left ventricular outflow tract causing obstruction. The forceps are retracting the anterior leaflet of the mitral valve, demonstrating the characteristic plaque of systolic anterior motion, manifest as endocardial fibrosis on the interventricular septum in a mirror-image pattern to the valve leaflet. There is patchy replacement fibrosis, and small thick-walled arterioles can be appreciated grossly, especially in the interventricular septum. IVS, interventricular septum; LV, left ventricle; RV, right ventricle. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

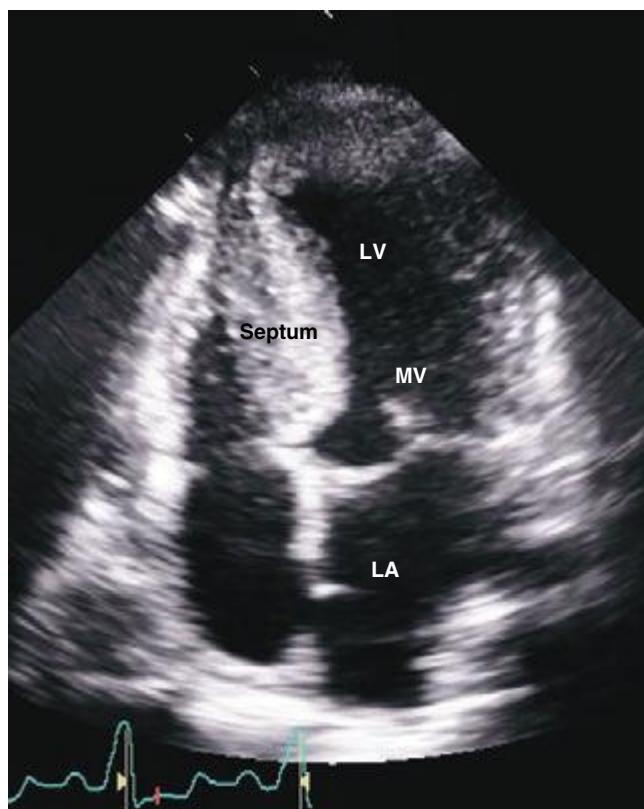


FIGURE 287-16 Hypertrophic cardiomyopathy. This echocardiogram of hypertrophic cardiomyopathy shows asymmetric hypertrophy of the septum compared to the lateral wall of the left ventricle (LV). The mitral valve (MV) is moving anteriorly toward the hypertrophied septum in systole. The left atrium (LA) is enlarged. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)

cardiomyopathy with or without obstruction. Prevalence in North America, Japan, and China is about 1:500. It is the leading cause of sudden death in the young and is an important cause of heart failure. Although pediatric presentation is associated with increased early morbidity and mortality, the prognosis for patients diagnosed as adults is generally favorable.

The clustering of hypertrophic cardiomyopathy within families has been appreciated since recognition of the disease approximately 55 years ago. Echocardiographic screening of families revealed an autosomal dominant pattern of inheritance. Initial genetic studies using linkage analysis in large families identified disease-causing mutations in sarcomeric genes. A sarcomere mutation is present in ~60% of patients with hypertrophic cardiomyopathy and is more common in those with familial disease and characteristic asymmetric septal hypertrophy. More than nine different sarcomere genes with over 1400 mutations have been implicated, although ~80% of patients have a mutation in either *MYH7* or *MYBPC3* (Table 287-3), most of which are unique to individual families ("private" mutations).

Hypertrophic cardiomyopathy is characterized by age-dependent and incomplete penetrance. The defining phenotype of left ventricular hypertrophy is rarely present at birth and usually develops later in life. Accordingly, screening of family members should begin in adolescence and extend through adulthood. In *MYBPC3* mutation carriers, the average age of disease development is 40 years, while 30% remain free from hypertrophy after 70 years. Related individuals who carry the *same* mutation may have a different extent and pattern of hypertrophy (e.g., asymmetric versus concentric), occurrence of outflow tract obstruction, and associated clinical outcomes (e.g., sudden death, atrial fibrillation).

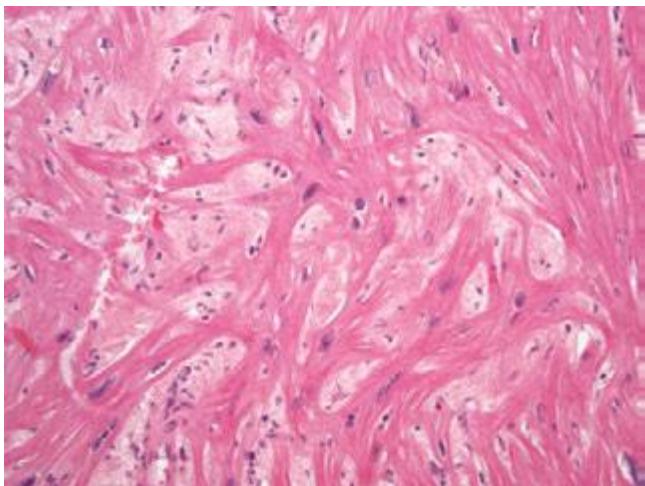


FIGURE 287-17 Hypertrophic cardiomyopathy. Microscopic image of hypertrophic cardiomyopathy showing the characteristic disordered myocyte architecture with swirling and branching rather than the usual parallel arrangement of myocyte fibers. Myocyte nuclei vary markedly in size and interstitial fibrosis is present. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

At the level of the sarcomere, hypertrophic cardiomyopathy mutations lead to enhanced calcium sensitivity, maximal force generation, and ATPase activity. Calcium handling is affected through modification of regulatory proteins. Sarcomere mutations lead to abnormal energetics and impaired relaxation, both directly and as a result of hypertrophy. Hypertrophic cardiomyopathy is characterized by misalignment and disarray of the enlarged myofibrils and myocytes (Fig. 287-17), which can also occur to a lesser extent in other cardiac diseases. Although hypertrophy is the defining feature of hypertrophic cardiomyopathy, fibrosis and microvascular disease are also present. Interstitial fibrosis is detectable before overt hypertrophy develops and likely results from early activation of profibrotic pathways. In the majority of patients with overt cardiomyopathy, focal areas of replacement fibrosis can be readily detected with MRI. These areas of “scar” may represent substrate for the development of ventricular arrhythmias. Increased thickness and decreased luminal area of the intramural vessels in hypertrophied myocardium contribute to microvascular ischemia and angina. Microinfarction of hypertrophied myocardium is a hypothesized mechanism for replacement scar formation.

Macroscopically, hypertrophy is typically manifest as nonuniform ventricular thickening (Fig. 287-15). The interventricular septum is the typical location of maximal hypertrophy, although other patterns of hypertrophic remodeling include concentric and midventricular. Hypertrophy confined to the ventricular apex (apical hypertrophic cardiomyopathy) is less often familial and has a different genetic substrate, with sarcomere mutations present in only ~15%. Left ventricular outflow tract obstruction represents the most common focus of diagnosis and intervention, although diastolic dysfunction, myocardial fibrosis, and microvascular ischemia also contribute to contractile dysfunction and elevated intracardiac pressures. Obstruction is present in ~30% of patients at rest and can be provoked by exercise in another ~30%. Systolic obstruction is initiated by drag forces, which push an anteriorly displaced and enlarged anterior mitral leaflet into contact with the hypertrophied ventricular septum. Mitral leaflet coaptation may ensue, leading to posteriorly directed mitral regurgitation. In order to maintain stroke volume across outflow tract obstruction, the ventricle generates higher pressures, leading to higher wall stress and myocardial oxygen demand. Smaller chamber size and increased contractility exacerbate the severity of obstruction. Conditions of low preload, such as dehydration, and low afterload, such as arterial vasodilation, may lead to transient hypotension and near-syncope. The systolic ejection murmur of left ventricular outflow tract obstruction is harsh and late peaking and can be enhanced by bedside maneuvers that diminish

ventricular volume and transiently worsen obstruction, such as standing from a squatting position or the Valsalva maneuver.

DIAGNOSIS

The substantial variability of hypertrophic cardiomyopathy pathology is reflected in the diversity of clinical presentations. Patients may be diagnosed after undergoing evaluations triggered by the abnormal physical findings (murmur) or symptoms of exertional dyspnea, angina, or syncope. Alternatively, diagnosis may follow evaluations prompted by the detection of disease in family members. Cardiac imaging (Fig. 287-16) is central to diagnosis due to the insensitivity of examination and ECG and the need to exclude other causes for hypertrophy. The identification of a disease-causing mutation in a proband can focus family evaluations on mutation carriers, but this strategy requires a high degree of certainty that the mutation is truly pathogenic and not a benign DNA variant. Biopsy is not needed to diagnose hypertrophic cardiomyopathy but can be used to exclude infiltrative and metabolic diseases. Rigorous athletic training (athlete’s heart) may cause intermediate degrees of physiologic hypertrophy difficult to differentiate from mild hypertrophic cardiomyopathy. Unlike hypertrophic cardiomyopathy, hypertrophy in the athlete’s heart regresses with cessation of training, and is accompanied by supernormal exercise capacity ($\text{VO}_{\text{2max}} > 50 \text{ mL/kg/min}$), mild ventricular dilation, and normal diastolic function.

TREATMENT

HYPERTROPHIC CARDIOMYOPATHY

Management focuses on treatment of symptoms and prevention of sudden death and stroke (Fig. 287-18). Left ventricular outflow tract obstruction can be controlled medically in the majority of patients. β -Adrenergic blocking agents and L-type calcium channel blockers (e.g., verapamil) are first-line agents that reduce the severity of obstruction by slowing heart rate, enhancing diastolic filling, and decreasing contractility. Persistent symptoms of exertional dyspnea or chest pain can sometimes be controlled with the addition of disopyramide, an antiarrhythmic agent with potent negative inotropic properties. Patients with or without obstruction may develop heart failure symptoms due to fluid retention and require diuretic therapies for venous congestion. Severe medically refractory symptoms develop in ~5% of patients, for whom surgical myectomy or alcohol septal ablation may be effective. Developed over 50 years ago, surgical myectomy effectively relieves outflow tract obstruction by excising part of the septal myocardium involved in the dynamic obstruction. In selected patients, perioperative mortality is extremely low with excellent long-term survival free from recurrent obstruction and symptoms. Mitral valve repair or replacement is usually unnecessary as associated eccentric mitral regurgitation resolves with myectomy alone. Alcohol septal ablation in patients with suitable coronary anatomy can relieve outflow tract obstruction via a controlled infarction of the proximal septum, which produces similar periprocedural outcomes and gradient reduction as surgical myectomy. Until long-term outcomes are demonstrated for this procedure, it is relegated primarily to patients who wish to avoid surgery or who have limiting comorbidities. Neither procedure has been shown to improve outcomes other than symptoms. With both procedures, the most common complication is the development of complete heart block necessitating permanent pacing. However, ventricular pacing as a primary therapy for outflow tract obstruction is ineffective and not generally advised.

Patients with hypertrophic cardiomyopathy have an increased risk of sudden cardiac death from ventricular tachyarrhythmias. Vigorous physical activity and competitive sport are prohibited. Factors that increase the risk of sudden death from a baseline of 0.5% per year are presented in Table 287-6. As sudden death has not been reduced by medical or procedural interventions, an implantable cardioverter-defibrillator is advised for patients with two or more risk factors and is advised on a selected basis for patient with one risk factor. Nevertheless, the positive predictive value of most risk factors is low, and many patients receiving a defibrillator

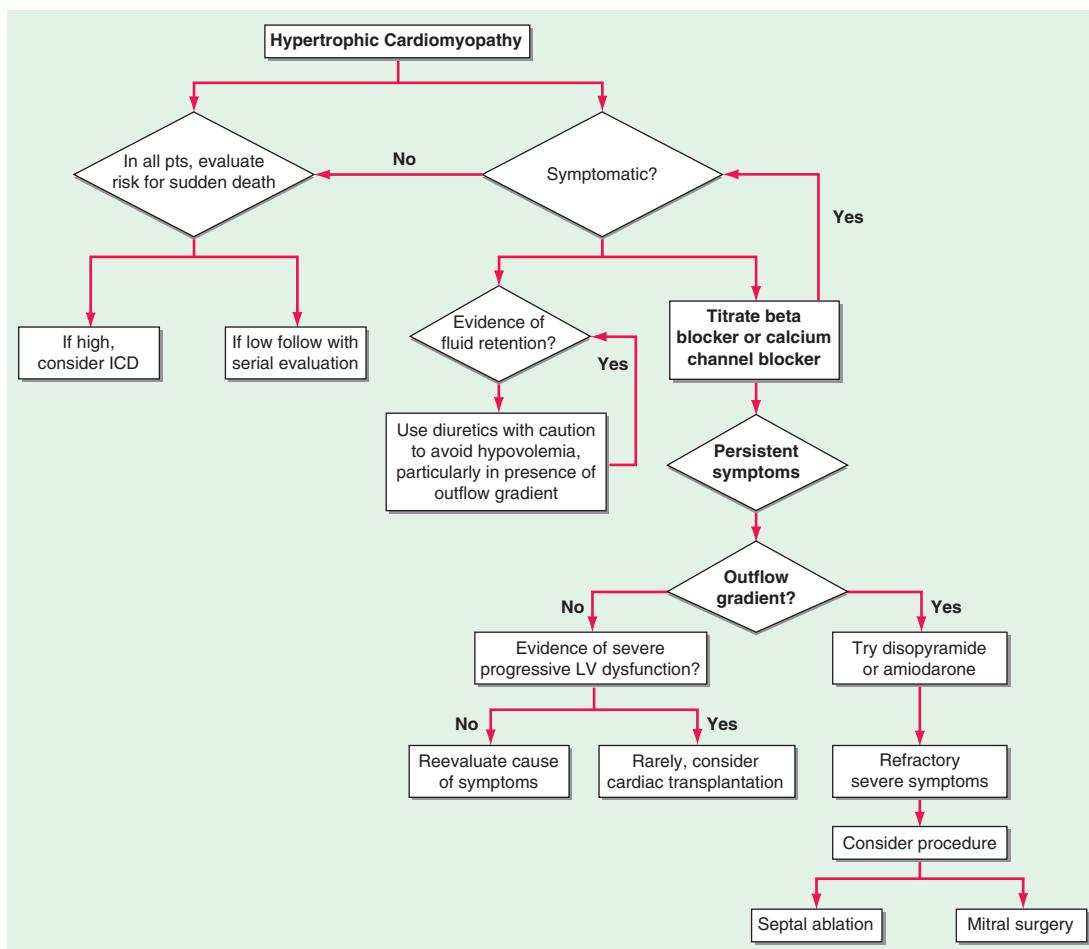


FIGURE 287-18 Treatment algorithm for hypertrophic cardiomyopathy depending on the presence and severity of symptoms and the presence of an intraventricular gradient with obstruction to outflow. Note that all patients with hypertrophic cardiomyopathy should be evaluated for atrial fibrillation and risk of sudden death, whether or not they require treatment for symptoms. ICD, implantable cardioverter-defibrillator; LV, left ventricular.

never receive an appropriate therapy. Long-term use of a defibrillator may be associated with serious device-related complications, particularly in young active patients. Refinement of sudden death risk through the application of contemporary technologies such as cardiac MRI is ongoing.

TABLE 287-6 RISK FACTORS FOR SUDDEN DEATH IN HYPERTROPHIC CARDIOMYOPATHY

Major Risk Factor	Screening Technique	
History of cardiac arrest or spontaneous sustained ventricular tachycardia ^a	History	
Syncope	Nonvagal, often with or after exertion	History
Family history of sudden cardiac death		Family history
Spontaneous nonsustained ventricular tachycardia ^b	>3 beats at rate >120	Exercise or 24- to 48-hour ambulatory recording
LV thickness >30 mm	Present in <10% of patients	Echocardiography
Abnormal blood pressure response to exercise ^b	Systolic blood pressure fall or failure to increase at peak exercise	Maximal upright exercise testing

^aImplantable cardioverter-defibrillator advised for patients with prior arrest or sustained ventricular tachycardia regardless of other risk factors. ^bPrognostic value most applicable to patients less than 40 years old.

Abbreviation: LV, left ventricle.

Atrial fibrillation is common in patients with hypertrophic cardiomyopathy and may lead to hemodynamic deterioration and embolic stroke. Rapid ventricular response is poorly tolerated and may worsen outflow tract obstruction. β -Adrenergic blocking agents and L-type calcium channel blockers slow AV nodal conduction and improve symptoms; cardiac glycosides should be avoided, as they may increase contractility and worsen obstruction. Symptoms exacerbated by atrial fibrillation may persist despite adequate rate control due to loss of AV synchrony and may require restoration of sinus rhythm. Disopyramide and amiodarone are the preferred antiarrhythmic agents, with radiofrequency ablation considered for medically refractory cases. Anticoagulation to prevent embolic stroke in atrial fibrillation is recommended.

PROGNOSIS The general prognosis for hypertrophic cardiomyopathy is good, better than in early studies of referral populations. For patients diagnosed as adults, survival is comparable to an age-matched population without cardiomyopathy. The sudden death risk is less than 1% per year; however, up to 1 in 20 patients will progress to overt systolic dysfunction with a reduced ejection fraction with or without dilated remodeling ("burned out" or end-stage hypertrophic cardiomyopathy). These patients suffer from low cardiac output and have a high risk of death from progressive heart failure and sudden death unless they undergo cardiac transplantation.

NORMAL FUNCTIONS OF THE PERICARDIUM

The normal pericardium is a double-layered sac; the visceral pericardium is a serous membrane that is separated by a small quantity (15–50 mL) of fluid, an ultrafiltrate of plasma, from the fibrous parietal pericardium. The normal pericardium, by exerting a restraining force, prevents sudden dilation of the cardiac chambers, especially the right atrium and ventricle, during exercise and with hypervolemia. It also restricts the anatomic position of the heart, and probably retards the spread of infections from the lungs and pleural cavities to the heart. Nevertheless, *total* absence of the pericardium, either congenital or after surgery, does not produce obvious clinical disease. In *partial* left pericardial defects, the main pulmonary artery and left atrium may bulge through the defect; very rarely, herniation and subsequent strangulation of the left atrium may cause sudden death.

ACUTE PERICARDITIS

Acute pericarditis, by far the most common pathologic process involving the pericardium (**Table 288-1**), has four principal diagnostic features:

- Chest pain* is usually present in acute infectious pericarditis and in many of the forms presumed to be related to hypersensitivity or autoimmunity. The pain of acute pericarditis is often severe, retrosternal, and left precordial, and referred to the neck, arms, or left shoulder. Frequently the pain is pleuritic, consequent to accompanying pleural inflammation (i.e., sharp and aggravated by inspiration and coughing), but sometimes it is steady, constricting, radiates into either arm or both arms, and resembles that of myocardial ischemia; therefore, confusion with acute myocardial infarction (AMI) is common. Characteristically, however, pericardial pain may be relieved by sitting up and leaning forward and is intensified by lying supine (**Chap. 19**). Pain is often absent in slowly developing tuberculous, postirradiation, and neoplastic, uremic, and constrictive pericarditis.
- The differentiation of AMI from acute pericarditis may become perplexing when, with acute pericarditis, serum biomarkers of myocardial damage such as troponin and creatine kinase-MB rise, presumably because of concomitant involvement of the epicardium in the inflammatory process (an epi-myocarditis) with resulting myocyte necrosis. However, these elevations, if they occur, are quite modest given the extensive electrocardiographic ST-segment elevation in pericarditis. This dissociation is useful in differentiating between these conditions.
- A *pericardial friction rub* is audible at some point in about 85% of patients with acute pericarditis, may have up to three components per cardiac cycle, is high-pitched, and is described as rasping, scratching, or grating (**Chap. 267**). It is heard most frequently at end expiration with the patient upright and leaning forward.

- The *electrocardiogram* (ECG) in acute pericarditis without massive effusion usually displays changes secondary to acute subepicardial inflammation (**Fig. 288-1**). It typically evolves through four stages. In stage 1, there is widespread elevation of the ST segments, often with upward concavity, involving two or three standard limb leads and V_2 to V_6 , with reciprocal depressions only in aVR and sometimes V_1 . Also, there is depression of the PR segment below the TP segment, reflecting atrial involvement. Usually there are no significant changes in QRS complexes. After several days, the ST segments return to normal (stage 2), and only then, or even later, do the T waves become inverted (stage 3). Weeks or months after the onset of acute pericarditis, the ECG returns to normal (stage 4). In contrast, in AMI, ST elevations are convex, and reciprocal depression is usually more prominent; these changes may return to normal within a

TABLE 288-1 CLASSIFICATION OF PERICARDITIS**Clinical Classification**

- Acute pericarditis (<6 weeks)
 - Fibrinous
 - Effusive (serous or sanguineous)
- Subacute pericarditis (6 weeks to 6 months)
 - Effusive-constrictive
 - Constrictive
- Chronic pericarditis (>6 months)
 - Constrictive
 - Effusive
 - Adhesive (nonconstrictive)

Etiologic Classification

- Infectious pericarditis
 - Viral (coxsackievirus A and B, echovirus, mumps, adenovirus, hepatitis, HIV)
 - Pyogenic (pneumococcus, *Streptococcus*, *Staphylococcus*, *Neisseria*, *Legionella*)
 - Tuberculous
 - Fungal (histoplasmosis, coccidioidomycosis, *Candida*, blastomycosis)
 - Other infections (syphilitic, protozoal, parasitic)
- Noninfectious pericarditis
 - Acute myocardial infarction
 - Uremia
 - Neoplasia
 - Primary tumors (benign or malignant, mesothelioma)
 - Tumors metastatic to pericardium (lung and breast cancer, lymphoma, leukemia)
 - Myxedema
 - Cholesterol
 - Chylopericardium
 - Trauma
 - Penetrating chest wall
 - Nonpenetrating
 - Aortic dissection (with leakage into pericardial sac)
 - Postirradiation
 - Familial Mediterranean fever
 - Familial pericarditis
 - Mulibrey nanism^a
 - Acute idiopathic
 - Whipple's disease
 - Sarcoidosis
- Pericarditis presumably related to hypersensitivity or autoimmunity
 - Rheumatic fever
 - Collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, scleroderma, acute rheumatic fever, granulomatosis with polyangiitis [Wegener's])
 - Drug-induced (e.g., procainamide, hydralazine, phenytoin, isoniazid, minoxidil, anticoagulants, methysergide)
 - Postcardiac injury
 - Postmyocardial infarction (Dressler's syndrome)
 - Postpericardiectomy
 - Posttraumatic

^aAn autosomal recessive syndrome characterized by growth failure, muscle hypotonia, hepatomegaly, ocular changes, enlarged cerebral ventricles, mental retardation, ventricular hypertrophy, and chronic constrictive pericarditis

day or two. Q waves may develop, with loss of R-wave amplitude, and T-wave inversions are usually seen within hours *before* the ST segments have become isoelectric (**Chaps. 294 and 295**).

- Pericardial effusion is usually associated with pain and/or the ECG changes mentioned above, as well as electrical alternans.

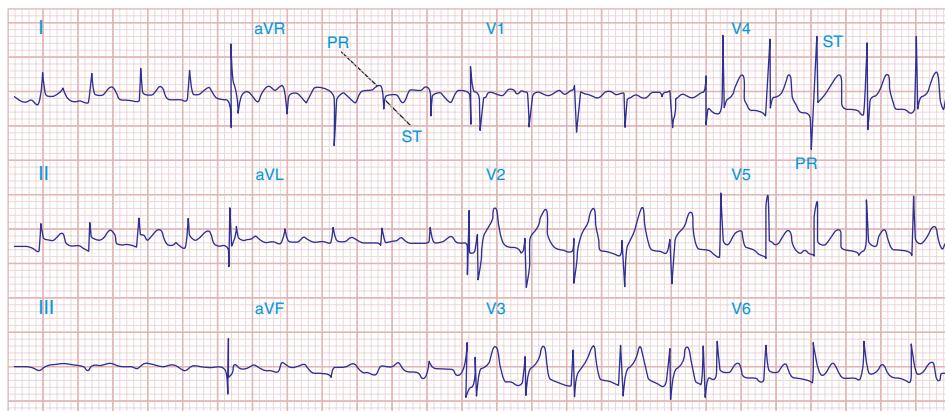


FIGURE 288-1 Acute pericarditis. There are diffuse ST-segment elevations (in this case in leads I, II, aVF, and V₂ to V₆) due to a ventricular current of injury. There is PR-segment deviation (opposite in polarity to the ST segment) due to a concomitant atrial injury current.

Pericardial effusion is especially important clinically when it develops within a relatively short time because it may lead to cardiac tamponade (see below). Differentiation from cardiac enlargement may be difficult on physical examination, but heart sounds may be fainter with pericardial effusion. The friction rub and the apex impulse may disappear. The base of the left lung may be compressed by pericardial fluid, producing *Ewart's sign*, a patch of dullness and increased fremitus (and egophony) beneath the angle of the left scapula. The chest roentgenogram may show enlargement of the cardiac silhouette, with a "water bottle" configuration, but may be normal.

Diagnosis *Echocardiography* (Chap. 270e) is the most widely used imaging technique. It is sensitive, specific, simple, noninvasive, may be performed at the bedside, and can identify accompanying cardiac tamponade (see below) (Fig. 288-2). The presence of pericardial fluid is recorded by two-dimensional transthoracic echocardiography as a relatively echo-free space between the posterior pericardium and left ventricular epicardium in patients with small effusions and as a space between the anterior right ventricle and the parietal pericardium just beneath the anterior chest wall. In patients with large effusions, the heart may swing freely within the pericardial sac. When severe, the extent of this motion alternates and may be associated with electrical alternans (Fig. 288-3). Echocardiography allows localization and identification of the quantity of pericardial fluid.

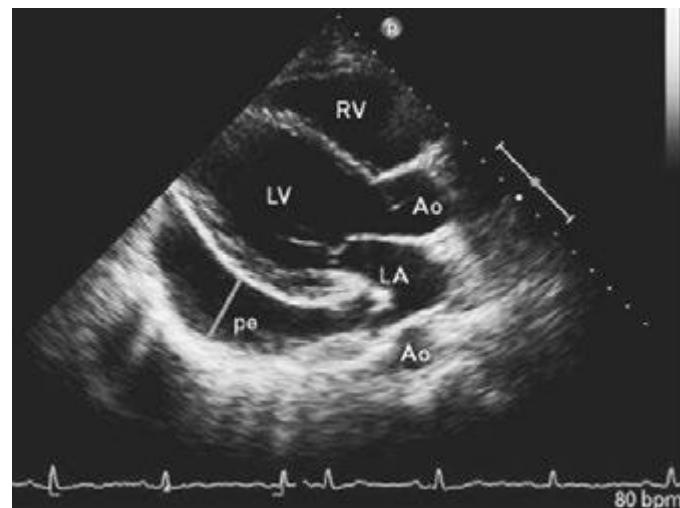


FIGURE 288-2 Two-dimensional echocardiogram in lateral view in a patient with a large pericardial effusion. Ao, aorta; LV, left ventricle; pe, pericardial effusion; RV, right ventricle. (From M Imazio: Curr Opin Cardiol 27:308, 2012.)

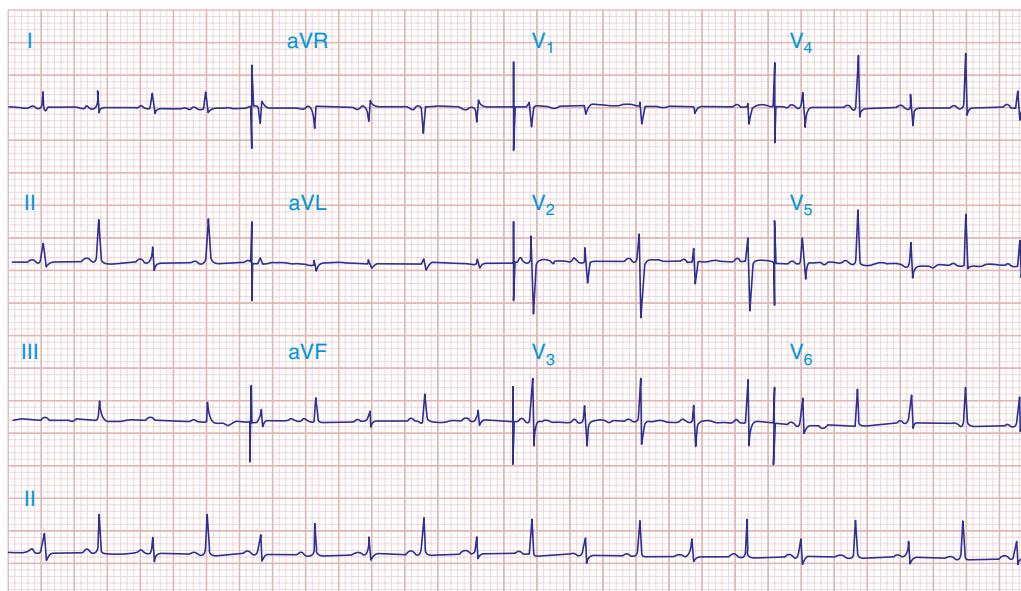


FIGURE 288-3 Electrical alternans. This tracing was obtained from a patient with a large pericardial effusion with tamponade. (Reproduced from DM Mirvis, AL Goldberger: Electrocardiography, in RO Bonow et al [eds]: Braunwald's Heart Disease, 9th ed. Philadelphia: Elsevier, 2012.)

The diagnosis of pericardial fluid or thickening may be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). These techniques may be superior to echocardiography in detecting loculated pericardial effusions, pericardial thickening, and the identification of pericardial masses.

TREATMENT ACUTE PERICARDITIS

There is no specific therapy for acute idiopathic pericarditis, but bed rest and anti-inflammatory treatment with aspirin (2–4 g/d), with gastric protection (e.g., omeprazole 20 mg/d), may be given. If this is ineffective, one of the nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (400–600 mg tid) or indomethacin (25–50 mg tid), should be tried. In responsive patients, these doses should be continued for 1–2 weeks and then tapered over several weeks. In patients who are unresponsive, colchicine (0.5 mg bid, given for 4–8 weeks) has been found to be effective, not only in acute pericarditis, but also in reducing the risk of recurrent pericarditis. Colchicine is concentrated in and interferes with the migration of neutrophils, is contraindicated in patients with hepatic or renal dysfunction, and may cause diarrhea and other gastrointestinal side effects. Glucocorticoids (e.g., prednisone 1 mg/kg per day) usually suppress the clinical manifestations of acute pericarditis in patients who have failed therapy with the anti-inflammatory therapies described above, but appear to increase the risk of subsequent recurrence. Therefore, full-dose corticosteroids should be given for only 2–4 days and then tapered. Anticoagulants should be avoided because their use could cause bleeding into the pericardial cavity and tamponade.

In patients with recurrences that are multiple, frequent, disabling, continue for more than 2 years, and are not prevented by colchicine and other NSAIDs and are not controlled by glucocorticoids,

pericardial stripping may be necessary to terminate the illness, and usually does so.

CARDIAC TAMPONADE

The accumulation of fluid in the pericardial space in a quantity sufficient to cause serious obstruction of the inflow of blood into the ventricles results in cardiac tamponade. This complication may be fatal if it is not recognized and treated promptly. The most common causes of tamponade are idiopathic pericarditis and pericarditis secondary to neoplastic disease. Tamponade may also result from bleeding into the pericardial space after leakage from an aortic dissection, cardiac operations, trauma, and treatment of patients with acute pericarditis with anticoagulants.

The three principal features of tamponade (*Beck's triad*) are hypotension, soft or absent heart sounds, and jugular venous distention with a prominent *x* descent but an absent *y* descent. The limitations of ventricular filling are responsible for a reduction of cardiac output. The quantity of fluid necessary to produce cardiac tamponade may be as small as 200 mL when the fluid develops rapidly to as much as >2000 mL in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to an increasing volume. Tamponade may also develop more slowly, and in these circumstances, the clinical manifestations can resemble those of heart failure, including dyspnea, orthopnea, and hepatic engorgement.

A high index of suspicion for cardiac tamponade is required because in many instances no obvious cause for pericardial disease is apparent, and this diagnosis should be considered in any patient with otherwise unexplained enlargement of the cardiac silhouette, hypotension, and elevation of jugular venous pressure. There may be reduction in amplitude of the QRS complexes, and *electrical alternans* of the P, QRS, or T waves should raise the suspicion of cardiac tamponade (Fig. 288-3).

Table 288-2 lists the features that distinguish acute cardiac tamponade from constrictive pericarditis.

TABLE 288-2 FEATURES THAT DISTINGUISH CARDIAC TAMPONADE FROM CONSTRICTIVE PERICARDITIS AND SIMILAR CLINICAL DISORDERS

Characteristic	Tamponade	Constrictive Pericarditis	Restrictive Cardiomyopathy	RVMI	Effusive Constrictive Pericarditis
Clinical					
Pulsus paradoxus	+++	+	+	+	+++
Jugular veins					
Prominent <i>y</i> descent	-	++	+	+	-
Prominent <i>x</i> descent	+++	++	+++	+	+++
Kussmaul's sign	-	+++	+	+++	++
Third heart sound	-	-	+	+	+
Pericardial knock	-	++	-	-	-
Electrocardiogram					
Low ECG voltage	++	++	++	-	++
Electrical alternans	++	-	-	-	+
Echocardiogram					
Thickened pericardium	-	+++	-	-	++
Pericardial calcification	-	++	-	-	
Pericardial effusion	+++	-	-	++	
RV size	Usually small	Usually normal	Usually normal	Enlarged	
RA and RV	+++	-	-	-	
Exaggerated respiratory variation in flow velocity	+++	+++	-	+++	
CT/MRI					
Thickened pericardium	-	+++	-	++	
Cardiac catheterization					
Equalization of diastolic pressures	+++	+++	-	++	

Abbreviations: +++, always present; ++, usually present; +, rare; -, absent; DC, diastolic collapse; ECG, electrocardiograph; RA, right atrium; RV, right ventricle; RVMI, right ventricular myocardial infarction.

Source: Adapted from GM Brockington et al: Cardiol Clin 8:645, 1990, with permission.

1574 Paradoxical Pulse This important clue to the presence of cardiac tamponade consists of a greater than normal (10 mmHg) inspiratory decline in systolic arterial pressure. When severe, it may be detected by palpating weakness or disappearance of the arterial pulse during inspiration, but usually sphygmomanometric measurement of systolic pressure during slow respiration is required.

Because both ventricles share a tight incompressible covering, i.e., the pericardial sac, the inspiratory enlargement of the right ventricle in cardiac tamponade compresses and reduces left ventricular volume; leftward bulging of the interventricular septum reduces further the left ventricular cavity as the right ventricle enlarges during inspiration. Thus, in cardiac tamponade, the normal inspiratory augmentation of right ventricular volume causes an exaggerated reduction of left ventricular volume, stroke volume, and systolic pressure. Paradoxical pulse also occurs in approximately one-third of patients with constrictive pericarditis (see below), and in some cases of hypovolemic shock, acute and chronic obstructive airway disease, and pulmonary embolus. Right ventricular infarction (Chap. 295) may resemble cardiac tamponade with hypotension, elevated jugular venous pressure, an absent y descent in the jugular venous pulse, and, occasionally, a paradoxical pulse (Table 288-2).

Low-pressure tamponade refers to mild tamponade in which the intrapericardial pressure is increased from its slightly subatmospheric levels to +5 to +10 mmHg; in some instances, hypovolemia coexists. As a consequence, the central venous pressure is normal or only slightly elevated, whereas arterial pressure is unaffected and there is no paradoxical pulse. These patients are asymptomatic or complain of mild weakness and dyspnea. The diagnosis is aided by echocardiography, and both hemodynamic and clinical manifestations improve after pericardiocentesis.

Diagnosis Because immediate treatment of cardiac tamponade may be lifesaving, prompt measures to establish the diagnosis by echocardiography should be undertaken. When pericardial effusion causes tamponade, Doppler ultrasound shows that tricuspid and pulmonic valve flow velocities increase markedly during inspiration, whereas pulmonic vein, mitral, and aortic flow velocities diminish (as in constrictive pericarditis, see below) (Fig. 288-4). In tamponade, there is late diastolic inward motion (collapse) of the right ventricular free wall and the right atrium. Transesophageal echocardiography, CT, or cardiac MRI may be necessary to diagnose a loculated effusion responsible for cardiac tamponade.

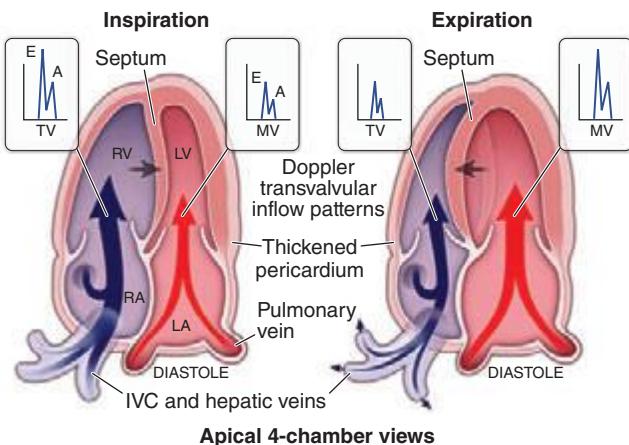


FIGURE 288-4 Constrictive pericarditis. Doppler schema of respiratory changes in mitral and tricuspid inflow. Reciprocal patterns of ventricular filling are assessed on pulsed Doppler examination of mitral valve (MV) and tricuspid valve (TV) inflow. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Courtesy of Bernard E. Bulwer, MD; with permission.)

TREATMENT CARDIAC TAMPONADE

Patients with acute pericarditis should be observed frequently for the development of an effusion; if a large effusion is present, pericardiocentesis should be carried out or the patient watched closely for signs of tamponade. Arterial and venous pressures should be monitored and serial echocardiograms obtained.

PERICARDIOCENTESIS

If manifestations of tamponade appear, echocardiographically guided pericardiocentesis using an apical, parasternal, or, most commonly, subxiphoid approach must be carried out at once because reduction of the elevated intrapericardial pressure may be lifesaving. Intravenous saline may be administered as the patient is being readied for the procedure, but the pericardiocentesis must not be delayed. If possible, intrapericardial pressure should be measured before fluid is withdrawn, and the pericardial cavity should be drained as completely as possible. A small, multiholed catheter advanced over the needle inserted into the pericardial cavity may be left in place to allow draining of the pericardial space if fluid reaccumulates. Surgical drainage through a limited (subxiphoid) thoracotomy may be required in recurrent tamponade, when it is necessary to remove loculated effusions, and/or when it is necessary to obtain tissue for diagnosis.

Pericardial fluid obtained from an effusion often has the physical characteristics of an exudate. Bloody fluid is most commonly due to neoplasm, renal failure, or dialysis in the United States and tuberculosis in developing nations but may also be found in the effusion of acute rheumatic fever, after cardiac injury, and after myocardial infarction. Transudative pericardial effusions may occur in heart failure.

The pericardial fluid should be analyzed for red and white blood cells and cytologic studies, and cultures should be obtained. The presence of DNA of *Mycobacterium tuberculosis* determined by the polymerase chain reaction strongly supports the diagnosis of tuberculous pericarditis (Chap. 202).

VIRAL OR IDIOPATHIC ACUTE PERICARDITIS

In many instances, acute pericarditis occurs in association with illnesses of known or presumed viral origin and probably is caused by the same agent. Commonly, there is an antecedent infection of the respiratory tract, and viral isolation and serologic studies are negative. In some cases, coxsackievirus A or B or the virus of influenza, echovirus, mumps, herpes simplex, chickenpox, adenovirus, or cytomegalovirus has been isolated from pericardial fluid and/or appropriate elevations in viral antibody titers have been noted. Pericardial effusion is a common cardiac manifestation of HIV; it is usually secondary to infection (often mycobacterial) or neoplasm, most often lymphoma. Frequently, a viral cause cannot be established, and the term *idiopathic acute pericarditis* is then appropriate.

Viral or idiopathic acute pericarditis occurs at all ages but is more common in young adults and is often associated with pleural effusions and pneumonitis. The almost simultaneous development of fever and precordial pain, often 10–12 days after a presumed viral illness, constitutes an important feature in the differentiation of acute pericarditis from AMI, in which chest pain precedes fever. The constitutional symptoms are usually mild to moderate, and a pericardial friction rub is often audible. The disease ordinarily runs its course in a few days to 4 weeks. The ST-segment alterations in the ECG usually disappear after 1 or more weeks, but the abnormal T waves may persist for several years and be a source of confusion in persons without a clear history of pericarditis. Pleuritis and pneumonitis frequently accompany viral or idiopathic acute pericarditis. Accumulation of some pericardial fluid is common, and both tamponade and constrictive pericarditis are possible, but infrequent, complications.

The most frequent complication is recurrent (relapsing) pericarditis, which occurs in about one-fourth of patients with acute idiopathic

pericarditis. In a smaller number, there are multiple recurrences. For treatment, see earlier section on treatment of acute pericarditis.

Postcardiac Injury Syndrome Acute pericarditis may appear in a variety of circumstances that have one common feature—previous injury to the myocardium with blood in the pericardial cavity. The syndrome may develop after a cardiac operation (postpericardiotomy syndrome), after blunt or penetrating cardiac trauma (Chap. 289e), or after perforation of the heart with a catheter. Rarely, it follows AMI.

The clinical picture mimics acute viral or idiopathic pericarditis. The principal symptom is the pain of acute pericarditis, which usually develops 1–4 weeks after the cardiac injury but earlier (1–3 days) after AMI. Recurrences are common and may occur up to 2 years or more following the injury. Fever, pleuritis, and pneumonitis are the outstanding features, and the bout of illness usually subsides in 1 or 2 weeks. The pericarditis may be of the fibrinous variety, or it may be a pericardial effusion, which is often serosanguineous but rarely causes tamponade. ECG changes typical of acute pericarditis may also occur. This syndrome is probably the result of a hypersensitivity reaction to antigen(s) that originate from injured myocardial tissue and/or pericardium.

Often no treatment is necessary aside from aspirin and analgesics. When the illness is severe or followed by a series of disabling recurrences, therapy with an NSAID, colchicine, or a glucocorticoid, such as described for treatment of acute pericarditis, is usually effective.

DIFFERENTIAL DIAGNOSIS

Because there is no specific test for *acute idiopathic pericarditis*, the diagnosis is one of exclusion. Consequently, all other disorders that may be associated with acute fibrinous pericarditis must be considered. A common diagnostic error is mistaking acute viral or idiopathic pericarditis for AMI and vice versa. When acute fibrinous pericarditis is associated with AMI (Chap. 295), it is characterized by fever, pain, and a friction rub in the first 4 days after the development of the infarct. ECG abnormalities (such as the appearance of Q waves, brief ST-segment elevations with reciprocal changes, and earlier T-wave changes in AMI) and the extent of the elevations of markers of myocardial necrosis (higher in AMI) are helpful in differentiating pericarditis from AMI.

Pericarditis secondary to postcardiac injury is differentiated from acute idiopathic pericarditis chiefly by timing. If it occurs within a few days or weeks of an AMI, a chest blow, a cardiac perforation, or a cardiac operation, it may be justified to conclude that the two are probably related.

It is important to distinguish *pericarditis due to collagen vascular disease* from acute idiopathic pericarditis. Most important in the differential diagnosis is the pericarditis due to systemic lupus erythematosus (SLE; Chap. 378) or drug-induced (procainamide or hydralazine) lupus. When pericarditis occurs in the absence of any obvious underlying disorder, the diagnosis of SLE may be suggested by a rise in the titer of antinuclear antibodies. Acute pericarditis is an occasional complication of *rheumatoid arthritis*, *scleroderma*, and *polyarteritis nodosa*, and other evidence of these diseases is usually obvious.

Pyogenic (purulent) pericarditis is usually secondary to cardiothoracic operations, by extension of infection from the lungs or pleural cavities, from rupture of the esophagus into the pericardial sac, or from rupture of a ring abscess in a patient with infective endocarditis. It may also complicate the viral, pyogenic, mycobacterial, and fungal infections that occur with HIV infection. It is generally accompanied by fever, chills, septicemia, and evidence of infection elsewhere and generally has a poor prognosis. The diagnosis is made by examination of the pericardial fluid. It requires drainage as well as vigorous antibiotic treatment.

Pericarditis of renal failure occurs in up to one-third of patients with chronic uremia (*uremic pericarditis*), and is also seen in patients undergoing chronic dialysis who have normal levels of blood urea and creatinine (*dialysis-associated pericarditis*). These two forms of pericarditis may be fibrinous and are generally associated with serosanguineous

effusions. A pericardial friction rub is common, but pain is usually absent or mild. Treatment with an NSAID and intensification of dialysis are usually adequate. Occasionally, tamponade occurs and pericardiocentesis is required. When the pericarditis of renal failure is recurrent or persistent, a pericardial window should be created or pericardectomy may be necessary.

Pericarditis due to *neoplastic diseases* results from extension or invasion of metastatic tumors (most commonly carcinoma of the lung and breast, malignant melanoma, lymphoma, and leukemia) to the pericardium; pain, atrial arrhythmias, and tamponade are complications that occur occasionally. Diagnosis is made by pericardial fluid cytology or pericardial biopsy. *Mediastinal irradiation* for neoplasm may cause acute pericarditis and/or chronic constrictive pericarditis. Unusual causes of acute pericarditis include syphilis, fungal infection (histoplasmosis, blastomycosis, aspergillosis, and candidiasis), and parasitic infestation (amebiasis, toxoplasmosis, echinococcosis, and trichinosis).

CHRONIC PERICARDIAL EFFUSIONS

Chronic pericardial effusions are sometimes encountered in patients without an antecedent history of acute pericarditis. They may cause few symptoms per se, and their presence may be detected by finding an enlarged cardiac silhouette on a chest roentgenogram. Tuberculosis is a common cause. *Myxedema* may be responsible for chronic pericardial effusion that is sometimes massive but rarely, if ever, causes cardiac tamponade. The cardiac silhouette may be markedly enlarged, and an echocardiogram distinguishes cardiomegaly from pericardial effusion. The diagnosis of myxedema can be confirmed by tests of thyroid function (Chap. 405). Myxedematous pericardial effusion responds to thyroid hormone replacement. Neoplasms, SLE, rheumatoid arthritis, mycotic infections, radiation therapy to the chest, pyogenic infections, and chylopericardium may also cause chronic pericardial effusion and should be considered and specifically sought in such patients.

Aspiration and analysis of the pericardial fluid are often helpful in diagnosis. Pericardial fluid should be analyzed as described in pericardiocentesis. Grossly sanguineous pericardial fluid results most commonly from a neoplasm, tuberculosis, renal failure, or slow leakage from an aortic dissection. Pericardiocentesis may resolve large effusions, but pericardectomy may be required in patients with recurrence. Intrapericardial instillation of sclerosing agents may be used to prevent reaccumulation of fluid.

CHRONIC CONSTRICTIVE PERICARDITIS

This disorder results when the healing of an acute fibrinous or serofibrinous pericarditis or the resorption of a chronic pericardial effusion is followed by obliteration of the pericardial cavity with the formation of granulation tissue. The latter gradually contracts and forms a firm scar encasing the heart, which may be calcified. In developing nations where the condition is prevalent, a high percentage of cases are of tuberculous origin, but this is now an uncommon cause in North America. Chronic constrictive pericarditis may follow acute or relapsing viral or idiopathic pericarditis, trauma with organized blood clot, or cardiac surgery of any type or result from mediastinal irradiation, purulent infection, histoplasmosis, neoplastic disease (especially breast cancer, lung cancer, and lymphoma), rheumatoid arthritis, SLE, or chronic renal failure treated by chronic dialysis. In many patients, the cause of the pericardial disease is undetermined, and in these patients, an asymptomatic or forgotten bout of viral pericarditis, acute or idiopathic, may have been the inciting event.

The basic physiologic abnormality in patients with chronic constrictive pericarditis is the inability of the ventriles to fill because of the limitations imposed by the rigid, thickened pericardium. Ventricular filling is unimpeded during early diastole but is reduced abruptly when the elastic limit of the pericardium is reached, whereas in cardiac tamponade, ventricular filling is impeded throughout diastole. In both conditions, ventricular end-diastolic and stroke volumes are reduced and the end-diastolic pressures in both ventricles and

the mean pressures in the atria, pulmonary veins, and systemic veins are all elevated to similar levels (i.e., within 5 mmHg of one another). Despite these hemodynamic changes, systolic function may be normal or only slightly impaired. However, in advanced cases, the fibrotic process may extend into the myocardium and cause myocardial scarring and atrophy, and venous congestion may then be due to the combined effects of the pericardial and myocardial lesions.

In constrictive pericarditis, the right and left atrial pressure pulses display an M-shaped contour, with prominent *x* and *y* descents. The *y* descent, which is absent or diminished in cardiac tamponade, is the most prominent deflection in constrictive pericarditis; it reflects rapid early filling of the ventricles. The *y* descent is interrupted by a rapid rise in atrial pressure during early diastole, when ventricular filling is impeded by the constricting pericardium. These characteristic changes are transmitted to the jugular veins, where they may be recognized by inspection. In constrictive pericarditis, the ventricular pressure pulses in both ventricles exhibit characteristic “square root” signs during diastole. These hemodynamic changes, although characteristic, are not pathognomonic of constrictive pericarditis and may also be observed in restrictive cardiomyopathies (Chap. 287, Table 287-2).

CLINICAL AND LABORATORY FINDINGS

Weakness, fatigue, weight gain, increased abdominal girth, abdominal discomfort, and edema are common. The patient often appears chronically ill, and in advanced cases, anasarca, skeletal muscle wasting, and cachexia may be present. Exertional dyspnea is common, and orthopnea may occur, although it is usually not severe. Acute left ventricular failure (acute pulmonary edema) is very uncommon. The cervical veins are distended and may remain so even after intensive diuretic treatment, and venous pressure may fail to decline during inspiration (*Kussmaul's sign*). The latter is common in chronic pericarditis but may also occur in tricuspid stenosis, right ventricular infarction, and restrictive cardiomyopathy.

The pulse pressure is normal or reduced. A paradoxical pulse can be detected in about one-third of cases. Congestive hepatomegaly is pronounced and may impair hepatic function and cause jaundice; ascites is common and is usually more prominent than dependent edema. The apical pulse is reduced and may retract in systole (*Broadbent's sign*). The heart sounds may be distant; an early third heart sound (i.e., a pericardial knock, occurring at the cardiac apex 0.09–0.12 s after aortic valve closure) with the abrupt cessation of ventricular filling is often conspicuous.

The ECG frequently displays low voltage of the QRS complexes and diffuse flattening or inversion of the T waves. Atrial fibrillation is present in about one-third of patients. The chest roentgenogram shows a normal or slightly enlarged heart. Pericardial calcification is most common in tuberculous pericarditis. Pericardial calcification may, however, occur in the absence of constriction, and constriction may occur without calcification.

Inasmuch as the usual physical signs of cardiac disease (murmurs, cardiac enlargement) may be inconspicuous or absent in chronic constrictive pericarditis, hepatic enlargement and dysfunction associated with jaundice and intractable ascites may lead to a mistaken diagnosis of hepatic cirrhosis. This error can be avoided if the neck veins are inspected and found to be distended.

The transthoracic echocardiogram typically shows pericardial thickening, dilation of the inferior vena cava and hepatic veins, and a sharp halt in ventricular filling in early diastole, with normal ventricular systolic function and flattening of the left ventricular posterior wall. There is a distinctive pattern of transvalvular flow velocity on Doppler echocardiography. During inspiration, there is an exaggerated reduction in blood flow velocity in the pulmonary veins and across the mitral valve and a leftward shift of the ventricular septum; the opposite occurs during expiration. Diastolic flow velocity in the inferior vena cava into the right atrium and across the tricuspid valve increases in an exaggerated manner during inspiration and declines during expiration (Fig. 288-4). However, echocardiography cannot definitively exclude the diagnosis of constrictive pericarditis. CT and MRI scanning (Fig. 288-5) are

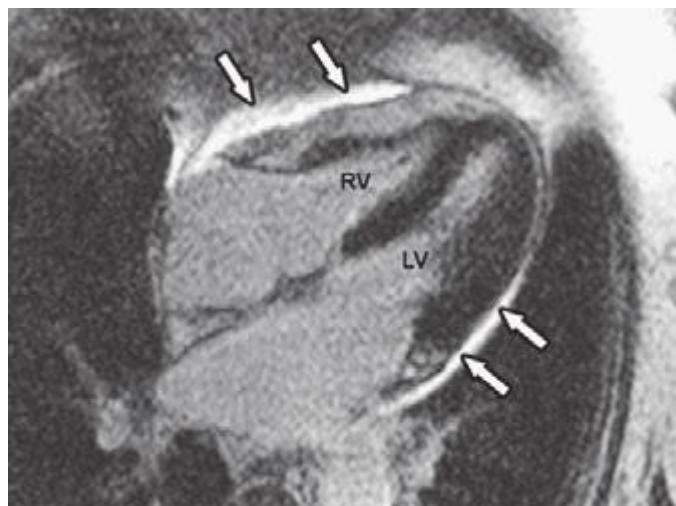


FIGURE 288-5 Magnetic resonance imaging in chronic constrictive pericarditis. The arrows point to a thickened pericardium, which shows late enhancement after gadolinium, characteristic of intense inflammation. LV, left ventricle; RV, right ventricle. (From RY Kwong: *Cardiovascular magnetic resonance imaging*, in RO Bonow et al [eds]: *Braunwald's Heart Disease*, 9th ed. Philadelphia: Elsevier, 2012.)

more accurate than echocardiography in establishing or excluding the presence of a thickened pericardium.

DIFFERENTIAL DIAGNOSIS

Like chronic constrictive pericarditis, cor pulmonale (Chap. 279) may be associated with severe systemic venous hypertension but little pulmonary congestion; the heart is usually not enlarged, and a paradoxical pulse may be present. However, in cor pulmonale, advanced parenchymal pulmonary disease is usually apparent and venous pressure falls during inspiration (i.e., Kussmaul's sign is negative). Tricuspid stenosis (Chap. 283) may also simulate chronic constrictive pericarditis; congestive hepatomegaly, splenomegaly, ascites, and venous distention may be equally prominent. However, in tricuspid stenosis, a characteristic murmur and the murmur of accompanying mitral stenosis are usually present.

Because constrictive pericarditis can be corrected surgically, it is important to distinguish chronic constrictive pericarditis from restrictive cardiomyopathy (Chap. 287), which has a similar physiologic abnormality (i.e., restriction of ventricular filling). The differentiating features are summarized in Table 288-2. When a patient has progressive, disabling, and unresponsive congestive heart failure and displays any of the features of constrictive heart disease, Doppler echocardiography to record respiratory effects on transvalvular flow and an MRI or CT scan should be obtained to detect or exclude constrictive pericarditis, because the latter is usually correctable.

TREATMENT CONSTRICITIVE PERICARDITIS

Pericardial resection is the only definitive treatment of constrictive pericarditis and should be as complete as possible. Dietary sodium restriction and diuretics are useful during preoperative preparation. Coronary arteriography should be carried out preoperatively in patients older than 50 years to exclude unsuspected accompanying coronary artery disease. The benefits derived from cardiac decortication are usually progressive over a period of months. The risk of this operation depends on the extent of penetration of the myocardium by the fibrotic and calcific process, the severity of myocardial atrophy, the extent of secondary impairment of hepatic and/or renal function, and the patient's general condition. Operative mortality is in the range of 5 to 10% even in experienced centers; the patients

with the most severe disease are at highest risk. Therefore, surgical treatment should, if possible, be carried out as early as possible in the course.

Subacute Effusive-Constrictive Pericarditis This form of pericardial disease is characterized by the combination of a tense effusion in the pericardial space and constriction of the heart by thickened pericardium. It shares a number of features with both chronic pericardial effusion producing cardiac compression and with pericardial constriction. It may be caused by tuberculosis (see below), multiple attacks of acute idiopathic pericarditis, radiation, traumatic pericarditis, renal failure, scleroderma, and neoplasms. The heart is generally enlarged, and a paradoxical pulse and a prominent x descent (without a prominent y descent) are present in the atrial and jugular venous pressure pulses. After pericardiocentesis, the physiologic findings may change from those of cardiac tamponade to those of pericardial constriction. Furthermore, the intrapericardial pressure and the central venous pressure may decline, but not to normal. The diagnosis can be established by pericardiocentesis followed by pericardial biopsy. Wide excision of both the visceral and parietal pericardium is usually effective therapy.

Tuberculous Pericardial Disease This chronic infection is a common cause of chronic pericardial effusion, although less so in North America than in the developing world where active tuberculosis is endemic. The clinical picture is that of a chronic, systemic illness in a patient with pericardial effusion. It is important to consider this diagnosis in a patient with known tuberculosis, with HIV, and with fever, chest pain, weight loss, and enlargement of the cardiac silhouette of undetermined origin. If the etiology of chronic pericardial effusion remains obscure despite detailed analysis of the pericardial fluid (see above), a pericardial biopsy, preferably by a limited thoracotomy, should be performed. If definitive evidence is still lacking but the specimen shows granulomas with caseation, antituberculous chemotherapy (Chap. 202) is indicated.

If the biopsy specimen shows a thickened pericardium after 2–4 weeks of antituberculin therapy, pericardectomy should be carried out to prevent the development of constriction. Tubercular cardiac constriction should be treated surgically while the patient is receiving antituberculous chemotherapy.

OTHER DISORDERS OF THE PERICARDIUM

Pericardial cysts appear as rounded or lobulated deformities of the cardiac silhouette, most commonly at the right cardiophrenic angle. They usually do not cause symptoms, and their major clinical significance lies in the possibility of confusion with a tumor, ventricular aneurysm, or massive cardiomegaly. *Tumors* involving the pericardium are most commonly secondary to malignant neoplasms originating in or invading the mediastinum, including carcinoma of the bronchus and breast, lymphoma, and melanoma. Mesothelioma is the most common *primary* malignant tumor. The usual clinical picture of malignant pericardial tumor is an insidiously developing, often bloody pericardial effusion. Surgical exploration is required to establish a definitive diagnosis and to carry out definitive or, more commonly, palliative treatment.

289e Tumors and Trauma of the Heart

Eric H. Awtry, Wilson S. Colucci

TUMORS OF THE HEART

PRIMARY TUMORS

Primary tumors of the heart are rare. Approximately three-quarters are histologically benign, and the majority of these tumors are myxomas. Malignant tumors, almost all of which are sarcomas, account for 25% of primary cardiac tumors. All cardiac tumors, regardless of pathologic type, have the potential to cause life-threatening complications. Many tumors are now surgically curable; thus, early diagnosis is imperative.

Clinical Presentation Cardiac tumors may present with a wide array of cardiac and noncardiac manifestations. These manifestations depend in large part on the location and size of the tumor and are often nonspecific features of more common forms of heart disease, such as chest pain, syncope, heart failure, murmurs, arrhythmias, conduction disturbances, and pericardial effusion with or without tamponade. Additionally, embolic phenomena and constitutional symptoms may occur.

Myxoma Myxomas are the most common type of primary cardiac tumor in adults, accounting for one-third to one-half of all cases at postmortem examination, and about three-quarters of the tumors treated surgically. They occur at all ages, most commonly in the third through sixth decades, with a female predilection. Approximately 90% of myxomas are sporadic; the remainder are familial with autosomal dominant transmission. The familial variety often occurs as part of a syndrome complex (Carney complex) that includes (1) myxomas (cardiac, skin, and/or breast), (2) lentigines and/or pigmented nevi, and (3) endocrine overactivity (primary nodular adrenal cortical disease with or without Cushing's syndrome, testicular tumors, and/or pituitary adenomas with gigantism or acromegaly). Certain constellations of findings have been referred to as the *NAME* syndrome (*nevi, atrial myxoma, myxoid neurofibroma, and ephelides*) or the *LAMB* syndrome (*lentigines, atrial myxoma, and blue nevi*), although these syndromes probably represent subsets of the Carney complex. The genetic basis of this complex has not been elucidated completely; however, patients frequently have inactivating mutations in the tumor-suppressor gene *PRKAR1A*, which encodes the protein kinase A type I- α regulatory subunit.

Pathologically, myxomas are gelatinous structures that consist of myxoma cells embedded in a stroma rich in glycosaminoglycans. Most are solitary, arise from the interatrial septum in the vicinity of the fossa ovalis (particularly the left atrium), and are often pedunculated on a fibrovascular stalk. In contrast to sporadic tumors, familial or syndromic tumors tend to occur in younger individuals, are often multiple, may be ventricular in location, and are more likely to recur after initial resection.

Myxomas commonly present with obstructive signs and symptoms. The most common clinical presentation mimics that of mitral valve disease: either stenosis owing to tumor prolapse into the mitral orifice or regurgitation resulting from tumor-induced valvular trauma. Ventricular myxomas may cause outflow obstruction similar to that caused by subaortic or subpulmonic stenosis. The symptoms and signs of myxoma may be sudden in onset or positional in nature, owing to the effects of gravity on tumor position. A characteristic low-pitched sound, a "tumor plop," may be appreciated on auscultation during early or mid-diastole and is thought to result from the impact of the tumor against the mitral valve or ventricular wall. Myxomas also may present with peripheral or pulmonary emboli or with constitutional signs and symptoms, including fever, weight loss, cachexia, malaise, arthralgias, rash, digital clubbing, Raynaud's phenomenon, hypergammaglobulinemia, anemia, polycythemia, leukocytosis, elevated erythrocyte sedimentation rate, thrombocytopenia, and thrombocytosis. These features account for the frequent misdiagnosis of patients with myxomas as having endocarditis, collagen vascular disease, or a paraneoplastic syndrome.

Two-dimensional transthoracic or omniplane transesophageal echocardiography is useful in the diagnosis of cardiac myxoma and allows assessment of tumor size and determination of the site of tumor attachment, both of which are important considerations in the planning of surgical excision (Fig. 289e-1). Computed tomography (CT) and magnetic resonance imaging (MRI) may provide important information regarding size, shape, composition, and surface characteristics of the tumor (Fig. 289e-2).

Although cardiac catheterization and angiography were previously performed routinely before tumor resection, they no longer are considered mandatory when adequate noninvasive information is available and other cardiac disorders (e.g., coronary artery disease) are not considered likely. Additionally, catheterization of the chamber from which the tumor arises carries the risk of tumor embolization. Because myxomas may be familial, echocardiographic screening of first-degree relatives is appropriate, particularly if the patient is young and has multiple tumors or evidence of myxoma syndrome.

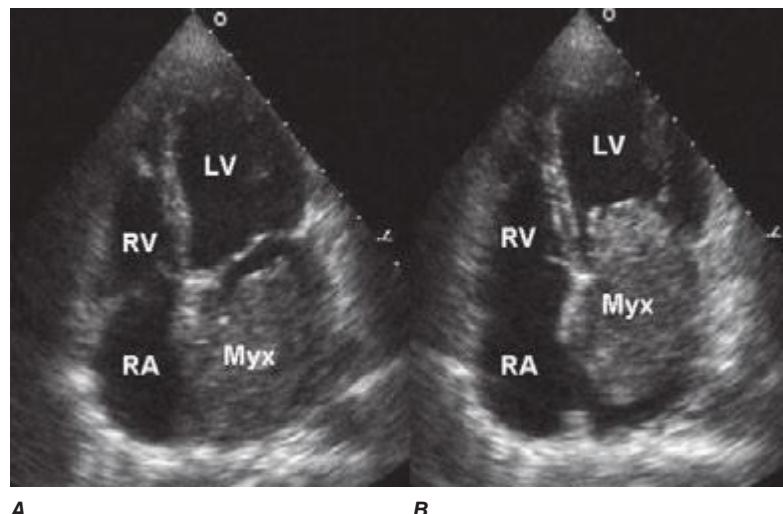


FIGURE 289e-1 Transthoracic echocardiogram demonstrating a large atrial myxoma. The myxoma (Myx) fills the entire left atrium in systole (A) and prolapses across the mitral valve and into the left ventricle (LV) during diastole (B). RA, right atrium; RV, right ventricle. (Courtesy of Dr. Michael Tsang; with permission.)

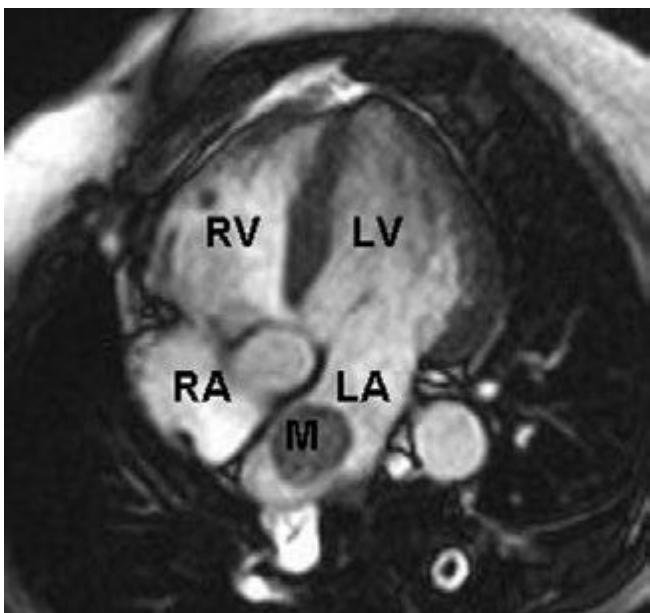


FIGURE 289e-2 Cardiac magnetic resonance imaging demonstrating a rounded mass (M) within the left atrium (LA). Pathologic evaluation at the time of surgery revealed it to be an atrial myxoma. LV, left ventricle; RA, right atrium; RV, right ventricle.

TREATMENT MYXOMA

Surgical excision using cardiopulmonary bypass is indicated regardless of tumor size and is generally curative. Myxomas recur in 12–22% of familial cases but in only 1–2% of sporadic cases. Tumor recurrence most likely is due to multifocal lesions in the former and inadequate resection in the latter.

Other Benign Tumors Cardiac *lipomas*, although relatively common, are usually incidental findings at postmortem examination; however, they may grow as large as 15 cm and may present with symptoms owing to mechanical interference with cardiac function, arrhythmias, or conduction disturbances or as an abnormality of the cardiac silhouette on chest x-ray. *Papillary fibroelastomas* are the most common tumors of the cardiac valves. Although usually clinically silent, they can cause valve dysfunction and may embolize distally, resulting in transient ischemic attacks, stroke, or myocardial infarction. In general, these tumors should be resected even when asymptomatic, although a more conservative approach may be considered for small, right-sided lesions. *Rhabdomyomas* and *fibromas* are the most common cardiac tumors in infants and children and usually occur in the ventricles, where they may produce mechanical obstruction to blood flow, thereby mimicking valvular stenosis, congestive heart failure (CHF), restrictive or hypertrophic cardiomyopathy, or pericardial constriction. Rhabdomyomas are probably hamartomatous growths, are multiple in 90% of cases, and are strongly associated with tuberous sclerosis. These tumors have a tendency to regress completely or partially; only tumors that cause obstruction require surgical resection. Fibromas are usually single, are often calcified, tend to grow and cause obstructive symptoms, and should be resected. *Hemangiomas* and *mesotheliomas* are generally small tumors, most often intramyocardial in location, and may cause atrioventricular (AV) conduction disturbances and even sudden death as a result of their propensity to develop in the region of the AV node. Other benign tumors arising from the heart include *teratoma*, *chemodectoma*, *neurilemoma*, *granular cell myoblastoma*, and *bronchogenic cysts*.

Sarcoma Almost all malignant primary cardiac tumors are sarcomas, which may be of several histologic types. In general, these tumors are characterized by rapid progression that culminates in the patient's death within weeks to months from the time of presentation as a result

of hemodynamic compromise, local invasion, or distant metastases. Sarcomas commonly involve the right side of the heart, are characterized by rapid growth, frequently invade the pericardial space, and may obstruct the cardiac chambers or vena cavae. Sarcomas also may occur on the left side of the heart and may be mistaken for myxomas.

TREATMENT SARCOMA

At the time of presentation, these tumors have often spread too extensively to allow for surgical excision. Although there are scattered reports of palliation with surgery, radiotherapy, and/or chemotherapy, the response of cardiac sarcomas to these therapies is generally poor. The one exception appears to be cardiac lymphosarcomas, which may respond to a combination of chemo- and radiotherapy.

TUMORS METASTATIC TO THE HEART

Tumors metastatic to the heart are much more common than primary tumors, and their incidence is likely to increase as the life expectancy of patients with various forms of malignant neoplasms is extended by more effective therapy. Although cardiac metastases may occur with any tumor type, the relative incidence is especially high in malignant melanoma and, to a somewhat lesser extent, leukemia and lymphoma. In absolute terms, the most common primary originating sites of cardiac metastases are carcinoma of the breast and lung, reflecting the high incidence of those cancers. Cardiac metastases almost always occur in the setting of widespread primary disease, and most often there is either primary or metastatic disease elsewhere in the thoracic cavity. Nevertheless, cardiac metastasis occasionally may be the initial presentation of an extrathoracic tumor.

Cardiac metastases may occur via hematogenous or lymphangitic spread or by direct tumor invasion. They generally manifest as small, firm nodules; diffuse infiltration also may occur, especially with sarcomas or hematologic neoplasms. The pericardium is most often involved, followed by myocardial involvement of any chamber and, rarely, by involvement of the endocardium or cardiac valves.

Cardiac metastases are clinically apparent only ~10% of the time, are usually not the cause of the patient's presentation, and rarely are the cause of death. The vast majority occur in the setting of a previously recognized malignant neoplasm. As with primary cardiac tumors, the clinical presentation reflects more the location and size of the tumor than its histologic type. When symptomatic, cardiac metastases may result in a variety of clinical features, including dyspnea, acute pericarditis, cardiac tamponade, ectopic tachyarrhythmias, heart block, and CHF. Importantly, many of these signs and symptoms may also result from myocarditis, pericarditis, or cardiomyopathy induced by radiotherapy or chemotherapy.

Electrocardiographic (ECG) findings are nonspecific. On chest x-ray, the cardiac silhouette is most often normal but may be enlarged or exhibit a bizarre contour. Echocardiography is useful for identifying pericardial effusions and visualizing larger metastases, although CT and radionuclide imaging with gallium or thallium may define the tumor burden more clearly. Cardiac MRI offers superb image quality and plays a central role in the diagnostic evaluation of cardiac metastases and cardiac tumors in general. Pericardiocentesis may allow for a specific cytologic diagnosis in patients with malignant pericardial effusions. Angiography is rarely necessary but may delineate discrete lesions.

TREATMENT TUMORS METASTATIC TO THE HEART

Most patients with cardiac metastases have advanced malignant disease; thus, therapy is generally palliative and consists of treatment of the primary tumor. Symptomatic malignant pericardial effusions should be drained by pericardiocentesis. Concomitant instillation of a sclerosing agent (e.g., tetracycline or bleomycin) may delay or prevent reaccumulation of the effusion, and creation of a pericardial window allows drainage of the effusion to the pleural or peritoneal space.

TRAUMATIC CARDIAC INJURY

Traumatic cardiac injury may be caused by either penetrating or nonpenetrating trauma. *Penetrating injuries* most often result from gunshot or knife wounds, and the site of entry is usually obvious. *Nonpenetrating injuries* most often occur during motor vehicle accidents, either from rapid deceleration or from impact of the chest against the steering wheel, and may be associated with significant cardiac injury even in the absence of external signs of thoracic trauma.

NONPENETRATING CARDIAC INJURY

Myocardial contusions are the most common form of nonpenetrating cardiac injury and may initially be overlooked in trauma patients as the clinical focus is directed toward other, more obvious injuries. Myocardial necrosis may occur as a direct result of the blunt injury or as a result of traumatic coronary laceration or thrombosis. The contused myocardium is pathologically similar to infarcted myocardium and may be associated with atrial or ventricular arrhythmias; conduction disturbances, including bundle branch block; or ECG abnormalities resembling those of infarction or pericarditis. Thus, it is important to consider contusion as a cause of otherwise unexplained ECG changes in a trauma patient. Serum creatine kinase, myocardial band (CK-MB) isoenzyme levels are increased in ~20% of patients who experience blunt chest trauma but may be falsely elevated in the presence of massive skeletal muscle injury. Cardiac troponin levels are more specific for identifying cardiac injury in this setting. Echocardiography is useful in detecting structural and functional sequelae of contusion, including wall motion abnormalities (most commonly involving the right ventricle, interventricular septum, or left ventricular apex), pericardial effusion, valvular dysfunction, and ventricular rupture.

Rupture of the cardiac valves or their supporting structures, most commonly of the tricuspid or mitral valve, leads to acute valvular incompetence. This complication is usually heralded by the development of a loud murmur, may be associated with rapidly progressive heart failure, and can be diagnosed by either transthoracic or transesophageal echocardiography.

The most serious consequence of nonpenetrating cardiac injury is myocardial rupture, which may result in hemopericardium and tamponade (free wall rupture) or intracardiac shunting (ventricular septal rupture). Although it generally is fatal, up to 40% of patients with cardiac rupture have been reported to survive long enough to reach a specialized trauma center. Hemopericardium also may result from traumatic rupture of a pericardial vessel or a coronary artery. Additionally, a pericardial effusion may develop weeks or even months after blunt chest trauma as a manifestation of the post-cardiac injury syndrome, which resembles the postpericardiotomy syndrome ([Chap. 288](#)).

Blunt, nonpenetrating, often innocent-appearing injuries to the chest may trigger ventricular fibrillation even in absence of overt signs of injury. This syndrome, referred to as *commotio cordis*, occurs most often in adolescents during sporting events (e.g., baseball, hockey, football, and lacrosse) and probably results from an impact to the chest wall overlying the heart during the susceptible phase of repolarization just before the peak of the T wave. Survival depends on prompt defibrillation. Sudden emotional or physical trauma, even in the absence of direct cardiac trauma, may precipitate a transient catecholamine-mediated

cardiomyopathy referred to as *tako-tsubo syndrome* or the *apical ballooning syndrome* ([Chap. 287](#)).

Rupture or transection of the aorta, usually just above the aortic valve or at the site of the ligamentum arteriosum, is a common consequence of nonpenetrating chest trauma and is the most common vascular deceleration injury. The clinical presentation is similar to that of aortic dissection ([Chap. 301](#)); the arterial pressure and pulse amplitude may be increased in the upper extremities and decreased in the lower extremities, and chest x-ray may reveal mediastinal widening. Occasionally, aortic rupture is contained by the aortic adventitia, resulting in a false, or *pseudo-*, aneurysm that may be discovered months or years after the initial injury.

PENETRATING CARDIAC INJURY

Penetrating injuries of the heart produced by knife or bullet wounds usually result in rapid clinical deterioration and frequently in death as a result of hemopericardium/pericardial tamponade or massive hemorrhage. Nonetheless, up to half of such patients may survive long enough to reach a specialized trauma center if immediate resuscitation is performed. Prognosis in these patients relates to the mechanism of injury, their clinical condition at presentation, and the specific cardiac chamber(s) involved. Iatrogenic cardiac or coronary arterial perforation may complicate placement of central venous or intracardiac catheters, pacemaker leads, or intracoronary stents and is associated with a better prognosis than are other forms of penetrating cardiac trauma.

Traumatic rupture of a great vessel from penetrating injury is usually associated with hemothorax and, less often, hemopericardium. Local hematoma formation may compress major vessels and produce ischemic symptoms, and AV fistulas may develop, occasionally resulting in high-output CHF.

Occasionally, patients who survive penetrating cardiac injuries may subsequently present with a new cardiac murmur or CHF as a result of mitral regurgitation or an intracardiac shunt (i.e., ventricular or atrial septal defect, aortopulmonary fistula, or coronary AV fistula) that was undetected at the time of the initial injury or developed subsequently. Therefore, trauma patients should be examined carefully several weeks after the injury. If a mechanical complication is suspected, it can be confirmed by echocardiography or cardiac catheterization.

TREATMENT TRAUMATIC CARDIAC INJURY

The treatment of an uncomplicated myocardial contusion is similar to the medical therapy for a myocardial infarction, except that anticoagulation is contraindicated, and should include monitoring for the development of arrhythmias and mechanical complications such as cardiac rupture ([Chap. 295](#)). Acute myocardial failure resulting from traumatic valve rupture usually requires urgent operative correction. Immediate thoracotomy should be carried out for most cases of penetrating injury, or if there is evidence of cardiac tamponade and/or shock regardless of the type of trauma. Pericardiocentesis may be lifesaving in patients with tamponade but is usually only a temporizing measure while awaiting definitive surgical therapy. Pericardial hemorrhage often leads to constriction ([Chap. 288](#)), which must be treated by surgical decortication.

290e Cardiac Manifestations of Systemic Disease

Eric H. Awtry, Wilson S. Colucci

The common systemic disorders that have associated cardiac manifestations are summarized in **Table 290e-1**.

DIABETES MELLITUS

(See also Chap. 417) Diabetes mellitus, both insulin- and non-insulin-dependent, is an independent risk factor for coronary artery disease (CAD; Chap. 291e) and accounts for 14–50% of new cases of cardiovascular disease. Furthermore, CAD is the most common cause of death in adults with diabetes mellitus. In the diabetic population, the incidence of CAD relates to the duration of diabetes and the level of glycemic control, and its pathogenesis involves endothelial dysfunction, increased lipoprotein peroxidation, increased inflammation, a prothrombotic state, and associated metabolic abnormalities.

Compared to their nondiabetic counterparts, diabetic patients are more likely to have a myocardial infarction, have a greater burden of CAD, have larger infarct size, and have more postinfarct complications, including heart failure, shock, and death. Importantly, diabetic patients are more likely to have atypical ischemic symptoms; nausea, dyspnea, pulmonary edema, arrhythmias, heart block, or syncope may be their anginal equivalent. Additionally, “silent ischemia,” resulting from autonomic nervous system dysfunction, is more common in diabetic patients, accounting for up to 90% of their ischemic episodes. Thus, one must have a low threshold for suspecting CAD in diabetic patients. The treatment of diabetic patients with CAD must include aggressive risk factor management (Chap. 418). Considerations regarding pharmacologic therapy and revascularization strategies are similar in diabetic and nondiabetic patients except that diabetic patients have higher morbidity and mortality rates associated with revascularization, have an increased risk of restenosis after percutaneous coronary intervention (PCI), and have improved survival when treated with surgical bypass compared with PCI for multivessel CAD.

Patients with diabetes mellitus also may have abnormal left ventricular systolic and diastolic function, reflecting concomitant epicardial CAD and/or hypertension, coronary microvascular disease, endothelial dysfunction, ventricular hypertrophy, and autonomic dysfunction. Furthermore, the increase in intramyocardial lipid deposition (predominantly nonesterified fatty acids) that is characteristic of diabetic states may contribute to both systolic and diastolic dysfunction by impairing insulin signaling, reducing trans-sarcolemma calcium flux, and inducing myocyte apoptosis. A restrictive cardiomyopathy may be present with abnormal myocardial relaxation and elevated ventricular filling pressures. Histologically, interstitial fibrosis is seen, and intramural arteries may demonstrate intimal thickening, hyaline deposition, and inflammatory changes. Diabetic patients have an increased risk of developing clinical heart failure, which probably contributes to their excessive cardiovascular morbidity and mortality rates. There is some evidence that insulin therapy may ameliorate diabetes-related myocardial dysfunction.

MALNUTRITION AND VITAMIN DEFICIENCY

Malnutrition (See also Chap. 97) In patients whose intake of protein, calories, or both is severely deficient, the heart may become thin, pale, and hypokinetic with myofibrillar atrophy and interstitial edema. The systolic pressure and cardiac output fall, and the pulse pressure narrows. Generalized edema is common and relates to a variety of factors, including reduced serum oncotic pressure and myocardial dysfunction. Such profound states of protein and caloric malnutrition, termed *kwashiorkor* and *marasmus*, respectively, are most common in underdeveloped countries. However, significant nutritional heart disease also may occur in developed nations, particularly in patients with chronic diseases such as AIDS, patients with anorexia nervosa, and patients with severe cardiac failure in whom gastrointestinal hypoperfusion and venous congestion may lead to anorexia and malabsorption. Open-heart surgery poses increased risk in malnourished patients; such patients may benefit from preoperative hyperalimentation.

Thiamine Deficiency (Beriberi) (See also Chap. 96e) Generalized malnutrition often is accompanied by thiamine deficiency; however, this hypovitaminosis also may occur in the presence of an adequate protein and caloric intake, particularly in East Asia, where polished rice

TABLE 290e-1 COMMON SYSTEMIC DISORDERS AND THEIR ASSOCIATED CARDIAC MANIFESTATIONS

Systemic Disorder	Common Cardiac Manifestations	Chapter
Diabetes mellitus	CAD, atypical angina, CMP, systolic or diastolic CHF	417
Protein-calorie malnutrition	Dilated CMP, CHF	97
Thiamine deficiency	High-output failure, dilated CMP	96e
Hyperhomocysteinemia	Premature atherosclerosis	96e
Obesity	CMP, systolic or diastolic CHF	415e
Hyperthyroidism	Palpitations, SVT, atrial fibrillation, hypertension	405
Hypothyroidism	Hypotension, bradycardia, dilated CMP, CHF, pericardial effusion	405
Malignant carcinoid	Tricuspid and pulmonary valve disease, right heart failure	113
Pheochromocytoma	Hypertension, palpitations, CHF	407
Acromegaly	Systolic or diastolic heart failure	401e
Rheumatoid arthritis	Pericarditis, pericardial effusions, coronary arteritis, myocarditis, valvulitis	380
Seronegative arthropathies	Aortitis, aortic and mitral insufficiency, conduction abnormalities	384
Systemic lupus erythematosus	Pericarditis, Libman-Sacks endocarditis, myocarditis, arterial and venous thrombosis	378
HIV	Myocarditis, dilated CMP, pericardial effusion	226
Amyloidosis	CHF, restrictive CMP, valvular regurgitation, pericardial effusion	137
Sarcoidosis	CHF, dilated or restrictive CMP, ventricular arrhythmias, heart block	390
Hemochromatosis	CHF, arrhythmias, heart block	428
Marfan syndrome	Aortic aneurysm and dissection, aortic insufficiency, mitral valve prolapse	427
Ehlers-Danlos syndrome	Aortic and coronary aneurysms, mitral and tricuspid valve prolapse	427
Systemic sclerosis	Pericardial effusion, CHF (systolic and diastolic), myocarditis, coronary microvascular vasospasm, tachyarrhythmias	382

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CMP, cardiomyopathy; SVT, supraventricular tachycardia.

deficient in thiamine may be a major dietary component. In Western nations where the use of thiamine-enriched flour is widespread, clinical thiamine deficiency is limited primarily to alcoholics, food faddists, and patients receiving chemotherapy. Nonetheless, when thiamine stores are measured using the thiamine-pyrophosphate effect (TPPE), thiamine deficiency has been found in 20–90% of patients with chronic heart failure. This deficiency appears to result from both reduced dietary intake and a diuretic-induced increase in the urinary excretion of thiamine. The acute administration of thiamine to these patients increases the left ventricular ejection fraction and the excretion of salt and water.

Clinically, patients with thiamine deficiency usually have evidence of generalized malnutrition, peripheral neuropathy, glossitis, and anemia. The classic associated cardiovascular syndrome is characterized by high-output heart failure, tachycardia, and often elevated biventricular filling pressures. The major cause of the high-output state is vasomotor depression leading to reduced systemic vascular resistance, the precise mechanism of which is not understood. The cardiac examination may reveal a wide pulse pressure, tachycardia, a third heart sound, and an apical systolic murmur. The electrocardiogram (ECG) may reveal decreased voltage, a prolonged QT interval, and T-wave abnormalities. The chest x-ray generally reveals cardiomegaly and signs of congestive heart failure (CHF). The response to thiamine is often dramatic, with an increase in systemic vascular resistance, a decrease in cardiac output, clearing of pulmonary congestion, and a reduction in heart size often occurring in 12–48 h. Although the response to inotropes and diuretics may be poor before thiamine therapy, these agents may be important *after* thiamine repletion, since the left ventricle may not be able to handle the increased work load presented by the return of vascular tone.

Vitamin B₆, B₁₂, and Folate Deficiency (See also Chap. 96e) Vitamin B₆, vitamin B₁₂, and folate are cofactors in the metabolism of homocysteine. Their deficiency probably contributes to the majority of cases of hyperhomocysteinemia, a disorder associated with increased atherosclerotic risk. Supplementation of these vitamins has reduced the incidence of hyperhomocysteinemia in the United States; however, the clinical cardiovascular benefit of normalizing elevated homocysteine levels has not been proved.

OBESITY

(See also Chap. 415e) Obesity is associated with an increased prevalence of hypertension, glucose intolerance, atherosclerotic CAD, atrial fibrillation, obstructive sleep apnea, and pulmonary hypertension, and is associated with increased cardiovascular morbidity and mortality rates. In addition, obese patients have a distinct hemodynamic profile characterized by increased total and central blood volumes, increased cardiac output, and elevated left ventricular filling pressure. The elevated cardiac output appears to be required to support the metabolic demands of the excess adipose tissue. Left ventricular filling pressure is often at the upper limits of normal at rest and rises excessively with exercise, contributing to exertional dyspnea. In part as a result of chronic volume overload, eccentric cardiac hypertrophy with cardiac dilation and ventricular diastolic and/or systolic dysfunction may develop. In addition, altered levels of adipokines secreted by adipose tissue may contribute to adverse myocardial remodeling via direct effects on cardiac myocytes and other cells. Pathologically, there is left and, in some cases, right ventricular hypertrophy and generalized cardiac dilation. Pulmonary congestion, peripheral edema, and exercise intolerance may all ensue; however, the recognition of these findings may be difficult in massively obese patients.

Treatment with angiotensin-converting enzyme inhibitors, sodium restriction, and diuretics may be useful to control heart failure symptoms. Weight reduction, however, is the most effective therapy and results in reduction in blood volume and the return of cardiac output toward normal. However, rapid weight reduction may be dangerous, as cardiac arrhythmias and sudden death owing to electrolyte imbalance have been described.

THYROID DISEASE

(See also Chap. 405) Thyroid hormone exerts a major influence on the cardiovascular system by a number of direct and indirect mechanisms, and not surprisingly, cardiovascular effects are prominent in both hypo- and hyperthyroidism. Thyroid hormone causes increases in total-body metabolism and oxygen consumption that indirectly increase the cardiac workload. In addition, thyroid hormone exerts direct inotropic, chronotropic, and dromotropic effects that are similar to those seen with adrenergic stimulation (e.g., tachycardia, increased cardiac output); they are mediated at least partly by both transcriptional and nontranscriptional effects of thyroid hormone on myosin, calcium-activated ATPase, Na⁺-K⁺-ATPase, and myocardial β-adrenergic receptors.

Hyperthyroidism Common cardiovascular manifestations of hyperthyroidism include palpitations, systolic hypertension, and fatigue. Sinus tachycardia is present in ~40% of hyperthyroid patients, and atrial fibrillation is present in ~15%. Physical examination may reveal a hyperdynamic precordium, a widened pulse pressure, increases in the intensity of the first heart sound and the pulmonic component of the second heart sound, and a third heart sound. An increased incidence of mitral valve prolapse has been described in hyperthyroid patients, in which case a midsystolic murmur may be heard at the left sternal border with or without a midsystolic click. A systolic pleuropericardial friction rub (*Means-Lerman scratch*) may be heard at the left second intercostal space during expiration and is thought to result from the hyperdynamic cardiac motion.

Elderly patients with hyperthyroidism may present with only cardiovascular manifestations of thyrotoxicosis such as sinus tachycardia, atrial fibrillation, and hypertension, all of which may be resistant to therapy until the hyperthyroidism is controlled. Angina pectoris and CHF are unusual with hyperthyroidism unless there is coexistent heart disease; in such cases, symptoms often resolve with treatment of the hyperthyroidism.

Hypothyroidism Cardiac manifestations of hypothyroidism include a reduction in cardiac output, stroke volume, heart rate, systolic blood pressure, and pulse pressure. Pericardial effusions are present in about one-third of patients, rarely progress to tamponade, and probably result from increased capillary permeability. Other clinical signs include cardiomegaly, bradycardia, weak arterial pulses, distant heart sounds, and pleural effusions. Although the signs and symptoms of myxedema may mimic those of CHF, in the absence of other cardiac disease, myocardial failure is uncommon. The ECG generally reveals sinus bradycardia and low voltage and may show prolongation of the QT interval, decreased P-wave voltage, prolonged AV conduction time, intraventricular conduction disturbances, and nonspecific ST-T-wave abnormalities. Chest x-ray may show cardiomegaly, often with a “water bottle” configuration; pleural effusions; and, in some cases, evidence of CHF. Pathologically, the heart is pale and dilated and often demonstrates myofibrillar swelling, loss of striations, and interstitial fibrosis.

Patients with hypothyroidism frequently have elevations of cholesterol and triglycerides, resulting in premature atherosclerotic CAD. Before treatment with thyroid hormone, patients with hypothyroidism frequently do not have angina pectoris, presumably because of the low metabolic demands caused by their condition. However, angina and myocardial infarction may be precipitated during initiation of thyroid hormone replacement, especially in elderly patients with underlying heart disease. Therefore, replacement should be done with care, starting with low doses that are increased gradually.

MALIGNANT CARCINOID

(See also Chap. 113) Carcinoid tumors most often originate in the small bowel and elaborate a variety of vasoactive amines (e.g., serotonin), kinins, indoles, and prostaglandins that are believed to be responsible for the diarrhea, flushing, and labile blood pressure that characterize the carcinoid syndrome. Some 50% of patients with carcinoid syndrome have cardiac involvement, usually manifesting as abnormalities of the tricuspid or pulmonic valves. These patients

invariably have hepatic metastases that allow vasoactive substances to circumvent hepatic metabolism. Left-sided cardiac involvement is rare and indicates either pulmonary carcinoid or an intracardiac shunt. Pathologically, carcinoid lesions are fibrous plaques that consist of smooth-muscle cells embedded in a stroma of glycosaminoglycans and collagen. They occur on the cardiac valves, where they cause valvular dysfunction, as well as on the endothelium of the cardiac chambers and great vessels.

Carcinoid heart disease most often presents as tricuspid regurgitation, pulmonic stenosis, or both. In some cases, a high cardiac output state may occur, presumably as a result of a decrease in systemic vascular resistance resulting from vasoactive substances released by the tumor. Treatment with somatostatin analogues (e.g., octreotide) or interferon α improves symptoms and survival in patients with carcinoid heart disease but does not appear to improve valvular abnormalities. Treatment with diuretics usually mitigates the symptoms of right heart failure; in some severely symptomatic patients, valve replacement is indicated. Coronary artery spasm, presumably due to a circulating vasoactive substance, may occur in patients with carcinoid syndrome.

PHEOCHROMOCYTOMA

(See also Chap. 407) In addition to causing labile or sustained hypertension, the high circulating levels of catecholamines resulting from a pheochromocytoma may cause direct myocardial injury. Focal myocardial necrosis and inflammatory cell infiltration are present in ~50% of patients who die with pheochromocytoma and may contribute to clinically significant left ventricular failure and pulmonary edema. In addition, associated hypertension results in left ventricular hypertrophy. Left ventricular dysfunction and CHF may resolve after removal of the tumor.

ACROMEGALY

(See also Chap. 401e) Exposure of the heart to excessive growth hormone may cause CHF as a result of high cardiac output, diastolic dysfunction owing to ventricular hypertrophy (with increased left ventricular chamber size or wall thickness), or global systolic dysfunction. Hypertension occurs in up to one-third of patients with acromegaly and is characterized by suppression of the renin-angiotensin-aldosterone axis and increases in total-body sodium and plasma volume. Some form of cardiac disease occurs in about one-third of patients with acromegaly and is associated with a doubling of the risk of cardiac death.

RHEUMATOID ARTHRITIS AND THE COLLAGEN VASCULAR DISEASES

Rheumatoid Arthritis (See also Chap. 380) Rheumatoid arthritis may be associated with inflammatory changes in any or all cardiac structures, although pericarditis is the most common clinical entity. Pericardial effusions are found on echocardiography in 10–50% of patients with rheumatoid arthritis, particularly those with subcutaneous nodules. Nonetheless, only a small fraction of these patients have symptomatic pericarditis, and when present, it usually follows a benign course, only occasionally progressing to cardiac tamponade or constrictive pericarditis. The pericardial fluid is generally exudative,

with decreased concentrations of complement and glucose and elevated cholesterol. Coronary arteritis with intimal inflammation and edema is present in ~20% of cases but only rarely results in angina pectoris or myocardial infarction. Inflammation and granuloma formation may affect the cardiac valves, most often the mitral and aortic valves, and may cause clinically significant regurgitation owing to valve deformity. Myocarditis is uncommon and rarely results in cardiac dysfunction.

Treatment is directed at the underlying rheumatoid arthritis and may include glucocorticoids. Urgent pericardiocentesis should be performed in patients with tamponade, but pericardectomy usually is required in cases of pericardial constriction.

Seronegative Arthropathies (See also Chap. 384) The seronegative arthropathies, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and the arthritides associated with ulcerative colitis and regional enteritis, are all strongly associated with the HLA-B27 histocompatibility antigen and may be accompanied by a pancarditis and proximal aortitis. The aortic inflammation usually is limited to the aortic root but may extend to involve the aortic valve, mitral valve, and ventricular myocardium, resulting in aortic and mitral regurgitation, conduction abnormalities, and ventricular dysfunction. One-tenth of these patients have significant aortic insufficiency, and one-third have conduction disturbances; both are more common in patients with peripheral joint involvement and long-standing disease. Treatment with aortic valve replacement and permanent pacemaker implantation may be required. Occasionally, aortic regurgitation precedes the onset of arthritis, and therefore, the diagnosis of a seronegative arthritis should be considered in young males with isolated aortic regurgitation.

Systemic Lupus Erythematosus (SLE) (See also Chap. 378) A significant percentage of patients with SLE have cardiac involvement. Pericarditis is common, occurring in about two-thirds of patients, and generally follows a benign course, although rarely tamponade or constriction may result. The characteristic endocardial lesions of SLE are verrucous valvular abnormalities known as *Libman-Sacks endocarditis*. They most often are located on the left-sided cardiac valves, particularly on the ventricular surface of the posterior mitral leaflet, and are made up almost entirely of fibrin. These lesions may embolize or become infected but rarely cause hemodynamically important valvular regurgitation. Myocarditis generally parallels the activity of the disease and, although common histologically, seldom results in clinical heart failure unless associated with hypertension. Although arteritis of epicardial coronary arteries may occur, it rarely results in myocardial ischemia. There is, however, an increased incidence of coronary atherosclerosis that probably is related more to associated risk factors and glucocorticoid use than to SLE itself. Patients with the antiphospholipid antibody syndrome may have a higher incidence of cardiovascular abnormalities, including valvular regurgitation, venous and arterial thrombosis, premature stroke, myocardial infarction, pulmonary hypertension, and cardiomyopathy.

SECTION 5 CORONARY AND PERIPHERAL VASCULAR DISEASE

291e The Pathogenesis, Prevention, and Treatment of Atherosclerosis

Peter Libby

PATHOGENESIS

Atherosclerosis remains the major cause of death and premature disability in developed societies. Moreover, current predictions estimate that by the year 2020 cardiovascular diseases, notably atherosclerosis, will become the leading global cause of total disease burden. Although many generalized or systemic risk factors predispose to its development, atherosclerosis affects various regions of the circulation preferentially and has distinct clinical manifestations that depend on the particular circulatory bed affected. Atherosclerosis of the coronary arteries commonly causes myocardial infarction (MI) (Chap. 295) and angina pectoris (Chap. 293). Atherosclerosis of the arteries supplying the central nervous system frequently provokes strokes and transient cerebral ischemia (Chap. 446). In the peripheral circulation, atherosclerosis causes intermittent claudication and gangrene and can jeopardize limb viability. Involvement of the splanchnic circulation can cause mesenteric ischemia. Atherosclerosis can affect the kidneys either directly (e.g., renal artery stenosis) or as a common site of atheroembolic disease (Chap. 301).

Even within a particular arterial bed, stenoses due to atherosclerosis tend to occur focally, typically in certain predisposed regions. In the coronary circulation, for example, the proximal left anterior descending coronary artery exhibits a particular predilection for developing atherosclerotic disease. Similarly, atherosclerosis preferentially affects the proximal portions of the renal arteries and, in the extracranial circulation to the brain, the carotid bifurcation. Indeed, atherosclerotic lesions often form at branch points of arteries, regions characterized by disturbed hydrodynamics. Not all manifestations of atherosclerosis result from stenotic, occlusive disease. Ectasia and the development of aneurysmal disease, for example, frequently occur in the aorta (Chap. 301). In addition to focal, flow-limiting stenoses, nonocclusive intimal atherosclerosis also occurs diffusely in affected arteries, as shown by intravascular imaging and postmortem studies.

Atherogenesis in humans typically occurs over a period of many years, usually many decades. Growth of atherosclerotic plaques probably does not occur in a smooth, linear fashion but discontinuously, with periods of relative quiescence punctuated by periods of rapid evolution. After a generally prolonged “silent” period, atherosclerosis may become clinically manifest. The clinical expressions of atherosclerosis may be *chronic*, as in the development of stable, effort-induced angina pectoris or predictable and reproducible intermittent claudication. Alternatively, a dramatic *acute* clinical event such as MI, stroke, or sudden cardiac death may first herald the presence of atherosclerosis. Other individuals may never experience clinical manifestations of arterial disease despite the presence of widespread atherosclerosis demonstrated postmortem.

INITIATION OF ATHEROSCLEROSIS

An integrated view of experimental results in animals and studies of human atherosclerosis suggests that the “fatty streak” represents the initial lesion of atherosclerosis. These early lesions most often seem to arise from focal increases in the content of lipoproteins within regions of the intima. In particular, the fraction of lipoproteins related to low-density lipoprotein (LDL) that bear apolipoprotein B appear causally related to atherosclerosis. This accumulation of lipoprotein particles may not result simply from increased permeability, or

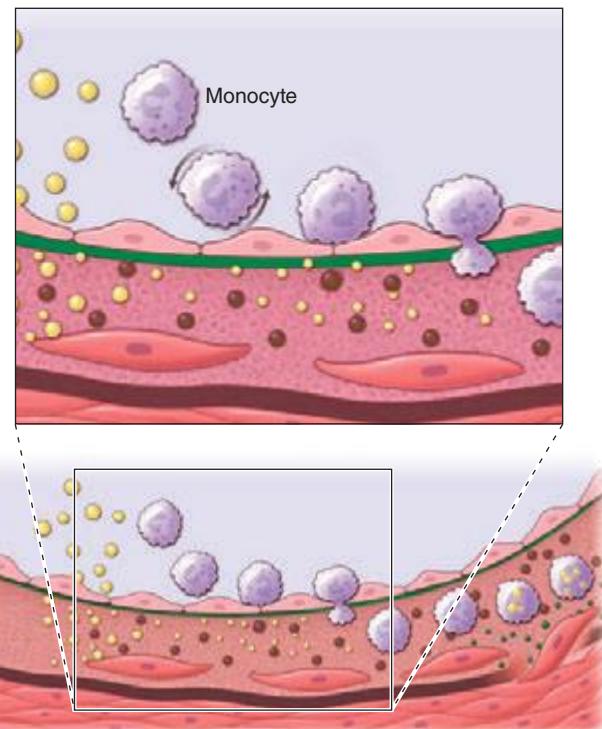


FIGURE 291e-1 Cross-sectional view of an artery depicting steps in development of an atheroma, from left to right. The upper panel shows a detail of the boxed area below. The endothelial monolayer overlying the intima contacts blood. Hypercholesterolemia promotes accumulation of low-density lipoprotein (LDL) particles (yellow spheres) in the intima. The lipoprotein particles often associate with constituents of the extracellular matrix, notably proteoglycans. Sequestration within the intima separates lipoproteins from some plasma antioxidants and favors oxidative modification. Such modified lipoprotein particles (darker spheres) may trigger a local inflammatory response that signals subsequent steps in lesion formation. The augmented expression of various adhesion molecules for leukocytes recruits monocytes to the site of a nascent arterial lesion.

Once adherent, some white blood cells migrate into the intima. The directed migration of leukocytes probably depends on chemoattractant factors, including modified lipoprotein particles themselves and chemoattractant cytokines (depicted by the smaller green spheres), such as the chemokine macrophage chemoattractant protein-1 produced by vascular wall cells in response to modified lipoproteins. Leukocytes in the evolving fatty streak can divide and exhibit augmented expression of receptors for modified lipoproteins (scavenger receptors). These mononuclear phagocytes ingest lipids and become foam cells, represented by a cytoplasm filled with lipid droplets. As the fatty streak evolves into a more complicated atherosclerotic lesion, smooth-muscle cells migrate from the media (bottom of lower panel hairline) through the internal elastic membrane (solid wavy line) and accumulate within the expanding intima, where they lay down extracellular matrix that forms the bulk of the advanced lesion (bottom panel, right side).

“leakiness,” of the overlying endothelium (Fig. 291e-1). Rather, the lipoproteins may collect in the intima of arteries because they bind to constituents of the extracellular matrix, increasing the residence time of the lipid-rich particles within the arterial wall. Lipoproteins that accumulate in the extracellular space of the intima of arteries often associate with proteoglycans of the arterial extracellular matrix, an interaction that may slow the egress of these lipid-rich particles from

the intima. Lipoprotein particles in the extracellular space of the intima, particularly those retained by binding to matrix macromolecules, may undergo oxidative modifications. Considerable evidence supports a pathogenic role for products of oxidized lipoproteins in atherogenesis. Lipoproteins sequestered from (plasma) antioxidants in the extracellular space of the intima become particularly susceptible to oxidative modification, giving rise to hydroperoxides, lysophospholipids, oxysterols, and aldehydic breakdown products of fatty acids and phospholipids. Modifications of the apoprotein moieties may include breaks in the peptide backbone as well as derivatization of certain amino acid residues. Local production of hypochlorous acid by myeloperoxidase associated with inflammatory cells within the plaque yields chlorinated species such as chlorotyrosyl moieties. Considerable evidence supports the presence of such oxidation products in atherosclerotic lesions.

Leukocyte Recruitment Accumulation of leukocytes characterizes the formation of early atherosclerotic lesions (Fig. 291e-1). Thus, from its very inception, atherogenesis involves elements of inflammation, a process that now provides a unifying theme in the pathogenesis of this disease. The inflammatory cell types typically found in the evolving atheroma include monocyte-derived macrophages and dendritic cells, T and B lymphocytes, and mast cells. Hypercholesterolemia augments the portion of particularly proinflammatory monocytes in blood that preferentially enter the nascent atheroma in mice. A number of adhesion molecules or receptors for leukocytes expressed on the surface of the arterial endothelial cell probably participate in the recruitment of leukocytes to the nascent atheroma. Proinflammatory cytokines can augment the expression of leukocyte adhesion molecules.

Laminar shear forces such as those encountered in most regions of normal arteries also can suppress the expression of leukocyte adhesion molecules. Sites of predilection for atherosclerotic lesions (e.g., distal to flow dividers) often have low shear stress and/or disturbed flow. Ordered, pulsatile laminar shear of normal blood flow augments the production of nitric oxide by endothelial cells. This molecule, in addition to its vasodilator properties, can act at the low levels constitutively produced by arterial endothelium as a local anti-inflammatory autacoid, e.g., limiting local adhesion molecule expression. Exposure of endothelial cells to laminar shear stress increases the transcription of Krüppel-like factor 2 (KLF2), which augments the activity of numerous salutary endothelial functions including nitric oxide synthase. Laminar shear stress also stimulates endothelial cells to produce superoxide dismutase, an antioxidant enzyme. These examples indicate how hemodynamic forces may influence the cellular events that underlie atherosclerotic lesion initiation and potentially explain the favored localization of atherosclerotic lesions at sites that experience disturbed flow or low shear stress.

Once captured on the surface of the arterial endothelial cell by adhesion receptors, the leukocytes penetrate the endothelial layer and take up residence in the intima. In addition to products of modified lipoproteins, cytokines (protein mediators of inflammation) can regulate the expression of adhesion molecules involved in leukocyte recruitment. For example, interleukin 1 (IL-1) and tumor necrosis factor (TNF) induce or augment the expression of leukocyte adhesion molecules on endothelial cells. Because products of lipoprotein oxidation can induce cytokine release from vascular wall cells, this pathway may provide an additional link between arterial accumulation of lipoproteins and leukocyte recruitment. Chemoattractant cytokines appear to direct the migration of leukocytes into the arterial wall.

Foam-Cell Formation Once resident within the intima, the mononuclear phagocytes mature into macrophages and become lipid-laden foam cells, a conversion that requires the uptake of lipoprotein particles by receptor-mediated endocytosis. One might suppose that the “classic” LDL receptor mediates this lipid uptake; however, humans or animals lacking effective LDL receptors due to genetic alterations (e.g., familial hypercholesterolemia) have abundant arterial lesions and extraarterial xanthomata rich in macrophage-derived foam cells. In addition, the exogenous cholesterol suppresses expression of the LDL receptor; thus, the level of this cell-surface receptor for LDL decreases under

conditions of cholesterol excess. Candidates for alternative receptors that can mediate lipid loading of foam cells include a number of macrophage “scavenger” receptors, which preferentially endocytose modified lipoproteins, and other receptors for oxidized LDL or very low-density lipoprotein (VLDL). Monocyte attachment to the endothelium, migration into the intima, and maturation to form lipid-laden macrophages thus represent key steps in the formation of the fatty streak, the precursor of fully formed atherosclerotic plaques.

ATHEROMA EVOLUTION AND COMPLICATIONS

Although the fatty streak commonly precedes the development of a more advanced atherosclerotic plaque, not all fatty streaks progress to form complex atheromata. By ingesting lipids from the extracellular space, the mononuclear phagocytes bearing such scavenger receptors may remove lipoproteins from the developing lesion. Some lipid-laden macrophages may leave the artery wall, exporting lipid in the process. Lipid accumulation, and hence the propensity to form an atheroma, ensues if the amount of lipid entering the artery wall exceeds that removed by mononuclear phagocytes or other pathways. Macrophages also proliferate in plaques in response to hematopoietic growth factors overexpressed in lesions, another aspect of the dynamic regulation and flux of cells during atherogenesis.

Export by phagocytes may constitute one response to local lipid overload in the evolving lesion. Another mechanism, reverse cholesterol transport mediated by high-density lipoproteins (HDLs), probably provides an independent pathway for lipid removal from atheroma. This transfer of cholesterol from the cell to the HDL particle involves specialized cell-surface molecules such as the ATP binding cassette (ABC) transporters. ABCA1, the gene mutated in Tangier disease, a condition characterized by very low HDL levels, transfers cholesterol from cells to nascent HDL particles and ABCG1 to mature HDL particles. “Reverse cholesterol transport” mediated by these ABC transporters allows HDL loaded with cholesterol to deliver it to hepatocytes by binding to scavenger receptor B1 or other receptors. The liver cell can metabolize the sterol to bile acids that can be excreted. Thus, macrophages may play a vital role in the dynamic economy of lipid accumulation in the arterial wall during atherogenesis.

Some lipid-laden foam cells within the expanding intimal lesion perish. Some foam cells may die as a result of programmed cell death, or *apoptosis*. This death of mononuclear phagocytes results in the formation of the lipid-rich center, often called the *necrotic core*, in established atherosclerotic plaques. Impaired clearance of dead foam cells (efferocytosis) in plaques may hasten lipid core formation. Macrophages loaded with modified lipoproteins may elaborate microparticles or exosomes (which may contain regulatory microRNAs), cytokines, and growth factors that can further signal some of the cellular events in lesion complication. Whereas accumulation of lipid-laden macrophages characterizes the fatty streak, buildup of fibrous tissue formed by extracellular matrix typifies the more advanced atherosclerotic lesion. The smooth-muscle cell synthesizes the bulk of the extracellular matrix of the complex atherosclerotic lesion. A number of growth factors or cytokines elaborated by mononuclear phagocytes can stimulate smooth-muscle cell proliferation and production of extracellular matrix. Cytokines found in the plaque, including IL-1 and TNF, can induce local production of growth factors, including forms of platelet-derived growth factor (PDGF), fibroblast growth factors, and others, which may contribute to plaque evolution and complication. Other cytokines, notably interferon γ (IFN- γ) derived from activated T cells within lesions, can limit the synthesis of interstitial forms of collagen by smooth-muscle cells. These examples illustrate how atherogenesis involves a complex mix of mediators that in the balance determines the characteristics of particular lesions.

The accumulation of smooth-muscle cells and their elaboration of extracellular matrix probably provide a critical transition, yielding a fibrofatty lesion in place of a simple accumulation of macrophage-derived foam cells. For example, PDGF elaborated by activated platelets, macrophages, and endothelial cells can stimulate the migration of smooth-muscle cells normally resident in the tunica media into the intima. Such growth factors and cytokines produced locally can

stimulate the proliferation of resident smooth-muscle cells or resident stem cells in the intima as well as those that may migrate in from the media. Transforming growth factor β (TGF- β), among other mediators, potently stimulates interstitial collagen production by smooth-muscle cells. These mediators may arise not only from neighboring vascular cells or leukocytes (a “paracrine” pathway), but also, in some instances, from the same cell that responds to the factor (an “auto-crine” pathway). Together, these alterations in smooth-muscle cells, signaled by these mediators acting at short distances, can hasten transformation of the fatty streak into a more fibrous smooth-muscle cell and extracellular matrix-rich lesion.

In addition to locally produced mediators, products of blood coagulation and thrombosis likely contribute to atheroma evolution and complication. This involvement justifies the use of the term *atherothrombosis* to convey the inextricable links between atherosclerosis and thrombosis. Fatty streak formation begins beneath a morphologically intact endothelium. In advanced fatty streaks, however, microscopic breaches in endothelial integrity may occur. Microthrombi rich in platelets can form at such sites of limited endothelial denudation, owing to exposure of the thrombogenic extracellular matrix of the underlying basement membrane. Activated platelets release numerous factors that can promote the fibrotic response, including PDGF and TGF- β . Thrombin not only generates fibrin during coagulation, but also stimulates protease-activated receptors that can signal smooth-muscle migration, proliferation, and extracellular matrix production. Many arterial mural microthrombi resolve without clinical manifestation by a process of local fibrinolysis, resorption, and endothelial repair, yet can lead to lesion progression by stimulating these profibrotic functions of smooth-muscle cells (Fig. 291e-2D).

Microvessels As atherosclerotic lesions advance, abundant plexi of microvessels develop in connection with the artery’s vasa vasorum. Newly developing microvascular networks may contribute to lesion complications in several ways. These blood vessels provide an abundant surface area for leukocyte trafficking and may serve as the portal for entry and exit of white blood cells from the established atheroma. Microvessels in the plaques may also furnish foci for intraplaque hemorrhage. Like the neovessels in the diabetic retina, microvessels in the atheroma may be friable and prone to rupture and can produce focal hemorrhage. Such a vascular leak can provoke thrombosis *in situ*, yielding local thrombin generation, which in turn can activate smooth-muscle and endothelial cells through ligation of protease-activated receptors. Atherosclerotic plaques often contain fibrin and hemosiderin, an indication that episodes of intraplaque hemorrhage contribute to plaque complications.

CALCIFICATION As they advance, atherosclerotic plaques also accumulate calcium. Microvesicles derived from lesional cells can stimulate calcification, and this process co-localizes with regions of heightened inflammation. Mineralization of the atherosclerotic plaque recapitulates many aspects of bone formation, including the regulatory participation of transcription factors such as Runx2.

Plaque Evolution Smooth-muscle cells and macrophages die in the atherosclerotic plaque. Indeed, complex atheromata often have a mostly fibrous character and lack the cellularity of less advanced lesions. This relative paucity of smooth-muscle cells in advanced atheromata may result from the predominance of cytostatic mediators such as TGF- β and IFN- γ (which can inhibit smooth-muscle cell proliferation) and also from smooth-muscle cell apoptosis. Thus, during the evolution of the atherosclerotic plaque, a complex and highly regulated balance between entry and egress of lipoproteins and leukocytes, cell proliferation and cell death, extracellular matrix production, and remodeling, as well as calcification and neovascularization, contribute to lesion formation. Many mediators related to atherogenic risk factors, including those derived from lipoproteins, cigarette smoking, and angiotensin II, provoke the production of proinflammatory cytokines and alter the behavior of the intrinsic vascular wall cells and infiltrating leukocytes that underlie the complex pathogenesis of these lesions. Thus, advances in vascular biology have led to increased

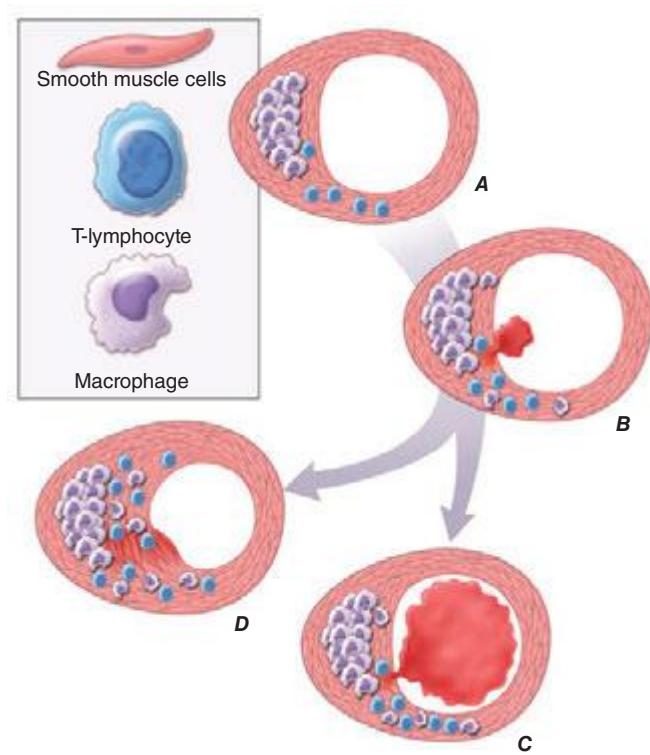


FIGURE 291e-2 Plaque rupture, thrombosis, and healing. **A.** Arterial remodeling during atherogenesis. During the initial part of the life history of an atheroma, growth is often outward, preserving the caliber of the lumen. This phenomenon of “compensatory enlargement” accounts in part for the tendency of coronary arteriography to underestimate the degree of atherosclerosis. **B.** Rupture of the plaque’s fibrous cap causes thrombosis. Physical disruption of the atherosclerotic plaque commonly causes arterial thrombosis by allowing blood coagulant factors to contact thrombogenic collagen found in the arterial extracellular matrix and tissue factor produced by macrophage-derived foam cells in the lipid core of lesions. In this manner, sites of plaque rupture form the nidus for thrombi. The normal artery wall has several fibrinolytic or antithrombotic mechanisms that tend to resist thrombosis and lyse clots that begin to form *in situ*. Such antithrombotic or thrombolytic molecules include thrombomodulin, tissue- and urokinase-type plasminogen activators, heparan sulfate proteoglycans, prostacyclin, and nitric oxide. **C.** When the clot overwhelms the endogenous fibrinolytic mechanisms, it may propagate and lead to arterial occlusion. The consequences of this occlusion depend on the degree of existing collateral vessels. In a patient with chronic multivessel occlusive coronary artery disease (CAD), collateral channels have often formed. In such circumstances, even a total arterial occlusion may not lead to myocardial infarction (MI), or it may produce an unexpectedly modest or a non-ST-segment elevation infarct because of collateral flow. In a patient with less advanced disease and without substantial stenotic lesions to provide a stimulus for collateral vessel formation, sudden plaque rupture and arterial occlusion commonly produces an ST-segment elevation infarction. These are the types of patients who may present with MI or sudden death as a first manifestation of coronary atherosclerosis. In some cases, the thrombus may lyse or organize into a mural thrombus without occluding the vessel. Such instances may be clinically silent. **D.** The subsequent thrombin-induced fibrosis and healing causes a fibroproliferative response that can lead to a more fibrous lesion that can produce an eccentric plaque that causes a hemodynamically significant stenosis. In this way, a nonocclusive mural thrombus, even if clinically silent or causing unstable angina rather than infarction, can provoke a healing response that can promote lesion fibrosis and luminal encroachment. Such a sequence of events may convert a “vulnerable” atheroma with a thin fibrous cap that is prone to rupture into a more “stable” fibrous plaque with a reinforced cap. Angioplasty of unstable coronary lesions may “stabilize” the lesions by a similar mechanism, producing a wound followed by healing.

understanding of the mechanisms that link risk factors to the pathogenesis of atherosclerosis and its complications.

PATHOPHYSIOLOGIC CONSEQUENCES OF ATHEROSCLEROSIS

Atherosclerotic lesions occur ubiquitously in Western societies, and the prevalence of this disease is on the rise globally. Most atheromata produce no symptoms, and many never cause clinical manifestations. Numerous patients with diffuse atherosclerosis may succumb to unrelated illnesses without ever having experienced a clinically significant manifestation of atherosclerosis. Arterial remodeling during atheroma formation accounts for some of this variability in the clinical expression of atherosclerotic disease (Fig. 291e-2A). During the initial phases of atheroma development, the plaque usually grows outward, in an abluminal direction. Vessels affected by atherogenesis tend to increase in diameter, a phenomenon known as *compensatory enlargement*, a type of vascular remodeling. The growing atheroma does not encroach on the arterial lumen until the burden of atherosclerotic plaque exceeds ~40% of the area encompassed by the internal elastic lamina. Thus, during much of its life history, an atheroma will not cause stenosis that can limit tissue perfusion.

Flow-limiting stenoses commonly form later in the history of the plaque. Many such plaques cause stable syndromes such as demand-induced angina pectoris or intermittent claudication in the extremities. In the coronary circulation and other circulations, even total vascular occlusion by an atheroma does not invariably lead to infarction. The hypoxic stimulus of repeated bouts of ischemia characteristically induces formation of collateral vessels in the myocardium, mitigating the consequences of an acute occlusion of an epicardial coronary artery. By contrast, many lesions that cause acute or unstable atherosclerotic syndromes, particularly in the coronary circulation, may arise from atherosclerotic plaques that do not produce a flow-limiting stenosis. Such lesions may produce only minimal luminal irregularities on traditional angiograms and often do not meet the traditional criteria for "significance" by arteriography. Thrombi arising from such nonocclusive stenoses may explain the frequency of MI as an initial manifestation of coronary artery disease (CAD) (in at least one-third of cases) in patients who report no prior history of angina pectoris, a syndrome usually caused by flow-limiting stenoses.

Plaque Instability and Rupture Postmortem studies afford considerable insight into the microanatomic substrate underlying the "instability" of plaques that do not cause critical stenoses. A superficial erosion of the endothelium or a frank plaque rupture or fissure usually produces the thrombus that causes episodes of unstable angina pectoris or the occlusive and relatively persistent thrombus that causes acute MI (Fig. 291e-2B). Rupture of the plaque's fibrous cap (Fig. 291e-2C) permits contact between coagulation factors in the blood and highly thrombogenic tissue factor expressed by macrophage foam cells in the plaque's lipid-rich core. If the ensuing thrombus is nonocclusive or transient, the episode of plaque disruption may not cause symptoms or may result in episodic ischemic symptoms such as rest angina. Occlusive thrombi that endure often cause acute MI, particularly in the absence of a well-developed collateral circulation that supplies the affected territory. Repetitive episodes of plaque disruption and healing provide one likely mechanism of transition of the fatty streak to a more complex fibrous lesion (Fig. 291e-2D). The healing process in arteries, as in skin wounds, involves the laying down of new extracellular matrix and fibrosis.

Not all atheromata exhibit the same propensity to rupture. Pathologic studies of culprit lesions that have caused acute MI reveal several characteristic features. Plaques that have caused thromboses tend to have thin fibrous caps, relatively large lipid cores, a high content of macrophages, outward remodeling, and spotty (rather than dense) calcification. Morphometric studies of such culprit lesions show that at sites of plaque rupture, macrophages and T lymphocytes predominate and contain relatively few smooth-muscle cells. The cells that concentrate at sites of plaque rupture bear markers of inflammatory activation. In addition, patients with active atherosclerosis and

acute coronary syndromes display signs of disseminated inflammation. Inflammatory mediators regulate processes that govern the integrity of the plaque's fibrous cap and, hence, its propensity to rupture. For example, the T cell-derived cytokine IFN- γ , which is found in atherosclerotic plaques, can inhibit growth and collagen synthesis of smooth-muscle cells, as noted above. Cytokines derived from activated macrophages and lesional T cells can boost production of proteolytic enzymes that can degrade the extracellular matrix of the plaque's fibrous cap. Thus, inflammatory mediators can impair the collagen synthesis required for maintenance and repair of the fibrous cap and trigger degradation of extracellular matrix macromolecules, processes that weaken the plaque's fibrous cap and enhance its susceptibility to rupture (so-called vulnerable plaques, Fig. 291e-3). In contrast to plaques with these features of vulnerability, those with a dense extracellular matrix and relatively thick fibrous cap without substantial tissue factor-rich lipid cores seem generally resistant to rupture and unlikely to provoke thrombosis.

Functional features of the atheromatous plaque, in addition to its degree of luminal encroachment, influence the clinical manifestations of this disease. This enhanced understanding of plaque biology provides insight into the diverse ways in which atherosclerosis can present clinically and the reasons why the disease may remain silent or stable for prolonged periods, punctuated by acute complications at certain times. Increased understanding of atherogenesis provides new insight into the mechanisms linking it to the risk factors discussed below, indicates the ways in which current therapies may improve outcomes, and suggests new targets for future intervention.

PREVENTION AND TREATMENT

THE CONCEPT OF ATHEROSCLEROTIC RISK FACTORS

The systematic study of risk factors for atherosclerosis emerged from a coalescence of experimental results, as well as from cross-sectional and ultimately longitudinal studies in humans. The prospective, community-based Framingham Heart Study provided rigorous support for the concept that hypercholesterolemia, hypertension, and other factors correlate with cardiovascular risk. Similar observational studies performed worldwide bolstered the concept of "risk factors" for cardiovascular disease.

From a practical viewpoint, the cardiovascular risk factors that have emerged from such studies fall into two categories: those modifiable by lifestyle and/or pharmacotherapy, and those that are immutable, such as age and sex. The weight of evidence supporting various risk factors differs. For example, hypercholesterolemia and hypertension certainly predict coronary risk, but the magnitude of the contributions of other so-called nontraditional risk factors, such as levels of homocysteine, levels of lipoprotein (a) [Lp(a)], and infection, remains controversial. Moreover, some biomarkers that predict cardiovascular risk may not participate in the causal pathway for the disease or its complications. Genetic studies using genome-wide association (GWAS) approaches and Mendelian randomization approaches have helped to distinguish between risk markers and factors that contribute causally to the disease. For example, recent genetic studies suggest that C-reactive protein (CRP) does not itself mediate atherogenesis, despite its ability to predict risk, whereas Lp(a) and apolipoprotein C3 have emerged as a causal risk factor. Table 291e-1 lists a number of risk factors implicated in atherosclerosis. The sections below will consider some of these factors and approaches to their modification.

Lipid Disorders

Abnormalities in plasma lipoproteins and derangements in lipid metabolism rank among the most firmly established and best understood risk factors for atherosclerosis. Chapter 421 describes the **lipoprotein classes and provides a detailed discussion of lipoprotein metabolism**.

The American College of Cardiology and American Heart Association (ACC/AHA) promulgated new guidelines on risk assessment, lifestyle measures, and cholesterol management in 2013. The panels that produced these guidelines followed an evidence-based approach.

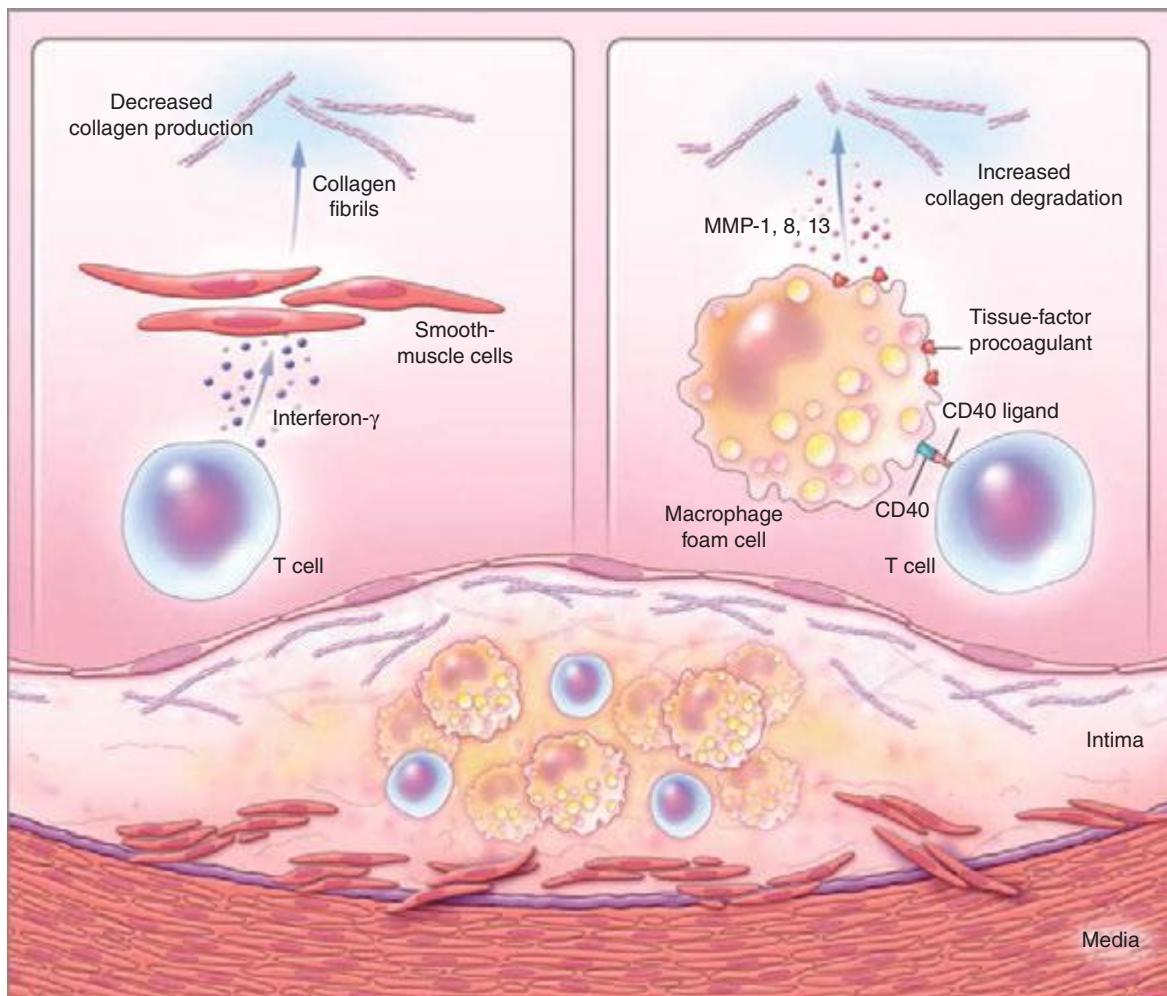


FIGURE 291e-3 Inflammatory pathways that predispose atherosclerotic plaques to rupture and provoke thrombosis. A cross-section of an atherosomatous plaque at the bottom of the figure shows the central lipid core that contains macrophage foam cells (yellow) and T cells (blue). The intima and media also contain arterial smooth-muscle cells (red), which are the source of arterial collagen (depicted as triple helical coiled structures). Activated T cells (of the type 1 helper T cell subtype) secrete cytokine interferon γ , which inhibits the production of the new, interstitial collagen that is required to repair and maintain the plaque's protective fibrous cap (upper left). The T cells can also activate the macrophages in the intimal lesion by expressing the inflammatory mediator CD40 ligand (CD154), which engages its cognate receptor (CD40) on the phagocyte. This inflammatory signalling causes overproduction of interstitial collagenases (matrix metalloproteinases [MMPs] 1, 8, and 13) that catalyze the initial rate-limiting step in collagen breakdown (top right). CD40 ligation also causes macrophages to overproduce tissue-factor procoagulant. Thus, inflammatory signalling puts the collagen in the plaque's fibrous cap in double jeopardy—decreasing synthesis and increasing breakdown—rendering the cap susceptible to rupture. Inflammatory activation also boosts tissue-factor production, which triggers thrombus formation in the disrupted plaque. These mechanisms link inflammation in the plaque to the thrombotic complications of atherosclerosis, including the acute coronary syndromes. (Adapted from P Libby: N Engl J Med 368:2004, 2013.)

The 2013 cholesterol guideline focused on 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) rather than other classes of lipid-modulating drugs, including fibric acid derivatives, cholesterol absorption inhibitors such as ezetimibe, and niacin products. The guideline cites the lack of contemporary randomized clinical trial evidence that supports the efficacy of these nonstatin lipid-modifying agents in cardiovascular event reduction. The cholesterol guideline defined four statin benefit groups (**Table 291e-2**): (1) all individuals who have clinical atherosclerotic cardiovascular disease (ASCVD), therefore considered “secondary prevention”; (2) those with LDL cholesterol ≥ 190 mg/dL without a secondary cause such as a high intake of saturated or *trans* fats, various drugs, or certain diseases; (3) individuals with diabetes without established cardiovascular disease who are 40–75 years old and have LDL cholesterol of 70–189 mg/dL; and (4) those without established ASCVD without diabetes who are 40–75 years old and who have LDL cholesterol of 70–189 mg/dL and a calculated ASCVD risk $\geq 7.5\%$. An online risk calculator based on pooled cohorts was provided to aid clinicians and patients in calculating their risk (<http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention->

Guidelines_UCM_457698_SubHomePage.jsp). Other validated risk calculators that incorporate family history of CAD and a marker of inflammation (high-sensitivity CRP [hsCRP]) that apply to U.S. women and men exist (<http://www.reynoldsriskscore.org>). Downloadable applications for risk calculation on handheld devices are readily available.

The 2013 guideline emphasized a patient-centered approach and recommended that clinicians and patients engage in a risk-benefit conversation before starting statin therapy and not rely solely on calculated risks or arbitrary category assignment. It further emphasizes that medications do not supplant a healthy lifestyle. The guideline also provides some practical suggestions regarding management of muscle symptoms attributed to statins, an issue of considerable concern to many patients and practitioners alike.

In a major departure from prior guidelines, the 2013 guideline eliminates LDL targets as goals of therapy. The panel did so because major clinical trials did not titrate therapy to a goal, but rather used fixed doses of statins. Instead, the new guideline suggests different intensities of statin therapy based on risk category (**Fig. 291e-4**).

The 2013 guideline focus on statins reflects an extensive body of rigorous evidence that supports the effectiveness of this class of drugs

TABLE 291e-1 MAJOR RISK FACTORS FOR ATHEROSCLEROSIS

High LDL cholesterol
Cigarette smoking
Hypertension (BP $\geq 140/90$ mmHg or on antihypertensive medication)
Low HDL cholesterol ^a (<1.0 mmol/L [<40 mg/dL])
Diabetes mellitus
Family history of premature CHD
Age (men ≥ 45 years; women ≥ 55 years)
Lifestyle risk factors
Obesity (BMI ≥ 30 kg/m ²)
Physical inactivity
Atherogenic diet
Emerging risk factors
Lipoprotein (a)
Prothrombotic factors
Proinflammatory factors
Impaired fasting glucose
Subclinical atherosclerosis

^aHDL cholesterol ≥ 1.6 mmol/L (≥ 60 mg/dL) has been viewed as a “negative” risk factor.

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

in cardiovascular event reduction and an acceptable risk-benefit relationship (Fig. 291e-5). Moreover, because almost all statins are now available as generic statins medications, cost has become much less of an impediment to their use.

The clinical use of effective pharmacologic strategies for lowering LDL has reduced cardiovascular events markedly, but a considerable burden of residual risk remains even in patients treated with high-intensity statins. Hence, current studies are evaluating other avenues to address the residual burden of cardiovascular disease that persists despite statin treatment. Inhibitors of genetic studies identified proprotein convertase subtilisin kexin-like 9 (PCSK9) as a regulator of LDL levels associated with cardiovascular outcomes. Interaction of the LDL receptor with PCSK9 hastens the receptor’s degradation, and hence yields higher circulating LDL concentrations. Genetic variants that lower PCSK9 activity appear to protect against cardiovascular events. Monoclonal antibodies that neutralize PCSK9 lower LDL levels even in statin-treated patients and are currently under investigation as novel therapeutics to lower cardiovascular risk.

LDL-lowering therapies do not appear to exert their beneficial effect on cardiovascular events by causing a marked “regression” of stenoses. Studies of lipid lowering monitored by angiography or by intravascular imaging modalities have shown at best a modest reduction in coronary artery stenoses over the duration of study, despite abundant evidence of event reduction. These results suggest that the beneficial mechanism of lipid lowering by statins does not require a substantial reduction in the fixed stenoses. Rather, the benefit may derive from “stabilization” of atherosclerotic lesions without substantially decreased stenosis.

Such stabilization of atherosclerotic lesions and the attendant decrease in coronary events may result from the egress of lipids or from favorably influencing aspects of the biology of atherogenesis discussed above. In addition, as sizable lesions may protrude abluminally rather than into the lumen due to complementary enlargement, shrinkage of such plaques may not be apparent on angiograms. The consistent benefit of statins may depend not only on their salutary effects on the lipid profile, but also on direct modulation of plaque biology independent of lipid lowering.

As the prevalence of metabolic syndrome and diabetes increases, many patients present with low concentrations of HDL (HDL cholesterol <1.0 mmol/L [<40 mg/dL]). A baseline measurement of HDL cholesterol indubitably correlates with future cardiovascular risk. Yet, the utility of therapies that raise HDL cholesterol levels in blood as effective interventions to reduce cardiovascular vascular events has come into question. Blood HDL levels vary inversely with those of triglycerides, and the independent role of HDL versus triglycerides as a cardiovascular risk factor remains unsettled. The 2013 guideline does not advocate any specific therapy for raising HDL. Indeed, multiple recent trials failed to show that raising HDL cholesterol levels improves cardiovascular outcomes, and recent genetic studies cast doubt on low HDL as a causal risk factor for atherosclerotic events. Weight loss and physical activity can raise HDL, and these lifestyle measures merit universal adoption (Table 291e-3). Nicotinic acid, particularly in combination with statins, can robustly raise HDL, but clinical trial data do not support the effectiveness of nicotinic acid in cardiovascular risk reduction. Agonists of nuclear receptors provide another potential avenue for raising HDL levels. Yet patients treated with peroxisome proliferator-activated receptors alpha and gamma (PPAR- α and - γ) agonists have not consistently shown improved cardiovascular outcomes, and at least some PPAR agonists have been associated with worsened cardiovascular outcomes. Other agents in clinical development raise HDL levels by inhibiting cholesteryl ester transfer protein (CETP). Two such agents have undergone large-scale clinical evaluation and have not shown efficacy in improving cardiovascular outcomes. Clinical studies currently under way will assess the effectiveness of two other CETP inhibitors that lack some of the adverse off-target actions encountered with the first agent tested.

The mechanism by which elevated LDL levels promote atherosclerosis may involve oxidative modification. Yet, rigorous and well-controlled clinical trials have failed to demonstrate that antioxidant vitamin therapy improves coronary heart disease (CHD) outcomes. In regard to nontraditional risk factors including homocysteine and infection, large-scale clinical trials using vitamins to lower homocysteine or using antibiotics have not reduced cardiovascular events. Therefore, the current evidence base does *not* support the use of vitamins or antibiotics to lower cardiovascular risk.

Hypertension (See also Chap. 298) A wealth of epidemiologic data support a relationship between hypertension and atherosclerotic risk, and extensive clinical trial evidence has established that pharmacologic treatment of hypertension can reduce the risk of stroke, heart failure, and CHD events.

Diabetes Mellitus, Insulin Resistance, and the Metabolic Syndrome (See also Chap. 417)

Most patients with diabetes mellitus die of atherosclerosis and its complications. Aging and rampant obesity underlie a current epidemic of type 2 diabetes mellitus. The abnormal lipoprotein profile associated with insulin resistance, known as *diabetic dyslipidemia*, accounts for part of the elevated cardiovascular risk in patients with type 2 diabetes. Although diabetic individuals often have LDL cholesterol levels near the average, the LDL particles tend to be smaller and denser and, therefore, more atherogenic. Other features of diabetic dyslipidemia include low HDL and elevated triglyceride levels. Hypertension also frequently accompanies obesity, insulin resistance, and dyslipidemia. This commonly encountered clinical cluster of risk factors has become known as the *metabolic syndrome* (Chap. 422). Despite legitimate concerns about whether clustered components confer more risk than the individual components, the metabolic syndrome concept may offer clinical utility.

TABLE 291e-2 SUMMARY OF THE FOUR STATIN BENEFIT GROUPS DESCRIBED IN THE 2013 ACC/AHA GUIDELINE ON THE TREATMENT OF BLOOD CHOLESTEROL TO REDUCE ATHEROSCLEROTIC CARDIOVASCULAR RISK IN ADULTS

- Clinical ASCVD “secondary prevention”
- LDL-C ≥ 190 mg/dL without secondary cause (e.g., saturated/trans fats, drugs, certain diseases)
- Primary prevention with diabetes mellitus: age 40–75 years, LDL-C 70–189 mg/dL
- Primary prevention without diabetes mellitus: age 40–75 years, LDL-C 70–189 mg/dL, estimated ASCVD risk $\geq 7.5\%$

Abbreviations: ACC/AHA, American College of Cardiology and American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Source: Adapted from NJ Stone et al: 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. J Am Coll Cardiol 2013; doi: 10.1016/j.jacc.2013.11.002.

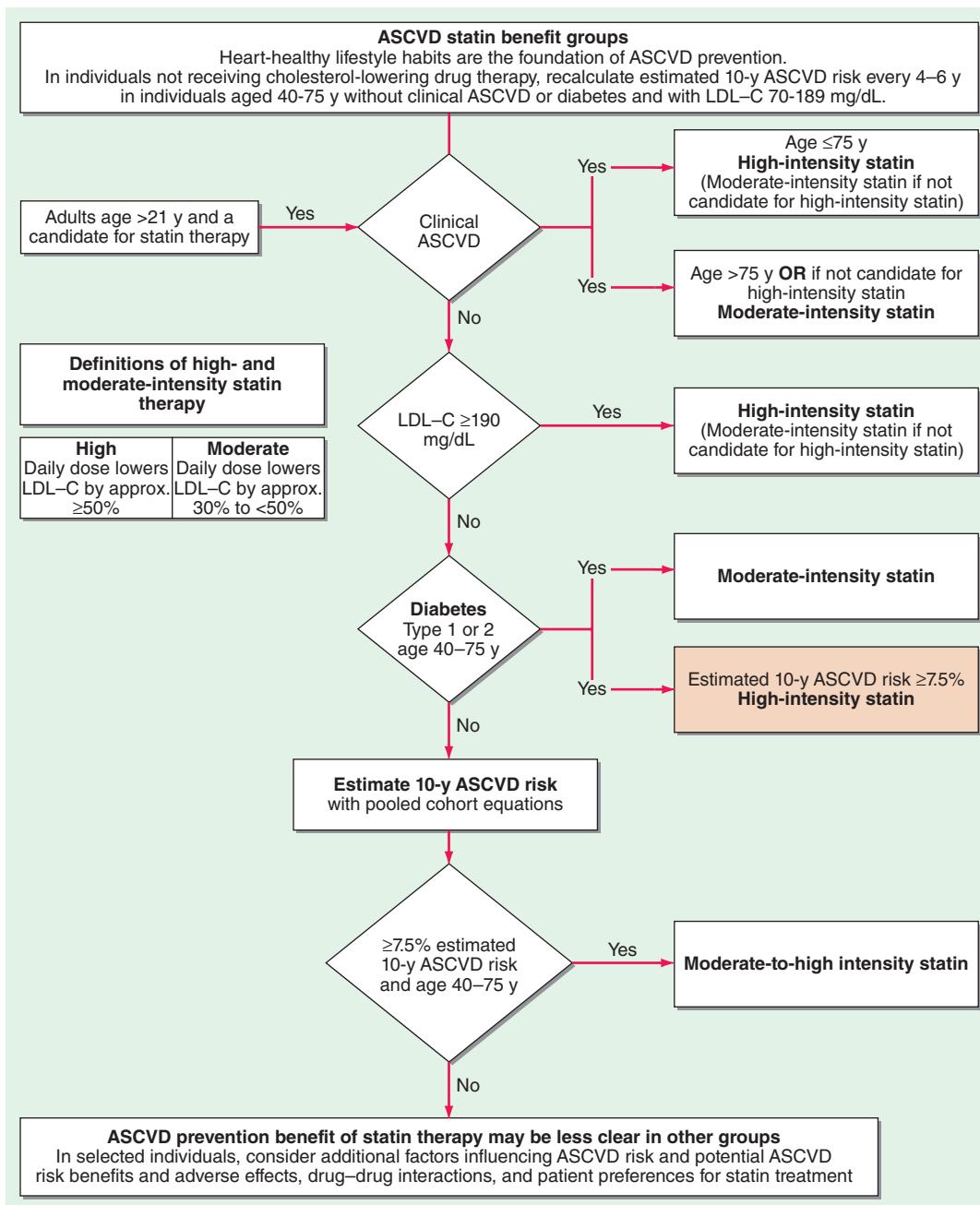


FIGURE 291e-4 Major recommendations for statin therapy for atherosclerotic cardiovascular disease (ASCVD) prevention. LDL-C, low-density lipoprotein cholesterol. (From NJ Stone et al: *J Am Coll Cardiol*, 2013, doi: 10.1016/j.jacc.2013.11.002.)

Therapeutic objectives for intervention in these patients include addressing the underlying causes, including obesity and low physical activity, by initiating lifestyle measures (see below). Establishing that strict glycemic control reduces the risk of macrovascular complications of diabetes has proved much more elusive than the beneficial effects on microvascular complications such as retinopathy and renal disease. Indeed, “tight” glycemic control may increase adverse events in patients with type 2 diabetes, lending even greater importance to aggressive control of other aspects of risk in this patient population. In this regard, multiple clinical trials have demonstrated unequivocal benefit of statin therapy in diabetic patients over all ranges of LDL cholesterol levels (but not those with end-stage renal disease or advanced heart failure). Among the oral hypoglycemic agents, metformin possesses the best evidence base for cardiovascular event reduction. The novel oral hypoglycemic agents tested in sufficiently powered trials, the dipeptidyl peptidase-4 (DPP-4) inhibitors saxagliptin and alogliptin, did not show cardiovascular benefit. Indeed, saxagliptin was associated

with a slight increase in heart failure. Diabetic populations appear to derive particular benefit from antihypertensive strategies that block the action of angiotensin II. Thus, the antihypertensive regimen for patients with the metabolic syndrome should include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers when possible. Many of these individuals will require more than one antihypertensive agent to reach the 2013 goals for individuals 18 years of age or older with diabetes to achieve a systolic blood pressure of less than 140 mmHg and a diastolic blood pressure of less than 90 mmHg.

Male Sex/Postmenopausal State Decades of observational studies have verified excess coronary risk in men compared with premenopausal women. After menopause, however, coronary risk accelerates in women. Although observational and experimental studies have suggested that estrogen therapy reduces coronary risk, large-scale randomized clinical trials have not demonstrated a net benefit of estrogen with or without progestins on CHD outcomes. In the Heart

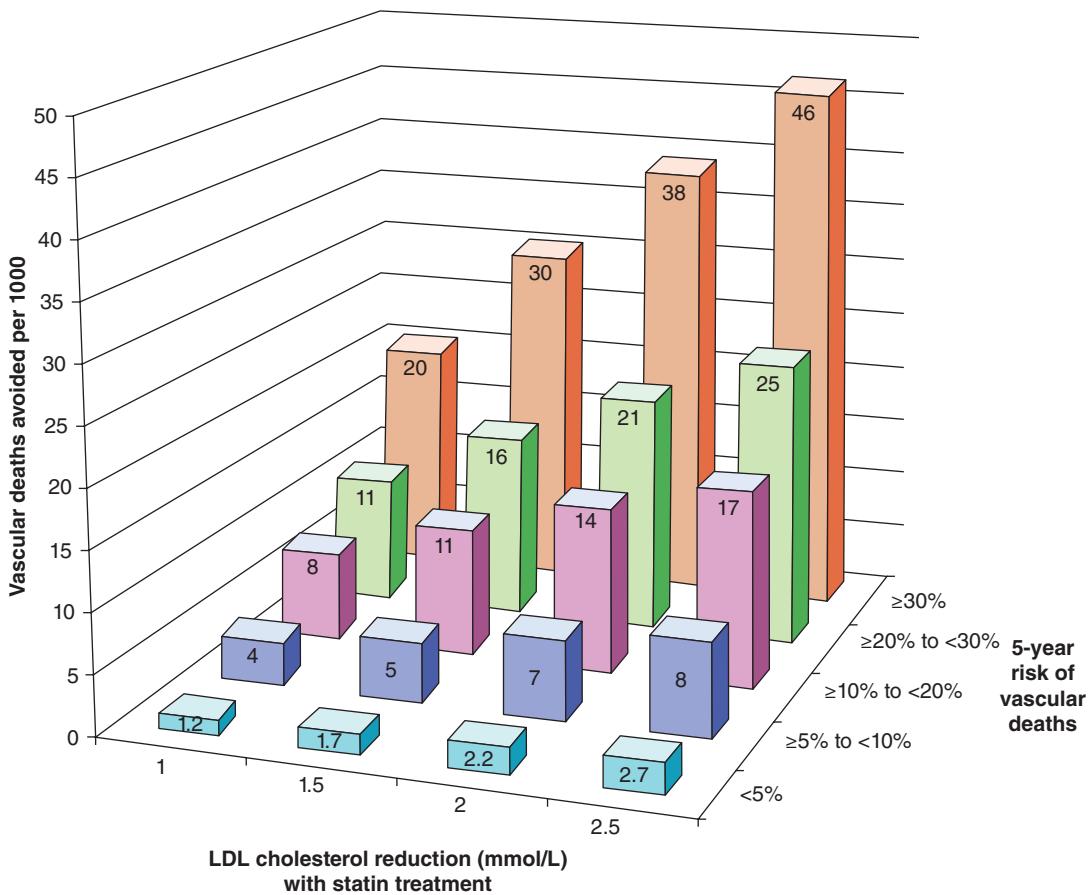


FIGURE 291e-5 The Cholesterol Treatment Trialists Collaboration meta-analyzed 27 randomized clinical trials evaluating statin therapy.

They found profound decreases in both major vascular events and vascular death (not shown) proportional to the magnitude of low-density lipoprotein (LDL) cholesterol reduction achieved with statin treatment. This diagram shows the results of this meta-analysis for vascular death. (From *Lancet* 380:581, 2012.)

and Estrogen/Progestin Replacement Study (HERS), postmenopausal female survivors of acute MI were randomized to an estrogen/progestin combination or to placebo. This study showed no overall reduction in recurrent coronary events in the active treatment arm. Indeed, early in the 5-year course of this trial, a trend occurred toward an increase

TABLE 291e-3 HEART HEALTHY NUTRITION AND PHYSICAL ACTIVITY BEHAVIORS RECOMMENDED IN THE 2013 ACC/AHA GUIDELINE ON LIFESTYLE MANAGEMENT TO REDUCE CARDIOVASCULAR RISK

The adult population should be encouraged to practice heart healthy lifestyle behaviors, including:

- Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; include low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limit intake of sodium, sweets, sugar-sweetened beverages, and red meats.
- Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus).
- Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet.
- Engage in 2 h and 30 min a week of moderate-intensity or 1 h and 15 min (75 min) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 min, preferably spread throughout the week.
- Achieve and maintain a healthy weight. Refer to the 2013 Obesity Expert Panel Report for recommendations on weight loss and maintenance.

Abbreviations: ACC/AHA, American College of Cardiology and American Heart Association; DASH, Dietary Approaches to Stop Hypertension; USDA, U.S. Department of Agriculture.

Source: Adapted from RH Eckel et al: 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk. *J Am Coll Cardiol* 2013; doi: 10.1016/j.jacc.2013.11.003.

in vascular events in the treated women. Extended follow-up of this cohort did not disclose an accrual of benefit in the treatment group. The Women's Health Initiative (WHI) study arm, using a similar estrogen plus progesterone regimen, was halted due to a small but significant hazard of cardiovascular events, stroke, and breast cancer. The estrogen without progestin arm of WHI (conducted in women without a uterus) was stopped early due to an increase in strokes, and failed to afford protection from MI or CHD death during observation over 7 years. The excess cardiovascular events in these trials may result from an increase in thromboembolism (Chap. 413). Physicians should work with women to provide information and help weigh the small but evident CHD risk of estrogen ± progestin versus the benefits for postmenopausal symptoms and osteoporosis, taking personal preferences into account. Post hoc analyses of observational studies suggest that estrogen therapy in women younger than or closer to menopause than the women enrolled in WHI might confer cardiovascular benefit. Thus, the timing in relation to menopause or the age at which estrogen therapy begins may influence its risk/benefit balance.

The lack of efficacy of estrogen therapy in cardiovascular risk reduction highlights the need for redoubled attention to known modifiable risk factors in women. Meta-analysis supports the efficacy of statins to reduce cardiovascular events in women in primary prevention, as well as in those who have already experienced a cardiovascular event.

Dysregulated Coagulation or Fibrinolysis Thrombosis ultimately causes the gravest complications of atherosclerosis. The propensity to form thrombi and/or lyse clots once they form influences the manifestations of atherosclerosis. Thrombosis provoked by atheroma rupture and subsequent healing may promote plaque growth. Certain individual characteristics can influence thrombosis or fibrinolysis and have received attention as potential coronary risk factors. For example,

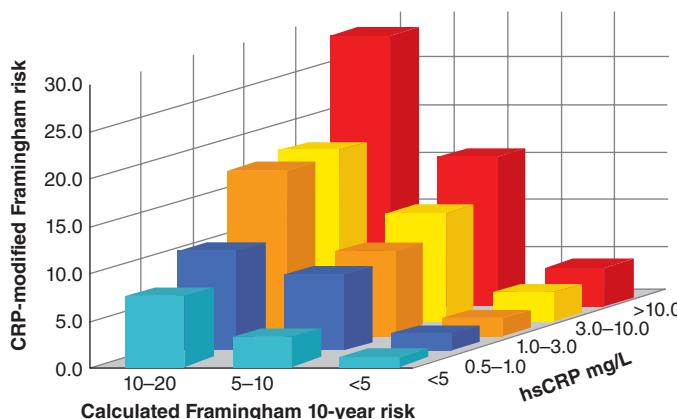


FIGURE 291e-6 C-reactive protein (CRP) level adds to the predictive value of the Framingham score. hsCRP, high-sensitivity measurement of CRP. (Adapted from PM Ridker et al: *Circulation* 109:2818, 2004.)

fibrinogen levels correlate with coronary risk and provide information about coronary risk independent of the lipoprotein profile.

The stability of an arterial thrombus depends on the balance between fibrinolytic factors, such as plasmin, and inhibitors of the fibrinolytic system, such as plasminogen activator inhibitor 1 (PAI-1). Individuals with diabetes mellitus or the metabolic syndrome have elevated levels of PAI-1 in plasma, and this probably contributes to the increased risk of thrombotic events. Lp(a) (Chap. 421) may modulate fibrinolysis, and individuals with elevated Lp(a) levels have increased CHD risk.

Aspirin reduces CHD events in several contexts. Chapter 293 discusses aspirin therapy in stable ischemic heart disease, Chap. 294 reviews recommendations for aspirin treatment in acute coronary syndromes, and Chap. 446 describes aspirin's role in preventing recurrent ischemic stroke. In primary prevention, pooled trial data show that low-dose aspirin treatment (81 mg/d to 325 mg on alternate days) can reduce the risk of a first MI in men. Although the Women's Health Study (WHS) showed that aspirin (100 mg on alternate days) reduced strokes by 17%, it did not prevent MI in women. Current AHA guidelines recommend the use of low-dose aspirin (75–160 mg/d) for women with high cardiovascular risk ($\geq 20\%$ 10-year risk), for men with a $\geq 10\%$ 10-year risk of CHD, and for all aspirin-tolerant patients with established cardiovascular disease who lack contraindications.

Inflammation An accumulation of clinical evidence shows that markers of inflammation correlate with coronary risk. For example, plasma levels of CRP, as measured by a high-sensitivity assay (hsCRP), prospectively predict the risk of MI. CRP levels also correlate with the outcome in patients with acute coronary syndromes. In contrast to several other novel risk factors, CRP adds predictive information to that derived from established risk factors, such as those included in the Framingham score (Fig. 291e-6). Mendelian randomization studies do not support a causal role for CRP in cardiovascular disease. Thus, CRP serves as a validated biomarker of risk, but probably not as a direct contributor to pathogenesis.

Elevations in acute-phase reactants such as fibrinogen and CRP reflect the overall inflammatory burden, not just vascular foci of inflammation. Visceral adipose tissue releases proinflammatory cytokines that drive CRP production and may represent a major extravascular

stimulus to the elevation of inflammatory markers in obese and overweight individuals. Indeed, CRP levels rise with body mass index (BMI) or visceral adipose depot as assessed by imaging, and weight reduction lowers CRP levels. Infectious agents might also furnish inflammatory stimuli related to cardiovascular risk.

Statin therapy likely reduces cardiovascular events in part by muting the inflammatory aspects of the pathogenesis of atherosclerosis. For example, in statin trials conducted in both primary (JUPITER) and secondary (PROVE-IT/TIMI-22) prevention populations, prespecified analyses showed that those who achieved lower levels of both LDL and CRP had better clinical outcomes than did those who only reached the lower level of either the inflammatory marker or the atherogenic lipoprotein (Fig. 291e-7). The anti-inflammatory effect of statins appears independent of LDL lowering, because these two variables correlated very poorly in individual subjects in multiple clinical trials.

Lifestyle Modification The prevention of atherosclerosis presents a long-term challenge to all health care professionals and for public health policy. Both individual practitioners and organizations providing health care should strive to help patients optimize their risk factor profiles long before atherosclerotic disease becomes manifest. The current accumulation of cardiovascular risk in youth and in certain minority populations presents a particularly vexing concern from a public health perspective.

The ACC/AHA 2013 Guideline on Lifestyle Management to Reduce Cardiovascular Risk relied on rigorous evidentiary reviews. Few lifestyle interventions have undergone rigorous evaluation in randomized clinical trials. Therefore, these guidelines reflected judicious analysis of carefully selected observational studies and of intervention studies that relied primarily on biomarkers or surrogate endpoints rather than "hard" cardiovascular outcomes. Table 291e-3 summarizes the ACC/AHA lifestyle recommendations.

The care plan for all patients seen by internists should include measures to assess and minimize cardiovascular risk. Physicians must counsel patients about the health risks of tobacco use and provide guidance and resources regarding smoking cessation. Similarly, physicians should advise all patients about prudent dietary and physical activity habits for maintaining ideal body weight. Both National Institutes of Health (NIH) and AHA statements recommend at least 30 min of moderate-intensity physical activity per day. Obesity, particularly the male pattern of centripetal or visceral fat accumulation, can contribute to the elements of the "metabolic syndrome" cluster. Physicians should encourage their patients to take personal responsibility for behavior related to modifiable risk factors for the development of premature atherosclerotic disease. Conscientious counseling and patient education may forestall the need for pharmacologic measures intended to reduce coronary risk.

Issues in Risk Assessment A growing panel of markers of coronary risk presents a perplexing array to the practitioner. Markers measured in peripheral blood include size fractions of LDL particles and concentrations of homocysteine, Lp(a), fibrinogen, CRP, PAI-1, myeloperoxidase, lipoprotein-associated phospholipase A₂, and imaging assessment of subclinical atherosclerosis, among many others. In general, such specialized tests add little to the information available from a careful history and physical examination combined with measurement of a plasma lipoprotein profile and fasting blood glucose. The hsCRP measurement may well prove an exception in view of its robustness in risk

Group	N	Rate
Placebo	7832	1.11
LDL \geq 70 mg/dL, hsCRP \geq 2 mg/L	1384	1.11
LDL < 70 mg/dL, hsCRP \geq 2 mg/L	2921	0.62
LDL \geq 70 mg/dL, hsCRP < 2 mg/L	726	0.54
LDL < 70 mg/dL, hsCRP < 2 mg/L	2685	0.38

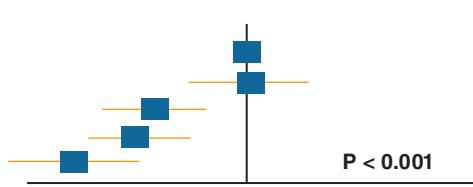


FIGURE 291e-7 Evidence from the JUPITER study that both low-density lipoprotein (LDL)-lowering and anti-inflammatory actions contribute to the benefit of statin therapy in primary prevention. See text for explanation. hsCRP, high-sensitivity measurement of C-reactive protein (CRP). (Adapted from PM Ridker et al: *Lancet* 373:1175, 2009.)

291e-10 prediction, ease of reproducible and standardized measurement, relative stability in individuals over time, ability to add to the risk information disclosed by standard measurements such as the components of the Framingham risk score, and most importantly, the demonstration in a large-scale trial (JUPITER) that allocating therapy can reduce cardiovascular events in those deemed ineligible by traditional risk assessment criteria. The addition of information regarding a family history of premature atherosclerosis (a simply obtained indicator of genetic susceptibility), together with the inflammation marker hsCRP, permits correct reclassification of risk in individuals, especially those whose Framingham scores place them at intermediate risk.

Available data do not support the routine use of imaging studies to screen for subclinical disease (e.g., measurement of carotid intima-media thickness, coronary artery calcification, and use of computed tomographic coronary angiograms [CTA]). Inappropriate use of such imaging modalities may promote excessive alarm in asymptomatic individuals and prompt invasive diagnostic and therapeutic procedures of unproven value for both asymptomatic atherosclerosis and incidental findings. Widespread application of such modalities for screening should await proof that targeting therapies based on their application provides clinical benefit.

The 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk recommends the use of newer risk markers if uncertainty persists after assessing quantitative risk using the pooled cohort calculator. The guideline states that family history, hsCRP, coronary artery calcium (CAC) score, or ankle-brachial index (ABI) may then be considered to inform treatment decision making. It discourages carotid intima-media thickness (CIMT) for routine measurement in clinical practice for risk assessment for a first ASCVD event. The guideline panel deemed the contribution to risk assessment for a first ASCVD event using apolipoprotein B (ApoB), chronic kidney disease, albuminuria, or cardiorespiratory fitness as uncertain at present.

Progress in human genetics holds considerable promise for risk prediction and for individualization of cardiovascular therapy. Many early reports identified single-nucleotide polymorphisms (SNPs) in candidate genes as predictors of cardiovascular risk. The validation of such genetic markers of risk and drug responsiveness in multiple populations often proved disappointing. The era of GWAS has led to discovery of sites of genetic variation that reproducibly indicate heightened cardiovascular risk (e.g., chromosome 9p21). The advent of technology that permits relatively rapid and inexpensive exome or whole-genome sequencing promises to identify new therapeutic targets, sharpen risk prediction, and deploy preventive or therapeutic measures in a more personalized manner. Despite this considerable promise, genetic scores for risk prediction have not yet demonstrated consistent improvement over algorithms that use traditional tools.

THE CHALLENGE OF IMPLEMENTATION: CHANGING PHYSICIAN AND PATIENT BEHAVIOR

Despite declining age-adjusted rates of coronary death, cardiovascular mortality worldwide is rising due to aging of the population and due to subsiding of communicable diseases and increased prevalence of risk factors in developing countries. Enormous challenges remain regarding translation of the current evidence base into practice. Physicians must learn how to help individuals adopt a healthy lifestyle in a culturally appropriate manner and to deploy their increasingly powerful pharmacologic tools most economically and effectively. The obstacles to implementation of current evidence-based prevention and treatment of atherosclerosis involve economics, education, physician awareness, and patient adherence to recommended regimens. Future goals in the treatment of atherosclerosis should include more widespread implementation of the current evidence-based guidelines regarding risk factor management and, when appropriate, drug therapy.

292e Atlas of Atherosclerosis

Peter Libby

Knowledge about the biology of human atherosclerosis and the risk factors for the disease has expanded considerably. The application of vascular biology to human atherosclerosis has revealed many new insights into the mechanisms that promote clinical events. The series of animated video presentations presented here illustrates some of the evolving information about risk factors for atherosclerosis and the pathophysiology of clinical events.

The importance of blood pressure as a risk factor for atherosclerosis and cardiovascular events has long been recognized. More recent clinical information has highlighted the importance of pulse pressure—the difference between the systolic pressure and minimum diastolic arterial pressure—as a prognostic indicator of cardiovascular risk. The video clip on pulse pressure explains the pathophysiology of this readily measured clinical variable.

Physicians possess a great deal of knowledge about the role of cholesterol in the prediction of atherosclerosis and its complications, but knowledge about the mechanism that links hypercholesterolemia to cardiovascular events has lagged the epidemiologic and observational findings. Low-density lipoprotein (LDL) provides an example of a well-understood cardiovascular risk factor. Several of the animations included in this series highlight the role of modified LDL as a trigger for inflammation and other aspects of the pathobiology of arterial plaques that lead to their aggravation and clinical events. Physicians have useful tools for modulating LDL, but other aspects of dyslipidemia are on the rise and provide a growing challenge to the practitioner. In particular, low levels of high-density lipoprotein (HDL) and elevated levels of triglycerides characterize the constellation of findings denoted by some as the “metabolic syndrome.” In the wake of increasing obesity worldwide, these features of the lipoprotein profile require renewed focus. Several of the animations in this collection discuss the concept of the metabolic syndrome and the role of lipid profile components other than LDL in atherogenesis.

The traditional approach to atherosclerosis focused on arterial stenoses as a cause of ischemia and cardiovascular events. Physicians now have effective revascularization modalities for addressing flow-limiting stenoses, but atherosclerotic plaques that do not cause stenoses nonetheless may precipitate clinical events, such as unstable angina and acute myocardial infarction. Thus, it is necessary to add to the traditional focus on stenosis an enlarged appreciation of the pathobiology of atherosclerosis that underlies many acute coronary syndromes. The animation on the development and complication of atherosclerotic plaque explains some of these emerging concepts in plaque

activation as they apply to the precipitation of thrombotic complications of atherosclerosis.

ACKNOWLEDGMENTS

From Peter Libby, MD: Changes and Challenges in Cardiovascular Protection: A Special CME Activity for Physicians. Created under an unrestricted educational grant from Merck & Co., Inc. Copyright © 2002, Cardinal Health; used with permission.

VIDEO 292e-1 Pulse pressure. Considerable evidence suggests that pulse pressure serves as an important risk factor for future cardiovascular events. This video clip explains the derivation of pulse pressure and some of the pathophysiology that determines this parameter. (With permission from the Academy for Health Care Education.)

VIDEO 292e-2 Plaque instability. Most coronary thromboses result from a physical disruption of the atherosclerotic plaque. This animation explains some of the current concepts of the pathophysiology of atherosclerotic plaque disruption and how it triggers arterial thrombosis.

VIDEO 292e-3 Lipoprotein menagerie. The lipid profile confers important information regarding cardiovascular risk and the effects of therapies; understanding lipoprotein metabolism provides insight into the pathophysiology of arterial disease. This animation presents the rudiments of lipoprotein metabolism that are important in clinical medicine.

VIDEO 292e-4 Formation and complication of atherosclerotic plaques. Physicians now understand the generation of atherosclerotic plaques as a dynamic process involving an interchange between cells of the artery wall, inflammatory cells recruited from blood, and risk factors such as lipoproteins. This animation reviews current thinking about how risk factors alter the biology of the artery wall and can incite initiation and progression of atherosclerosis. It also discusses the importance of inflammation in these processes and portrays the role of inflammation in plaque disruption and thrombosis. Finally, this animation depicts the concept of stabilization of atherosclerotic plaques by interventions such as lipid lowering.

VIDEO 292e-5 Atherogenesis. This video clip highlights some of the current thinking about mechanisms of atherogenesis.

VIDEO 292e-6 Metabolic syndrome. A number of important cardiovascular risk factors tend to cluster in a pattern that has been described by some as the metabolic syndrome. Although controversy persists regarding whether cardiovascular risk due to these factors is additive or synergistic, their clinical importance is growing. This animation discusses some of the metabolic derangements that underlie the metabolic syndrome.

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Ischemic Heart Disease

Elliott M. Antman, Joseph Loscalzo

Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery. [Chapter 291e](#) deals with the development and treatment of atherosclerosis. This chapter focuses on the chronic manifestations and treatment of IHD. The subsequent chapters address the acute phases of IHD.

EPIDEMIOLOGY AND GLOBAL TRENDS

 IHD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world.

IHD is the most common, serious, chronic, life-threatening illness in the United States, where 13 million persons have IHD, >6 million have angina pectoris, and >7 million have sustained a myocardial infarction. Genetic factors, a high-fat and energy-rich diet, smoking, and a sedentary lifestyle are associated with the emergence of IHD ([Chap. 291e](#)). In the United States and Western Europe, IHD is growing among low-income groups, but primary prevention has delayed the disease to later in life in all socioeconomic groups. Despite these sobering statistics, it is worth noting that epidemiologic data show a decline in the rate of deaths due to IHD, about half of which is attributable to treatments and half to prevention by risk factor modification.

Obesity, insulin resistance, and type 2 diabetes mellitus are increasing and are powerful risk factors for IHD. These trends are occurring in the general context of population growth and as a result of the increase in the average age of the world's population. With urbanization in countries with emerging economies and a growing middle class, elements of the energy-rich Western diet are being adopted. As a result, the prevalence of risk factors for IHD and the prevalence of IHD itself are both increasing rapidly, so that in analyses of the global burden of disease, there is a shift from communicable to noncommunicable diseases. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India and the Middle East. In light of the projection of large increases in IHD throughout the world, IHD is likely to become the most common cause of death worldwide by 2020.

PATHOPHYSIOLOGY

Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. In normal conditions, for any given level of a demand for oxygen, the myocardium will control the supply of oxygen-rich blood to prevent underperfusion of myocytes and the subsequent development of ischemia and infarction. The major determinants of myocardial oxygen demand (MVO_2) are heart rate, myocardial contractility, and myocardial wall tension (stress). An adequate supply of oxygen to the myocardium requires a satisfactory level of oxygen-carrying capacity of the blood (determined by the inspired level of oxygen, pulmonary function, and hemoglobin concentration and function) and an adequate level of coronary blood flow. Blood flows through the coronary arteries in a phasic fashion, with the majority occurring during diastole. About 75% of the total coronary resistance to flow occurs across three sets of arteries: (1) large epicardial arteries ($Resistance\ 1 = R_1$), (2) prearteriolar vessels (R_2), and (3) arteriolar and intramyocardial capillary vessels (R_3). In the absence of significant flow-limiting atherosclerotic

obstructions, R_1 is trivial; the major determinant of coronary resistance is found in R_2 and R_3 .

The normal coronary circulation is dominated and controlled by the heart's requirements for oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance (and, therefore, blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate a great capacity for dilation (R_2 and R_3 decrease). For example, the changing oxygen needs of the heart with exercise and emotional stress affect coronary vascular resistance and in this manner regulate the supply of oxygen and substrate to the myocardium (*metabolic regulation*). The coronary resistance vessels also adapt to physiologic alterations in blood pressure to maintain coronary blood flow at levels appropriate to myocardial needs (*autoregulation*).

By reducing the lumen of the coronary arteries, atherosclerosis limits its appropriate increases in perfusion when the demand for flow is augmented, as occurs during exertion or excitement. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow also can be limited by spasm (see Prinzmetal's angina in [Chap. 294](#)), arterial thrombi, and, rarely, coronary emboli as well as by ostial narrowing due to aortitis. Congenital abnormalities such as the origin of the left anterior descending coronary artery from the pulmonary artery may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults.

Myocardial ischemia also can occur if myocardial oxygen demands are markedly increased and particularly when coronary blood flow may be limited, as occurs in severe left ventricular hypertrophy due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis largely owing to subendocardial ischemia ([Chap. 283](#)). A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxyhemoglobin, rarely causes myocardial ischemia by itself but may lower the threshold for ischemia in patients with moderate coronary obstruction.

Not infrequently, two or more causes of ischemia coexist in a patient, such as an increase in oxygen demand due to left ventricular hypertrophy secondary to hypertension and a reduction in oxygen supply secondary to coronary atherosclerosis and anemia. Abnormal constriction or failure of normal dilation of the coronary resistance vessels also can cause ischemia. When it causes angina, this condition is referred to as *microvascular angina*.

CORONARY ATHEROSCLEROSIS

Epicardial coronary arteries are the major site of atherosclerotic disease. The major risk factors for atherosclerosis (high levels of plasma low-density lipoprotein [LDL], low plasma high-density lipoprotein [HDL], cigarette smoking, hypertension, and diabetes mellitus [[Chap. 291e](#)]) disturb the normal functions of the vascular endothelium. These functions include local control of vascular tone, maintenance of an antithrombotic surface, and control of inflammatory cell adhesion and diapedesis. The loss of these defenses leads to inappropriate constriction, luminal thrombus formation, and abnormal interactions between blood cells, especially monocytes and platelets, and the activated vascular endothelium. Functional changes in the vascular milieu ultimately result in the subintimal collections of fat, smooth muscle cells, fibroblasts, and intercellular matrix that define the atherosclerotic plaque. Rather than viewing atherosclerosis strictly as a vascular problem, it is useful to consider it in the context of alterations in the nature of the circulating blood (hyperglycemia; increased concentrations of LDL cholesterol, tissue factor, fibrinogen, von Willebrand factor, coagulation factor VII, and platelet microparticles). The combination of a "vulnerable vessel" in a patient with "vulnerable blood" promotes a state of hypercoagulability and hypofibrinolysis. This is especially true in patients with diabetes mellitus.

Atherosclerosis develops at irregular rates in different segments of the epicardial coronary tree and leads eventually to segmental reductions in cross-sectional area, i.e., plaque formation. There is also a

predisposition for atherosclerotic plaques to develop at sites of increased turbulence in coronary flow, such as at branch points in the epicardial arteries. When a stenosis reduces the diameter of an epicardial artery by 50%, there is a limitation of the ability to increase flow to meet increased myocardial demand. When the diameter is reduced by ~80%, blood flow at rest may be reduced, and further minor decreases in the stenotic orifice area can reduce coronary flow dramatically to cause myocardial ischemia at rest or with minimal stress.

Segmental atherosclerotic narrowing of epicardial coronary arteries is caused most commonly by the formation of a plaque, which is subject to rupture or erosion of the cap separating the plaque from the bloodstream. Upon exposure of the plaque contents to blood, two important and interrelated processes are set in motion: (1) platelets are activated and aggregate, and (2) the coagulation cascade is activated, leading to deposition of fibrin strands. A thrombus composed of platelet aggregates and fibrin strands traps red blood cells and can reduce coronary blood flow, leading to the clinical manifestations of myocardial ischemia.

The location of the obstruction influences the quantity of myocardium rendered ischemic and determines the severity of the clinical manifestations. Thus, critical obstructions in vessels, such as the left main coronary artery and the proximal left anterior descending coronary artery, are particularly hazardous. Chronic severe coronary narrowing and myocardial ischemia frequently are accompanied by the development of collateral vessels, especially when the narrowing develops gradually. When well developed, such vessels can by themselves provide sufficient blood flow to sustain the viability of the myocardium at rest but not during conditions of increased demand.

With progressive worsening of a stenosis in a proximal epicardial artery, the distal resistance vessels (when they function normally) dilate to reduce vascular resistance and maintain coronary blood flow. A pressure gradient develops across the proximal stenosis, and poststenotic pressure falls. When the resistance vessels are maximally dilated, myocardial blood flow becomes dependent on the pressure in the coronary artery distal to the obstruction. In these circumstances, ischemia, manifest clinically by angina or electrocardiographically by ST-segment deviation, can be precipitated by increases in myocardial oxygen demand caused by physical activity, emotional stress, and/or tachycardia. Changes in the caliber of the stenosed coronary artery due to physiologic vasomotion, loss of endothelial control of dilation (as occurs in atherosclerosis), pathologic spasm (Prinzmetal's angina), or small platelet-rich plugs also can upset the critical balance between oxygen supply and demand and thereby precipitate myocardial ischemia.

EFFECTS OF ISCHEMIA

During episodes of inadequate perfusion caused by coronary atherosclerosis, myocardial tissue oxygen tension falls and may cause transient disturbances of the mechanical, biochemical, and electrical functions of the myocardium ([Fig. 293-1](#)). Coronary atherosclerosis is a focal process that usually causes nonuniform ischemia. During ischemia, regional disturbances of ventricular contractility cause segmental hypokinesia, akinesia, or, in severe cases, bulging (dyskinesia), which can reduce myocardial pump function.

The abrupt development of severe ischemia, as occurs with total or subtotal coronary occlusion, is associated with almost instantaneous failure of normal muscle relaxation and then contraction. The relatively poor perfusion of the subendocardium causes more intense ischemia of this portion of the wall (compared with the subepicardial region). Ischemia of large portions of the ventricle causes transient left ventricular failure, and if the papillary muscle apparatus is involved, mitral regurgitation can occur. When ischemia is transient, it may be associated with angina pectoris; when it is prolonged, it can lead to myocardial necrosis and scarring with or without the clinical picture of acute myocardial infarction ([Chap. 295](#)).

A wide range of abnormalities in cell metabolism, function, and structure underlie these mechanical disturbances during ischemia. The normal myocardium metabolizes fatty acids and glucose to carbon

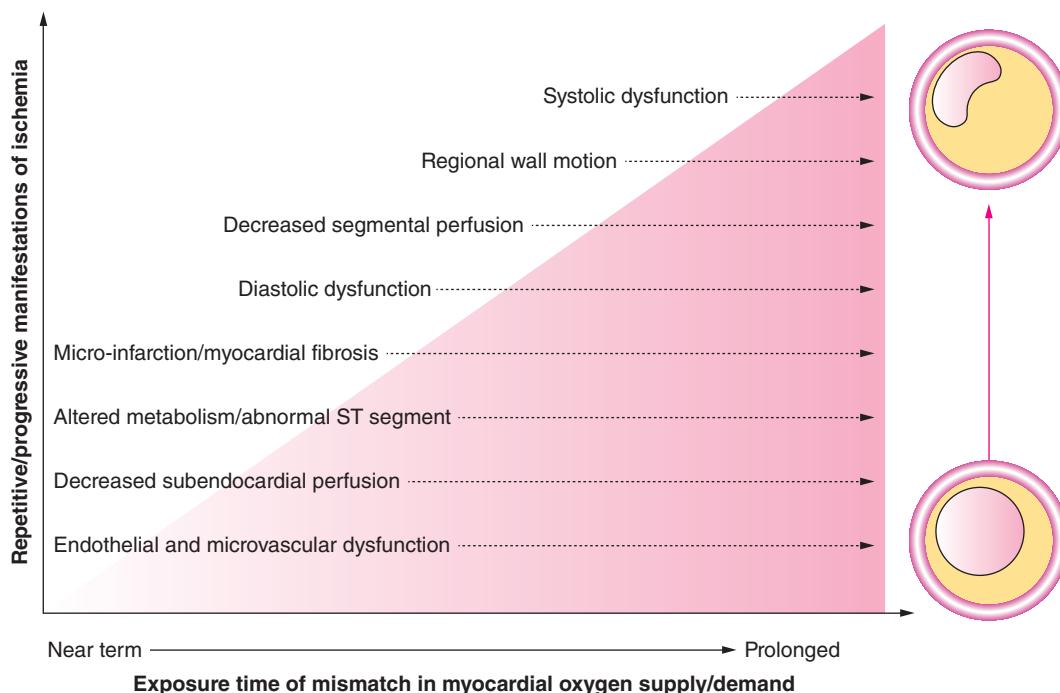


FIGURE 293-1 Cascade of mechanisms and manifestations of ischemia. (Modified from LJ Shaw et al: J Am Coll Cardiol 54:1561, 2009. Original figure illustration by Rob Flewell.)

dioxide and water. With severe oxygen deprivation, fatty acids cannot be oxidized, and glucose is converted to lactate; intracellular pH is reduced, as are the myocardial stores of high-energy phosphates, i.e., ATP and creatine phosphate. Impaired cell membrane function leads to the leakage of potassium and the uptake of sodium by myocytes as well as an increase in cytosolic calcium. The severity and duration of the imbalance between myocardial oxygen supply and demand determine whether the damage is reversible (≤ 20 min for total occlusion in the absence of collaterals) or permanent, with subsequent myocardial necrosis (> 20 min).

Ischemia also causes characteristic changes in the electrocardiogram (ECG) such as repolarization abnormalities, as evidenced by inversion of T waves and, when more severe, displacement of ST segments (Chap. 268). Transient T-wave inversion probably reflects non-transmural, intramyocardial ischemia; transient ST-segment depression often reflects patchy subendocardial ischemia; and ST-segment elevation is thought to be caused by more severe transmural ischemia. Another important consequence of myocardial ischemia is electrical instability, which may lead to isolated ventricular premature beats or even ventricular tachycardia or ventricular fibrillation (Chap. 277). Most patients who die suddenly from IHD do so as a result of ischemia-induced ventricular tachyarrhythmias (Chap. 327).

ASYMPTOMATIC VERSUS SYMPTOMATIC IHD

Although the prevalence is decreasing, postmortem studies of accident victims and military casualties in Western countries still show that coronary atherosclerosis can begin before age 20 and is present even among adults who were asymptomatic during life. Exercise stress tests in asymptomatic persons may show evidence of silent myocardial ischemia, i.e., exercise-induced ECG changes not accompanied by angina pectoris; coronary angiographic studies of such persons may reveal coronary artery plaques and previously unrecognized obstructions (Chap. 272). Postmortem examination of patients with such obstructions without a history of clinical manifestations of myocardial ischemia often shows macroscopic scars secondary to myocardial infarction in regions supplied by diseased coronary arteries, with or without collateral circulation. According to population studies, ~25% of patients who survive acute myocardial infarction may not come to medical attention, and these patients have the same adverse prognosis as do those who present with the classic clinical picture of acute

myocardial infarction (Chap. 295). Sudden death may be unheralded and is a common presenting manifestation of IHD (Chap. 327).

Patients with IHD also can present with cardiomegaly and heart failure secondary to ischemic damage of the left ventricular myocardium that may have caused no symptoms before the development of heart failure; this condition is referred to as *ischemic cardiomyopathy*. In contrast to the asymptomatic phase of IHD, the symptomatic phase is characterized by chest discomfort due to either angina pectoris or acute myocardial infarction (Chap. 295). Having entered the symptomatic phase, the patient may exhibit a stable or progressive course, revert to the asymptomatic stage, or die suddenly.

STABLE ANGINA PECTORIS

This episodic clinical syndrome is due to transient myocardial ischemia. Various diseases that cause myocardial ischemia and the numerous forms of discomfort with which it may be confused are discussed in Chap. 19. Males constitute ~70% of all patients with angina pectoris and an even greater proportion of those less than 50 years of age. It is, however, important to note that angina pectoris in women is often atypical in presentation (see below).

HISTORY

The typical patient with angina is a man >50 years or a woman >60 years of age who complains of episodes of chest discomfort, usually described as heaviness, pressure, squeezing, smothering, or choking and only rarely as frank pain. When the patient is asked to localize the sensation, he or she typically places a hand over the sternum, sometimes with a clenched fist, to indicate a squeezing, central, substernal discomfort (Levine's sign). Angina is usually crescendo-decrescendo in nature, typically lasts 2 to 5 min, and can radiate to either shoulder and to both arms (especially the ulnar surfaces of the forearm and hand). It also can arise in or radiate to the back, interscapular region, root of the neck, jaw, teeth, and epigastrium. Angina is rarely localized below the umbilicus or above the mandible. A useful finding in assessing a patient with chest discomfort is the fact that myocardial ischemic discomfort does not radiate to the trapezius muscles; that radiation pattern is more typical of pericarditis.

Although episodes of angina typically are caused by exertion (e.g., exercise, hurrying, or sexual activity) or emotion (e.g., stress, anger,

fright, or frustration) and are relieved by rest, they also may occur at rest ([Chap. 294](#)) and while the patient is recumbent (angina decubitus). The patient may be awakened at night by typical chest discomfort and dyspnea. Nocturnal angina may be due to episodic tachycardia, diminished oxygenation as the respiratory pattern changes during sleep, or expansion of the intrathoracic blood volume that occurs with recumbency; the latter causes an increase in cardiac size (end-diastolic volume), wall tension, and myocardial oxygen demand that can lead to ischemia and transient left ventricular failure.

The threshold for the development of angina pectoris may vary by time of day and emotional state. Many patients report a fixed threshold for angina, which occurs predictably at a certain level of activity, such as climbing two flights of stairs at a normal pace. In these patients, coronary stenosis and myocardial oxygen supply are fixed, and ischemia is precipitated by an increase in myocardial oxygen demand; they are said to have stable exertional angina. In other patients, the threshold for angina may vary considerably within any particular day and from day to day. In such patients, variations in myocardial oxygen supply, most likely due to changes in coronary vasomotor tone, may play an important role in defining the pattern of angina. A patient may report symptoms upon minor exertion in the morning (a short walk or shaving) yet by midday be capable of much greater effort without symptoms. Angina may also be precipitated by unfamiliar tasks, a heavy meal, exposure to cold, or a combination of these factors.

Exertional angina typically is relieved in 1–5 min by slowing or ceasing activities and even more rapidly by rest and sublingual nitroglycerin (see below). Indeed, the diagnosis of angina should be suspect if it does not respond to the combination of these measures. The severity of angina can be conveniently summarized by the Canadian Cardiac Society functional classification ([Table 293-1](#)). Its impact on the patient's functional capacity can be described by using the New York Heart Association functional classification (Table 293-1).

TABLE 293-1 CARDIOVASCULAR DISEASE CLASSIFICATION CHART

Class	New York Heart Association Functional Classification	Canadian Cardiovascular Society Functional Classification
I	Patients have cardiac disease but <i>without</i> the resulting <i>limitations</i> of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, <i>does not cause angina</i> . Angina present with strenuous or rapid or prolonged exertion at work or recreation.
II	Patients have cardiac disease resulting in <i>slight limitation</i> of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	<i>Slight limitation</i> of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or when under emotional stress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
III	Patients have cardiac disease resulting in <i>marked limitation</i> of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	<i>Marked limitation</i> of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions.
IV	Patients have cardiac disease resulting in <i>inability</i> to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	<i>Inability</i> to carry on any physical activity without discomfort—anginal syndrome <i>may</i> be present at rest.

Source: Modified from L Goldman et al: Circulation 64:1227, 1981.

Sharp, fleeting chest pain or a prolonged, dull ache localized to the left submammary area is rarely due to myocardial ischemia. However, especially in women and diabetic patients, angina pectoris may be atypical in location and not strictly related to provoking factors. In addition, this symptom may exacerbate and remit over days, weeks, or months. Its occurrence can be seasonal, occurring more frequently in the winter in temperate climates. Anginal “equivalents” are symptoms of myocardial ischemia other than angina. They include dyspnea, nausea, fatigue, and faintness and are more common in the elderly and in diabetic patients.

Systematic questioning of a patient with suspected IHD is important to uncover the features of an unstable syndrome associated with increased risk, such as angina occurring with less exertion than in the past, occurring at rest, or awakening the patient from sleep. Since coronary atherosclerosis often is accompanied by similar lesions in other arteries, a patient with angina should be questioned and examined for peripheral arterial disease (intermittent claudication [[Chap. 302](#)]), stroke, or transient ischemic attacks ([Chap. 446](#)). It is also important to uncover a family history of premature IHD (<55 years in first-degree male relatives and <65 in female relatives) and the presence of diabetes mellitus, hyperlipidemia, hypertension, cigarette smoking, and other risk factors for coronary atherosclerosis ([Chap. 291e](#)).

The history of typical angina pectoris establishes the diagnosis of IHD until proven otherwise. The coexistence of advanced age, male sex, the postmenopausal state, and risk factors for atherosclerosis increase the likelihood of hemodynamically significant coronary disease. A particularly challenging problem is the evaluation and management of patients with persistent ischemic-type chest discomfort but no flow-limiting obstructions in their epicardial coronary arteries. This situation arises more often in women than in men. Potential etiologies include microvascular coronary disease (detectable on coronary reactivity testing in response to vasoactive agents such as intracoronary adenosine, acetylcholine, and nitroglycerin) and abnormal cardiac nociception. Treatment of microvascular coronary disease should focus on efforts to improve endothelial function, including nitrates, beta blockers, calcium antagonists, statins, and angiotensin-converting enzyme (ACE) inhibitors. Abnormal cardiac nociception is more difficult to manage and may be ameliorated in some cases by imipramine.

PHYSICAL EXAMINATION

The physical examination is often normal in patients with stable angina when they are asymptomatic. However, because of the increased likelihood of IHD in patients with diabetes and/or peripheral arterial disease, clinicians should search for evidence of atherosclerotic disease at other sites, such as an abdominal aortic aneurysm, carotid arterial bruits, and diminished arterial pulses in the lower extremities. The physical examination also should include a search for evidence of risk factors for atherosclerosis such as xanthelasmas and xanthomas ([Chap. 291e](#)). Evidence for peripheral arterial disease should be sought by evaluating the pulse contour at multiple locations and comparing the blood pressure between the arms and between the arms and the legs (ankle-brachial index). Examination of the fundi may reveal an increased light reflex and arteriovenous nicking as evidence of hypertension. There also may be signs of anemia, thyroid disease, and nicotine stains on the fingertips from cigarette smoking.

Palpation may reveal cardiac enlargement and abnormal contraction of the cardiac impulse (left ventricular dyskinesia). Auscultation can uncover arterial bruits, a third and/or fourth heart sound, and, if acute ischemia or previous infarction has impaired papillary muscle function, an apical systolic murmur due to mitral regurgitation. These auscultatory signs are best appreciated with the patient in the left lateral decubitus position. Aortic stenosis, aortic regurgitation ([Chap. 283](#)), pulmonary hypertension ([Chap. 304](#)), and hypertrophic cardiomyopathy ([Chap. 287](#)) must be excluded, since these disorders may cause angina in the absence of coronary atherosclerosis. Examination during an anginal attack is useful, since ischemia can cause transient left ventricular failure with the appearance of a third

and/or fourth heart sound, a dyskinetic cardiac apex, mitral regurgitation, and even pulmonary edema. Tenderness of the chest wall, localization of the discomfort with a single fingertip on the chest, or reproduction of the pain with palpation of the chest makes it unlikely that the pain is caused by myocardial ischemia. A protuberant abdomen may indicate that the patient has the metabolic syndrome and is at increased risk for atherosclerosis.

LABORATORY EXAMINATION

Although the diagnosis of IHD can be made with a high degree of confidence from the history and physical examination, a number of simple laboratory tests can be helpful. The urine should be examined for evidence of diabetes mellitus and renal disease (including microalbuminuria) since these conditions accelerate atherosclerosis. Similarly, examination of the blood should include measurements of lipids (cholesterol—total, LDL, HDL—and triglycerides), glucose (hemoglobin A_{1c}), creatinine, hematocrit, and, if indicated based on the physical examination, thyroid function. A chest x-ray is important as it may show the consequences of IHD, i.e., cardiac enlargement, ventricular aneurysm, or signs of heart failure. These signs can support the diagnosis of IHD and are important in assessing the degree of cardiac damage. Evidence exists that an elevated level of high-sensitivity C-reactive protein (CRP) (specifically, between 0 and 3 mg/dL) is an independent risk factor for IHD and may be useful in therapeutic decision making about the initiation of hypolipidemic treatment. The major benefit of high-sensitivity CRP is in reclassifying the risk of IHD in patients in the “intermediate” risk category on the basis of traditional risk factors.

ELECTROCARDIOGRAM

A 12-lead ECG recorded at rest may be normal in patients with typical angina pectoris, but there may also be signs of an old myocardial infarction (Chap. 268). Although repolarization abnormalities, i.e., ST-segment and T-wave changes, as well as left ventricular hypertrophy and disturbances of cardiac rhythm or intraventricular conduction are suggestive of IHD, they are nonspecific, since they also can occur in pericardial, myocardial, and valvular heart disease or, in the case of the former, transiently with anxiety, changes in posture, drugs, or esophageal disease. The presence of left ventricular hypertrophy (LVH) is a significant indication of increased risk of adverse outcomes from IHD. Of note, even though LVH and cardiac rhythm disturbances are nonspecific indicators of the development of IHD, they may be contributing factors to episodes of angina in patients in whom IHD has developed as a consequence of conventional risk factors. Dynamic ST-segment and T-wave changes that accompany episodes of angina pectoris and disappear thereafter are more specific.

STRESS TESTING

Electrocardiographic The most widely used test for both the diagnosis of IHD and the estimation of risk and prognosis involves recording the 12-lead ECG before, during, and after exercise, usually on a treadmill (Fig. 293-2). The test consists of a standardized incremental increase in external workload (Table 293-2) while symptoms, the ECG, and arm blood pressure are monitored. Exercise duration is usually symptom-limited, and the test is discontinued upon evidence of chest discomfort, severe shortness of breath, dizziness, severe fatigue, ST-segment depression >0.2 mV (2 mm), a fall in systolic blood pressure >10 mmHg, or the development of a ventricular tachyarrhythmia. This test is used to discover any limitation in exercise performance, detect typical ECG signs of myocardial ischemia, and establish their relationship to chest discomfort. The ischemic ST-segment response generally is defined as flat or downsloping depression of the ST segment >0.1 mV below baseline (i.e., the PR segment) and lasting longer than 0.08 s (Fig. 293-1). Upsloping or junctional ST-segment changes are not considered characteristic of ischemia and do not constitute a positive test. Although T-wave abnormalities, conduction disturbances, and ventricular arrhythmias that develop during exercise should be noted, they are also not diagnostic. Negative exercise tests in which the target heart rate (85% of maximal predicted heart rate for age and sex) is not achieved are considered nondiagnostic.

In interpreting ECG stress tests, the probability that coronary artery disease (CAD) exists in the patient or population under study (i.e., pretest probability) should be considered. Overall, false-positive or false-negative results occur in one-third of cases. However, a positive result on exercise indicates that the likelihood of CAD is 98% in males who are >50 years with a history of typical angina pectoris and who develop chest discomfort during the test. The likelihood decreases if the patient has atypical or no chest pain by history and/or during the test.

The incidence of false-positive tests is significantly increased in patients with low probabilities of IHD, such as asymptomatic men age <40 or premenopausal women with no risk factors for premature atherosclerosis. It is also increased in patients taking cardioactive drugs, such as digitalis and antiarrhythmic agents, and in those with intraventricular conduction disturbances, resting ST-segment and T-wave abnormalities, ventricular hypertrophy, or abnormal serum potassium levels. Obstructive disease limited to the circumflex coronary artery may result in a false-negative stress test since the lateral portion of the heart that this vessel supplies is not well represented on the surface 12-lead ECG. Since the overall sensitivity of exercise stress electrocardiography is only ~75%, a negative result does not exclude CAD, although it makes the likelihood of three-vessel or left main CAD extremely unlikely.

A medical professional should be present throughout the exercise test. It is important to measure total duration of exercise, the times to the onset of ischemic ST-segment change and chest discomfort, the external work performed (generally expressed as the stage of exercise), and the internal cardiac work performed, i.e., by the heart rate–blood pressure product. The depth of the ST-segment depression and the time needed for recovery of these ECG changes are also important. Because the risks of exercise testing are small but real—estimated at one fatality and two nonfatal complications per 10,000 tests—equipment for resuscitation should be available. Modified (heart rate-limited rather than symptom-limited) exercise tests can be performed safely in patients as early as 6 days after uncomplicated myocardial infarction (Table 293-2). Contraindications to exercise stress testing include rest angina within 48 h, unstable rhythm, severe aortic stenosis, acute myocarditis, uncontrolled heart failure, severe pulmonary hypertension, and active infective endocarditis.

The normal response to graded exercise includes progressive increases in heart rate and blood pressure. Failure of the blood pressure to increase or an actual decrease with signs of ischemia during the test is an important adverse prognostic sign, since it may reflect ischemia-induced global left ventricular dysfunction. The development of angina and/or severe (>0.2 mV) ST-segment depression at a low workload, i.e., before completion of stage II of the Bruce protocol, and/or ST-segment depression that persists >5 min after the termination of exercise increases the specificity of the test and suggests severe IHD and a high risk of future adverse events.

Cardiac Imaging (See also Chap. 270e) When the resting ECG is abnormal (e.g., preexcitation syndrome, >1 mm of resting ST-segment depression, left bundle branch block, paced ventricular rhythm), information gained from an exercise test can be enhanced by stress myocardial radionuclide perfusion imaging after the intravenous administration of thallium-201 or 99m-technetium sestamibi during exercise (or with pharmacologic) stress. Contemporary data also suggest positron emission tomography (PET) imaging (with exercise or pharmacologic stress) using N-13 ammonia or rubidium-82 nuclide as another technique for assessing perfusion. Images obtained immediately after cessation of exercise to detect regional ischemia are compared with those obtained at rest to confirm reversible ischemia and regions of persistently absent uptake that signify infarction.

A sizable fraction of patients who need noninvasive stress testing to identify myocardial ischemia and increased risk of coronary events cannot exercise because of peripheral vascular or musculoskeletal disease, exertional dyspnea, or deconditioning. In these circumstances, an intravenous pharmacologic challenge is used in place of exercise. For example, dipyridamole or adenosine can be given to create a coronary “steal” by temporarily increasing flow in nondiseased

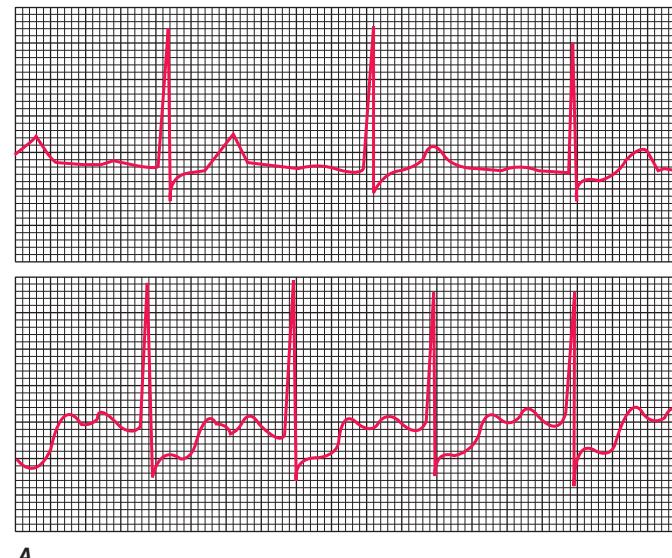
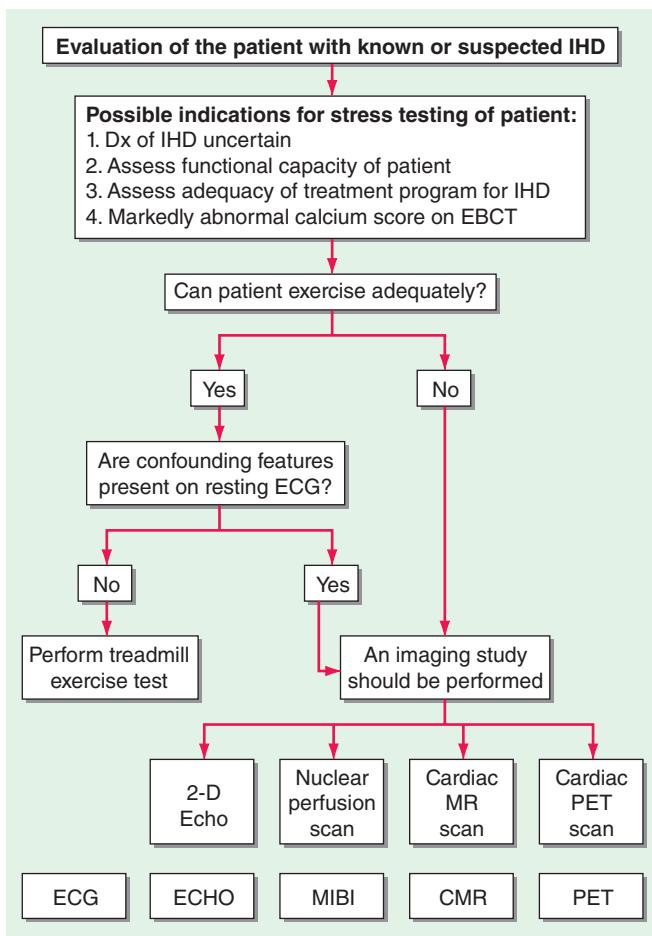


FIGURE 293-2 Evaluation of the patient with known or suspected ischemic heart disease. On the left of the figure is an algorithm for identifying patients who should be referred for stress testing and the decision pathway for determining whether a standard treadmill exercise with electrocardiogram (ECG) monitoring alone is adequate. A specialized imaging study is necessary if the patient cannot exercise adequately (pharmacologic challenge is given) or if there are confounding features on the resting ECG (symptom-limited treadmill exercise may be used to stress the coronary circulation). Panels B–E, continued on the next page, are examples of the data obtained with ECG monitoring and specialized imaging procedures. CMR, cardiac magnetic resonance; EBCT, electron beam computed tomography; ECHO, echocardiography; IHD, ischemic heart disease; MIBI, methoxyisobutyl isonitrite; MR, magnetic resonance; PET, positron emission tomography. **A.** Lead V₄ at rest (top panel) and after 4.5 min of exercise (bottom panel). There is 3 mm (0.3 mV) of horizontal ST-segment depression, indicating a positive test for ischemia. (Modified from BR Chaitman, in E Braunwald et al [eds]: *Heart Disease*, 8th ed, Philadelphia, Saunders, 2008.) **B.** A 45-year-old avid jogger who began experiencing classic substernal chest pressure underwent an exercise echo study. With exercise the patient's heart rate increased from 52 to 153 beats/min. The left ventricular chamber dilated with exercise, and the septal and apical portions became akinetic to dyskinetic (red arrow). These findings are strongly suggestive of a significant flow-limiting stenosis in the proximal left anterior descending artery, which was confirmed at coronary angiography. (Modified from SD Solomon, in E. Braunwald et al [eds]: *Primary Cardiology*, 2nd ed, Philadelphia, Saunders, 2003.) **C.** Stress and rest myocardial perfusion single-photon emission computed tomography images obtained with 99m-technetium sestamibi in a patient with chest pain and dyspnea on exertion. The images demonstrate a medium-size and severe stress perfusion defect involving the inferolateral and basal inferior walls, showing nearly complete reversibility, consistent with moderate ischemia in the right coronary artery territory (red arrows). (Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.) **D.** A patient with a prior myocardial infarction presented with recurrent chest discomfort. On cardiac magnetic resonance (CMR) cine imaging, a large area of anterior akinesia was noted (marked by the arrows in the top left and right images, systolic frame only). This area of akinesia was matched by a larger extent of late gadolinium-DTPA enhancements consistent with a large transmural myocardial infarction (marked by arrows in the middle left and right images). Resting (bottom left) and adenosine vasodilating stress (bottom right) first-pass perfusion images revealed reversible perfusion abnormality that extended to the inferior septum. This patient was found to have an occluded proximal left anterior descending coronary artery with extensive collateral formation. This case illustrates the utility of different modalities in a CMR examination in characterizing ischemic and infarcted myocardium. DTPA, diethylenetriamine penta-acetic acid. (Images provided by Dr. Raymond Kwong, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.) **E.** Stress and rest myocardial perfusion PET images obtained with rubidium-82 in a patient with chest pain on exertion. The images demonstrate a large and severe stress perfusion defect involving the mid and apical anterior, anterolateral, and anteroseptal walls and the left ventricular apex, showing complete reversibility, consistent with extensive and severe ischemia in the mid-left anterior descending coronary artery territory (red arrows). (Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.)

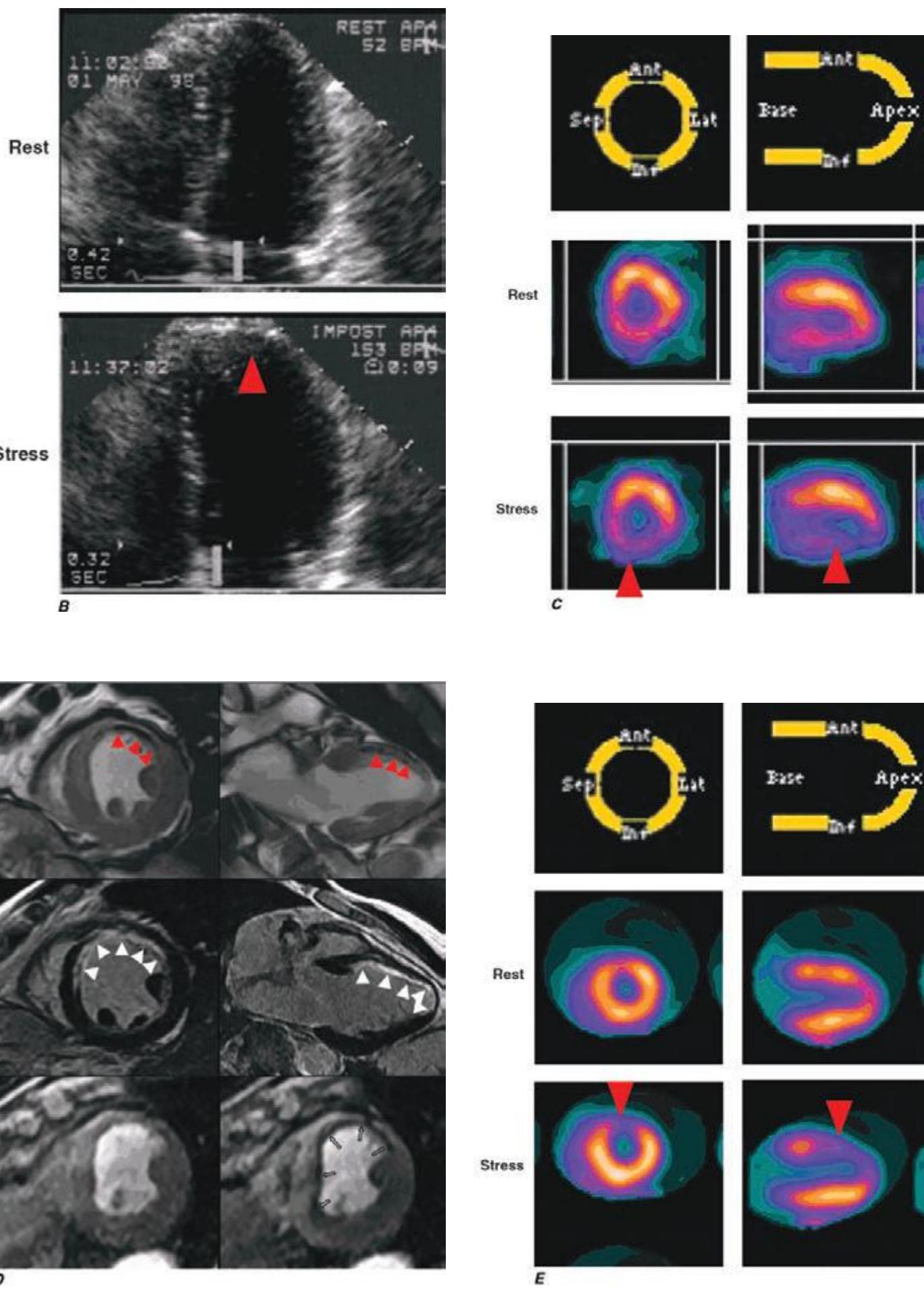


FIGURE 293-2 (Continued)

TABLE 293-2 RELATION OF METABOLIC EQUIVALENT TASKS (METS) TO STAGES IN VARIOUS TESTING PROTOCOLS

Functional Class	Clinical Status	O_2 Cost mL/kg/min	METs	Treadmill Protocols			
				BRUCE Modified 3 min Stages		BRUCE 3 min Stages	
NORMAL AND I	HEALTHY, DEPENDENT ON AGE, ACTIVITY	SEDENTARY HEALTHY	SYNTHETIC	MPH	%GR	MPH	%GR
				6.0	22	6.0	22
				5.5	20	5.2	20
				5.0	18	5.0	18
				56.0	16		
				52.5	15		
				49.0	14		
				45.5	13	4.2	16
				42.0	12		
				38.5	11	3.4	14
II		LIMITED	SYNTHETIC	35.0	10		
				31.5	9		
III		SYNTHETIC	SYNTHETIC	28.0	8		
				24.5	7	2.5	12
IV		SYNTHETIC	SYNTHETIC	21.0	6		
				17.5	5	1.7	10
				14.0	4		
				10.5	3	1.7	5
				7.0	2	1.7	0
				3.5	1		

Abbreviations: GR, grade; MPH, miles per hour.

Source: Modified from GF Fletcher et al: Circulation 104:1694, 2001.

segments of the coronary vasculature at the expense of diseased segments. Alternatively, a graded incremental infusion of dobutamine may be administered to increase MVO_2 . A variety of imaging options are available to accompany these pharmacologic stressors (Fig. 293-2). The development of a transient perfusion defect with a tracer such as thallium-201 or 99m-technetium sestamibi is used to detect myocardial ischemia.

Echocardiography is used to assess left ventricular function in patients with chronic stable angina and patients with a history of a prior myocardial infarction, pathologic Q waves, or clinical evidence of heart failure. Two-dimensional echocardiography can assess both global and regional wall motion abnormalities of the left ventricle that are transient when due to ischemia. Stress (exercise or dobutamine) echocardiography may cause the emergence of regions of akinesis or dyskinesis that are not present at rest. Stress echocardiography, like stress myocardial perfusion imaging, is more sensitive than exercise electrocardiography in the diagnosis of IHD. Cardiac magnetic resonance (CMR) stress testing is also evolving as an alternative to radioisotope, PET, or echocardiographic stress imaging. CMR stress testing performed with dobutamine infusion can be used to assess wall motion abnormalities accompanying ischemia, as well as myocardial perfusion. CMR can be used to provide more complete ventricular evaluation using multislice magnetic resonance imaging (MRI) studies.

Atherosclerotic plaques become progressively calcified over time, and coronary calcification in general increases with age. For this reason, methods for detecting coronary calcium have been developed as a measure of the presence of coronary atherosclerosis. These methods involve computed tomography (CT) applications that achieve rapid acquisition of images (electron beam [EBCT] and multidetector [MDCT] detection). Coronary calcium detected by these imaging techniques most commonly is quantified by using the Agatston score, which is based on the area and density of calcification. Although the diagnostic accuracy of this imaging method is high (sensitivity, 90–94%; specificity, 95–97%; negative predictive value, 93–99%), its prognostic utility has not been defined. Thus, its role in CT, EBCT, and MDCT scans for the detection and management of patients with IHD has not been clarified.

CORONARY ARTERIOGRAPHY

(See also Chap. 272) This diagnostic method outlines the lumina of the coronary arteries and can be used to detect or exclude serious coronary obstruction. However, coronary arteriography provides no information about the arterial wall, and severe atherosclerosis that does not encroach on the lumen may go undetected. Of note, atherosclerotic plaques characteristically are scattered throughout the coronary tree, tend to occur more frequently at branch points, and grow progressively in the intima and media of an epicardial coronary artery at first without encroaching on the lumen, causing an outward bulging of the artery—a process referred to as remodeling (Chap. 291e). Later in the course of the disease, further growth causes luminal narrowing.

Indications Coronary arteriography is indicated in (1) patients with chronic stable angina pectoris who are severely symptomatic despite medical therapy and are being considered for revascularization, i.e., a percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); (2) patients with troublesome symptoms that present diagnostic difficulties in whom there is a need to confirm or rule out the diagnosis of IHD; (3) patients with known or possible angina pectoris who have survived cardiac arrest; (4) patients with angina or evidence of ischemia on noninvasive testing with clinical or laboratory evidence of ventricular dysfunction; and (5) patients judged to be at high risk of sustaining coronary events based on signs of severe ischemia on noninvasive testing, regardless of the presence or severity of symptoms (see below).

Examples of other indications for coronary arteriography include the following:

1. Patients with chest discomfort suggestive of angina pectoris but a negative or nondiagnostic stress test who require a definitive diagnosis for guiding medical management, alleviating psychological stress, career or family planning, or insurance purposes.
2. Patients who have been admitted repeatedly to the hospital for a suspected acute coronary syndrome (Chaps. 294 and 295), but in whom this diagnosis has not been established and in whom the presence or absence of CAD should be determined.

3. Patients with careers that involve the safety of others (e.g., pilots, firefighters, police) who have questionable symptoms or suspicious or positive noninvasive tests and in whom there are reasonable doubts about the state of the coronary arteries.
4. Patients with aortic stenosis or hypertrophic cardiomyopathy and angina in whom the chest pain could be due to IHD.
5. Male patients >45 years and females >55 years who are to undergo a cardiac operation such as valve replacement or repair and who may or may not have clinical evidence of myocardial ischemia.
6. Patients after myocardial infarction, especially those who are at high risk after myocardial infarction because of the recurrence of angina or the presence of heart failure, frequent ventricular premature contractions, or signs of ischemia on the stress test.
7. Patients with angina pectoris, regardless of severity, in whom noninvasive testing indicates a high risk of coronary events (poor exercise performance or severe ischemia).
8. Patients in whom coronary spasm or another nonatherosclerotic cause of myocardial ischemia (e.g., coronary artery anomaly, Kawasaki disease) is suspected.

Noninvasive alternatives to diagnostic coronary arteriography include CT angiography and CMR angiography ([Chap. 270e](#)). Although these new imaging techniques can provide information about obstructive lesions in the epicardial coronary arteries, their exact role in clinical practice has not been rigorously defined. Important aspects of their use that should be noted include the substantially higher radiation exposure with CT angiography compared to conventional diagnostic arteriography and the limitations on CMR imposed by cardiac movement during the cardiac cycle, especially at high heart rates.

PROGNOSIS

The principal prognostic indicators in patients known to have IHD are age, the functional state of the left ventricle, the location(s) and severity of coronary artery narrowing, and the severity or activity of myocardial ischemia. Angina pectoris of recent onset, unstable angina ([Chap. 294](#)), early postmyocardial infarction angina, angina that is unresponsive or poorly responsive to medical therapy, and angina accompanied by symptoms of congestive heart failure all indicate an increased risk for adverse coronary events. The same is true for the physical signs of heart failure, episodes of pulmonary edema, transient third heart sounds, and mitral regurgitation and for echocardiographic or radioisotopic (or roentgenographic) evidence of cardiac enlargement and reduced (<0.40) ejection fraction.

Most important, any of the following signs during noninvasive testing indicates a high risk for coronary events: inability to exercise for 6 min, i.e., stage II (Bruce protocol) of the exercise test; a strongly positive exercise test showing onset of myocardial ischemia at low workloads (≥ 0.1 mV ST-segment depression before completion of stage II, ≥ 0.2 mV ST-segment depression at any stage, ST-segment depression for >5 min after the cessation of exercise, a decline in systolic pressure >10 mmHg during exercise, or the development of ventricular tachyarrhythmias during exercise); the development of large or multiple perfusion defects or increased lung uptake during stress radioisotope perfusion imaging; and a decrease in left ventricular ejection fraction during exercise on radionuclide ventriculography or during stress echocardiography. Conversely, patients who can complete stage III of the Bruce exercise protocol and have a normal stress perfusion scan or negative stress echocardiographic evaluation are at very low risk for future coronary events. The finding of frequent episodes of ST-segment deviation on ambulatory ECG monitoring (even in the absence of symptoms) is also an adverse prognostic finding.

On cardiac catheterization, elevations of left ventricular end-diastolic pressure and ventricular volume and reduced ejection fraction are the most important signs of left ventricular dysfunction and are associated with a poor prognosis. Patients with chest discomfort but normal left ventricular function and normal coronary arteries have an excellent prognosis. Obstructive lesions of the left main ($>50\%$ luminal diameter) or left anterior descending coronary artery proximal to the origin of the first septal artery are associated with

a greater risk than are lesions of the right or left circumflex coronary artery because of the greater quantity of myocardium at risk. Atherosclerotic plaques in epicardial arteries with fissuring or filling defects indicate increased risk. These lesions go through phases of inflammatory cellular activity, degeneration, endothelial dysfunction, abnormal vasomotion, platelet aggregation, and fissuring or hemorrhage. These factors can temporarily worsen the stenosis and cause thrombosis and/or abnormal reactivity of the vessel wall, thus exacerbating the manifestations of ischemia. The recent onset of symptoms, the development of severe ischemia during stress testing (see above), and unstable angina pectoris ([Chap. 294](#)) all reflect episodes of rapid progression in coronary lesions.

With any degree of obstructive CAD, mortality is greatly increased when left ventricular function is impaired; conversely, at any level of left ventricular function, the prognosis is influenced importantly by the quantity of myocardium perfused by critically obstructed vessels. Therefore, it is essential to collect all the evidence substantiating past myocardial damage (evidence of myocardial infarction on ECG, echocardiography, radioisotope imaging, or left ventriculography), residual left ventricular function (ejection fraction and wall motion), and risk of future damage from coronary events (extent of coronary disease and severity of ischemia defined by noninvasive stress testing). The larger the quantity of established myocardial necrosis is, the less the heart is able to withstand additional damage and the poorer the prognosis is. Risk estimation must include age, presenting symptoms, all risk factors, signs of arterial disease, existing cardiac damage, and signs of impending damage (i.e., ischemia).

The greater the number and severity of risk factors for coronary atherosclerosis (advanced age [>75 years], hypertension, dyslipidemia, diabetes, morbid obesity, accompanying peripheral and/or cerebrovascular disease, previous myocardial infarction), the worse the prognosis of an angina patient. Evidence exists that elevated levels of CRP in the plasma, extensive coronary calcification on electron beam CT (see above), and increased carotid intimal thickening on ultrasound examination also indicate an increased risk of coronary events.

TREATMENT STABLE ANGINA PECTORIS

Once the diagnosis of IHD has been made, each patient must be evaluated individually with respect to his or her level of understanding, expectations and goals, control of symptoms, and prevention of adverse clinical outcomes such as myocardial infarction and premature death. The degree of disability and the physical and emotional stress that precipitates angina must be recorded carefully to set treatment goals. The management plan should include the following components: (1) explanation of the problem and reassurance about the ability to formulate a treatment plan, (2) identification and treatment of aggravating conditions, (3) recommendations for adaptation of activity as needed, (4) treatment of risk factors that will decrease the occurrence of adverse coronary outcomes, (5) drug therapy for angina, and (6) consideration of revascularization.

EXPLANATION AND REASSURANCE

Patients with IHD need to understand their condition and realize that a long and productive life is possible even though they have angina pectoris or have experienced and recovered from an acute myocardial infarction. Offering results of clinical trials showing improved outcomes can be of great value in encouraging patients to resume or maintain activity and return to work. A planned program of rehabilitation can encourage patients to lose weight, improve exercise tolerance, and control risk factors with more confidence.

IDENTIFICATION AND TREATMENT OF AGGRAVATING CONDITIONS

A number of conditions may increase oxygen demand or decrease oxygen supply to the myocardium and may precipitate or exacerbate angina in patients with IHD. Left ventricular hypertrophy,

aortic valve disease, and hypertrophic cardiomyopathy may cause or contribute to angina and should be excluded or treated. Obesity, hypertension, and hyperthyroidism should be treated aggressively to reduce the frequency and severity of anginal episodes. Decreased myocardial oxygen supply may be due to reduced oxygenation of the arterial blood (e.g., in pulmonary disease or, when carboxyhemoglobin is present, due to cigarette or cigar smoking) or decreased oxygen-carrying capacity (e.g., in anemia). Correction of these abnormalities, if present, may reduce or even eliminate angina pectoris.

ADAPTATION OF ACTIVITY

Myocardial ischemia is caused by a discrepancy between the demand of the heart muscle for oxygen and the ability of the coronary circulation to meet that demand. Most patients can be helped to understand this concept and utilize it in the rational programming of activity. Many tasks that ordinarily evoke angina may be accomplished without symptoms simply by reducing the speed at which they are performed. Patients must appreciate the diurnal variation in their tolerance of certain activities and should reduce their energy requirements in the morning, immediately after meals, and in cold or inclement weather. On occasion, it may be necessary to recommend a change in employment or residence to avoid physical stress.

Physical conditioning usually improves the exercise tolerance of patients with angina and has substantial psychological benefits. A regular program of isotonic exercise that is within the limits of the individual patient's threshold for the development of angina pectoris and that does not exceed 80% of the heart rate associated with ischemia on exercise testing should be strongly encouraged. Based on the results of an exercise test, the number of metabolic equivalent tasks (METs) performed at the onset of ischemia can be estimated (Table 293-2) and a practical exercise prescription can be formulated to permit daily activities that will fall below the ischemic threshold (Table 293-3).

TREATMENT OF RISK FACTORS

A family history of premature IHD is an important indicator of increased risk and should trigger a search for treatable risk factors such as hyperlipidemia, hypertension, and diabetes mellitus. Obesity impairs the treatment of other risk factors and increases the risk of adverse coronary events. In addition, obesity often is accompanied by three other risk factors: diabetes mellitus, hypertension, and hyperlipidemia. The treatment of obesity and these accompanying risk factors is an important component of any management plan. A diet low in saturated and *trans*-unsaturated fatty acids and a reduced caloric intake to achieve optimal body weight are a cornerstone in the management of chronic IHD. It is especially important to emphasize weight loss and regular exercise in patients with the metabolic syndrome or overt diabetes mellitus.

Cigarette smoking accelerates coronary atherosclerosis in both sexes and at all ages and increases the risk of thrombosis, plaque instability, myocardial infarction, and death (Chap. 291e). In addition, by increasing myocardial oxygen needs and reducing oxygen supply, it aggravates angina. Smoking cessation studies have demonstrated important benefits with a significant decline in the occurrence of these adverse outcomes. The physician's message must be clear and strong and supported by programs that achieve and monitor abstinence (Chap. 470). Hypertension (Chap. 298) is associated with an increased risk of adverse clinical events from coronary atherosclerosis as well as stroke. In addition, the left ventricular hypertrophy that results from sustained hypertension aggravates ischemia. There is evidence that long-term effective treatment of hypertension can decrease the occurrence of adverse coronary events.

Diabetes mellitus (Chap. 417) accelerates coronary and peripheral atherosclerosis and is frequently associated with dyslipidemias and increases in the risk of angina, myocardial infarction, and sudden coronary death. Aggressive control of the dyslipidemia (target LDL cholesterol <70 mg/dL) and hypertension (target blood pressure 120/80 mmHg) that are frequently found in diabetic patients is highly effective and therefore essential, as described below.

TABLE 293-3 ENERGY REQUIREMENTS FOR SOME COMMON ACTIVITIES

Less Than 3 METs	3–5 METs	5–7 METs	7–9 METs	More Than 9 METs
Self-Care				
Washing/shaving	Cleaning windows	Easy digging in garden	Heavy shoveling	Carrying loads up stairs (objects more than 90 lb)
Dressing	Raking	Level hand lawn mowing	Carrying objects (60–90 lb)	Climbing stairs (quickly)
Light housekeeping	Power lawn mowing	Carrying objects (30–60 lb)		Shoveling heavy snow
Desk work	Bed making/stripping			
Driving auto	Carrying objects (15–30 lb)			
Occupational				
Sitting (clerical/assembly)	Stocking shelves (light objects)	Carpentry (exterior)	Digging ditches (pick and shovel)	Heavy labor
Desk work	Light welding/carpentry	Shoveling dirt		
Standing (store clerk)		Sawing wood		
Recreational				
Golf (cart)	Dancing (social)	Tennis (singles)	Canoeing	Squash
Knitting	Golf (walking)	Snow skiing (downhill)	Mountain climbing	Ski touring
	Sailing	Light backpacking		Vigorous basketball
	Tennis (doubles)	Basketball		
		Stream fishing		
Physical Conditioning				
Walking (2 mph)	Level walking (3–4 mph)	Level walking (4.5–5.0 mph)	Level jogging (5 mph)	Running more than 6 mph
Stationary bike	Level biking (6–8 mph)	Bicycling (9–10 mph)	Swimming (crawl stroke)	Bicycling (more than 13 mph)
Very light calisthenics	Light calisthenics	Swimming, breast stroke	Rowing machine	Rope jumping
			Heavy calisthenics	Walking uphill (5 mph)
			Bicycling (12 mph)	

Abbreviation: METs, metabolic equivalent tasks.

Source: Modified from WL Haskell: Rehabilitation of the coronary patient, in NK Wenger, HK Hellerstein (eds): *Design and Implementation of Cardiac Conditioning Program*. New York, Churchill Livingstone, 1978.

The treatment of dyslipidemia is central in aiming for long-term relief from angina, reduced need for revascularization, and reduction in myocardial infarction and death. The control of lipids can be achieved by the combination of a diet low in saturated and trans-unsaturated fatty acids, exercise, and weight loss. Nearly always, HMG-CoA reductase inhibitors (statins) are required and can lower LDL cholesterol (25–50%), raise HDL cholesterol (5–9%), and lower triglycerides (5–30%). A powerful treatment effect of statins on atherosclerosis, IHD, and outcomes is seen regardless of the pretreatment LDL cholesterol level. Fibrates or niacin can be used to raise HDL cholesterol and lower triglycerides ([Chaps. 291e and 421](#)). Controlled trials with lipid-regulating regimens have shown equal proportional benefit for men, women, the elderly, diabetic patients, and smokers.

Compliance with the health-promoting behaviors listed above is generally very poor, and a conscientious physician must not underestimate the major effort required to meet this challenge. Many patients who are discharged from the hospital with proven coronary disease do not receive adequate treatment for dyslipidemia. In light of the proof that treating dyslipidemia brings major benefits, physicians need to establish treatment pathways, monitor compliance, and follow up regularly.

RISK REDUCTION IN WOMEN WITH IHD

The incidence of clinical IHD in premenopausal women is very low; however, after menopause, the atherogenic risk factors increase (e.g., increased LDL, reduced HDL) and the rate of clinical coronary events accelerates to the levels observed in men. Women have not given up cigarette smoking as effectively as have men. Diabetes mellitus, which is more common in women, greatly increases the occurrence of clinical IHD and amplifies the deleterious effects of hypertension, hyperlipidemia, and smoking. Cardiac catheterization and coronary revascularization are underused in women and are performed at a later and more severe stage of the disease than in men. When cholesterol lowering, beta blockers after myocardial infarction, and coronary artery bypass grafting are applied in the appropriate patient groups, women benefit to the same degree as men.

DRUG THERAPY

The commonly used drugs for the treatment of angina pectoris are summarized in [Tables 293-4 through 293-6](#). Pharmacotherapy for IHD is designed to reduce the frequency of anginal episodes, myocardial infarction, and coronary death. There is a wealth of trial

data to emphasize how important this medical management is when added to the health-promoting behaviors discussed above. To achieve maximum benefit from medical therapy for IHD, it is frequently necessary to combine agents from different classes and titrate the doses as guided by the individual profile of risk factors, symptoms, hemodynamic responses, and side effects.

NITRATES

The organic nitrates are a valuable class of drugs in the management of angina pectoris ([Table 293-4](#)). Their major mechanisms of action include systemic venodilation with concomitant reduction in left ventricular end-diastolic volume and pressure, thereby reducing myocardial wall tension and oxygen requirements; dilation of epicardial coronary vessels; and increased blood flow in collateral vessels. When metabolized, organic nitrates release nitric oxide (NO) that binds to guanylyl cyclase in vascular smooth muscle cells, leading to an increase in cyclic guanosine monophosphate, which causes relaxation of vascular smooth muscle. Nitrates also exert antithrombotic activity by NO-dependent activation of platelet guanylyl cyclase, impairment of intraplatelet calcium flux, and platelet activation.

The absorption of these agents is most rapid and complete through the mucous membranes. For this reason, nitroglycerin is most commonly administered sublingually in tablets of 0.4 or 0.6 mg. Patients with angina should be instructed to take the medication both to relieve angina and also approximately 5 min before stress that is likely to induce an episode. The value of this prophylactic use of the drug cannot be overemphasized.

Nitrates improve exercise tolerance in patients with chronic angina and relieve ischemia in patients with unstable angina as well as patients with Prinzmetal's variant angina ([Chap. 294](#)). A diary of angina and nitroglycerin use may be valuable for detecting changes in the frequency, severity, or threshold for discomfort that may signify the development of unstable angina pectoris and/or herald an impending myocardial infarction.

Long-Acting Nitrates None of the long-acting nitrates are as effective as sublingual nitroglycerin for the acute relief of angina. These organic nitrate preparations can be swallowed, chewed, or administered as a patch or paste by the transdermal route ([Table 293-4](#)). They can provide effective plasma levels for up to 24 h, but the therapeutic response is highly variable. Different preparations and/or administration during the daytime should be tried only to prevent discomfort while avoiding side effects such as headache and dizziness. Individual dose titration is important to prevent side effects. To minimize the effects of tolerance, the minimum effective dose should be used and a minimum of 8 h each day kept free of the drug to restore any useful response(s).

β-Adrenergic Blockers These drugs represent an important component of the pharmacologic treatment of angina pectoris ([Table 293-5](#)). They reduce myocardial oxygen demand by inhibiting the increases in heart rate, arterial pressure, and myocardial contractility caused by adrenergic activation. Beta blockade reduces these variables most strikingly during exercise but causes only small reductions at rest. Long-acting beta-blocking drugs or sustained-release formulations offer the advantage of once-daily dosing ([Table 293-5](#)). The therapeutic aims include relief of angina and ischemia. These drugs also can reduce mortality and reinfarction rates in patients after myocardial infarction and are moderately effective antihypertensive agents.

Relative contraindications include asthma and reversible airway obstruction in patients with chronic lung disease, atrioventricular conduction disturbances, severe bradycardia, Raynaud's phenomenon, and a history of mental depression. Side effects include fatigue, reduced exercise tolerance, nightmares, impotence, cold extremities, intermittent claudication, bradycardia (sometimes severe), impaired atrioventricular conduction, left ventricular failure, bronchial asthma, worsening claudication, and intensification of the hypoglycemia produced by oral hypoglycemic agents and insulin.

TABLE 293-4 NITRATE THERAPY IN PATIENTS WITH ISCHEMIC HEART DISEASE

Preparation of Agent	Dose	Schedule
Nitroglycerin ^a		
Ointment	0.5–2 inches	Two or three times daily
Transdermal patch	0.2–0.8 mg/h	Every 24 h; remove at bedtime for 12–14 h
Sublingual tablet	0.3–0.6 mg	As needed, up to three doses 5 min apart
Spray	One or two sprays	As needed, up to three doses 5 min apart
Isosorbide dinitrate ^a		
Oral	10–40 mg	Two or three times daily
Oral sustained release	80–120 mg	Once or twice daily (eccentric schedules)
Isosorbide 5-mononitrate		
Oral	20 mg	Twice daily (given 7–8 h apart)
Oral sustained release	30–240 mg	Once daily

^aA 10- to 12-h nitrate-free interval is recommended.

Source: Modified from DA Morrow, WE Boden: Stable ischemic heart disease. In RO Bonow et al (eds): *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 9th edition. Philadelphia, Saunders, 2012, p. 1224.

TABLE 293-5 PROPERTIES OF BETA BLOCKERS IN CLINICAL USE FOR ISCHEMIC HEART DISEASE

Drugs	Selectivity	Partial Agonist Activity	Usual Dose for Angina
Acetbutolol	β_1	Yes	200–600 mg twice daily
Atenolol	β_1	No	50–200 mg/d
Betaxolol	β_1	No	10–20 mg/d
Bisoprolol	β_1	No	10 mg/d
Esmolol (intravenous) ^a	β_1	No	50–300 μ g/kg/min
Labetalol ^b	None	Yes	200–600 mg twice daily
Metoprolol	β_1	No	50–200 mg twice daily
Nadolol	None	No	40–80 mg/d
Nebivolol	β_1 (at low doses)	No	5–40 mg/d
Pindolol	None	Yes	2.5–7.5 mg 3 times daily
Propranolol	None	No	80–120 mg twice daily
Timolol	None	No	10 mg twice daily

^aEsmolol is an ultra-short-acting beta blocker that is administered as a continuous intravenous infusion. Its rapid offset of action makes esmolol an attractive agent to use in patients with relative contraindications to beta blockade. ^bLabetalol is a combined alpha and beta blocker.

Note: This list of beta blockers that may be used to treat patients with angina pectoris is arranged alphabetically. The agents for which there is the greatest clinical experience include atenolol, metoprolol, and propranolol. It is preferable to use a sustained-release formulation that may be taken once daily to improve the patient's compliance with the regimen.

Source: Modified from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003.

Reducing the dose or even discontinuation may be necessary if these side effects develop and persist. Since sudden discontinuation can intensify ischemia, the doses should be tapered over 2 weeks. Beta blockers with relative β_1 -receptor specificity such as metoprolol and atenolol may be preferable in patients with mild bronchial obstruction and insulin-requiring diabetes mellitus.

Calcium Channel Blockers Calcium channel blockers (Table 293-6) are coronary vasodilators that produce variable and dose-dependent reductions in myocardial oxygen demand, contractility, and arterial pressure. These combined pharmacologic effects are advantageous and make these agents as effective as beta blockers in the treatment of angina pectoris. They are indicated when beta blockers are contraindicated, poorly tolerated, or ineffective. Because of differences in the dose-response relationship on cardiac electrical activity between the dihydropyridine and nondihydropyridine calcium channel blockers, verapamil and diltiazem may produce symptomatic disturbances in cardiac conduction and bradyarrhythmias. They also exert negative inotropic actions and are more

likely to aggravate left ventricular failure, particularly when used in patients with left ventricular dysfunction, especially if the patients are also receiving beta blockers. Although useful effects usually are achieved when calcium channel blockers are combined with beta blockers and nitrates, individual titration of the doses is essential with these combinations. Variant (Prinzmetal's) angina responds particularly well to calcium channel blockers (especially members of the dihydropyridine class), supplemented when necessary by nitrates (*Chap. 294*).

Verapamil ordinarily should not be combined with beta blockers because of the combined adverse effects on heart rate and contractility. Diltiazem can be combined with beta blockers in patients with normal ventricular function and no conduction disturbances. Amlodipine and beta blockers have complementary actions on coronary blood supply and myocardial oxygen demands. Whereas the former decreases blood pressure and dilates coronary arteries, the latter slows heart rate and decreases contractility. Amlodipine and the other second-generation dihydropyridine calcium antagonists (nicardipine, isradipine, long-acting nifedipine, and felodipine) are

TABLE 293-6 CALCIUM CHANNEL BLOCKERS IN CLINICAL USE FOR ISCHEMIC HEART DISEASE

Drugs	Usual Dose	Duration of Action	Side Effects
Dihydropyridines			
Amlodipine	5–10 mg qd	Long	Headache, edema
Felodipine	5–10 mg qd	Long	Headache, edema
Isradipine	2.5–10 mg bid	Medium	Headache, fatigue
Nicardipine	20–40 mg tid	Short	Headache, dizziness, flushing, edema
Nifedipine	Immediate release: 30–90 mg daily orally Slow release: 30–180 mg orally	Short	Hypotension, dizziness, flushing, nausea, constipation, edema
Nisoldipine	20–40 mg qd	Short	Similar to nifedipine
Nondihydropyridines			
Diltiazem	Immediate release: 30–80 mg 4 times daily Slow release: 120–320 mg qd	Short Long	Hypotension, dizziness, flushing, bradycardia, edema
Verapamil	Immediate release: 80–160 mg tid Slow release: 120–480 mg qd	Short Long	Hypotension, myocardial depression, heart failure, edema, bradycardia

^aMay be associated with increased risk of mortality if administered during acute myocardial infarction.

Note: This list of calcium channel blockers that may be used to treat patients with angina pectoris is divided into two broad classes, dihydropyridines and nondihydropyridines, and arranged alphabetically within each class. Among the dihydropyridines, the greatest clinical experience has been obtained with amlodipine and nifedipine. After the initial period of dose titration with a short-acting formulation, it is preferable to switch to a sustained-release formulation that may be taken once daily to improve patient compliance with the regimen.

Source: Modified from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003.

1590 potent vasodilators and are useful in the simultaneous treatment of angina and hypertension. Short-acting dihydropyridines should be avoided because of the risk of precipitating infarction, particularly in the absence of concomitant beta blocker therapy.

Choice Between Beta Blockers and Calcium Channel Blockers for Initial Therapy

Since beta blockers have been shown to improve life expectancy after acute myocardial infarction ([Chaps. 294 and 295](#)) and calcium channel blockers have not, the former may also be preferable in patients with angina and a damaged left ventricle. However, calcium channel blockers are indicated in patients with the following: (1) inadequate responsiveness to the combination of beta blockers and nitrates; many of these patients do well with a combination of a beta blocker and a dihydropyridine calcium channel blocker; (2) adverse reactions to beta blockers such as depression, sexual disturbances, and fatigue; (3) angina and a history of asthma or chronic obstructive pulmonary disease; (4) sick-sinus syndrome or significant atrioventricular conduction disturbances; (5) Prinzmetal's angina; or (6) symptomatic peripheral arterial disease.

Antiplatelet Drugs Aspirin is an irreversible inhibitor of platelet cyclooxygenase and thereby interferes with platelet activation. Chronic administration of 75–325 mg orally per day has been shown to reduce coronary events in asymptomatic adult men over age 50, patients with chronic stable angina, and patients who have or have survived unstable angina and myocardial infarction. There is a dose-dependent increase in bleeding when aspirin is used chronically. It is preferable to use an enteric-coated formulation in the range of 81–162 mg/d. Administration of this drug should be considered in all patients with IHD in the absence of gastrointestinal bleeding, allergy, or dyspepsia. Clopidogrel (300–600 mg loading and 75 mg/d) is an oral agent that blocks P2Y12 ADP receptor-mediated platelet aggregation. It provides benefits similar to those of aspirin in patients with stable chronic IHD and may be substituted for aspirin if aspirin causes the side effects listed above. Clopidogrel combined with aspirin reduces death and coronary ischemic events in patients with an acute coronary syndrome ([Chap. 294](#)) and also reduces the risk of thrombus formation in patients undergoing implantation of a stent in a coronary artery ([Chap. 296e](#)). Alternative antiplatelet agents that block the P2Y12 platelet receptor such as prasugrel and ticagrelor have been shown to be more effective than clopidogrel for prevention of ischemic events after placement of a stent for an acute coronary syndrome but are associated with an increased risk of bleeding. Although combined treatment with clopidogrel and aspirin for at least a year is recommended in patients with an acute coronary syndrome treated with implantation of a drug-eluting stent, studies have not shown any benefit from the routine addition of clopidogrel to aspirin in patients with chronic stable IHD.

OTHER THERAPIES

The angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of survivors of myocardial infarction, patients with hypertension or chronic IHD including angina pectoris, and those at high risk of vascular diseases such as diabetes. The benefits of ACE inhibitors are most evident in IHD patients at increased risk, especially if diabetes mellitus or left ventricle dysfunction is present, and those who have not achieved adequate control of blood pressure and LDL cholesterol on beta blockers and statins. However, the routine administration of ACE inhibitors to IHD patients who have normal left ventricular function and have achieved blood pressure and LDL goals on other therapies does not reduce the incidence of events and therefore is not cost-effective.

Despite treatment with nitrates, beta blockers, or calcium channel blockers, some patients with IHD continue to experience angina, and additional medical therapy is now available to alleviate their symptoms. Ranolazine, a piperazine derivative, may be useful for patients with chronic angina despite standard medical therapy. Its antianginal action is believed to occur via inhibition of the late inward sodium current (I_{Na}). The benefits of I_{Na} inhibition include

limitation of the Na overload of ischemic myocytes and prevention of Ca^{2+} overload via the Na^+-Ca^{2+} exchanger. A dose of 500–1000 mg orally twice daily is usually well tolerated. Ranolazine is contraindicated in patients with hepatic impairment or with conditions or drugs associated with QT_c prolongation and when drugs that inhibit the CYP3A metabolic system (e.g., ketoconazole, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and large quantities of grapefruit juice) are being used.

Nonsteroidal anti-inflammatory drug (NSAID) use in patients with IHD may be associated with a small but finite increased risk of myocardial infarction and mortality. For this reason, they generally should be avoided in IHD patients. If they are required for symptom relief, it is advisable to coadminister aspirin and strive to use an NSAID associated with the lowest risk of cardiovascular events, in the lowest dose required, and for the shortest period of time.

Another class of agents opens ATP-sensitive potassium channels in myocytes, leading to a reduction of free intracellular calcium ions. The major drug in this class is nicorandil, which typically is administered orally in a dose of 20 mg twice daily for prevention of angina. (Nicorandil is not available for use in the United States but is used in several other countries.)

Angina and Heart Failure Transient left ventricular failure with angina can be controlled by the use of nitrates. For patients with established congestive heart failure, the increased left ventricular wall tension raises myocardial oxygen demand. Treatment of congestive heart failure with an ACE inhibitor, a diuretic, and digoxin ([Chap. 279](#)) reduces heart size, wall tension, and myocardial oxygen demand, which helps control angina and ischemia. If the symptoms and signs of heart failure are controlled, an effort should be made to use beta blockers not only for angina but because trials in heart failure have shown significant improvement in survival. A trial of the intravenous ultra-short-acting beta blocker esmolol may be useful to establish the safety of beta blockade in selected patients. Nocturnal angina often can be relieved by the treatment of heart failure.

The combination of congestive heart failure and angina in patients with IHD usually indicates a poor prognosis and warrants serious consideration of cardiac catheterization and coronary revascularization.

CORONARY REVASCULARIZATION

Clinical trials have confirmed that with the initial diagnosis of stable IHD, it is first appropriate to initiate a thorough medical regimen as described above. Revascularization should be considered in the presence of unstable phases of the disease, intractable symptoms, severe ischemia or high-risk coronary anatomy, diabetes, and impaired left ventricular (LV) function. *Revascularization should be employed in conjunction with but not replace the continuing need to modify risk factors and assess medical therapy.* An algorithm for integrating medical therapy and revascularization options in patients with IHD is shown in [Fig. 293-3](#).

PERCUTANEOUS CORONARY INTERVENTION

(See also [Chap. 296e](#)) Percutaneous coronary intervention (PCI) involving balloon dilatation usually accompanied by coronary stenting is widely used to achieve revascularization of the myocardium in patients with symptomatic IHD and suitable stenoses of epicardial coronary arteries. Whereas patients with stenosis of the left main coronary artery and those with three-vessel IHD (especially with diabetes and/or impaired LV function) who require revascularization are best treated with CABG, PCI is widely employed in patients with symptoms and evidence of ischemia due to stenoses of one or two vessels and even in selected patients with three-vessel disease (and, perhaps, in some patients with left main disease) and may offer many advantages over surgery.

Indications and Patient Selection The most common clinical indication for PCI is symptom-limiting angina pectoris, despite medical therapy, accompanied by evidence of ischemia during a stress test. PCI is more effective than medical therapy for the relief of angina. PCI improves

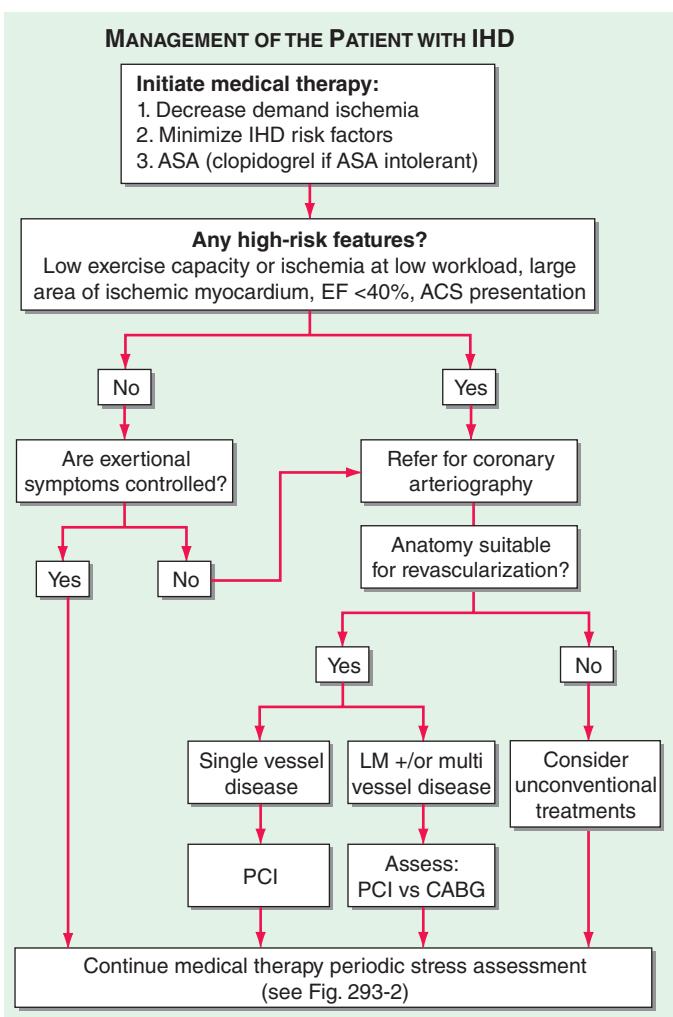


FIGURE 293-3 Algorithm for management of a patient with ischemic heart disease. All patients should receive the core elements of medical therapy as shown at the top of the algorithm. If high-risk features are present, as established by the clinical history, exercise test data, and imaging studies, the patient should be referred for coronary arteriography. Based on the number and location of the diseased vessels and their suitability for revascularization, the patient is treated with a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery or should be considered for unconventional treatments. See text for further discussion. ACS, acute coronary syndrome; ASA, aspirin; EF, ejection fraction; IHD, ischemic heart disease; LM, left main.

outcomes in patients with unstable angina or when used early in the course of myocardial infarction with and without cardiogenic shock. However, in patients with stable exertional angina, clinical trials have confirmed that PCI does not reduce the occurrence of death or myocardial infarction compared to optimum medical therapy. PCI can be used to treat stenoses in native coronary arteries as well as in bypass grafts in patients who have recurrent angina after CABG.

Risks When coronary stenoses are discrete and symmetric, two and even three vessels can be treated in sequence. However, case selection is essential to avoid a prohibitive risk of complications, which are usually due to dissection or thrombosis with vessel occlusion, uncontrolled ischemia, and ventricular failure (Chap. 296e). Oral aspirin, a P2Y12 antagonist, and an antithrombin agent are given to reduce coronary thrombus formation. Left main coronary artery stenosis generally is regarded as a contraindication to PCI; such patients should be treated with CABG. In selected cases such as patients with prohibitive surgical risks, PCI of an unprotected left main can be considered, but such a procedure should be performed only by a highly skilled

operator; importantly, there are regional differences in the use of this approach internationally.

Efficacy Primary success, i.e., adequate dilation (an increase in luminal diameter >20% to a residual diameter obstruction <50%) with relief of angina, is achieved in >95% of cases. Recurrent stenosis of the dilated vessels occurs in ~20% of cases within 6 months of PCI with bare metal stents, and angina will recur within 6 months in 10% of cases. Restenosis is more common in patients with diabetes mellitus, arteries with small caliber, incomplete dilation of the stenosis, long stents, occluded vessels, obstructed vein grafts, dilation of the left anterior descending coronary artery, and stenoses containing thrombi. In diseased vein grafts, procedural success has been improved by the use of capture devices or filters that prevent embolization, ischemia, and infarction.

It is usual clinical practice to administer aspirin indefinitely and a P2Y12 antagonist for 1–3 months after the implantation of a bare metal stent. Although aspirin in combination with a thienopyridine may help prevent coronary thrombosis during and shortly after PCI with stenting, there is no evidence that these medications reduce the incidence of restenosis.

The use of drug-eluting stents that locally deliver antiproliferative drugs can reduce restenosis to less than 10%. Advances in PCI, especially the availability of drug-eluting stents, have vastly extended the use of this revascularization option in patients with IHD. Of note, however, the delayed endothelial healing in the region of a drug-eluting stent also extends the period during which the patient is at risk for subacute stent thrombosis. Current recommendations are to administer aspirin indefinitely and a P2Y12 antagonist daily for at least 1 year after implantation of a drug-eluting stent. When a situation arises in which temporary discontinuation of antiplatelet therapy is necessary, the clinical circumstances should be reviewed with the operator who performed the PCI and a coordinated plan should be established for minimizing the risk of late stent thrombosis; central to this plan is the discontinuation of antiplatelet therapy for the shortest acceptable period. The risk of stent thrombosis is dependent on stent size and length, complexity of the lesions, age, diabetes, and technique. However, compliance with dual antiplatelet therapy and individual responsiveness to platelet inhibition are very important factors as well.

Successful PCI produces effective relief of angina in >95% of cases. The majority of patients with symptomatic IHD who require revascularization can be treated initially by PCI. Successful PCI is less invasive and expensive than CABG and permits savings in the *initial* cost of care. Successful PCI avoids the risk of stroke associated with CABG surgery, allows earlier return to work, and allows the resumption of an active life. However, the early health-related and economic benefit of PCI is reduced over time because of the greater need for follow-up and the increased need for repeat procedures. When directly compared in patients with diabetes or three-vessel or left main CAD, CABG was superior to PCI in preventing major adverse cardiac or cerebrovascular events over a 12-month follow-up.

CORONARY ARTERY BYPASS GRAFTING

Anastomosis of one or both of the internal mammary arteries or a radial artery to the coronary artery distal to the obstructive lesion is the preferred procedure. For additional obstructions that cannot be bypassed by an artery, a section of a vein (usually the saphenous) is used to form a connection between the aorta and the coronary artery distal to the obstructive lesion.

Although some indications for CABG are controversial, certain areas of agreement exist:

1. The operation is relatively safe, with mortality rates <1% in patients without serious comorbid disease and normal LV function and when the procedure is performed by an experienced surgical team.
2. Intraoperative and postoperative mortality rates increase with the severity of ventricular dysfunction, comorbidities, age >80 years, and lack of surgical experience. The effectiveness and risk of CABG vary widely depending on case selection and the skill and experience of the surgical team.

3. Occlusion of venous grafts is observed in 10–20% of patients during the first postoperative year and in approximately 2% per year during 5- to 7-year follow-up and 4% per year thereafter. Long-term patency rates are considerably higher for internal mammary and radial artery implantations than for saphenous vein grafts. In patients with left anterior descending coronary artery obstruction, survival is better when coronary bypass involves the internal mammary artery rather than a saphenous vein. Graft patency and outcomes are improved by meticulous treatment of risk factors, particularly dyslipidemia.
4. Angina is abolished or greatly reduced in ~90% of patients after complete revascularization. Although this usually is associated with graft patency and restoration of blood flow, the pain may also have been alleviated as a result of infarction of the ischemic segment or a placebo effect. Within 3 years, angina recurs in about one-fourth of patients but is rarely severe.
5. Survival may be improved by operation in patients with stenosis of the left main coronary artery as well as in patients with three- or two-vessel disease with significant obstruction of the proximal left anterior descending coronary artery. The survival benefit is greater in patients with abnormal LV function (ejection fraction <50%). Survival *may* also be improved in the following patients: (a) patients with obstructive CAD who have survived sudden cardiac death or sustained ventricular tachycardia; (b) patients who have undergone previous CABG and have multiple saphenous vein graft stenoses, especially of a graft supplying the left anterior descending coronary artery; and (c) patients with recurrent stenosis after PCI and high-risk criteria on noninvasive testing.
6. Minimally invasive CABG through a small thoracotomy and/or off-pump surgery can reduce morbidity and shorten convalescence in suitable patients but does not appear to reduce significantly the risk of neurocognitive dysfunction postoperatively.
7. Among patients with type 2 diabetes mellitus and multivessel coronary disease, CABG surgery plus optimal medical therapy is superior to optimal medical therapy alone in preventing major cardiovascular events, a benefit mediated largely by a significant reduction in nonfatal myocardial infarction. The benefits of CABG are especially evident in diabetic patients treated with an insulin-sensitizing strategy as opposed to an insulin-providing strategy. CABG has also been shown to be superior to PCI (including the use of drug-eluting stents) in preventing death, myocardial infarction, and repeat revascularization in patients with diabetes mellitus and multivessel IHD.

Indications for CABG usually are based on the severity of symptoms, coronary anatomy, and ventricular function. The ideal candidate is male, <80 years of age, has no other complicating disease, and has troublesome or disabling angina that is not adequately controlled by medical therapy or does not tolerate medical therapy. The patient wishes to lead a more active life and has severe stenoses of two or three epicardial coronary arteries with objective evidence of myocardial ischemia as a cause of the chest discomfort. Great symptomatic benefit can be anticipated in such patients. Congestive heart failure and/or LV dysfunction, advanced age (>80 years), reoperation, urgent need for surgery, and the presence of diabetes mellitus are all associated with a higher perioperative mortality rate.

LV dysfunction can be due to noncontractile or hypocontractile segments that are viable but are chronically ischemic (hibernating myocardium). As a consequence of chronic reduction in myocardial blood flow, these segments downregulate their contractile function. They can be detected by using radionuclide scans of myocardial perfusion and metabolism, PET, cardiac MRI, or delayed scanning with thallium-201 or by improvement of regional functional impairment provoked by low-dose dobutamine. In such patients, revascularization improves myocardial blood flow, can return function, and can improve survival.

The Choice Between PCI and CABG All the clinical characteristics of each individual patient must be used to decide on the method of revascularization (e.g., LV function, diabetes, lesion complexity). A number of randomized clinical trials have compared PCI and CABG in patients

with multivessel CAD who were suitable technically for both procedures. The redevelopment of angina requiring repeat coronary angiography and repeat revascularization is higher with PCI. This is a result of restenosis in the stented segment (a problem largely solved with drug-eluting stents) and the development of new stenoses in unstented portions of the coronary vasculature. It has been argued that PCI with stenting focuses on culprit lesions, whereas a bypass graft to the target vessel also provides a conduit around future culprit lesions proximal to the anastomosis of the graft to the native vessel (Fig. 293-4). By contrast, stroke rates are lower with PCI.

Based on available evidence, it is now recommended that patients with an unacceptable level of angina despite optimal medical management be considered for coronary revascularization. Patients with single- or two-vessel disease with normal LV function and anatomically suitable lesions ordinarily are advised to undergo PCI (Chap. 296e). Patients with three-vessel disease (or two-vessel disease that includes the proximal left descending coronary artery) and impaired global LV function (LV ejection fraction <50%) or diabetes mellitus and those with left main CAD or other lesions unsuitable for catheter-based procedures should be considered for CABG as the initial method of revascularization. In light of the complexity of the decision making, it is desirable to have a multidisciplinary team, including a cardiologist and a cardiac surgeon in conjunction with the patient's primary care physician, provide input along with ascertaining the patient's preferences before committing to a particular revascularization option.

UNCONVENTIONAL TREATMENTS FOR IHD

On occasion clinicians will encounter a patient who has persistent disabling angina despite maximally tolerated medical therapy and for whom revascularization is not an option (e.g., small diffusely diseased vessels not amenable to stent implantation or acceptable targets for bypass grafting). In such situations, unconventional treatments should be considered.

Enhanced external counterpulsation utilizes pneumatic cuffs on the lower extremities to provide diastolic augmentation and systolic unloading of blood pressure to decrease cardiac work and oxygen consumption while enhancing coronary blood flow. Clinical trials have shown that regular application improves angina, exercise capacity, and regional myocardial perfusion. Experimental approaches such as gene and stem cell therapies are also under active study.

ASYMPTOMATIC (SILENT) ISCHEMIA

Obstructive CAD, acute myocardial infarction, and transient myocardial ischemia are frequently asymptomatic. During continuous ambulatory ECG monitoring, the majority of ambulatory patients with typical chronic stable angina are found to have objective evidence of myocardial ischemia (ST-segment depression) during episodes of chest discomfort while they are active outside the hospital. In addition, many of these patients also have more frequent episodes of asymptomatic ischemia. Frequent episodes of ischemia (symptomatic and asymptomatic) during daily life appear to be associated with an increased likelihood of adverse coronary events (death and myocardial infarction). In addition, patients with asymptomatic ischemia after a myocardial infarction are at greater risk for a second coronary event. The widespread use of exercise ECG during routine examinations has also identified some of these previously unrecognized patients with asymptomatic CAD. Longitudinal studies have demonstrated an increased incidence of coronary events in asymptomatic patients with positive exercise tests.

TREATMENT ASYMPTOMATIC ISCHEMIA

The management of patients with asymptomatic ischemia must be individualized. When coronary disease has been confirmed, the aggressive treatment of hypertension and dyslipidemia is essential and will decrease the risk of infarction and death. In addition, the

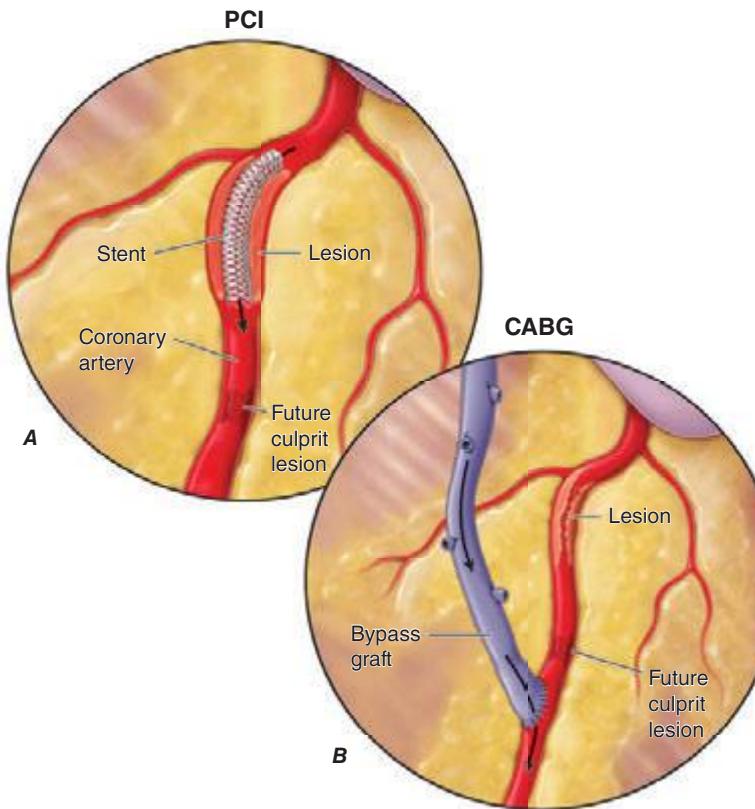


FIGURE 293-4 Difference in the approach to the lesion with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). PCI is targeted at the “culprit” lesion or lesions, whereas CABG is directed at the epicardial vessel, including the culprit lesion or lesions and future culprits, proximal to the insertion of the vein graft, a difference that may account for the superiority of CABG, at least in the intermediate term, in patients with multivessel disease. (Reproduced from BJ Gersh, RL Frye: N Engl J Med 352:2235, 2005.)

physician should consider the following: (1) the degree of positivity of the stress test, particularly the stage of exercise at which ECG signs of ischemia appear; the magnitude and number of the ischemic zones of myocardium on imaging; and the change in LV ejection fraction that occurs on radionuclide ventriculography or echocardiography during ischemia and/or during exercise; (2) the ECG leads showing a positive response, with changes in the anterior precordial leads indicating a less favorable prognosis than changes in the inferior leads; and (3) the patient’s age, occupation, and general medical condition.

Most would agree that an asymptomatic 45-year-old commercial airline pilot with significant (0.4-mV) ST-segment depression in leads V₁ to V₄ during mild exercise should undergo coronary arteriography, whereas an asymptomatic, sedentary 85-year-old retiree with 0.1-mV ST-segment depression in leads II and III during maximal activity need not. However, there is no consensus about the most appropriate approach in the large majority of patients for whom the situation is less extreme. Asymptomatic patients with silent ischemia, three-vessel CAD, and impaired LV function may be considered appropriate candidates for CABG.

The treatment of risk factors, particularly lipid lowering and blood pressure control as described above, and the use of aspirin, statins, and beta blockers after infarction have been shown to reduce events and improve outcomes in asymptomatic as well as symptomatic patients with ischemia and proven CAD. Although the incidence of asymptomatic ischemia can be reduced by treatment with beta blockers, calcium channel blockers, and long-acting nitrates, it is not clear whether this is necessary or desirable in patients who have not had a myocardial infarction.

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Non-ST-Segment Elevation Acute Coronary Syndrome (Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina)

Christopher P. Cannon, Eugene Braunwald

Patients with ischemic heart disease fall into two large groups: patients with chronic coronary artery disease (CAD) who most commonly present with stable angina (Chap. 293) and patients with acute coronary syndromes (ACSS). These include patients with acute myocardial infarction with ST-segment elevation (STEMI) on their presenting electrocardiogram (Chap. 295) and those with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). The latter include patients with non-ST-segment elevation myocardial infarction (NSTEMI), who, by definition, have evidence of myocyte necrosis, and those with unstable angina (UA), who do not. The relative incidence of NSTEMI compared to STEMI appears to be increasing (Fig. 294-1). Every year in the United States, approximately 1.1 million patients are admitted to hospitals with NSTE-ACS as compared with ~300,000 patients with acute STEMI. Women comprise more than one-third of patients with NSTE-ACS, but less than one-fourth of patients with STEMI.

PATHOPHYSIOLOGY

NSTE-ACS is most commonly caused by an imbalance between oxygen supply and oxygen demand resulting from a partially occluding thrombus forming on a disrupted atherosclerotic coronary plaque

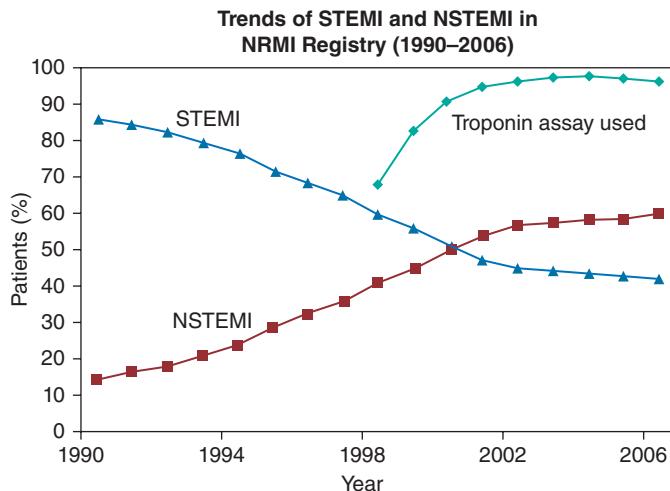


FIGURE 294-1 Trends of incidence of ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) and of frequency of use of troponin assay to diagnose acute myocardial infarction. NRMI, National Registry of Myocardial Infarction. (From N Arora, RG Brindis, CP Cannon: Acute coronary syndrome in North America, in Theroux P [ed]: Acute Coronary Syndromes, 2nd ed. Philadelphia: Elsevier, 2011.)

or on eroded coronary artery endothelium. Severe ischemia or myocardial necrosis may occur consequent to the reduction of coronary blood flow caused by the thrombus and by downstream embolization of platelet aggregates and/or atherosclerotic debris. Other causes of NSTE-ACS include: (1) dynamic obstruction (e.g., coronary spasm, as in Prinzmetal's variant angina [see "Prinzmetal's Variant Angina" later]); (2) severe mechanical obstruction due to progressive coronary atherosclerosis; and (3) increased myocardial oxygen demand produced by conditions such as fever, tachycardia, and thyrotoxicosis in the presence of fixed epicardial coronary obstruction. More than one of these processes may be involved.

Among patients with NSTE-ACS studied at angiography, approximately 10% have stenosis of the left main coronary artery, 35% have three-vessel CAD, 20% have two-vessel disease, 20% have single-vessel disease, and 15% have no apparent critical epicardial coronary artery stenosis; some of the latter may have obstruction of the coronary microcirculation and/or spasm. The "culprit lesion" responsible for ischemia may show an eccentric stenosis with scalloped or overhanging edges and a narrow neck on coronary angiography. Optical coherence tomography (an invasive technique) and contrast-enhanced coronary computed tomographic angiography (CCTA), a noninvasive technique (Fig. 294-2), have shown that culprit lesions are composed of a lipid-rich core with a thin fibrous cap. Patients with NSTE-ACS frequently have multiple such plaques that are at risk of disruption (vulnerable plaques).

CLINICAL PRESENTATION

Diagnosis The diagnosis of NSTE-ACS is based largely on the clinical presentation. Typically, chest discomfort is severe and has at least one of three features: (1) it occurs at rest (or with minimal exertion), lasting >10 minutes; (2) it is of relatively recent onset (i.e., within the prior 2 weeks); and/or (3) it occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previous episodes). The diagnosis of NSTEMI is established if a patient with these clinical features develops evidence of myocardial necrosis, as reflected in abnormally elevated levels of biomarkers of cardiac necrosis (see below).

History and Physical Examination The chest discomfort, often severe enough to be described as frank pain, is typically located in the substernal region or sometimes in the epigastrium, and radiates to the left

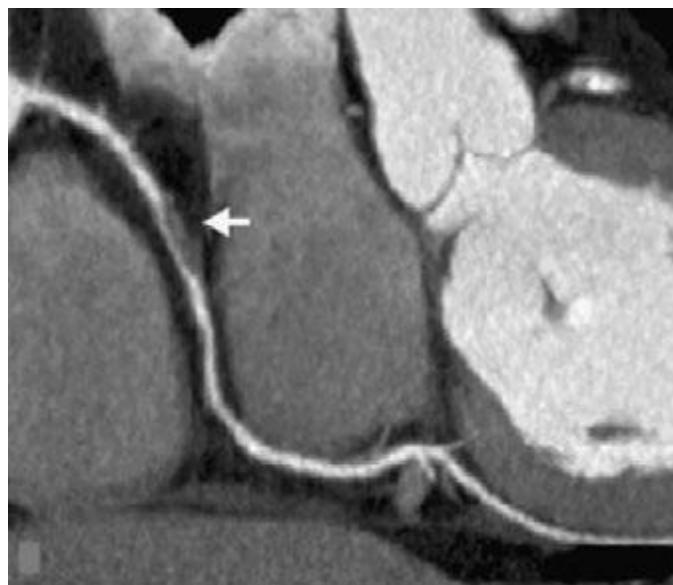


FIGURE 294-2 Coronary computed tomographic angiogram showing an obstructive plaque in the right coronary artery. (From PJ de Feyter, K Nieman. Multislice computed tomography in acute coronary syndromes, in Theroux P [ed]: Acute Coronary Syndromes, 2nd ed. Philadelphia: Elsevier, 2011.)

arm, left shoulder, and/or neck. Anginal "equivalents" such as dyspnea, epigastric discomfort, nausea, or weakness may occur instead of chest pain and appear to be more frequent in women, the elderly, and patients with diabetes mellitus. The physical examination resembles that in patients with stable angina (Chap. 293) and may be unremarkable. If the patient has a large area of myocardial ischemia or a large NSTEMI, the physical findings can include diaphoresis; pale, cool skin; sinus tachycardia; a third and/or fourth heart sound; basilar rales; and, sometimes, hypotension.

Electrocardiogram ST-segment depression occurs in 20 to 25% of patients; it may be transient in patients without biomarker evidence of myocardial necrosis, but may be persistent for several days in NSTEMI. T-wave changes are common but are less specific signs of ischemia, unless they are new and deep T-wave inversions (≥ 0.3 mV).

Cardiac Biomarkers Patients with NSTEMI have elevated biomarkers of necrosis, such as cardiac troponin I or T, which are specific, sensitive, and the preferred markers of myocardial necrosis. The MB isoform of creatine kinase (CK-MB) is a less sensitive alternative. Elevated levels of these markers distinguish patients with NSTEMI from those with UA. There is a characteristic temporal rise and fall of the plasma concentration of these markers and a direct relationship between the degree of elevation and mortality (see Fig. 294-4B). However, in patients *without* a clear clinical history of myocardial ischemia, minor cardiac troponin (cTn) elevations have been reported and can be caused by congestive heart failure, myocarditis, or pulmonary embolism, or using high-sensitivity assays, they may occur in ostensibly normal subjects. Thus, in patients with an *unclear* history, small elevations of cTn, especially if they are persistent, may not be diagnostic of an ACS.

With more widespread measurement of troponin, especially using high-sensitivity assays, an increasing fraction of patients with NSTE-ACS are found to have NSTEMI, whereas the fraction of patients with UA is dwindling.

DIAGNOSTIC EVALUATION

In addition to the clinical examination, three major noninvasive tools are used in the evaluation of NSTEMI-ACS: the electrocardiogram (ECG), cardiac biomarkers, and stress testing. CCTA is an additional emerging option (Fig. 294-2). The goals are to: (1) recognize or exclude myocardial infarction (MI) using cardiac biomarkers, preferably cTn;

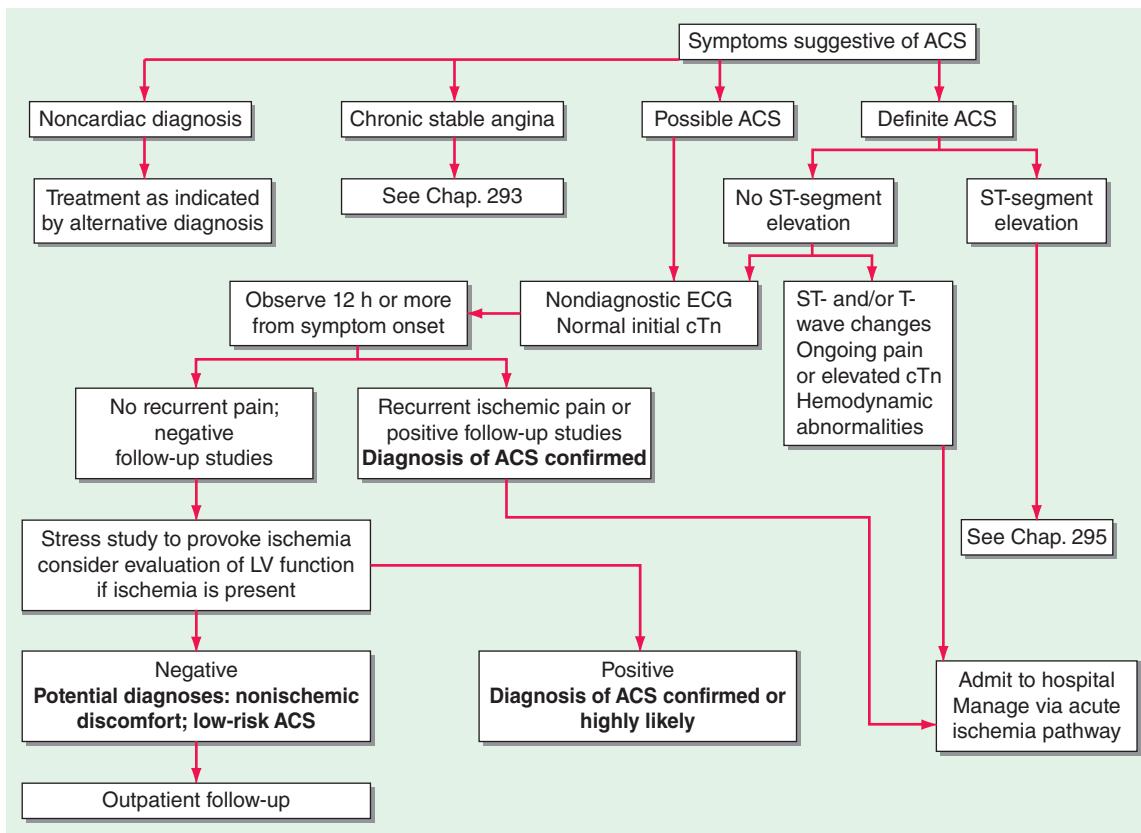


FIGURE 294-3 Algorithm for evaluation and management of patients with suspected acute coronary syndrome (ACS). Follow-up studies refer to ST deviations and elevation of troponin levels. cTn, cardiac troponin; ECG, electrocardiogram; LV, left ventricular. (Modified from JL Anderson et al: *J Am Coll Cardiol* 61:e179, 2013.)

(2) detect rest ischemia (using serial or continuous ECGs); and (3) detect significant coronary obstruction at rest with CCTA and myocardial ischemia using stress testing ([Chap. 270e](#)).

Patients with a low likelihood of ischemia are usually managed with an emergency department-based critical pathway (which, in some institutions, is carried out in a “chest pain unit”) ([Fig. 294-3](#)). Evaluation of such patients includes clinical monitoring for recurrent ischemic discomfort and continuous monitoring of ECGs and cardiac markers, typically obtained at baseline and at 4–6 h and 12 h after presentation. If new elevations in cardiac markers or ST-T-wave changes on the ECG are noted, the patient should be admitted to the hospital. Patients who remain pain free with negative markers may proceed to stress testing to determine the presence of ischemia or CCTA to detect coronary luminal obstruction ([Fig. 294-2](#)).

RISK STRATIFICATION

Patients with documented NSTE-ACS exhibit a wide spectrum of early (30 days) risk of death, ranging from 1 to 10%, and a recurrent ACS rate of 5 to 15% during the first year. Assessment of risk can be accomplished by clinical risk scoring systems such as that developed from the Thrombolysis in Myocardial Infarction (TIMI) Trials, which includes seven independent risk factors ([Fig. 294-4A](#)). The presence of an abnormally elevated cTn is especially important, as is its peak level, which correlates with the extent of myocardial damage ([Fig. 294-4B](#)). Other risk factors include diabetes mellitus, left ventricular dysfunction, renal dysfunction, and elevated levels of B-type natriuretic peptides and C-reactive protein. Multimarker strategies are now gaining favor, both to define more fully the pathophysiologic mechanisms underlying a given patient’s presentation and to stratify the patient’s risk further. Patients with ACS without elevated levels of cTn (infrequently encountered with the new sensitive troponin assays) are considered to have UA and have a more favorable prognosis than those with cTn elevations (NSTEMI).

Early risk assessment is useful both in predicting the risk of recurrent cardiac events and in identifying patients who would derive the greatest benefit from an early invasive strategy. For example, in the TACTICS-TIMI 18 Trial, an early invasive strategy conferred a 40% reduction in recurrent cardiac events in patients with an elevated cTn level, whereas no benefit was observed in those without detectable troponin.

TREATMENT

NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME (NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION AND UNSTABLE ANGINA)

MEDICAL TREATMENT

Patients should be placed at bed rest with continuous ECG monitoring for ST-segment deviation and cardiac arrhythmias. Ambulation is permitted if the patient shows no recurrence of ischemia (symptoms or ECG changes) and does not develop an elevation of a biomarker of necrosis for 12–24 h. Medical therapy involves simultaneous anti-ischemic and antithrombotic treatments and consideration of coronary revascularization.

ANTI-ISCHEMIC TREATMENT (TABLE 294-1)

To provide relief and prevention of recurrence of chest pain, initial treatment should include bed rest, nitrates, beta adrenergic blockers, and inhaled oxygen in the presence of hypoxemia.

Nitrates These should first be given sublingually or by buccal spray (0.3–0.6 mg) if the patient is experiencing ischemic pain. If pain persists after three doses given 5 min apart, intravenous nitroglycerin (5–10 µg/min using nonabsorbing tubing) is recommended. The rate of the infusion may be increased by 10 µg/min every 3–5 min until symptoms are relieved, systolic arterial pressure falls to

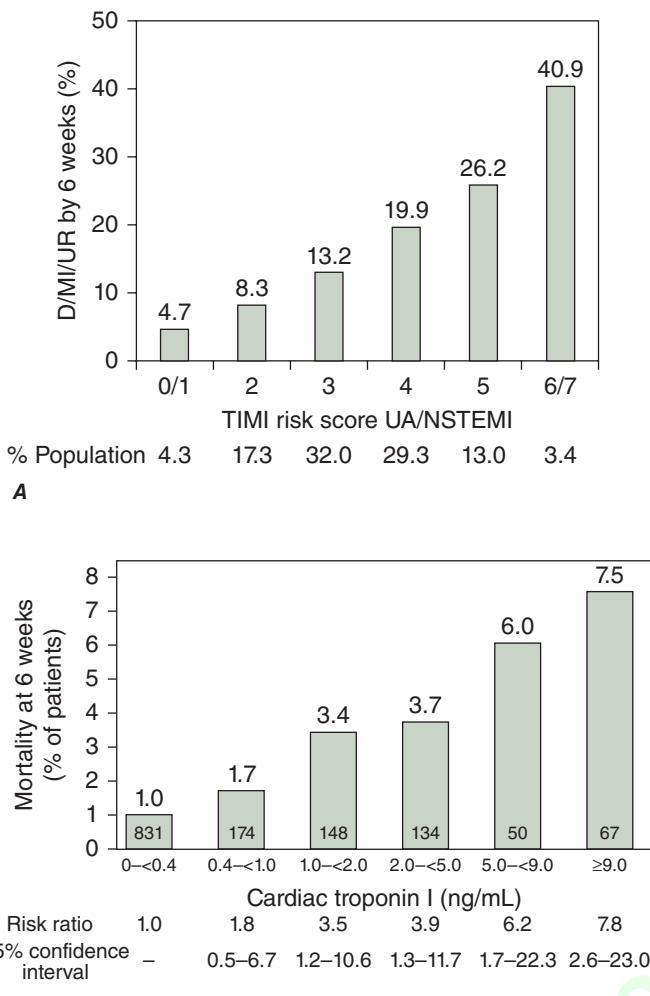


FIGURE 294-4 **A.** Death (D), myocardial infarction (MI), or need for urgent revascularization (UR) through 6 weeks by Thrombolysis in Myocardial Infarction (TIMI) Risk Score in the unfractionated heparin arm of the TIMI 11B trial. (From EM Antman et al: JAMA 284:835, 2000.) **B.** Mortality rate at 42 days by baseline cardiac troponin I levels in the TIMI 3B trial. (From EM Antman et al: N Engl J Med 335:1342, 1996.)

<100 mmHg, or the dose reaches 200 µg/min. Topical or oral nitrates (**Chap. 293**) can be used when the pain has resolved, or they may replace intravenous nitroglycerin when the patient has been pain-free for 12–24 h. The only absolute contraindications to the use of nitrates are hypotension or the use of sildenafil or other phosphodiesterase-5 inhibitors within the previous 24–48 h.

Beta Adrenergic Blockers and Other Agents Beta blockers are the other mainstay of anti-ischemic treatment. They may be started by the intravenous route in patients with severe ischemia, but this is contraindicated in the presence of heart failure. Ordinarily, oral beta blockade targeted to a heart rate of 50–60 beats/min is recommended. Heart rate–slowing calcium channel blockers, e.g., verapamil or diltiazem, are recommended for patients who have persistent symptoms or ECG signs of ischemia after treatment with full-dose nitrates and beta blockers and in patients with contraindications to either class of these agents. Additional medical therapy includes angiotensin-converting enzyme (ACE) inhibitors or, if these are not tolerated, angiotensin receptor blockers. Early administration of intensive HMG-CoA reductase inhibitors (statins), such as atorvastatin 80 mg/d, prior to percutaneous coronary intervention (PCI), and continued thereafter, has been shown to reduce complications of the procedure and recurrences of ACS.

ANTITHROMBOTIC THERAPY (TABLE 294-2)

This is the second major cornerstone of treatment. There are two components of antithrombotic therapy: antiplatelet drugs and anticoagulants.

Antiplatelet Drugs (See Chap. 143) Initial treatment should begin with the platelet cyclooxygenase inhibitor aspirin. The typical initial dose is 325 mg/d, with lower doses (75–100 mg/d) recommended thereafter. Contraindications are active bleeding or aspirin intolerance. “Aspirin resistance” has been noted in 2–8% of patients but frequently has been related to noncompliance.

In the absence of a high risk for bleeding, patients with NSTE-ACS, irrespective of whether an invasive or conservative strategy (see below) is selected, should receive a platelet P2Y₁₂ receptor blocker to inhibit platelet activation. The thienopyridine clopidogrel is an inactive prodrug that is converted into an active metabolite that causes irreversible blockade of the platelet P2Y₁₂ receptor. When added to aspirin, so-called dual antiplatelet therapy, it has been shown to confer a 20% relative reduction in cardiovascular death, MI, or stroke, compared to aspirin alone, but to be associated with a moderate (absolute 1%) increase in major bleeding.

Continued benefit of treatment with the combination of aspirin and clopidogrel has been observed both in patients treated conservatively and in those who underwent PCI. This regimen should continue for at least 1 year in patients with NSTE-ACS, especially those with a drug-eluting stent, to prevent stent thrombosis. Up to one-third of patients have an inadequate response to clopidogrel, and a substantial proportion of these cases are related to a genetic variant of the cytochrome P450 system. A variant of the 2C19 gene leads to reduced conversion of clopidogrel into its active metabolite, which, in turn, reduces platelet inhibition and is associated with increases in the incidence of adverse cardiovascular events. Alternate P2Y₁₂ blockers, such as prasugrel or ticagrelor (see below) used with aspirin, should be considered in patients with NSTE-ACS who develop a coronary event while receiving clopidogrel and aspirin or who are hypo responsive to clopidogrel as identified by platelet and/or genetic testing, although such testing is not yet widespread.

A second P2Y₁₂ blocker, prasugrel, also a thienopyridine, achieves a more rapid onset and higher level of platelet inhibition than clopidogrel. It has been approved for ACS patients following angiography in whom PCI is planned. It should be administered at a loading dose of 60 mg followed by 10 mg/d for up to 15 months. The TRITON-TIMI 38 trial showed that relative to clopidogrel, prasugrel reduced the risk of cardiovascular death, MI, or stroke significantly, albeit with an increase in major bleeding. Stent thrombosis was reduced by half. This agent is contraindicated in patients with prior stroke or transient ischemic attack or at high risk for bleeding. It has not been found to be effective in patients treated by a conservative strategy (see below).

Ticagrelor is a novel, potent, reversible platelet P2Y₁₂ inhibitor. It has been shown in the PLATO trial to reduce the risk of cardiovascular death, MI, or stroke compared with clopidogrel in ACS patients who are treated by either an invasive or a conservative strategy. This agent reduced mortality but increased the risk of bleeding not associated with coronary artery bypass grafting. After a loading dose of 180 mg, 90 mg bid is administered as maintenance.

Prior to the development of the oral P2Y₁₂ receptor blockers, many trials had shown the benefit of intravenous glycoprotein IIb/IIIa inhibitors. Their benefit, however, has been small (i.e., only a 10% reduction in death or MI, with a significant increase in major bleeding). Two recent studies failed to show a benefit of routine early initiation of a drug in this class compared with their use only in patients who undergo PCI. The addition of these agents to aspirin and a P2Y₁₂ inhibitor (i.e., triple antiplatelet therapy) should be reserved for unstable patients with recurrent rest pain, elevated cTn, and ECG changes, as well as those who have a coronary thrombus evident on angiography when they undergo PCI.

TABLE 294-1 DRUGS COMMONLY USED IN INTENSIVE MEDICAL MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA AND NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Drug Category	Clinical Condition	When to Avoid ^a	Dosage
Nitrates	Administer sublingually, and, if symptoms persist, intravenously	Hypotension	Topical, oral, or buccal nitrates are acceptable alternatives for patients without ongoing or refractory symptoms
		Patient receiving sildenafil or other PDE-5 inhibitor	5–10 µg/min by continuous infusion titrated up to 75–100 µg/min until relief of symptoms or limiting side effects (headache or hypotension with a systolic blood pressure <90 mmHg or more than 30% below starting mean arterial pressure levels if significant hypertension is present)
Beta blockers ^b	Unstable angina	PR interval (ECG) <0.24 s 2° or 3° atrioventricular block Heart rate <60 beats/min Systolic pressure <90 mmHg Shock Left ventricular failure Severe reactive airway disease	Metoprolol 25–50 mg by mouth every 6 h If needed, and no heart failure, 5-mg increments by slow (over 1–2 min) IV administration
Calcium channel blockers	Patients whose symptoms are not relieved by adequate doses of nitrates and beta blockers, or in patients unable to tolerate adequate doses of one or both of these agents, or in patients with variant angina	Pulmonary edema Evidence of left ventricular dysfunction (for diltiazem or verapamil)	Dependent on specific agent
Morphine sulfate	Patients whose symptoms are not relieved after three serial sublingual nitroglycerin tablets or whose symptoms recur with adequate anti-ischemic therapy	Hypotension Respiratory depression Confusion Obtundation	2–5 mg IV dose May be repeated every 5–30 min as needed to relieve symptoms and maintain patient comfort

^aAllergy or prior intolerance is a contraindication for all categories of drugs listed in this chart. ^bChoice of the specific agent is not as important as ensuring that appropriate candidates receive this therapy. If there are concerns about patient intolerance due to existing pulmonary disease, especially asthma, left ventricular dysfunction, risk of hypotension, or severe bradycardia, initial selection should favor a short-acting agent, such as propranolol or metoprolol or the ultra-short-acting agent esmolol. Mild wheezing or a history of chronic obstructive pulmonary disease should prompt a trial of a short-acting agent at a reduced dose (e.g., 2.5 mg IV metoprolol, 12.5 mg oral metoprolol, or 25 µg/kg per min esmolol as initial doses) rather than complete avoidance of beta blocker therapy.

Note: Some of the recommendations in this guide suggest the use of agents for purposes or in doses other than those specified by the U.S. Food and Drug Administration. Such recommendations are made after consideration of concerns regarding nonapproved indications. Where made, such recommendations are based on more recent clinical trials or expert consensus. 2°, second-degree; 3°, third-degree; ECG, electrocardiogram; IV, intravenous.

Source: Modified from J Anderson et al: J Am Coll Cardiol 61:e179, 2013.

Anticoagulants (See Chap. 143) Four options are available for anti-coagulant therapy to be added to antiplatelet agents: (1) unfractionated heparin (UFH), long the mainstay of therapy; (2) the low-molecular-weight heparin (LMWH), enoxaparin, which has been shown to be superior to UFH in reducing recurrent cardiac events, especially in patients managed by a conservative strategy but with some increase in bleeding; (3) bivalirudin, a direct thrombin inhibitor that is similar in efficacy to either UFH or LMWH but causes less bleeding and is used just prior to and/or during PCI; and (4) the indirect factor Xa inhibitor, fondaparinux, which is equivalent in efficacy to enoxaparin but appears to have a lower risk of major bleeding.

Excessive bleeding is the most important adverse effect of all antithrombotic agents, including both antiplatelet agents and anticoagulants. Therefore, attention must be directed to the doses of antithrombotic agents, accounting for body weight, creatinine clearance, and a previous history of excessive bleeding, as a means of reducing the risk of bleeding. Patients who have experienced a stroke are at higher risk of intracranial bleeding with potent antiplatelet agents and combinations of antithrombotic drugs.

INVASIVE VERSUS CONSERVATIVE STRATEGY

Multiple clinical trials have demonstrated the benefit of an early invasive strategy in high-risk patients (i.e., patients with multiple

clinical risk factors, ST-segment deviation, and/or positive biomarkers) (Table 294-3). In this strategy, following treatment with anti-ischemic and antithrombotic agents, coronary arteriography is carried out within ~48 h of presentation, followed by coronary revascularization (PCI or coronary artery bypass grafting), depending on the coronary anatomy. In low-risk patients, the outcomes from an invasive strategy are similar to those obtained from a conservative strategy. The latter consists of anti-ischemic and anti-thrombotic therapy followed by “watchful waiting,” in which the patient is closely observed and coronary arteriography is carried out only if rest pain or ST-segment changes recur, a biomarker of necrosis becomes positive, or there is evidence of severe ischemia on a stress test.

LONG-TERM MANAGEMENT

The time of hospital discharge is a “teachable moment” for the patient with NSTE-ACS, when the physician can review and optimize the medical regimen. Risk-factor modification is key, and the caregiver should discuss with the patient the importance of smoking cessation, achieving optimal weight, daily exercise, blood-pressure control, following an appropriate diet, control of hyperglycemia (in diabetic patients), and lipid management as recommended for patients with chronic stable angina (Chap. 293).

TABLE 294-2 CLINICAL USE OF ANTITHROMBOTIC THERAPY

Oral Antiplatelet Therapy	
Aspirin	Initial dose of 325 mg nonenteric formulation followed by 75–100 mg/d of an enteric or a nonenteric formulation
Clopidogrel	Loading dose of 300–600 mg followed by 75 mg/d
Prasugrel	Pre-PCI: Loading dose 60 mg followed by 10 mg/d
Ticagrelor	Loading dose of 180 mg followed by 90 mg twice daily
Intravenous Antiplatelet Therapy	
Abciximab	0.25 mg/kg bolus followed by infusion of 0.125 µg/kg per min (maximum 10 µg/min) for 12–24 h
Eptifibatide	180 µg/kg bolus followed 10 min later by second bolus of 180 µg with infusion of 2.0 µg/kg per min for 72–96 h following first bolus
Tirofiban	25 µg/kg per min followed by infusion of 0.15 µg/kg per min for 48–96 h
Heparins ^a	
Unfractionated heparin (UFH)	^b Bolus 70–100 U/kg (maximum 5000 U) IV followed by infusion of 12–15 U/kg per h (initial maximum 1000 U/h) titrated to ACT 250–300 s
Enoxaparin	1 mg/kg SC every 12 h; the first dose may be preceded by a 30-mg IV bolus; renal adjustment to 1 mg/kg once daily if creatine clearance <30 cc/min
Fondaparinux	2.5 mg SC qd
Bivalirudin	Initial IV bolus of 0.75 mg/kg and an infusion of 1.75 mg/kg per h.

^aOther low-molecular-weight heparins exist beyond those listed. ^bIf no glycoprotein IIb/IIIa inhibitor planned.

Abbreviations: ACT, activated clotting time for HemoTec; IV, intravenous; SC, subcutaneously.

Source: Modified from J Anderson et al: J Am Coll Cardiol 61:e179, 2013.

There is evidence of benefit with long-term therapy with five classes of drugs that are directed at different components of the atherothrombotic process. Beta blockers, statins (at a high dose, e.g., atorvastatin 80 mg/d), and ACE inhibitors or angiotensin receptor blockers are recommended for long-term plaque stabilization. Antiplatelet therapy,

now recommended to be the combination of low-dose (75–100 mg/d) aspirin and a P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor) for 1 year, with aspirin continued thereafter, prevents or reduces the severity of any thrombosis that would occur if a plaque were to rupture.

Registries have shown that women and racial minorities, as well as patients with NSTE-ACS at high risk, including the elderly and patients with diabetes or chronic kidney disease, are less likely to receive evidence-based pharmacologic and interventional therapies with resultant poorer clinical outcomes and quality of life. Special attention should be directed to these groups.

PRINZMETAL'S VARIANT ANGINA

In 1959 Prinzmetal et al. described a syndrome of severe ischemic pain that usually occurs at rest and is associated with transient ST-segment elevation. Prinzmetal's variant angina (PVA) is caused by focal spasm of an epicardial coronary artery, leading to severe transient myocardial ischemia and occasionally infarction. The cause of the spasm is not well defined, but it may be related to hypercontractility of vascular smooth muscle due to adrenergic vasoconstrictors, leukotrienes, or serotonin. For reasons that are not clear, the prevalence of PVA has decreased substantially during the past few decades.

Clinical and Angiographic Manifestations Patients with PVA are generally younger and have fewer coronary risk factors (with the exception of cigarette smoking) than do patients with NSTE-ACS. Cardiac examination is usually unremarkable in the absence of ischemia. The clinical diagnosis of PVA is made by the detection of transient ST-segment elevation with rest pain. Many patients also exhibit multiple episodes of asymptomatic ST-segment elevation (*silent ischemia*). Small elevations of troponin may occur in patients with prolonged attacks.

Coronary angiography demonstrates transient coronary spasm as the diagnostic hallmark of PVA. Atherosclerotic plaques in at least one proximal coronary artery occur in about half of patients, and in these patients, spasm usually occurs within 1 cm of the plaque. Focal spasm is most common in the right coronary artery, and it may occur at one or more sites in one artery or in multiple arteries simultaneously. Hyperventilation or intracoronary acetylcholine has been used to provoke focal coronary stenosis on angiography or to provoke rest angina with ST-segment elevation to establish the diagnosis.

TREATMENT PRINZMETAL'S VARIANT ANGINA

Nitrates and calcium channel blockers are the main therapeutic agents. Aspirin may actually increase the severity of ischemic episodes, possibly as a result of the sensitivity of coronary tone to modest changes in the synthesis of prostacyclin. The response to beta blockers is variable. Coronary revascularization may be helpful in patients who also have discrete, flow-limiting, proximal fixed obstructive lesions.

Prognosis Many patients with PVA pass through an acute, active phase, with frequent episodes of angina and cardiac events during the first 6 months after presentation. Survival at 5 years is excellent (~90–95%). Patients with no or mild fixed coronary obstruction tend to experience a more benign course than do patients with associated severe obstructive lesions. Nonfatal MI occurs in up to 20% of patients by 5 years. Patients with PVA who develop serious arrhythmias during spontaneous episodes of pain are at a higher risk for sudden cardiac death. In most patients who survive an infarction or the initial 3- to 6-month period of frequent episodes, there is a tendency for symptoms and cardiac events to diminish over time.

TABLE 294-3 CLASS I RECOMMENDATIONS FOR USE OF AN EARLY INVASIVE STRATEGY IN PATIENTS WITH NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME^a

Class I (Level of Evidence: A) Indications

- Recurrent angina at rest/low-level activity despite treatment
- Elevated TnT or Tnl
- New ST-segment depression
- CHF symptoms, rales, MR
- EF <0.40
- Sustained VT
- PCI <6 months, prior CABG
- High-risk findings from noninvasive testing
- Hemodynamic instability
- Mild-to-moderate renal dysfunction
- Diabetes mellitus
- High TIMI Risk Score (>3)^b

^aAny one of the high-risk indicators. ^bSee Antman (JAMA 284:835, 2000).

Abbreviations: CABG, coronary artery bypass grafting; CHF, congestive heart failure; EF, ejection fraction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; Tnl, troponin I; TnT, troponin T; VT, ventricular tachycardia.

Source: Modified from J Anderson et al: J Am Coll Cardiol 61:e179, 2013.

295 ST-Segment Elevation Myocardial Infarction

Elliott M. Antman, Joseph Loscalzo

Acute myocardial infarction (AMI) is one of the most common diagnoses in hospitalized patients in industrialized countries. In the United States, approximately 525,000 patients experience a new AMI, and 190,000 experience a recurrent AMI each year. More than half of AMI-related deaths occur before the stricken individual reaches the hospital. The in-hospital mortality rate after admission for AMI has declined from 10% to about 6% over the past decade. The 1-year mortality rate after AMI is about 15%. Mortality is approximately fourfold higher in elderly patients (over age 75) as compared with younger patients.

When patients with prolonged ischemic discomfort at rest are first seen, the working clinical diagnosis is that they are suffering from an acute coronary syndrome (Fig. 295-1). The 12-lead electrocardiogram (ECG) is a pivotal diagnostic and triage tool because it is at the center of the decision pathway for management; it permits distinction of those patients presenting with ST-segment elevation from those presenting without ST-segment elevation. Serum cardiac biomarkers are obtained to distinguish unstable angina (UA) from non-ST-segment elevation myocardial infarction (NSTEMI) and to assess the magnitude of an ST-segment elevation myocardial infarction (STEMI). This chapter focuses on the evaluation and management of patients with STEMI, while Chap. 294 discusses UA/NSTEMI.

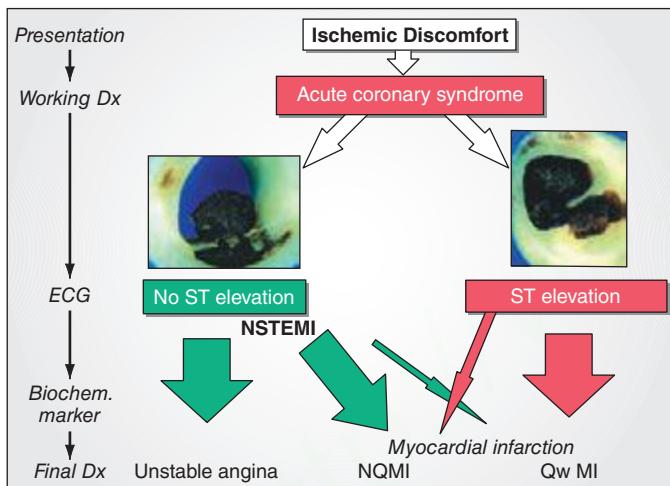


FIGURE 295-1 Acute coronary syndromes. Following disruption of a vulnerable plaque, patients experience ischemic discomfort resulting from a reduction of flow through the affected epicardial coronary artery. The flow reduction may be caused by a completely occlusive thrombus (right) or subtotally occlusive thrombus (left). Patients with ischemic discomfort may present with or without ST-segment elevation. Of patients with ST-segment elevation, the majority (wide red arrow) ultimately develop a Q wave on the ECG (Qw MI), while a minority (thin red arrow) do not develop Q wave and, in older literature, were said to have sustained a non-Q-wave MI (NQMI). Patients who present without ST-segment elevation are suffering from either unstable angina or a non-ST-segment elevation MI (NSTEMI) (wide green arrows), a distinction that is ultimately made based on the presence or absence of a serum cardiac marker such as CK-MB or a cardiac troponin detected in the blood. The majority of patients presenting with NSTEMI do not develop a Q wave on the ECG; a minority develop a Qw MI (thin green arrow). Dx, diagnosis; ECG, electrocardiogram; MI, myocardial infarction. (Adapted from CW Hamm et al: Lancet 358:1533, 2001, and MJ Davies: Heart 83:361, 2000; with permission from the BMJ Publishing Group.)

PATHOPHYSIOLOGY: ROLE OF ACUTE PLAQUE RUPTURE

1599

STEMI usually occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously affected by atherosclerosis. Slowly developing, high-grade coronary artery stenoses do not typically precipitate STEMI because of the development of a rich collateral network over time. Instead, STEMI occurs when a coronary artery thrombus develops rapidly at a site of vascular injury. This injury is produced or facilitated by factors such as cigarette smoking, hypertension, and lipid accumulation. In most cases, STEMI occurs when the surface of an atherosclerotic plaque becomes disrupted (exposing its contents to the blood) and conditions (local or systemic) favor thrombogenesis. A mural thrombus forms at the site of plaque disruption, and the involved coronary artery becomes occluded. Histologic studies indicate that the coronary plaques prone to disruption are those with a rich lipid core and a thin fibrous cap (Chap. 291e). After an initial platelet monolayer forms at the site of the disrupted plaque, various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation. After agonist stimulation of platelets, thromboxane A₂ (a potent local vasoconstrictor) is released, further platelet activation occurs, and potential resistance to fibrinolysis develops.

In addition to the generation of thromboxane A₂, activation of platelets by agonists promotes a conformational change in the glycoprotein IIb/IIIa receptor (Chap. 140). Once converted to its functional state, this receptor develops a high affinity for soluble adhesive proteins (i.e., integrins) such as fibrinogen. Since fibrinogen is a multivalent molecule, it can bind to two different platelets simultaneously, resulting in platelet cross-linking and aggregation.

The coagulation cascade is activated on exposure of tissue factor in damaged endothelial cells at the site of the disrupted plaque. Factors VII and X are activated, ultimately leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to fibrin (Chap. 141). Fluid-phase and clot-bound thrombin participates in an autoamplification reaction leading to further activation of the coagulation cascade. The culprit coronary artery eventually becomes occluded by a thrombus containing platelet aggregates and fibrin strands.

In rare cases, STEMI may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic—particularly inflammatory—diseases. The amount of myocardial damage caused by coronary occlusion depends on (1) the territory supplied by the affected vessel, (2) whether or not the vessel becomes totally occluded, (3) the duration of coronary occlusion, (4) the quantity of blood supplied by collateral vessels to the affected tissue, (5) the demand for oxygen of the myocardium whose blood supply has been suddenly limited, (6) endogenous factors that can produce early spontaneous lysis of the occlusive thrombus, and (7) the adequacy of myocardial perfusion in the infarct zone when flow is restored in the occluded epicardial coronary artery.

Patients at increased risk for developing STEMI include those with multiple coronary risk factors (Chap. 291e) and those with UA (Chap. 294). Less common underlying medical conditions predisposing patients to STEMI include hypercoagulability, collagen vascular disease, cocaine abuse, and intracardiac thrombi or masses that can produce coronary emboli.

There have been major advances in the management of STEMI with recognition that the “chain of survival” involves a highly integrated system starting with prehospital care and extending to early hospital management so as to provide expeditious implementation of a reperfusion strategy.

CLINICAL PRESENTATION

In up to one-half of cases, a precipitating factor appears to be present before STEMI, such as vigorous physical exercise, emotional stress, or a medical or surgical illness. Although STEMI may commence at any time of the day or night, circadian variations have been reported such that clusters are seen in the morning within a few hours of awakening.

Pain is the most common presenting complaint in patients with STEMI. The pain is deep and visceral; adjectives commonly used to

describe it are *heavy, squeezing, and crushing*, although, occasionally, it is described as stabbing or burning ([Chap. 19](#)). It is similar in character to the discomfort of angina pectoris ([Chap. 293](#)) but commonly occurs at rest, is usually more severe, and lasts longer. Typically, the pain involves the central portion of the chest and/or the epigastrium, and, on occasion, it radiates to the arms. Less common sites of radiation include the abdomen, back, lower jaw, and neck. The frequent location of the pain beneath the xiphoid and epigastrium and the patients' denial that they may be suffering a heart attack are chiefly responsible for the common mistaken impression of indigestion. The pain of STEMI may radiate as high as the occipital area but not below the umbilicus. It is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and a sense of impending doom. The pain may commence when the patient is at rest, but when it begins during a period of exertion, it does not usually subside with cessation of activity, in contrast to angina pectoris.

The pain of STEMI can simulate pain from acute pericarditis ([Chap. 288](#)), pulmonary embolism ([Chap. 300](#)), acute aortic dissection ([Chap. 301](#)), costochondritis, and gastrointestinal disorders. These conditions should therefore be considered in the differential diagnosis. Radiation of discomfort to the trapezius is not seen in patients with STEMI and may be a useful distinguishing feature that suggests pericarditis is the correct diagnosis. However, *pain is not uniformly present in patients with STEMI*. The proportion of painless STEMIs is greater in patients with diabetes mellitus, and it increases with age. In the elderly, STEMI may present as sudden-onset breathlessness, which may progress to pulmonary edema. Other less common presentations, with or without pain, include sudden loss of consciousness, a confusional state, a sensation of profound weakness, the appearance of an arrhythmia, evidence of peripheral embolism, or merely an unexplained drop in arterial pressure.

PHYSICAL FINDINGS

Most patients are anxious and restless, attempting unsuccessfully to relieve the pain by moving about in bed, altering their position, and stretching. Pallor associated with perspiration and coolness of the extremities occurs commonly. The combination of substernal chest pain persisting for >30 min and diaphoresis strongly suggests STEMI. Although many patients have a normal pulse rate and blood pressure within the first hour of STEMI, about one-fourth of patients with anterior infarction have manifestations of sympathetic nervous system hyperactivity (tachycardia and/or hypertension), and up to one-half with inferior infarction show evidence of parasympathetic hyperactivity (bradycardia and/or hypotension).

The precordium is usually quiet, and the apical impulse may be difficult to palpate. In patients with anterior wall infarction, an abnormal systolic pulsation caused by dyskinetic bulging of infarcted myocardium may develop in the periapical area within the first days of the illness and then may resolve. Other physical signs of ventricular dysfunction include fourth and third heart sounds, decreased intensity of the first heart sound, and paradoxical splitting of the second heart sound ([Chap. 267](#)). A transient midsystolic or late systolic apical systolic murmur due to dysfunction of the mitral valve apparatus may be present. A pericardial friction rub may be heard in patients with transmural STEMI at some time in the course of the disease, if they are examined frequently. The carotid pulse is often decreased in volume, reflecting reduced stroke volume. Temperature elevations up to 38°C may be observed during the first week after STEMI. The arterial pressure is variable; in most patients with transmural infarction, systolic pressure declines by approximately 10–15 mmHg from the preinfarction state.

LABORATORY FINDINGS

STEMI progresses through the following temporal stages: (1) acute (first few hours–7 days), (2) healing (7–28 days), and (3) healed (≥29 days). When evaluating the results of diagnostic tests for STEMI, the temporal phase of the infarction must be considered. The laboratory tests of value in confirming the diagnosis may be divided into four groups: (1) ECG, (2) serum cardiac biomarkers, (3) cardiac imaging, and (4) nonspecific indices of tissue necrosis and inflammation.

ELECTROCARDIOGRAM

The electrocardiographic manifestations of STEMI are described in [Chap. 268](#). During the initial stage, total occlusion of an epicardial coronary artery produces ST-segment elevation. Most patients initially presenting with ST-segment elevation ultimately evolve Q waves on the ECG. However, Q waves in the leads overlying the infarct zone may vary in magnitude and even appear only transiently, depending on the reperfusion status of the ischemic myocardium and restoration of transmembrane potentials over time. A small proportion of patients initially presenting with ST-segment elevation will not develop Q waves when the obstructing thrombus is not totally occlusive, obstruction is transient, or if a rich collateral network is present. Among patients presenting with ischemic discomfort but *without* ST-segment elevation, if a serum cardiac biomarker of necrosis (see below) is detected, the diagnosis of NSTEMI is ultimately made ([Fig. 295-1](#)). A minority of patients who present initially without ST-segment elevation may develop a Q-wave MI. Previously, it was believed that transmural myocardial infarction (MI) is present if the ECG demonstrates Q waves or loss of R waves, and nontransmural MI may be present if the ECG shows only transient ST-segment and T-wave changes. However, electrocardiographic-pathologic correlations are far from perfect and terms such as *Q-wave MI, non-Q-wave MI, transmural MI, and nontransmural MI*, have been replaced by STEMI and NSTEMI ([Fig. 295-1](#)). Contemporary studies using magnetic resonance imaging (MRI) suggest that the development of a Q wave on the ECG is more dependent on the volume of infarcted tissue rather than the transmurality of infarction.

SERUM CARDIAC BIOMARKERS

Certain proteins, called serum cardiac biomarkers, are released from necrotic heart muscle after STEMI. The rate of liberation of specific proteins differs depending on their intracellular location, their molecular weight, and the local blood and lymphatic flow. Cardiac biomarkers become detectable in the peripheral blood once the capacity of the cardiac lymphatics to clear the interstitium of the infarct zone is exceeded and spillover into the venous circulation occurs. The temporal pattern of protein release is of diagnostic importance. The criteria for AMI require a rise and/or fall in cardiac biomarker values with at least one value above the 99th percentile of the upper reference limit for normal individuals.

Cardiac-specific troponin T (cTnT) and *cardiac-specific troponin I* (cTnI) have amino-acid sequences different from those of the skeletal muscle forms of these proteins. These differences permitted the development of quantitative assays for cTnT and cTnI with highly specific monoclonal antibodies. Since cTnT and cTnI are not normally detectable in the blood of healthy individuals but may increase after STEMI to levels many times higher than the upper reference limit (the highest value seen in 99% of a reference population not suffering from MI), the measurement of cTnT or cTnI is of considerable diagnostic usefulness, and they are now the preferred biochemical markers for MI ([Fig. 295-2](#)). With improvements in the assays for the cardiac-specific troponins, it is now possible to detect concentrations <1 ng/L in patients without ischemic-type chest discomfort. The cardiac troponins are particularly valuable when there is clinical suspicion of either skeletal muscle injury or a small MI that may be below the detection limit for creatine phosphokinase (CK) and its MB isoenzyme (CK-MB) measurements, and they are, therefore, of particular value in distinguishing UA from NSTEMI. In practical terms, the high-sensitivity troponin assays are of less immediate value in patients with STEMI. Contemporary urgent reperfusion strategies necessitate making a decision (based largely on a combination of clinical and ECG findings) before the results of blood tests have returned from the laboratory. Levels of cTnI and cTnT may remain elevated for 7–10 days after STEMI.

CK rises within 4–8 h and generally returns to normal by 48–72 h ([Fig. 295-2](#)). An important drawback of total CK measurement is its lack of specificity for STEMI, as CK may be elevated with skeletal muscle disease or trauma, including intramuscular injection. The MB isoenzyme of CK has the advantage over total CK that it is not present in significant concentrations in extracardiac tissue and, therefore,

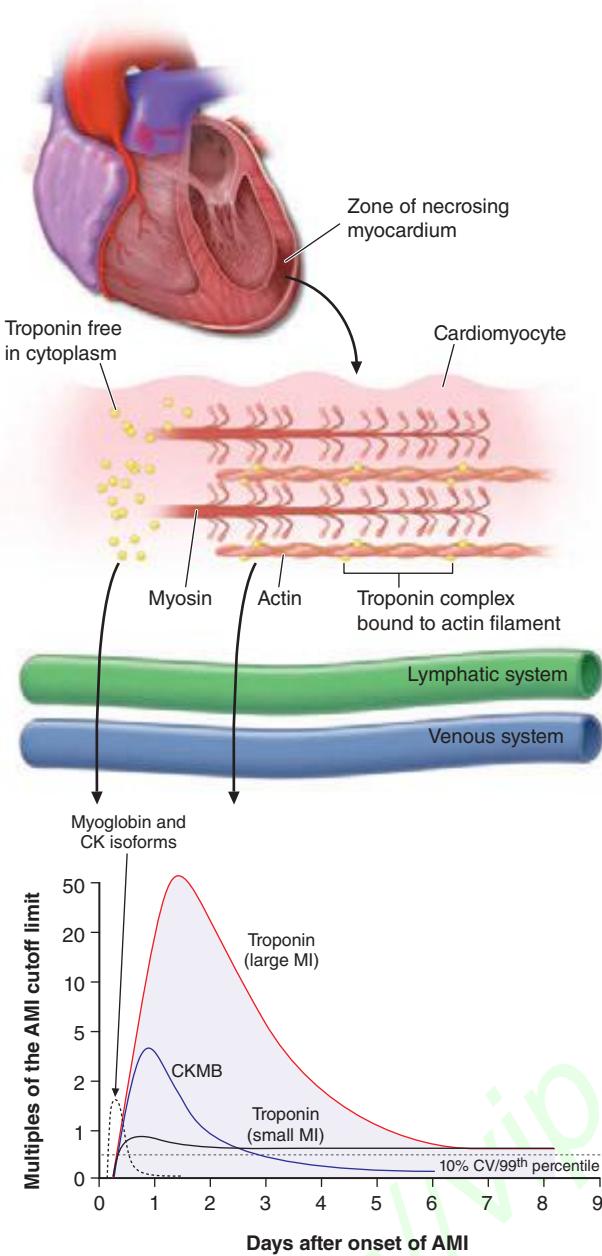


FIGURE 295-2 The zone of necrosing myocardium is shown at the top of the figure, followed in the middle portion of the figure by a diagram of a cardiomyocyte that is in the process of releasing biomarkers. The biomarkers that are released into the interstitium are first cleared by lymphatics followed subsequently by spillover into the venous system. After disruption of the sarcolemmal membrane of the cardiomyocyte, the cytoplasmic pool of biomarkers is released first (left-most arrow in bottom portion of figure). Markers such as myoglobin and CK isoforms are rapidly released, and blood levels rise quickly above the cutoff limit; this is then followed by a more protracted release of biomarkers from the disintegrating myofilaments that may continue for several days. Cardiac troponin levels rise to about 20 to 50 times the upper reference limit (the 99th percentile of values in a reference control group) in patients who have a “classic” acute myocardial infarction (MI) and sustain sufficient myocardial necrosis to result in abnormally elevated levels of the MB fraction of creatine kinase (CK-MB). Clinicians can now diagnose episodes of microinfarction by sensitive assays that detect cardiac troponin elevations above the upper reference limit, even though CK-MB levels may still be in the normal reference range (not shown). CV, coefficient of variation. (Modified from EM Antman: Decision making with cardiac troponin tests. *N Engl J Med* 346:2079, 2002 and AS Jaffe, L Babuin, FS Apple: Biomarkers in acute cardiac disease: The present and the future. *J Am Coll Cardiol* 48:1, 2006.)

is considerably more specific. However, cardiac surgery, myocarditis, and electrical cardioversion often result in elevated serum levels of the MB isoenzyme. A ratio (relative index) of CK-MB mass to CK activity ≥ 2.5 suggests but is not diagnostic of a myocardial rather than a skeletal muscle source for the CK-MB elevation.

Many hospitals are using cTnT or cTnI rather than CK-MB as the routine serum cardiac marker for diagnosis of STEMI, although any of these analytes remain clinically acceptable. It is *not* cost-effective to measure both a cardiac-specific troponin and CK-MB at all time points in every patient.

While it has long been recognized that the total quantity of protein released correlates with the size of the infarct, the peak protein concentration correlates only weakly with infarct size. Recanalization of a coronary artery occlusion (either spontaneously or by mechanical or pharmacologic means) in the early hours of STEMI causes earlier peaking of biomarker measurements (Fig. 295-2) because of a rapid washout from the interstitium of the infarct zone, quickly overwhelming lymphatic clearance of the proteins.

The *nonspecific reaction* to myocardial injury is associated with polymorphonuclear leukocytosis, which appears within a few hours after the onset of pain and persists for 3–7 days; the white blood cell count often reaches levels of 12,000–15,000/ μ L. The erythrocyte sedimentation rate rises more slowly than the white blood cell count, peaking during the first week and sometimes remaining elevated for 1 or 2 weeks.

CARDIAC IMAGING

Abnormalities of wall motion on *two-dimensional echocardiography* (Chap. 270e) are almost universally present. Although acute STEMI cannot be distinguished from an old myocardial scar or from acute severe ischemia by echocardiography, the ease and safety of the procedure make its use appealing as a screening tool in the Emergency Department setting. When the ECG is not diagnostic of STEMI, early detection of the presence or absence of wall motion abnormalities by echocardiography can aid in management decisions, such as whether the patient should receive reperfusion therapy (e.g., fibrinolysis or a percutaneous coronary intervention [PCI]). Echocardiographic estimation of left ventricular (LV) function is useful prognostically; detection of reduced function serves as an indication for therapy with an inhibitor of the renin-angiotensin-aldosterone system. Echocardiography may also identify the presence of right ventricular (RV) infarction, ventricular aneurysm, pericardial effusion, and LV thrombus. In addition, Doppler echocardiography is useful in the detection and quantitation of a ventricular septal defect and mitral regurgitation, two serious complications of STEMI.

Several *radionuclide imaging techniques* (Chap. 270e) are available for evaluating patients with suspected STEMI. However, these imaging modalities are used less often than echocardiography because they are more cumbersome and lack sensitivity and specificity in many clinical circumstances. Myocardial perfusion imaging with [^{201}Tl] or [$^{99\text{m}}\text{Tc}$]-sestamibi, which are distributed in proportion to myocardial blood flow and concentrated by viable myocardium (Chap. 293), reveals a defect (“cold spot”) in most patients during the first few hours after development of a transmural infarct. Although perfusion scanning is extremely sensitive, it cannot distinguish acute infarcts from chronic scars and, thus, is not specific for the diagnosis of *acute MI*. Radionuclide ventriculography, carried out with [$^{99\text{m}}\text{Tc}$]-labeled red blood cells, frequently demonstrates wall motion disorders and reduction in the ventricular ejection fraction in patients with STEMI. While of value in assessing the hemodynamic consequences of infarction and in aiding in the diagnosis of RV infarction when the RV ejection fraction is depressed, this technique is nonspecific, as many cardiac abnormalities other than MI alter the radionuclide ventriculogram.

MI can be detected accurately with high-resolution cardiac MRI (Chap. 270e) using a technique referred to as late enhancement. A standard imaging agent (gadolinium) is administered and images are obtained after a 10-min delay. Since little gadolinium enters normal myocardium, where there are tightly packed myocytes, but does percolate into the expanded intercellular region of the infarct zone, there

TABLE 295-1 DEFINITION OF MYOCARDIAL INFARCTION**Criteria for Acute Myocardial Infarction**

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
 - Symptoms of ischemia
 - New or presumed new significant ST-segment T-wave (ST-T) changes or new left bundle branch block (LBBB)
 - Development of pathologic Q waves in the electrocardiogram (ECG)
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
 - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes of new LBBB, but death occurred before cardiac biomarkers were obtained or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI)-related MI is arbitrarily defined by elevation of cTn values ($>5 \times$ 99th percentile URL) in patients with normal baseline values (\leq 99th percentile URL) or a rise of cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes, or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG)-related MI is arbitrarily defined by elevation of cardiac biomarker values ($>10 \times$ 99th percentile URL) in patients with normal baseline cTn values (\leq 99th percentile URL). In addition, either (i) new pathologic Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for Prior Myocardial Infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathologic Q waves with or without symptoms in the absence of nonischemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a nonischemic cause.
- Pathologic findings of a prior MI.

Source: K Thygesen: Eur Heart J 33:2551, 2012.

is a bright signal in areas of infarction that appears in stark contrast to the dark areas of normal myocardium.

An Expert Consensus Task Force for the Universal Definition of Myocardial Infarction has provided a comprehensive set of criteria for the definition of MI that integrates the clinical and laboratory findings discussed earlier ([Table 295-1](#)) as well as a classification of MI into five types that reflect the clinical circumstances in which it may occur ([Table 295-2](#)).

INITIAL MANAGEMENT

PREHOSPITAL CARE

The prognosis in STEMI is largely related to the occurrence of two general classes of complications: (1) electrical complications (arrhythmias) and (2) mechanical complications (“pump failure”). Most out-of-hospital deaths from STEMI are due to the sudden development of ventricular fibrillation. The vast majority of deaths due to ventricular fibrillation occur within the first 24 h of the onset of symptoms, and of these, over half occur in the first hour. Therefore, the major elements of prehospital care of patients with suspected STEMI include (1) recognition of symptoms by the patient and prompt seeking of medical attention; (2) rapid deployment of an emergency medical team capable

TABLE 295-2 CLASSIFICATION OF MYOCARDIAL INFARCTION**Type I: Spontaneous Myocardial Infarction**

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe coronary artery disease (CAD) but on occasion nonobstructive or no CAD.

Type 2: Myocardial Infarction Secondary to an Ischemic Imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy.

Type 3: Myocardial Infarction Resulting in Death When Biomarker Values Are Unavailable

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic electrocardiogram (ECG) changes or new left bundle branch block (LBBB), but death occurring before blood samples could be obtained or before cardiac biomarker could rise, or in rare cases, cardiac biomarkers were not collected.

Type 4a: Myocardial Infarction Related to Percutaneous Coronary Intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cardiac troponin (cTn) values $>5 \times$ 99th percentile upper reference limit (URL) in patients with normal baseline values (\leq 99th percentile URL) or a rise of cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.

Type 4b: Myocardial Infarction Related to Stent Thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

Type 5: Myocardial Infarction Related to Coronary Artery Bypass Grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values $>10 \times$ 99th percentile URL in patients with normal baseline cTn values (\leq 99th percentile URL). In addition, either (i) new pathologic Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Source: K Thygesen: Eur Heart J 33:2551, 2012.

of performing resuscitative maneuvers, including defibrillation; (3) expeditious transportation of the patient to a hospital facility that is continuously staffed by physicians and nurses skilled in managing arrhythmias and providing advanced cardiac life support; and (4) expeditious implementation of reperfusion therapy ([Fig. 295-3](#)). The greatest delay usually occurs not during transportation to the hospital but, rather, between the onset of pain and the patient’s decision to call for help. This delay can best be reduced by health care professionals educating the public concerning the significance of chest discomfort and the importance of seeking early medical attention. Regular office visits with patients having a history of or who are at risk for ischemic heart disease are important “teachable moments” for clinicians to review the symptoms of STEMI and the appropriate action plan.

Increasingly, monitoring and treatment are carried out by trained personnel in the ambulance, further shortening the time between the onset of the infarction and appropriate treatment. General guidelines for initiation of fibrinolysis in the prehospital setting include the ability to transmit 12-lead ECGs to confirm the diagnosis, the presence of paramedics in the ambulance, training of paramedics in the interpretation of ECGs and management of STEMI, and online medical command and control that can authorize the initiation of treatment in the field.

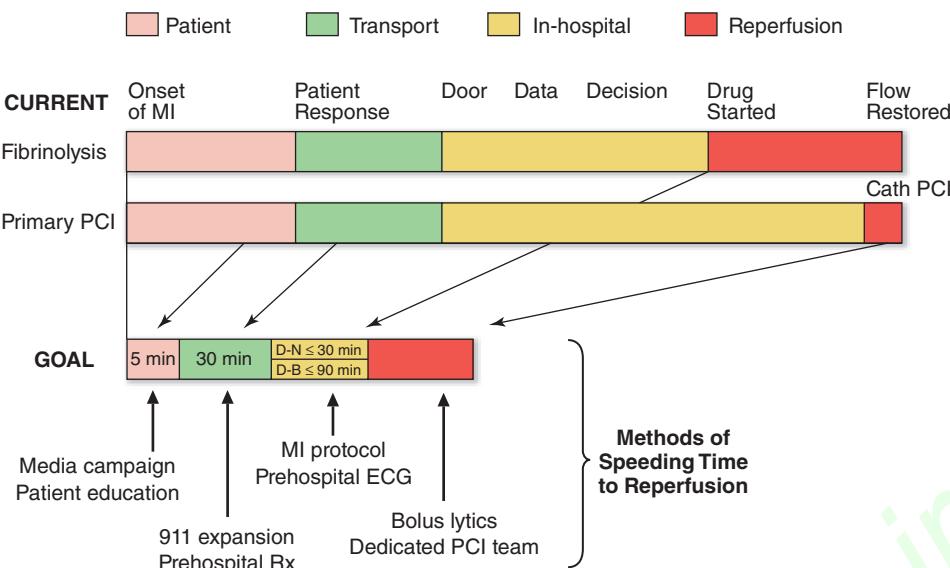


FIGURE 295-3 Major components of time delay between onset of symptoms from ST-segment elevation myocardial infarction and restoration of flow in the infarct-related artery. Plotted sequentially from left to right are the times for patients to recognize symptoms and seek medical attention, transportation to the hospital, in-hospital decision making, implementation of reperfusion strategy, and restoration of flow once the reperfusion strategy has been initiated. The time to initiate fibrinolytic therapy is the “door-to-needle” (D-N) time; this is followed by the period of time required for pharmacologic restoration of flow. More time is required to move the patient to the catheterization laboratory for a percutaneous coronary intervention (PCI) procedure, referred to as the “door-to-balloon” (D-B) time, but restoration of flow in the epicardial infarct-related artery occurs promptly after PCI. At the bottom is a variety of methods for speeding the time to reperfusion along with the goals for the time intervals for the various components of the time delay. (Adapted from CP Cannon et al: J Thromb Thrombol 1:27, 1994.)

MANAGEMENT IN THE EMERGENCY DEPARTMENT

In the Emergency Department, the goals for the management of patients with suspected STEMI include control of cardiac discomfort, rapid identification of patients who are candidates for urgent reperfusion therapy, triage of lower-risk patients to the appropriate location in the hospital, and avoidance of inappropriate discharge of patients with STEMI. Many aspects of the treatment of STEMI are initiated in the Emergency Department and then continued during the in-hospital phase of management (Fig. 295-4). The overarching goal is to minimize the time from first medical contact to initiation of reperfusion therapy. This may involve transfer from a non-PCI hospital to one that is PCI capable, with a goal of initiating PCI within 120 min of first medical contact (Fig. 295-4).

Aspirin is essential in the management of patients with suspected STEMI and is effective across the entire spectrum of acute coronary syndromes (Fig. 295-1). Rapid inhibition of cyclooxygenase-1 in platelets followed by a reduction of thromboxane A₂ levels is achieved by buccal absorption of a chewed 160–325-mg tablet in the Emergency Department. This measure should be followed by daily oral administration of aspirin in a dose of 75–162 mg.

In patients whose arterial O₂ saturation is normal, supplemental O₂ is of limited if any clinical benefit and therefore is not cost-effective. However, when hypoxemia is present, O₂ should be administered by nasal prongs or face mask (2–4 L/min) for the first 6–12 h after infarction; the patient should then be reassessed to determine if there is a continued need for such treatment.

CONTROL OF DISCOMFORT

Sublingual nitroglycerin can be given safely to most patients with STEMI. Up to three doses of 0.4 mg should be administered at about 5-min intervals. In addition to diminishing or abolishing chest discomfort, nitroglycerin may be capable of both decreasing myocardial oxygen demand (by lowering preload) and increasing myocardial oxygen supply (by dilating infarct-related coronary vessels or collateral vessels). In patients whose initially favorable response to sublingual nitroglycerin is followed by the return of chest discomfort, particularly

if accompanied by other evidence of ongoing ischemia such as further ST-segment or T-wave shifts, the use of intravenous nitroglycerin should be considered. Therapy with nitrates should be avoided in patients who present with low systolic arterial pressure (<90 mmHg) or in whom there is clinical suspicion of RV infarction (inferior infarction on ECG, elevated jugular venous pressure, clear lungs, and hypotension). Nitrates should not be administered to patients who have taken a phosphodiesterase-5 inhibitor for erectile dysfunction within the preceding 24 h, because it may potentiate the hypotensive effects of nitrates. An idiosyncratic reaction to nitrates, consisting of sudden marked hypotension, sometimes occurs but can usually be reversed promptly by the rapid administration of intravenous atropine.

Morphine is a very effective analgesic for the pain associated with STEMI. However, it may reduce sympathetically mediated arteriolar and venous constriction, and the resulting venous pooling may reduce cardiac output and arterial pressure. These hemodynamic disturbances usually respond promptly to elevation of the legs, but in some patients, volume expansion with intravenous saline is required. The patient may experience diaphoresis and nausea, but these events usually pass and are replaced by a feeling of well-being associated with the relief of pain. Morphine also has a vagotonic effect and may cause bradycardia or advanced degrees of heart block, particularly in patients with inferior infarction. These side effects usually respond to atropine (0.5 mg intravenously). Morphine is routinely administered by repetitive (every 5 min) intravenous injection of small doses (2–4 mg), rather than by the subcutaneous administration of a larger quantity, because absorption may be unpredictable by the latter route.

Intravenous beta blockers are also useful in the control of the pain of STEMI. These drugs control pain effectively in some patients, presumably by diminishing myocardial O₂ demand and hence ischemia. More important, there is evidence that intravenous beta blockers reduce the risks of reinfarction and ventricular fibrillation (see “Beta-Adrenoceptor Blockers” below). However, patient selection is important when considering beta blockers for STEMI. Oral beta blocker therapy should be initiated in the first 24 h for patients who do not have any of the following: (1) signs of heart failure, (2) evidence of a low-output state, (3) increased risk for cardiogenic shock, or (4) other

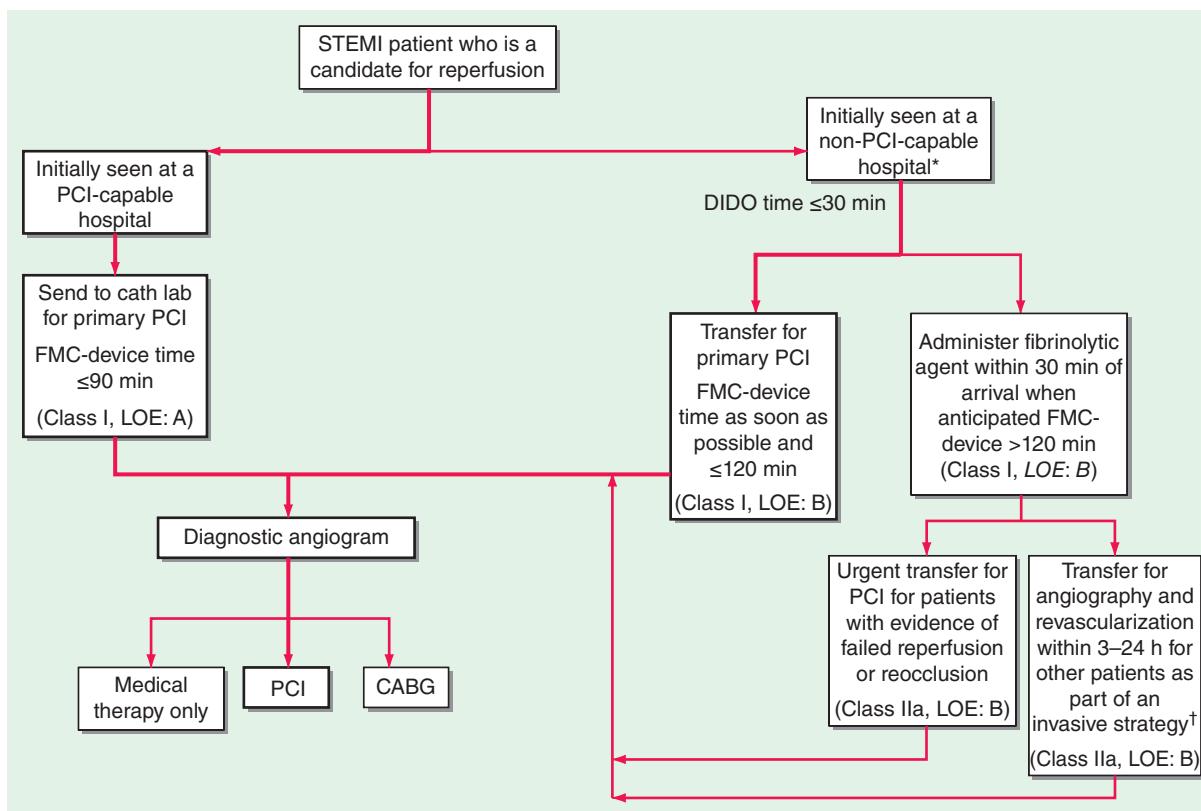


FIGURE 295-4 Reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI). The bold arrows and boxes are the preferred strategies. Performance of percutaneous coronary intervention (PCI) is dictated by an anatomically appropriate culprit stenosis. *Patients with cardiogenic shock or severe heart failure initially seen at a non-PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of time delay from myocardial infarction (MI) onset (Class I, LOE: B). †Angiography and revascularization should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy. CABG, coronary artery bypass graft; DIDO, door-in-door-out; FMC, first medical contact; LOE, level of evidence; STEMI, ST-elevation myocardial infarction. (Adapted with permission from P O'Gara et al: Circulation 127:e362, 2013.)

relative contraindications to beta blockade (PR interval greater than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airway disease). A commonly employed regimen is metoprolol, 5 mg every 2–5 min for a total of three doses, provided the patient has a heart rate >60 beats/min, systolic pressure >100 mmHg, a PR interval <0.24 s, and rales that are no higher than 10 cm up from the diaphragm. Fifteen minutes after the last intravenous dose, an oral regimen is initiated of 50 mg every 6 h for 48 h, followed by 100 mg every 12 h.

Unlike beta blockers, calcium antagonists are of little value in the acute setting, and there is evidence that short-acting dihydropyridines may be associated with an increased mortality risk.

MANAGEMENT STRATEGIES

The primary tool for screening patients and making triage decisions is the initial 12-lead ECG. When ST-segment elevation of at least 2 mm in two contiguous precordial leads and 1 mm in two adjacent limb leads is present, a patient should be considered a candidate for *reperfusion therapy* (Fig. 295-4). The process of selecting patients for fibrinolysis versus primary PCI (angioplasty or stenting; Chap. 296e) is discussed below. In the absence of ST-segment elevation, fibrinolysis is not helpful, and evidence exists suggesting that it may be harmful.

LIMITATION OF INFARCT SIZE

The quantity of myocardium that becomes necrotic as a consequence of a coronary artery occlusion is determined by factors other than just the site of occlusion. While the central zone of the infarct contains necrotic tissue that is irretrievably lost, the fate of the surrounding ischemic myocardium (ischemic penumbra) may be improved by timely restoration of coronary perfusion, reduction of myocardial

O₂ demands, prevention of the accumulation of noxious metabolites, and blunting of the impact of mediators of reperfusion injury (e.g., calcium overload and oxygen-derived free radicals). Up to one-third of patients with STEMI may achieve *spontaneous* reperfusion of the infarct-related coronary artery within 24 h and experience improved healing of infarcted tissue. Reperfusion, either pharmacologically (by fibrinolysis) or by PCI, accelerates the opening of infarct-related arteries in those patients in whom spontaneous fibrinolysis ultimately would have occurred and also greatly increases the number of patients in whom restoration of flow in the infarct-related artery is accomplished. Timely restoration of flow in the epicardial infarct-related artery combined with improved perfusion of the downstream zone of infarcted myocardium results in a limitation of infarct size. Protection of the ischemic myocardium by the maintenance of an optimal balance between myocardial O₂ supply and demand through pain control, treatment of congestive heart failure (CHF), and minimization of tachycardia and hypertension extends the “window” of time for the salvage of myocardium by reperfusion strategies.

Glucocorticoids and nonsteroidal anti-inflammatory agents, with the exception of aspirin, should be avoided in patients with STEMI. They can impair infarct healing and increase the risk of myocardial rupture, and their use may result in a larger infarct scar. In addition, they can increase coronary vascular resistance, thereby potentially reducing flow to ischemic myocardium.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

(See also Chap. 296e) PCI, usually angioplasty and/or stenting without preceding fibrinolysis, referred to as *primary PCI*, is effective in restoring perfusion in STEMI when carried out on an emergency basis in the first few hours of MI. It has the advantage of being applicable to patients who have contraindications to fibrinolytic therapy (see below)

but otherwise are considered appropriate candidates for reperfusion. It appears to be more effective than fibrinolysis in opening occluded coronary arteries and, *when performed by experienced operators in dedicated medical centers*, is associated with better short-term and long-term clinical outcomes. Compared with fibrinolysis, primary PCI is generally preferred when the diagnosis is in doubt, cardiogenic shock is present, bleeding risk is increased, or symptoms have been present for at least 2–3 h when the clot is more mature and less easily lysed by fibrinolytic drugs. However, PCI is expensive in terms of personnel and facilities, and its applicability is limited by its availability, around the clock, in only a minority of hospitals (Fig. 295-4).

FIBRINOLYSIS

If no contraindications are present (see below), fibrinolytic therapy should ideally be initiated within 30 min of presentation (i.e., door-to-needle time ≤ 30 min). The principal goal of fibrinolysis is prompt restoration of full coronary arterial patency. The fibrinolytic agents tissue plasminogen activator (tPA), streptokinase, tenecteplase (TNK), and reteplase (rPA) have been approved by the U.S. Food and Drug Administration for intravenous use in patients with STEMI. These drugs all act by promoting the conversion of plasminogen to plasmin, which subsequently lyses fibrin thrombi. Although considerable emphasis was first placed on a distinction between more fibrin-specific agents, such as tPA, and non-fibrin-specific agents, such as streptokinase, it is now recognized that these differences are only relative, as some degree of systemic fibrinolysis occurs with the former agents. TNK and rPA are referred to as *bolus fibrinolytics* since their administration does not require a prolonged intravenous infusion.

When assessed angiographically, flow in the culprit coronary artery is described by a simple qualitative scale called the *Thrombolysis in Myocardial Infarction (TIMI) grading system*: grade 0 indicates complete occlusion of the infarct-related artery; grade 1 indicates some penetration of the contrast material beyond the point of obstruction but without perfusion of the distal coronary bed; grade 2 indicates perfusion of the entire infarct vessel into the distal bed, but with flow that is delayed compared with that of a normal artery; and grade 3 indicates full perfusion of the infarct vessel with normal flow. The latter is the goal of reperfusion therapy, because full perfusion of the infarct-related coronary artery yields far better results in terms of limiting infarct size, maintenance of LV function, and reduction of both short- and long-term mortality rates. Additional methods of angiographic assessment of the efficacy of fibrinolysis include counting the number of frames on the cine film required for dye to flow from the origin of the infarct-related artery to a landmark in the distal vascular bed (*TIMI frame count*) and determining the rate of entry and exit of contrast dye from the microvasculature in the myocardial infarct zone (*TIMI myocardial perfusion grade*). These methods have an even tighter correlation with outcomes after STEMI than the more commonly employed TIMI flow grade.

tPA and the other relatively fibrin-specific plasminogen activators, rPA and TNK, are more effective than streptokinase at restoring full perfusion—i.e., TIMI grade 3 coronary flow—and have a small edge in improving survival as well. The current recommended regimen of tPA consists of a 15-mg bolus followed by 50 mg intravenously over the first 30 min, followed by 35 mg over the next 60 min. Streptokinase is administered as 1.5 million units (MU) intravenously over 1 h. rPA is administered in a double-bolus regimen consisting of a 10-MU bolus given over 2–3 min, followed by a second 10-MU bolus 30 min later. TNK is given as a single weight-based intravenous bolus of 0.53 mg/kg over 10 s. In addition to the fibrinolytic agents discussed earlier, pharmacologic reperfusion typically involves adjunctive antiplatelet and antithrombotic drugs, as discussed subsequently.

Clear contraindications to the use of fibrinolytic agents include a history of cerebrovascular hemorrhage at any time, a nonhemorrhagic stroke or other cerebrovascular event within the past year, marked hypertension (a reliably determined systolic arterial pressure >180 mmHg and/or a diastolic pressure >110 mmHg) at any time during the acute presentation, suspicion of aortic dissection, and active internal bleeding (excluding menses). While advanced age is associated with

an increase in hemorrhagic complications, the benefit of fibrinolytic therapy in the elderly appears to justify its use if no other contraindications are present and the amount of myocardium in jeopardy appears to be substantial.

Relative contraindications to fibrinolytic therapy, which require assessment of the risk-to-benefit ratio, include current use of anti-coagulants (international normalized ratio ≥ 2), a recent (<2 weeks) invasive or surgical procedure or prolonged (>10 min) cardiopulmonary resuscitation, known bleeding diathesis, pregnancy, a hemorrhagic ophthalmic condition (e.g., hemorrhagic diabetic retinopathy), active peptic ulcer disease, and a history of severe hypertension that is currently adequately controlled. Because of the risk of an allergic reaction, patients should not receive streptokinase if that agent had been received within the preceding 5 days to 2 years.

Allergic reactions to streptokinase occur in ~2% of patients who receive it. While a minor degree of hypotension occurs in 4–10% of patients given this agent, marked hypotension occurs, although rarely, in association with severe allergic reactions.

Hemorrhage is the most frequent and potentially the most serious complication. Because bleeding episodes that require transfusion are more common when patients require invasive procedures, unnecessary venous or arterial interventions should be avoided in patients receiving fibrinolytic agents. Hemorrhagic stroke is the most serious complication and occurs in ~0.5–0.9% of patients being treated with these agents. This rate increases with advancing age, with patients >70 years experiencing roughly twice the rate of intracranial hemorrhage as those <65 years. Large-scale trials have suggested that the rate of intracranial hemorrhage with tPA or rPA is slightly higher than with streptokinase.

INTEGRATED REPERFUSION STRATEGY

Evidence has emerged that suggests PCI plays an increasingly important role in the management of STEMI. Prior approaches that segregated the pharmacologic and catheter-based approaches to reperfusion have now been replaced with an integrated approach to triage and transfer of STEMI patients to receive PCI (Fig. 295-4). To achieve the degree of integration required to care for a patient with STEMI, all communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of emergency medical services and hospital-based activities.

Cardiac catheterization and coronary angiography should be carried out after fibrinolytic therapy if there is evidence of either (1) failure of reperfusion (persistent chest pain and ST-segment elevation >90 min), in which case a *rescue PCI* should be considered; or (2) coronary artery reocclusion (re-elevation of ST segments and/or recurrent chest pain) or the development of recurrent ischemia (such as recurrent angina in the early hospital course or a positive exercise stress test before discharge), in which case an *urgent PCI* should be considered. Routine angiography and *elective PCI* even in asymptomatic patients following administration of fibrinolytic therapy are used with less frequency, given the numerous technologic advances that have occurred in the catheterization laboratory and the increasing number of skilled interventionalists. Coronary artery bypass surgery should be reserved for patients whose coronary anatomy is unsuited to PCI but in whom revascularization appears to be advisable because of extensive jeopardized myocardium or recurrent ischemia.

HOSPITAL PHASE MANAGEMENT

CORONARY CARE UNITS

These units are routinely equipped with a system that permits continuous monitoring of the cardiac rhythm of each patient and hemodynamic monitoring in selected patients. Defibrillators, respirators, noninvasive transthoracic pacemakers, and facilities for introducing pacing catheters and flow-directed balloon-tipped catheters are also usually available. Equally important is the organization of a highly trained team of nurses who can recognize arrhythmias; adjust the dosage of antiarrhythmic, vasoactive, and anticoagulant drugs; and perform cardiac resuscitation, including electroshock, when necessary.

Patients should be admitted to a coronary care unit early in their illness when it is expected that they will derive benefit from the sophisticated and expensive care provided. The availability of electrocardiographic monitoring and trained personnel outside the coronary care unit has made it possible to admit lower-risk patients (e.g., those not hemodynamically compromised and without active arrhythmias) to “intermediate care units.”

The duration of stay in the coronary care unit is dictated by the ongoing need for intensive care. If symptoms are controlled with oral therapy, patients may be transferred out of the coronary care unit. Also, patients who have a confirmed STEMI but who are considered to be at low risk (no prior infarction and no persistent chest discomfort, CHF, hypotension, or cardiac arrhythmias) may be safely transferred out of the coronary care unit within 24 h.

Activity Factors that increase the work of the heart during the initial hours of infarction may increase the size of the infarct. Therefore, patients with STEMI should be kept at bed rest for the first 6–12 h. However, in the absence of complications, patients should be encouraged, under supervision, to resume an upright posture by dangling their feet over the side of the bed and sitting in a chair within the first 24 h. This practice is psychologically beneficial and usually results in a reduction in the pulmonary capillary wedge pressure. In the absence of hypotension and other complications, by the second or third day, patients typically are ambulating in their room with increasing duration and frequency, and they may shower or stand at the sink to bathe. By day 3 after infarction, patients should be increasing their ambulation progressively to a goal of 185 m (600 ft) at least three times a day.

Diet Because of the risk of emesis and aspiration soon after STEMI, patients should receive either nothing or only clear liquids by mouth for the first 4–12 h. The typical coronary care unit diet should provide ≤30% of total calories as fat and have a cholesterol content of ≤300 mg/d. Complex carbohydrates should make up 50–55% of total calories. Portions should not be unusually large, and the menu should be enriched with foods that are high in potassium, magnesium, and fiber, but low in sodium. Diabetes mellitus and hypertriglyceridemia are managed by restriction of concentrated sweets in the diet.

Bowel Management Bed rest and the effect of the narcotics used for the relief of pain often lead to constipation. A bedside commode rather than a bedpan, a diet rich in bulk, and the routine use of a stool softener such as dioctyl sodium sulfosuccinate (200 mg/d) are recommended. If the patient remains constipated despite these measures, a laxative can be prescribed. Contrary to prior belief, it is safe to perform a gentle rectal examination on patients with STEMI.

Sedation Many patients require sedation during hospitalization to withstand the period of enforced inactivity with tranquility. Diazepam (5 mg), oxazepam (15–30 mg), or lorazepam (0.5–2 mg), given three to four times daily, is usually effective. An additional dose of any of the above medications may be given at night to ensure adequate sleep. Attention to this problem is especially important during the first few days in the coronary care unit, where the atmosphere of 24-h vigilance may interfere with the patient’s sleep. However, sedation is no substitute for reassuring, quiet surroundings. Many drugs used in the coronary care unit, such as atropine, H₂ blockers, and narcotics, can produce delirium, particularly in the elderly. This effect should not be confused with agitation, and it is wise to conduct a thorough review of the patient’s medications before arbitrarily prescribing additional doses of anxiolytics.

PHARMACOTHERAPY

ANTITHROMBOTIC AGENTS

The use of antiplatelet and anticoagulant therapy during the initial phase of STEMI is based on extensive laboratory and clinical evidence that thrombosis plays an important role in the pathogenesis of this condition. The primary goal of treatment with antiplatelet and anticoagulant agents is to maintain patency of the infarct-related artery, in conjunction with reperfusion strategies. A secondary goal is to reduce the patient’s tendency to thrombosis and, thus, the likelihood of mural

thrombus formation or deep venous thrombosis, either of which could result in pulmonary embolism. The degree to which antiplatelet and anticoagulant therapy achieves these goals partly determines how effectively it reduces the risk of mortality from STEMI.

As noted previously (see “Management in the Emergency Department” earlier), aspirin is the standard antiplatelet agent for patients with STEMI. The most compelling evidence for the benefits of antiplatelet therapy (mainly with aspirin) in STEMI is found in the comprehensive overview by the Antiplatelet Trialists’ Collaboration. Data from nearly 20,000 patients with MI enrolled in 15 randomized trials were pooled and revealed a relative reduction of 27% in the mortality rate, from 14.2% in control patients to 10.4% in patients receiving antiplatelet agents.

Inhibitors of the P2Y₁₂ ADP receptor prevent activation and aggregation of platelets. The addition of the P2Y₁₂ inhibitor clopidogrel to background treatment with aspirin to STEMI patients reduces the risk of clinical events (death, reinfarction, stroke) and, in patients receiving fibrinolytic therapy, has been shown to prevent reocclusion of a successfully reperfused infarct artery. New P2Y₁₂ ADP receptor antagonists, such as prasugrel and ticagrelor, are more effective than clopidogrel in preventing ischemic complications in STEMI patients undergoing PCI, but are associated with an increased risk of bleeding. Glycoprotein IIb/IIIa receptor inhibitors appear useful for preventing thrombotic complications in patients with STEMI undergoing PCI.

The standard anticoagulant agent used in clinical practice is unfractionated heparin (UFH). The available data suggest that when UFH is added to a regimen of aspirin and a non-fibrin-specific thrombolytic agent such as streptokinase, additional mortality benefit occurs (about 5 lives saved per 1000 patients treated). It appears that the immediate administration of intravenous UFH, in addition to a regimen of aspirin and relatively fibrin-specific fibrinolytic agents (tPA, rPA, or TNK), helps to maintain patency of the infarct-related artery. This effect is achieved at the cost of a small increased risk of bleeding. The recommended dose of UFH is an initial bolus of 60 U/kg (maximum 4000 U) followed by an initial infusion of 12 U/kg per hour (maximum 1000 U/h). The activated partial thromboplastin time during maintenance therapy should be 1.5–2 times the control value.

Alternatives to UFH for anticoagulation of patients with STEMI are the low-molecular-weight heparin (LMWH) preparations, a synthetic version of the critical pentasaccharide sequence (fondaparinux), and the direct antithrombin bivalirudin. Advantages of LMWHs include high bioavailability permitting administration subcutaneously, reliable anticoagulation without monitoring, and greater antiXa:IIa activity. Enoxaparin has been shown to reduce significantly the composite endpoints of death/nonfatal reinfarction and death/nonfatal reinfarction/urgent revascularization compared with UFH in STEMI patients who receive fibrinolysis. Treatment with enoxaparin is associated with higher rates of serious bleeding, but net clinical benefit—a composite endpoint that combines efficacy and safety—still favors enoxaparin over UFH. Interpretation of the data on fondaparinux is difficult because of the complex nature of the pivotal clinical trial evaluating it in STEMI (OASIS-6). Fondaparinux appears superior to placebo in STEMI patients not receiving reperfusion therapy, but its relative efficacy and safety compared with UFH is less certain. Due to the risk of catheter thrombosis, fondaparinux should not be used alone at the time of coronary angiography and PCI but should be combined with another anticoagulant with antithrombin activity such as UFH or bivalirudin. Contemporary trials of bivalirudin used an open-label design to evaluate its efficacy and safety compared with UFH plus a glycoprotein IIb/IIIa inhibitor. Bivalirudin was associated with a lower rate of bleeding, largely driven by reductions in vascular access site hematomas ≥5 cm or the administration of blood transfusions.

Patients with an anterior location of the infarction, severe LV dysfunction, heart failure, a history of embolism, two-dimensional echocardiographic evidence of mural thrombus, or atrial fibrillation are at increased risk of systemic or pulmonary thromboembolism. Such individuals should receive full therapeutic levels of anticoagulant therapy (LMWH or UFH) while hospitalized, followed by at least 3 months of warfarin therapy.

BETA-ADRENOCEPTOR BLOCKERS

The benefits of beta blockers in patients with STEMI can be divided into those that occur immediately when the drug is given acutely and those that accrue over the long term when the drug is given for secondary prevention after an infarction. Acute intravenous beta blockade improves the myocardial O₂ supply-demand relationship, decreases pain, reduces infarct size, and decreases the incidence of serious ventricular arrhythmias. In patients who undergo fibrinolysis soon after the onset of chest pain, no incremental reduction in mortality rate is seen with beta blockers, but recurrent ischemia and reinfarction are reduced.

Thus, beta-blocker therapy after STEMI is useful for most patients (including those treated with an angiotensin-converting enzyme [ACE] inhibitor) except those in whom it is specifically contraindicated (patients with heart failure or severely compromised LV function, heart block, orthostatic hypotension, or a history of asthma) and perhaps those whose excellent long-term prognosis (defined as an expected mortality rate of <1% per year, patients <55 years, no previous MI, with normal ventricular function, no complex ventricular ectopy, and no angina) markedly diminishes any potential benefit.

INHIBITION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

ACE inhibitors reduce the mortality rate after STEMI, and the mortality benefits are additive to those achieved with aspirin and beta blockers. The maximum benefit is seen in high-risk patients (those who are elderly or who have an anterior infarction, a prior infarction, and/or globally depressed LV function), but evidence suggests that a short-term benefit occurs when ACE inhibitors are prescribed unselectively to all hemodynamically stable patients with STEMI (i.e., those with a systolic pressure >100 mmHg). The mechanism involves a reduction in ventricular remodeling after infarction (see “Ventricular Dysfunction” later) with a subsequent reduction in the risk of CHF. The rate of recurrent infarction may also be lower in patients treated chronically with ACE inhibitors after infarction.

Before hospital discharge, LV function should be assessed with an imaging study. ACE inhibitors should be continued indefinitely in patients who have clinically evident CHF, in patients in whom an imaging study shows a reduction in global LV function or a large regional wall motion abnormality, or in those who are hypertensive.

Angiotensin receptor blockers (ARBs) should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiologic signs of heart failure. Long-term aldosterone blockade should be prescribed for STEMI patients without significant renal dysfunction (creatinine ≥ 2.5 mg/dL in men and ≥ 2.0 mg/dL in women) or hyperkalemia (potassium ≥ 5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LV ejection fraction $\leq 40\%$, and have either symptomatic heart failure or diabetes mellitus. A multidrug regimen for inhibiting the renin-angiotensin-aldosterone system has been shown to reduce both heart failure-related and sudden cardiac death-related cardiovascular mortality after STEMI, but has not been as thoroughly explored as ACE inhibitors in STEMI patients.

OTHER AGENTS

Favorable effects on the ischemic process and ventricular remodeling (see below) previously led many physicians to routinely use *intravenous nitroglycerin* (5–10 µg/min initial dose and up to 200 µg/min as long as hemodynamic stability is maintained) for the first 24–48 h after the onset of infarction. However, the benefits of routine use of intravenous nitroglycerin are less in the contemporary era where beta-adrenoceptor blockers and ACE inhibitors are routinely prescribed for patients with STEMI.

Results of multiple trials of different calcium antagonists have failed to establish a role for these agents in the treatment of most patients with STEMI. Therefore, the routine use of calcium antagonists cannot be recommended. Strict control of blood glucose in diabetic patients with STEMI has been shown to reduce the mortality rate. Serum magnesium should be measured in all patients on admission, and any demonstrated deficits should be corrected to minimize the risk of arrhythmias.

COMPLICATIONS AND THEIR MANAGEMENT

VENTRICULAR DYSFUNCTION

After STEMI, the left ventricle undergoes a series of changes in shape, size, and thickness in both the infarcted and noninfarcted segments. This process is referred to as *ventricular remodeling* and generally precedes the development of clinically evident CHF in the months to years after infarction. Soon after STEMI, the left ventricle begins to dilate. Acutely, this results from expansion of the infarct, i.e., slippage of muscle bundles, disruption of normal myocardial cells, and tissue loss within the necrotic zone, resulting in disproportionate thinning and elongation of the infarct zone. Later, lengthening of the noninfarcted segments occurs as well. The overall chamber enlargement that occurs is related to the size and location of the infarct, with greater dilation following infarction of the anterior wall and apex of the left ventricle and causing more marked hemodynamic impairment, more frequent heart failure, and a poorer prognosis. Progressive dilation and its clinical consequences may be ameliorated by therapy with ACE inhibitors and other vasodilators (e.g., nitrates). In patients with an ejection fraction <40%, regardless of whether or not heart failure is present, ACE inhibitors or ARBs should be prescribed (see “Inhibition of the Renin-Angiotensin-Aldosterone System” earlier).

HEMODYNAMIC ASSESSMENT

Pump failure is now the primary cause of in-hospital death from STEMI. The extent of infarction correlates well with the degree of pump failure and with mortality, both early (within 10 days of infarction) and later. The most common clinical signs are pulmonary rales and S₃ and S₄ gallop sounds. Pulmonary congestion is also frequently seen on the chest roentgenogram. Elevated LV filling pressure and elevated pulmonary artery pressure are the characteristic hemodynamic findings, but these findings may result from a reduction of ventricular compliance (diastolic failure) and/or a reduction of stroke volume with secondary cardiac dilation (systolic failure) (Chap. 279).

A classification originally proposed by Killip divides patients into four groups: class I, no signs of pulmonary or venous congestion; class II, moderate heart failure as evidenced by rales at the lung bases, S₃ gallop, tachypnea, or signs of failure of the right side of the heart, including venous and hepatic congestion; class III, severe heart failure, pulmonary edema; and class IV, shock with systolic pressure <90 mmHg and evidence of peripheral vasoconstriction, peripheral cyanosis, mental confusion, and oliguria. When this classification was established in 1967, the expected hospital mortality rate of patients in these classes was as follows: class I, 0–5%; class II, 10–20%; class III, 35–45%; and class IV, 85–95%. With advances in management, the mortality rate in each class has fallen, perhaps by as much as one-third to one-half.

Hemodynamic evidence of abnormal global LV function appears when contraction is seriously impaired in 20–25% of the left ventricle. Infarction of $\geq 40\%$ of the left ventricle usually results in cardiogenic shock (Chap. 326). Positioning of a balloon flotation (Swan-Ganz) catheter in the pulmonary artery permits monitoring of LV filling pressure; this technique is useful in patients who exhibit hypotension and/or clinical evidence of CHF. Cardiac output can also be determined with a pulmonary artery catheter. With the addition of intra-arterial pressure monitoring, systemic vascular resistance can be calculated as a guide to adjusting vasopressor and vasodilator therapy. Some patients with STEMI have markedly elevated LV filling pressures (>22 mmHg) and normal cardiac indices (2.6–3.6 L/[min/m²]), while others have relatively low LV filling pressures (<15 mmHg) and reduced cardiac indices. The former patients usually benefit from diuresis, while the latter may respond to volume expansion.

HYPOVOLEMIA

This is an easily corrected condition that may contribute to the hypotension and vascular collapse associated with STEMI in some patients. It may be secondary to previous diuretic use, to reduced fluid intake during the early stages of the illness, and/or to vomiting associated with pain or medications. Consequently, hypovolemia should be identified and corrected in patients with STEMI and hypotension before

1608 more vigorous forms of therapy are begun. Central venous pressure reflects RV rather than LV filling pressure and is an inadequate guide for adjustment of blood volume, because LV function is almost always affected much more adversely than RV function in patients with STEMI. The optimal LV filling or pulmonary artery wedge pressure may vary considerably among patients. Each patient's ideal level (generally ~20 mmHg) is reached by cautious fluid administration during careful monitoring of oxygenation and cardiac output. Eventually, the cardiac output level plateaus, and further increases in LV filling pressure only increase congestive symptoms and decrease systemic oxygenation without raising arterial pressure.

TREATMENT CONGESTIVE HEART FAILURE

The management of CHF in association with STEMI is similar to that of acute heart failure secondary to other forms of heart disease (avoidance of hypoxemia, diuresis, afterload reduction, inotropic support) (**Chap. 279**), except that the benefits of digitalis administration to patients with STEMI are unimpressive. By contrast, diuretic agents are extremely effective, as they diminish pulmonary congestion in the presence of systolic and/or diastolic heart failure. LV filling pressure falls and orthopnea and dyspnea improve after the intravenous administration of furosemide or other loop diuretics. These drugs should be used with caution, however, as they can result in a massive diuresis with associated decreases in plasma volume, cardiac output, systemic blood pressure, and, hence, coronary perfusion. Nitrates in various forms may be used to decrease preload and congestive symptoms. Oral isosorbide dinitrate, topical nitroglycerin ointment, and intravenous nitroglycerin all have the advantage over a diuretic of lowering preload through venodilation without decreasing the total plasma volume. In addition, nitrates may improve ventricular compliance if ischemia is present, as ischemia causes an elevation of LV filling pressure. Vasodilators must be used with caution to prevent serious hypotension. As noted earlier, ACE inhibitors are an ideal class of drugs for management of ventricular dysfunction after STEMI, especially for the long term. (See "Inhibition of the Renin-Angiotensin-Aldosterone System" earlier.)

CARDIOGENIC SHOCK

Prompt reperfusion, efforts to reduce infarct size and treatment of ongoing ischemia and other complications of MI appear to have reduced the incidence of cardiogenic shock from 20% to about 7%. Only 10% of patients with this condition present with it on admission, while 90% develop it during hospitalization. Typically, patients who develop cardiogenic shock have severe multivessel coronary artery disease with evidence of "piecemeal" necrosis extending outward from the original infarct zone. **The evaluation and management of cardiogenic shock and severe power failure after STEMI are discussed in detail in Chap. 326.**

RIGHT VENTRICULAR INFARCTION

Approximately one-third of patients with inferior infarction demonstrate at least a minor degree of RV necrosis. An occasional patient with inferoposterior LV infarction also has extensive RV infarction, and rare patients present with infarction limited primarily to the RV. Clinically significant RV infarction causes signs of severe RV failure (jugular venous distention, Kussmaul's sign, hepatomegaly [**Chap. 267**]) with or without hypotension. ST-segment elevations of right-sided precordial ECG leads, particularly lead V_4R , are frequently present in the first 24 h in patients with RV infarction. Two-dimensional echocardiography is helpful in determining the degree of RV dysfunction. Catheterization of the right side of the heart often reveals a distinctive hemodynamic pattern resembling constrictive pericarditis (steep right atrial "y" descent and an early diastolic dip and plateau in RV waveforms) (**Chap. 288**). Therapy consists of volume expansion to maintain adequate RV preload and efforts to improve LV performance

with attendant reduction in pulmonary capillary wedge and pulmonary arterial pressures.

ARRHYTHMIAS

(**See also Chaps. 274 and 276**) The incidence of arrhythmias after STEMI is higher in patients seen early after the onset of symptoms. The mechanisms responsible for infarction-related arrhythmias include autonomic nervous system imbalance, electrolyte disturbances, ischemia, and slowed conduction in zones of ischemic myocardium. An arrhythmia can usually be managed successfully if trained personnel and appropriate equipment are available when it develops. Since most deaths from arrhythmia occur during the first few hours after infarction, the effectiveness of treatment relates directly to the speed with which patients come under medical observation. The prompt management of arrhythmias constitutes a significant advance in the treatment of STEMI.

Ventricular Premature Beats Infrequent, sporadic ventricular premature depolarizations occur in almost all patients with STEMI and do not require therapy. Whereas in the past, frequent, multifocal, or early diastolic ventricular extrasystoles (so-called warning arrhythmias) were routinely treated with antiarrhythmic drugs to reduce the risk of development of ventricular tachycardia and ventricular fibrillation, pharmacologic therapy is now reserved for patients with sustained ventricular arrhythmias. Prophylactic antiarrhythmic therapy (either intravenous lidocaine early or oral agents later) is contraindicated for ventricular premature beats in the absence of clinically important ventricular tachyarrhythmias, because such therapy may actually increase the mortality rate. Beta-adrenoceptor blocking agents are effective in abolishing ventricular ectopic activity in patients with STEMI and in the prevention of ventricular fibrillation. As described earlier (see "Beta-Adrenoceptor Blockers"), they should be used routinely in patients without contraindications. In addition, hypokalemia and hypomagnesemia are risk factors for ventricular fibrillation in patients with STEMI; to reduce the risk, the serum potassium concentration should be adjusted to approximately 4.5 mmol/L and magnesium to about 2.0 mmol/L.

Ventricular Tachycardia and Fibrillation Within the first 24 h of STEMI, ventricular tachycardia and fibrillation can occur without prior warning arrhythmias. The occurrence of ventricular fibrillation can be reduced by prophylactic administration of intravenous lidocaine. However, prophylactic use of lidocaine has not been shown to reduce overall mortality from STEMI. In fact, in addition to causing possible noncardiac complications, lidocaine may predispose to an excess risk of bradycardia and asystole. For these reasons, and with earlier treatment of active ischemia, more frequent use of beta-blocking agents, and the nearly universal success of electrical cardioversion or defibrillation, routine prophylactic antiarrhythmic drug therapy *is no longer recommended*.

Sustained ventricular tachycardia that is well tolerated hemodynamically should be treated with an intravenous regimen of amiodarone (bolus of 150 mg over 10 min, followed by infusion of 1.0 mg/min for 6 h and then 0.5 mg/min) or procainamide (bolus of 15 mg/kg over 20–30 min; infusion of 1–4 mg/min); if it does not stop promptly, electroversion should be used (**Chap. 276**). An unsynchronized discharge of 200–300 J (monophasic waveform; approximately 50% of these energies with biphasic waveforms) is used immediately in patients with ventricular fibrillation or when ventricular tachycardia causes hemodynamic deterioration. Ventricular tachycardia or fibrillation that is refractory to electroshock may be more responsive after the patient is treated with epinephrine (1 mg intravenously or 10 mL of a 1:10,000 solution via the intracardiac route) or amiodarone (a 75–150-mg bolus).

Ventricular arrhythmias, including the unusual form of ventricular tachycardia known as torsades des pointes (**Chaps. 276 and 277**), may occur in patients with STEMI as a consequence of other concurrent problems (such as hypoxia, hypokalemia, or other electrolyte disturbances) or of the toxic effects of an agent being administered to the patient (such as digoxin or quinidine). A search for such secondary causes should always be undertaken.

Although the in-hospital mortality rate is increased, the long-term survival is excellent in patients who survive to hospital discharge after *primary* ventricular fibrillation; i.e., ventricular fibrillation that is a primary response to acute ischemia that occurs during the first 48 h and is not associated with predisposing factors such as CHF, shock, bundle branch block, or ventricular aneurysm. This result is in sharp contrast to the poor prognosis for patients who develop ventricular fibrillation *secondary* to severe pump failure. For patients who develop ventricular tachycardia or ventricular fibrillation late in their hospital course (i.e., after the first 48 h), the mortality rate is increased both in-hospital and during long-term follow-up. Such patients should be considered for electrophysiologic study and implantation of a cardioverter-defibrillator (ICD) (Chap. 276). A more challenging issue is the prevention of sudden cardiac death from ventricular fibrillation late after STEMI in patients who have not exhibited sustained ventricular tachyarrhythmias during their index hospitalization. An algorithm for selection of patients who warrant prophylactic implantation of an ICD is shown in Fig. 295-5.

Accelerated Idioventricular Rhythm Accelerated idioventricular rhythm (AIVR, “slow ventricular tachycardia”), a ventricular rhythm with a rate of 60–100 beats/min, often occurs transiently during fibrinolytic therapy at the time of reperfusion. For the most part, AIVR, whether it occurs in association with fibrinolytic therapy or spontaneously, is benign and does not presage the development of classic ventricular tachycardia. Most episodes of AIVR do not require treatment if the patient is monitored carefully, as degeneration into a more serious arrhythmia is rare.

Supraventricular Arrhythmias Sinus tachycardia is the most common supraventricular arrhythmia. If it occurs secondary to another cause

(such as anemia, fever, heart failure, or a metabolic derangement), the primary problem should be treated first. However, if it appears to be due to sympathetic overstimulation (e.g., as part of a hyperdynamic state), then treatment with a beta blocker is indicated. Other common arrhythmias in this group are atrial flutter and atrial fibrillation, which are often secondary to LV failure. Digoxin is usually the treatment of choice for supraventricular arrhythmias if heart failure is present. If heart failure is absent, beta blockers, verapamil, or diltiazem are suitable alternatives for controlling the ventricular rate, as they may also help to control ischemia. If the abnormal rhythm persists for >2 h with a ventricular rate >120 beats/min, or if tachycardia induces heart failure, shock, or ischemia (as manifested by recurrent pain or ECG changes), a synchronized electroshock (100–200 J monophasic waveform) should be used.

Accelerated junctional rhythms have diverse causes but may occur in patients with inferoposterior infarction. Digitalis excess must be ruled out. In some patients with severely compromised LV function, the loss of appropriately timed atrial systole results in a marked reduction of cardiac output. Right atrial or coronary sinus pacing is indicated in such instances.

Sinus Bradycardia Treatment of sinus bradycardia is indicated if hemodynamic compromise results from the slow heart rate. Atropine is the most useful drug for increasing heart rate and should be given intravenously in doses of 0.5 mg initially. If the rate remains <50–60 beats/min, additional doses of 0.2 mg, up to a total of 2.0 mg, may be given. Persistent bradycardia (<40 beats/min) despite atropine may be treated with electrical pacing. Isoproterenol should be avoided.

Atrioventricular and Intraventricular Conduction Disturbances (See also Chap. 274) Both the in-hospital mortality rate and the postdischarge mortality rate of patients who have complete atrioventricular (AV) block in association with anterior infarction are markedly higher than those of patients who develop AV block with inferior infarction. This difference is related to the fact that heart block in inferior infarction is commonly a result of increased vagal tone and/or the release of adenosine and therefore is transient. In anterior wall infarction, however, heart block is usually related to ischemic malfunction of the conduction system, which is commonly associated with extensive myocardial necrosis.

Temporary electrical pacing provides an effective means of increasing the heart rate of patients with bradycardia due to AV block. However, acceleration of the heart rate may have only a limited impact on prognosis in patients with anterior wall infarction and complete heart block in whom the large size of the infarct is the major factor determining outcome. It should be carried out if it improves hemodynamics. Pacing does appear to be beneficial in patients with inferoposterior infarction who have complete heart block associated with heart failure, hypotension, marked bradycardia, or significant ventricular ectopic activity. A subgroup of these patients, those with RV infarction, often respond poorly to ventricular pacing because of the loss of the atrial contribution to ventricular filling. In such patients, dual-chamber AV sequential pacing may be required.

External noninvasive electrodes should be positioned in a “demand” mode for patients with sinus bradycardia (rate <50 beats/min) that is unresponsive to drug therapy, Mobitz II second-degree AV block, third-degree heart block, or bilateral bundle branch block (e.g., right bundle branch block plus left anterior fascicular block). Retrospective studies suggest that permanent pacing may reduce the long-term risk of sudden death due to bradyarrhythmias in the rare patient who develops combined persistent bifascicular and transient third-degree heart block during the acute phase of MI.

OTHER COMPLICATIONS

Recurrent Chest Discomfort Because recurrent or persistent ischemia often heralds extension of the original infarct or reinfarction in a new myocardial zone and is associated with a near tripling of mortality after STEMI, patients with these symptoms should be referred for prompt coronary arteriography and mechanical revascularization.

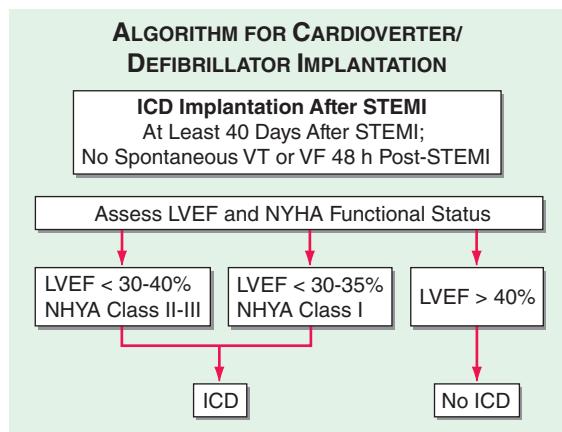


FIGURE 295-5 Algorithm for assessment of need for implantation of a cardioverter-defibrillator. The appropriate management is selected based on measurement of left ventricular ejection fraction and assessment of the New York Heart Association (NYHA) functional class. Patients with depressed left ventricular function at least 40 days after ST-segment elevation myocardial infarction (STEMI) are referred for insertion of an implantable cardioverter-defibrillator (ICD) if the left ventricular ejection fraction (LVEF) is <30–40% and they are in NYHA class II–III or if the LVEF is <30–35% and they are in NYHA class I functional status. Patients with preserved left ventricular function (LVEF >40%) do not receive an ICD regardless of NYHA functional class. All patients are treated with medical therapy after STEMI. VF, ventricular fibrillation; VT, ventricular tachycardia. (Adapted from data contained in DP Zipes et al: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death; a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines [Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death]. J Am Coll Cardiol 48:1064, 2006.)

1610 Administration of a fibrinolytic agent is an alternative to early mechanical revascularization.

Pericarditis (See also Chap. 288) Pericardial friction rubs and/or pericardial pain are frequently encountered in patients with STEMI involving the epicardium. This complication can usually be managed with aspirin (650 mg four times daily). It is important to diagnose the chest pain of pericarditis accurately, because failure to recognize it may lead to the erroneous diagnosis of recurrent ischemic pain and/or infarct extension, with resulting inappropriate use of anticoagulants, nitrates, beta blockers, or coronary arteriography. When it occurs, complaints of pain radiating to either trapezius muscle is helpful, because such a pattern of discomfort is typical of pericarditis but rarely occurs with ischemic discomfort. Anticoagulants potentially could cause tamponade in the presence of acute pericarditis (as manifested by either pain or persistent rub) and therefore should not be used unless there is a compelling indication.

Thromboembolism Clinically apparent thromboembolism complicates STEMI in ~10% of cases, but embolic lesions are found in 20% of patients in necropsy series, suggesting that thromboembolism is often clinically silent. Thromboembolism is considered to be an important contributing cause of death in 25% of patients with STEMI who die after admission to the hospital. Arterial emboli originate from LV mural thrombi, while most pulmonary emboli arise in the leg veins.

Thromboembolism typically occurs in association with large infarcts (especially anterior), CHF, and an LV thrombus detected by echocardiography. The incidence of arterial embolism from a clot originating in the ventricle at the site of an infarction is small but real. Two-dimensional echocardiography reveals LV thrombi in about one-third of patients with anterior wall infarction but in few patients with inferior or posterior infarction. Arterial embolism often presents as a major complication, such as hemiparesis when the cerebral circulation is involved or hypertension if the renal circulation is compromised. When a thrombus has been clearly demonstrated by echocardiographic or other techniques or when a large area of regional wall motion abnormality is seen even in the absence of a detectable mural thrombus, systemic anticoagulation should be undertaken (in the absence of contraindications), as the incidence of embolic complications appears to be markedly lowered by such therapy. The appropriate duration of therapy is unknown, but 3–6 months is probably prudent.

Left Ventricular Aneurysm The term *ventricular aneurysm* is usually used to describe *dyskinesis* or local expansile paradoxical wall motion. Normally functioning myocardial fibers must shorten more if stroke volume and cardiac output are to be maintained in patients with ventricular aneurysm; if they cannot, overall ventricular function is impaired. True aneurysms are composed of scar tissue and neither predispose to nor are associated with cardiac rupture.

The complications of LV aneurysm do not usually occur for weeks to months after STEMI; they include CHF, arterial embolism, and ventricular arrhythmias. Apical aneurysms are the most common and the most easily detected by clinical examination. The physical finding of greatest value is a double, diffuse, or displaced apical impulse. Ventricular aneurysms are readily detected by two-dimensional echocardiography, which may also reveal a mural thrombus in an aneurysm.

Rarely, myocardial rupture may be contained by a local area of pericardium, along with organizing thrombus and hematoma. Over time, this *pseudoaneurysm* enlarges, maintaining communication with the LV cavity through a narrow neck. Because a pseudoaneurysm often ruptures spontaneously, it should be surgically repaired if recognized.

POSTINFARCTION RISK STRATIFICATION AND MANAGEMENT

Many clinical and laboratory factors have been identified that are associated with an increase in cardiovascular risk after initial recovery from STEMI. Some of the most important factors include persistent ischemia (spontaneous or provoked), depressed LV ejection fraction (<40%), rales above the lung bases on physical examination or congestion on

chest radiograph, and symptomatic ventricular arrhythmias. Other features associated with increased risk include a history of previous MI, age >75, diabetes mellitus, prolonged sinus tachycardia, hypotension, ST-segment changes at rest without angina (“silent ischemia”), an abnormal signal-averaged ECG, nonpatency of the infarct-related coronary artery (if angiography is undertaken), and persistent advanced heart block or a new intraventricular conduction abnormality on the ECG. Therapy must be individualized on the basis of the relative importance of the risk(s) present.

The goal of preventing reinfarction and death after recovery from STEMI has led to strategies to evaluate risk after infarction. In stable patients, submaximal exercise stress testing may be carried out before hospital discharge to detect residual ischemia and ventricular ectopy and to provide the patient with a guideline for exercise in the early recovery period. Alternatively, or in addition, a maximal (symptom-limited) exercise stress test may be carried out 4–6 weeks after infarction. Evaluation of LV function is usually warranted as well. Recognition of a depressed LV ejection fraction by echocardiography or radionuclide ventriculography identifies patients who should receive medications to inhibit the renin-angiotensin-aldosterone system. Patients in whom angina is induced at relatively low workloads, those who have a large reversible defect on perfusion imaging or a depressed ejection fraction, those with demonstrable ischemia, and those in whom exercise provokes symptomatic ventricular arrhythmias should be considered at high risk for recurrent MI or death from arrhythmia (Fig. 295-5). Cardiac catheterization with coronary angiography and/or invasive electrophysiologic evaluation is advised.

Exercise tests also aid in formulating an individualized exercise prescription, which can be much more vigorous in patients who tolerate exercise without any of the previously mentioned adverse signs. In addition, predischarge stress testing may provide an important psychological benefit, building the patient’s confidence by demonstrating a reasonable exercise tolerance.

In many hospitals, a cardiac rehabilitation program with progressive exercise is initiated in the hospital and continued after discharge. Ideally, such programs should include an educational component that informs patients about their disease and its risk factors.

The usual duration of hospitalization for an uncomplicated STEMI is about 5 days. The remainder of the convalescent phase may be accomplished at home. During the first 1–2 weeks, the patient should be encouraged to increase activity by walking about the house and outdoors in good weather. Normal sexual activity may be resumed during this period. After 2 weeks, the physician must regulate the patient’s activity on the basis of exercise tolerance. Most patients will be able to return to work within 2–4 weeks.

SECONDARY PREVENTION

Various secondary preventive measures are at least partly responsible for the improvement in the long-term mortality and morbidity rates after STEMI. Long-term treatment with an antiplatelet agent (usually aspirin) after STEMI is associated with a 25% reduction in the risk of recurrent infarction, stroke, or cardiovascular mortality (36 fewer events for every 1000 patients treated). An alternative antiplatelet agent that may be used for secondary prevention in patients intolerant of aspirin is clopidogrel (75 mg orally daily). ACE inhibitors or ARBs and, in appropriate patients, aldosterone antagonists should be used indefinitely by patients with clinically evident heart failure, a moderate decrease in global ejection fraction, or a large regional wall motion abnormality to prevent late ventricular remodeling and recurrent ischemic events.

The chronic routine use of oral beta-adrenoceptor blockers for at least 2 years after STEMI is supported by well-conducted, placebo-controlled trials.

Evidence suggests that warfarin lowers the risk of late mortality and the incidence of reinfarction after STEMI. Most physicians prescribe aspirin routinely for all patients without contraindications and add warfarin for patients at increased risk of embolism (see “Thromboembolism” earlier). Several studies suggest that in patients

<75 years old a low dose of aspirin (75–81 mg/d) in combination with warfarin administered to achieve an international normalized ratio >2.0 is more effective than aspirin alone for preventing recurrent MI and embolic cerebrovascular accident. However, there is an increased risk of bleeding and a high rate of discontinuation of warfarin that has limited clinical acceptance of combination antithrombotic therapy. There is increased risk of bleeding when warfarin is added to dual antiplatelet therapy (aspirin and clopidogrel). However, patients who have had a stent implanted and have an indication for anticoagulation should receive dual antiplatelet therapies in combination with warfarin. Such patients should also receive a proton pump inhibitor to minimize the risk of gastrointestinal bleeding and should have regular monitoring of their hemoglobin levels and stool hematest while on combination antithrombotic therapy.

Finally, risk factors for *atherosclerosis* (Chap. 265e) should be discussed with the patient and, when possible, favorably modified.

296e Percutaneous Coronary Interventions and Other Interventional Procedures

David P. Faxon, Deepak L. Bhatt

Percutaneous transluminal coronary angioplasty (PTCA) was first introduced by Andreas Gruentzig in 1977 as an alternative to coronary bypass surgery. The concept was initially demonstrated by Charles Dotter in 1964 in peripheral vessels. The development of a small inelastic balloon catheter by Gruentzig allowed expansion of the technique into smaller peripheral and coronary vessels. Initial coronary experience was limited to single-vessel coronary disease and discrete proximal lesions due to the technical limitations of the equipment. Advances in technology and greater operator experience allowed the procedure to grow rapidly with expanded use in patients with more complex lesions and multivessel disease. The introduction of coronary stents in 1994 was one of the major advances in the field. These devices reduced acute complications and reduced by half the significant problem of restenosis (or recurrence of the stenosis). Further reductions in restenosis were achieved by the introduction of drug-eluting stents in 2003. These stents slowly release antiproliferative drugs directly into the plaque over a few months. Percutaneous coronary intervention (PCI) is the most common revascularization procedure in the United States and is performed more than twice as often as coronary artery bypass surgery: nearly 600,000 patients a year.

Interventional cardiology is a separate discipline in cardiology that requires a dedicated 1-year interventional cardiology fellowship following a 3-year general cardiology fellowship in order to obtain a separate board certification. The discipline has also expanded to include interventions for structural heart disease including treatment of congenital heart disease and valvular heart disease; it also includes interventions to treat peripheral vascular disease, including atherosclerotic and nonatherosclerotic lesions in the carotid, renal, aortic, and peripheral circulations.

TECHNIQUE

The initial procedure is performed in a similar manner as a diagnostic cardiac catheterization (Chap. 272). Arterial access is obtained via the femoral or radial artery. To prevent thrombotic complications during the procedure, patients who are anticipated to need an angioplasty

are given aspirin (325 mg) and may be given clopidogrel (loading dose of 300–600 mg), prasugrel (loading dose of 60 mg), or ticagrelor (loading dose of 180 mg) before the procedure. During the procedure, anticoagulation is achieved by administration of unfractionated heparin, enoxaparin (a low-molecular-weight heparin), or bivalirudin (a direct thrombin inhibitor). The latter has gained popularity due to the significant reduction in bleeding complications. In patients with ST-elevation myocardial infarction, high-risk acute coronary syndrome, or a large thrombus in the coronary artery, an intravenous glycoprotein IIb/IIIa inhibitor (abciximab, tirofiban, or eptifibatide) may also be given.

Following placement of an introducing sheath, preformed guiding catheters are used to cannulate selectively the origins of the coronary arteries. Through the guiding catheter, a flexible, steerable guidewire is negotiated down the coronary artery lumen using fluoroscopic guidance; it is then advanced through the stenosis and into the vessel beyond. This guidewire then serves as a “rail” over which angioplasty balloons, stents, or other therapeutic devices can be advanced to enlarge the narrowed segment of coronary artery. The artery is usually dilated with a balloon catheter followed by placement of a stent. The catheters and introducing sheath are removed and the artery manually held or closed using one of several femoral arterial closure devices to achieve hemostasis. Because PCI is performed under local anesthesia and mild sedation, it requires only a short (1-day) hospitalization or less.

Angioplasty works by stretching the artery and displacing the plaque away from the lumen, enlarging the entire vessel (Figs. 296e-1 and 296e-2). The procedure rarely results in embolization of atherosclerotic material. Owing to inelastic elements in the plaque, the stretching of the vessel by the balloon results in small localized dissections that can protrude into the lumen and be a nidus for acute thrombus formation. If the dissections are severe, then they can obstruct the lumen or induce a thrombotic occlusion of the artery (acute closure). Stents have largely prevented this complication by holding the dissection flaps up against the vessel wall (Fig. 296e-1).

Stents are currently used in more than 90% of coronary angioplasty procedures. Stents are wire meshes (usually made of stainless steel) that are compressed over a deflated angioplasty balloon. When the balloon is inflated, the stent is enlarged to approximate the “normal” vessel lumen. The balloon is then deflated and removed, leaving the stent behind to provide a permanent scaffold in the artery. Owing to the design of the struts, these devices are flexible, allowing their passage through diseased and tortuous coronary vessels. Stents are rigid enough to prevent elastic recoil of the vessel and have dramatically improved the success and safety of the procedure as a result.

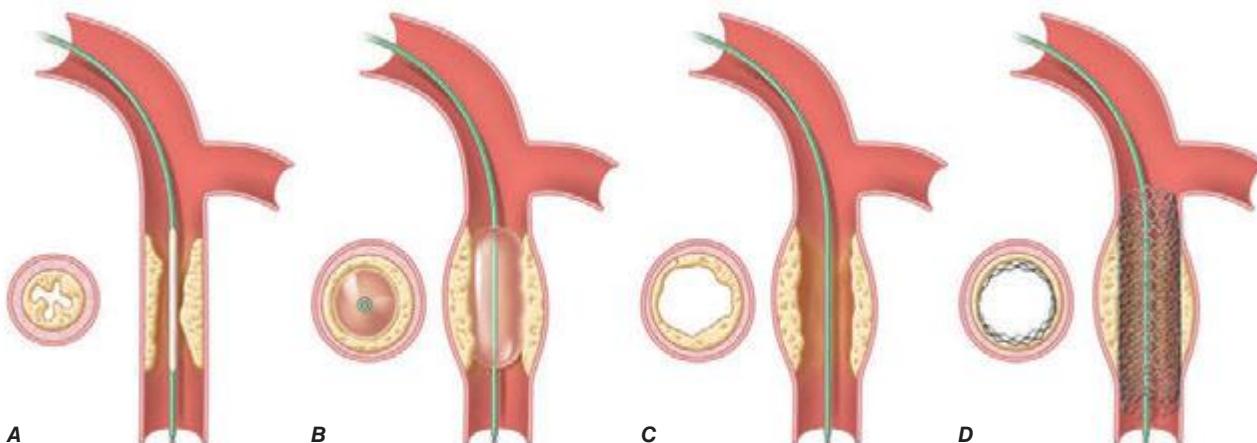


FIGURE 296e-1 Schematic diagram of the primary mechanisms of balloon angioplasty and stenting. **A.** A balloon angioplasty catheter is positioned into the stenosis over a guidewire under fluoroscopic guidance. **B.** The balloon is inflated temporarily occluding the vessel. **C.** The lumen is enlarged primarily by stretching the vessel, often resulting in small dissections in the neointima. **D.** A stent mounted on a deflated balloon is placed into the lesion and pressed against the vessel wall with balloon inflation (not shown). The balloon is deflated and removed, leaving the stent permanently against the wall acting as a scaffold to hold the dissections against the wall and prevent vessel recoil. (Adapted from EJ Topol: Textbook of Cardiovascular Medicine, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2002.)

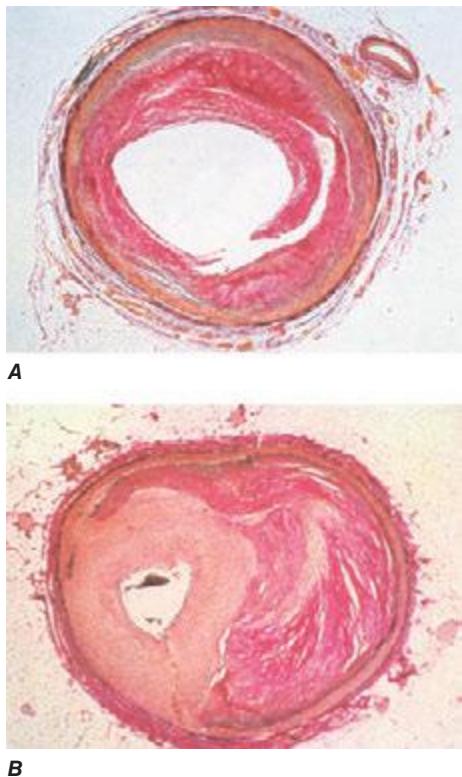


FIGURE 296e-2 Pathology of acute effects of balloon angioplasty with intimal dissection and vessel stretching (**A**) and an example of neointimal hyperplasia and restenosis showing renarrowing of the vessel (**B**). (Panel A from M Ueda et al: Eur Heart J 12:937, 1991; with permission. Panel B from CE Essed et al: Br Heart J 49:393, 1983; with permission.)

Drug-eluting stents further enhanced the efficacy of PCI. An antiproliferative agent is attached to the metal stent by use of a thin polymer coating. The antiproliferative drug elutes from the stent over a 1- to 3-month period after implantation. Drug-eluting stents have been shown to reduce clinical restenosis by 50%, so that in uncomplicated lesions symptomatic restenosis occurs in 5–10% of patients. Not surprisingly, this led to the rapid acceptance of these devices; currently 80–90% of all stents implanted are drug-eluting. The first-generation devices were coated with either sirolimus or paclitaxel. Second-generation drug-eluting stents use newer agents such as everolimus, biolimus, and zotarolimus. These second-generation drug-eluting stents appear to be more effective with fewer complications, such as early or late stent thrombosis, than the first-generation devices and, therefore, have replaced the first-generation stents. Biodegradable polymers that are used to attach the drugs to the stents may be superior to permanent polymers in preventing late stent thrombosis and are under investigation. In addition, the everolimus-eluting biodegradable vascular scaffold (BVS) stent has been shown to be safe and effective with gradual degradation over several years with return of normal vessel function. It is currently approved in Europe. Additional stents are under investigation. Other interventional devices include atherectomy devices and thrombectomy catheters. These devices are designed to remove atherosclerotic plaque or thrombus and are used in conjunction with balloon dilatation and stent placement. Rotational atherectomy is the most commonly used adjunctive device and is modeled after a dentist's drill, with small round burrs of 1.25–2.5 mm at the tip of a flexible wire shaft. They are passed over the guidewire up to the stenosis and drill away atherosclerotic material. Because the atherosclerotic particles are $\leq 25 \mu\text{m}$, they pass through the coronary microcirculation and rarely cause problems. The device is particularly useful in heavily calcified plaques that are resistant to balloon dilatation. Given the current advances in stents, rotational atherectomy is infrequently used. Directional atherectomy catheters are not used in the coronaries any longer but are used in peripheral arterial disease.

In acute ST-elevation myocardial infarction, specialized catheters without a balloon are used to aspirate thrombus in order to prevent embolization down the coronary vessel and to improve blood flow before angioplasty and stent placement. Some data suggest that manual catheter thrombus aspiration may reduce mortality in addition to improving blood flow in primary PCI.

PCI of degenerated saphenous vein graft lesions has been associated with a significant incidence of distal embolization of atherosclerotic material, unlike PCI of native vessel disease. A number of distal protection devices have been shown to significantly reduce embolization and myocardial infarction in this setting. Most devices work by using a collapsible wire filter at the end of a guidewire that is expanded in the distal vessel before PCI. If atherosclerotic debris is dislodged, the basket captures the material, and at the end of the PCI, the basket is pulled into a delivery catheter and the debris safely removed from the patient.

SUCCESS AND COMPLICATIONS

A successful procedure (angiographic success), defined as a reduction of the stenosis to less than a 20% diameter narrowing, occurs in 95–99% of patients. Lower success rates are seen in patients with tortuous, small, or calcified vessels or chronic total occlusions. Chronic total occlusions have the lowest success rates (60–70%), and their recanalization is usually not attempted unless the occlusion is recent (within 3 months) or there are favorable anatomic features. Improvements in equipment and technique have increased the success rates of recanalization of chronic total occlusions.

Serious complications are rare but include a mortality rate of 0.1–0.3% for elective cases, a large myocardial infarction in less than 3%, and stroke in less than 0.1%. Patients who are elderly (>65 years), undergoing an emergent or urgent procedure, have chronic kidney disease, present with an ST-segment elevation myocardial infarction (STEMI), or are in shock have significantly higher risk. Scoring systems can help to estimate the risk of the procedure. Myocardial infarction during PCI can occur for multiple reasons including an acute occluding thrombus, severe coronary dissection, embolization of thrombus or atherosclerotic material, or closure of a side branch vessel at the site of angioplasty. Most myocardial infarctions are small and only detected by a rise in the creatine phosphokinase (CPK) or troponin level after the procedure. Only those with significant enzyme elevations (more than three to five times the upper limit of normal) are associated with a less favorable long-term outcome. Coronary stents have largely prevented coronary dissections due to the scaffolding effect of the stent.

Metallic stents are also prone to stent thrombosis (1–3%), either acute (<24 h) or subacute (1–30 days), which can be ameliorated by greater attention to full initial stent deployment and the use of dual antiplatelet therapy (DAPT) (aspirin, plus a platelet P2Y₁₂ receptor blocker [clopidogrel, prasugrel, or ticagrelor]). Late (30 days–1 year) and very late stent thromboses (>1 year) occur very infrequently with stents but are slightly more common with first-generation drug-eluting stents, necessitating DAPT for up to 1 year or longer. Use of the second-generation stents is associated with lower rates of late and very late stent thromboses, and shorter durations of DAPT may be possible. Premature discontinuation of DAPT, particularly in the first month after implantation, is associated with a significantly increased risk for stent thrombosis (three- to ninefold greater). Stent thrombosis results in death in 10–20% and myocardial infarction in 30–70% of patients. Elective surgery that requires discontinuation of antiplatelet therapy after drug-eluting stent implantation should be postponed until after 6 months and preferably after 1 year, if at all possible.

Restenosis, or renarrowing of the dilated coronary stenosis, is the most common complication of angioplasty and occurs in 20–50% of patients with balloon angioplasty alone, 10–30% of patients with bare metal stents, and 5–15% of patients with drug-eluting stents within the first year. The fact that stent placement provides a larger acute luminal area than balloon angioplasty alone reduces the incidence of subsequent restenosis. Drug-eluting stents further reduce restenosis through a reduction in excessive neointimal growth over the stent. If restenosis does not occur, the long-term outcome is excellent

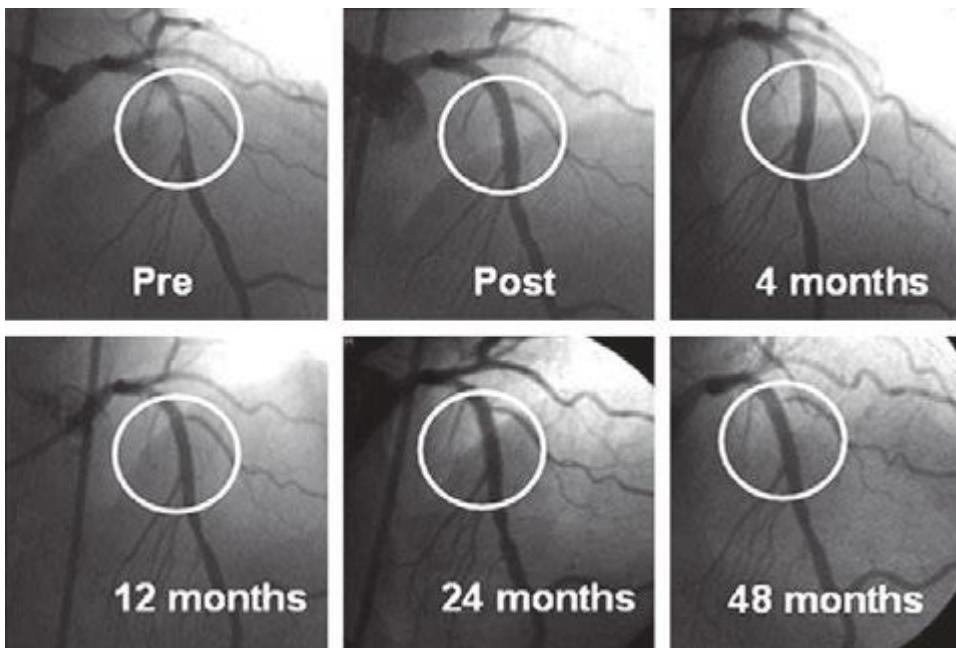


FIGURE 296e-3 Long-term results from one of the first patients to receive a sirolimus-eluting stent from early Sao Paulo experience. (From: GW Stone, in D Baim [ed]: *Cardiac Catheterization, Angiography and Intervention*, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2006; with permission.)

(**Fig. 296e-3**). Clinical restenosis is recognized by recurrence of angina or symptoms within 9 months of the procedure. Less frequently, patients with restenosis can present with non-ST-segment elevation myocardial infarction (NSTEMI) (10%) or STEMI (2%) as well. Clinical restenosis requires confirmation of a significant stenosis at the site of the prior PCI. *Target lesion revascularization* (TLR) or *target vessel revascularization* (TVR) is defined as angiographic restenosis with repeat PCI or coronary artery bypass grafting (CABG). By angiography, the incidence of restenosis is significantly higher than clinical restenosis (TLR or TVR) because many patients have mild restenosis that does not result in a recurrence of symptoms. The management of clinical restenosis is usually to repeat the PCI with balloon dilatation and placement of a drug-eluting stent. Once a patient has had restenosis, the risk of a second restenosis is further increased. The risk factors for restenosis are diabetes, myocardial infarction, long lesions, small-diameter vessels, and suboptimal initial PCI result.

INDICATIONS

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines extensively review the indications for PCI in patients with stable angina, unstable angina, NSTEMI, and STEMI and should be referred to for a comprehensive discussion of the indications. Briefly, the two principal indications for coronary revascularization in patients with *chronic stable angina* (**Chap. 293**) are (1) to improve anginal symptoms in patients who remain symptomatic despite adequate medical therapy and (2) to reduce mortality rates in patients with severe coronary disease. In patients with stable angina who are well controlled on medical therapy, studies such as the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trials have shown that initial revascularization does not lead to better outcomes and can be safely delayed until symptoms worsen or evidence of severe ischemia on noninvasive testing occurs. When revascularization is indicated, the choice of PCI or CABG depends on a number of clinical and anatomic factors (**Fig. 296e-4**). The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial compared PCI with the paclitaxel drug-eluting stent to CABG in 1800 patients with three-vessel coronary disease or left main disease. The study found no difference in death or myocardial infarction at 1 year,

but repeat revascularization was significantly higher in the stent-treated group (13.5 vs. 5.9%), while stroke was significantly higher in the surgical group (2.2 vs. 0.6%). The primary endpoint of death, myocardial infarction, stroke, or revascularization was significantly better with CABG, particularly in those with the most extensive coronary artery disease. The 3-year results confirm these findings. The Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial randomized 1900 patients with diabetes and multivessel disease and showed a significantly lower primary endpoint of death, myocardial infarction, or stroke with CABG than PCI. These studies support CABG for those with the most severe left main and three-vessel disease or those with diabetes. Lesser degrees of multivessel disease in patients with or without diabetes have an equal outcome with PCI.

The choice of PCI versus CABG is also related to the anticipated procedural success and complications of PCI and the risks of CABG. For PCI, the

characteristics of the coronary anatomy are critically important. The location of the lesion in the vessel (proximal or distal), the degree of tortuosity, and the size of the vessel are considered. In addition, the

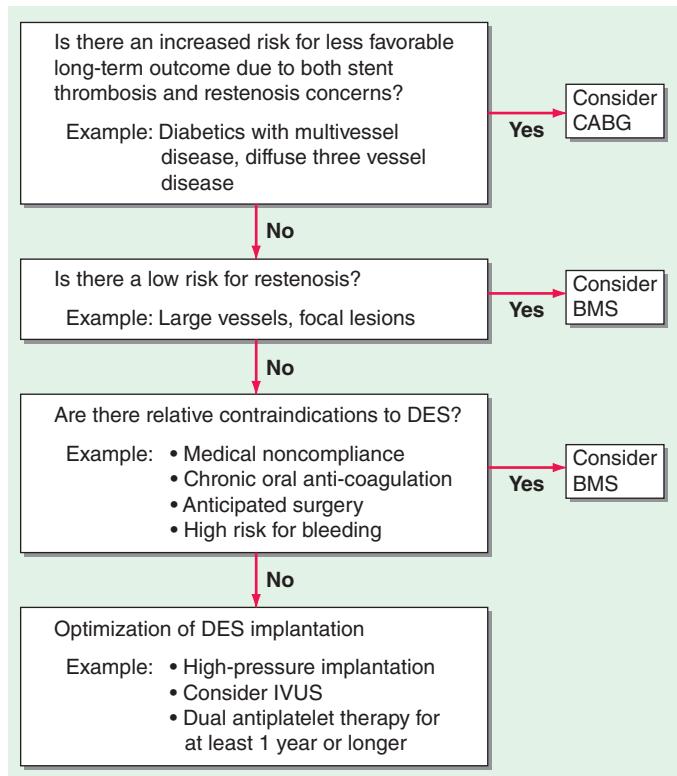


FIGURE 296e-4 In patients requiring revascularization, several factors need to be considered in choosing between bare metal stents, drug-eluting stents, or coronary artery bypass surgery. ACS, acute coronary syndrome; BMS, bare metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; IVUS, intravascular ultrasound; STEMI, ST-segment elevation myocardial infarction. (From AA Bavry, DL Bhatt: *Circulation* 116:696, 2007; with permission.)

lesion characteristics, including the degree of the stenosis, the presence of calcium, lesion length, and presence of thrombus, are assessed. The most common reason to decide not to do PCI is that the lesion felt to be responsible for the patient's symptoms is not treatable. This is most commonly due to the presence of a chronic total occlusion (>3 months in duration). In this setting, the historical success rate has been low (30–70%) and complications are more common. A lesion classification to characterize the likelihood of success or failure of PCI has been developed by the ACC/AHA. Lesions with the highest success are called type A lesions (such as proximal noncalcified subtotal lesions), and those with the lowest success or highest complication rate are type C lesions (such as chronic total occlusions). Intermediate lesions are classified as type B1 or B2 depending on the number of unfavorable characteristics. Approximately 25–30% of patients will not be candidates for PCI due to unfavorable anatomy, whereas only 5% of CABG patients will not be candidates for surgery due to coronary anatomy. The primary reason for being considered inoperable with CABG is the presence of severe comorbidities such as advanced age, frailty, severe chronic obstructive pulmonary disease (COPD), or poor left ventricular function.

Another consideration in choosing a revascularization strategy is the degree of revascularization. In patients with multivessel disease, bypass grafts can usually be placed to all vessels with significant stenosis, whereas PCI may be able to treat only some of the lesions due to the presence of unfavorable anatomy. Assessment of the significance of intermediate lesions using fractional flow reserve (FFR) ([Chap. 272](#)) can assist in determining which lesions should be revascularized. The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial showed a 30% reduction in adverse events when revascularization by PCI was restricted to those lesions that were hemodynamically significant (FFR ≤ 0.80) rather than when guided by angiography alone. Thus, complete revascularization of all functionally significant lesions should be favored and considered when choosing the optimal revascularization strategy. Given the multiple factors that need to be considered in choosing the best revascularization for an individual patient with multivessel disease, it is optimal to have a discussion among the cardiac surgeon, interventional cardiologist, and the physicians caring for the patient (so-called Heart Team) to properly weigh the choices.

Patients with acute coronary syndrome are at excess risk of short- and long-term mortality. Randomized clinical trials have shown that PCI is superior to intensive medical therapy in reducing mortality and myocardial infarction, with the benefit largely confined to those patients who are high risk. High-risk patients are defined as those with any one of the following: refractory ischemia, recurrent angina, positive cardiac-specific enzymes, new ST-segment depression, low ejection fraction, severe arrhythmias, or a recent PCI or CABG. PCI is preferred over surgical therapy in most high-risk patients with acute coronary syndromes unless they have severe multivessel disease or the culprit lesion responsible for the unstable presentation cannot be adequately treated. In STEMI, thrombolysis or PCI (primary PCI) are effective methods to restore coronary blood flow and salvage myocardium within the first 12 h after onset of chest pain. Because PCI is more effective in restoring flow than thrombolysis, it is preferred if readily available. PCI is also performed following thrombolysis to facilitate adequate reperfusion or as a rescue procedure in those who do not achieve reperfusion from thrombolysis or in those who develop cardiogenic shock.

OTHER INTERVENTIONAL TECHNIQUES

STRUCTURAL HEART DISEASE

Interventional treatment for structural heart disease (adult congenital heart disease and valvular heart disease) is a significant and growing component of the field of interventional cardiology.

The most common adult congenital lesion to be treated with percutaneous techniques is closure of atrial septal defects ([Chap. 282](#)). The procedure is done as in a diagnostic right heart catheterization with the passage of a catheter up the femoral vein into the right atrium. With echo and fluoroscopic guidance, the size and location of the defect can

be accurately defined, and closure is accomplished using one of several approved devices. All devices use a left atrial and right atrial wire mesh or covered disk that are pulled together to capture the atrial septum around the defect and seal it off. The Amplatzer Septal Occluder device (AGA Medical, Minneapolis, Minnesota) is the most commonly used in the United States. The success rate in selected patients is 85–95%, and the device complications are rare and include device embolization, infection, or erosion. Closure of patent foramen ovale (PFO) is done in a similar way. PFO closure may be considered in patients who have had recurrent paradoxical stroke or transient ischemic attack (TIA) despite adequate medical therapy including anticoagulation or antiplatelet therapy. The benefit, however, has not been proven. The CLOSURE I trial randomized 909 patients with cryptogenic stroke or TIA who had a PFO. Closure did not reduce the primary endpoint of death within 30 days or death following a neurologic cause during 2 years of follow-up or stroke/TIA within 2 years. Other trials have confirmed these findings. The use in the treatment of migraine is under clinical investigation and is not an approved indication.

Similar devices can also be used to close patent ductus arteriosus and ventricular septal defects. Other congenital diseases that can be treated percutaneously include coarctation of the aorta, pulmonic stenosis, peripheral pulmonary stenosis, and other abnormal communications between the cardiac chambers or vessels.

The treatment of valvular heart disease is the most rapidly growing area in interventional cardiology. Until recently, the only available techniques were balloon valvuloplasty for the treatment of aortic, mitral, or pulmonic stenosis ([Chap. 283](#)). Mitral valvuloplasty is the preferred treatment for symptomatic patients with rheumatic mitral stenosis who have favorable anatomy. The outcome in these patients is equal to that of surgical commissurotomy. The success is highly related to the echocardiographic appearance of the valve. The most favorable setting is commissural fusion without calcification or subchordal fusion and the absence of significant mitral regurgitation. Access is obtained from the femoral vein using a transseptal technique in which a long metal catheter with a needle tip is advanced from the femoral vein through the right atrium and atrial septum at the level of the foramen ovale into the left atrium. A guidewire is advanced into the left ventricle, and a balloon-dilatation catheter is negotiated across the mitral valve and inflated to a predetermined size to enlarge the valve. The most commonly used dilatation catheter is the Inoue balloon. The technique splits the commissural fusion and commonly results in a doubling of the mitral valve area. The success of the procedure in favorable anatomy is 95% and severe complications are rare (1–2%). The most common complications are tamponade due to puncture into the pericardium or the creation of severe mitral regurgitation.

For regurgitant valvular lesions, only severe mitral regurgitation can be effectively treated percutaneously using the MitraClip (Abbott, Abbott Park, Ill) device. The procedure involves the passage of a catheter into the left atrium using the transseptal technique. A special catheter with a metallic clip on the end is passed through the mitral valve and retracted to catch and clip together the mid portion of the anterior and posterior mitral valve leaflet. The clip creates a double opening in the mitral valve and thereby reduces mitral regurgitation similar to the surgical Alfieri repair. In the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) trial, the device was less effective than surgical repair or replacement but was shown to be safe. It is currently used for patients who are not good candidates for surgical repair, particularly when the regurgitation is due to functional causes.

Severe aortic stenosis can be treated with balloon valvuloplasty as well. In this setting, the valvuloplasty balloon catheter is placed retrograde across the aortic valve from the femoral artery and briefly inflated to stretch open the valve. The success is much less favorable, with only 50% achieving an aortic valve area of >1 cm² and a restenosis rate of 25–50% after 6–12 months. This poor success rate has limited its use to patients who are not surgical candidates or as a bridge to surgery or transcatheter aortic valve replacement (TAVR). In this setting, the intermediate-term mortality rate of the procedure is high (10%). Repeat aortic valvuloplasty as a treatment for aortic valve restenosis has been reported.

Percutaneous aortic valve replacement (TAVR) has been shown to be an effective treatment for high-risk and inoperable patients with aortic stenosis. Currently, two valve models, the Edwards SAPIEN valve (Edwards Lifescience, Irvine, California) and the CoreValve ReValving system (Medtronic, Minneapolis, Minnesota) are available. In more than 10,000 cases worldwide, follow-up shows no evidence of restenosis or severe prosthetic valve dysfunction in the midterm. The CoreValve is self-expanding, while the Edwards valve is balloon expanded. The cannulas are large (14–22 French), and retrograde access via the femoral artery is most commonly chosen, if possible. In patients with peripheral artery disease, access via the subclavian artery or transapically through a surgical incision can be used. Following balloon valvuloplasty, the valve is positioned across the valve and deployed with postdeployment balloon inflation to ensure full contact with the aortic annulus. The success rate is 80–90%, and the 30-day mortality rate is 10–15%, not unexpectedly as only high-risk patients are undergoing the procedure currently. The Placement of Aortic Transcatheter Valve (PARTNER) randomized trial of the Edwards valve showed a 55% reduction in 1-year mortality and major adverse events in the extreme-risk group randomized to TAVR compared to medical therapy. In a separate randomized trial, high-risk patients had a similar outcome to surgical valve replacement at 1 year. As a result, this valve is approved for both high-risk and extreme-risk patients with severe aortic stenosis.

Pulmonic stenosis can also be effectively treated with balloon valvuloplasty and percutaneously replaced with the Melody stent (Medtronic). Tricuspid valve interventions remain experimental.

PERIPHERAL ARTERY INTERVENTIONS

The use of percutaneous interventions to treat symptomatic patients with arterial obstruction in the carotid, renal, aortic, and peripheral vessels is also part of the field of interventional cardiology. Randomized clinical trial data already support the use of carotid stenting in patients at high risk of complications from carotid endarterectomy (Fig. 296e-5). Recent trials suggest similar outcomes with carotid stenting and carotid endarterectomy in patients at average risk, although depending on the patient's risk for perioperative stroke or myocardial infarction, one procedure may be preferred over the other. The success rate of peripheral artery interventional procedures has been improving, including for long segments of occlusive disease historically treated by peripheral bypass surgery (Fig. 296e-6). Peripheral intervention is increasingly part of the training of an interventional cardiologist, and most programs now require an additional year of training after the interventional cardiology training year. The techniques and outcomes are described in detail in the chapter on peripheral vascular disease (Chap. 302).

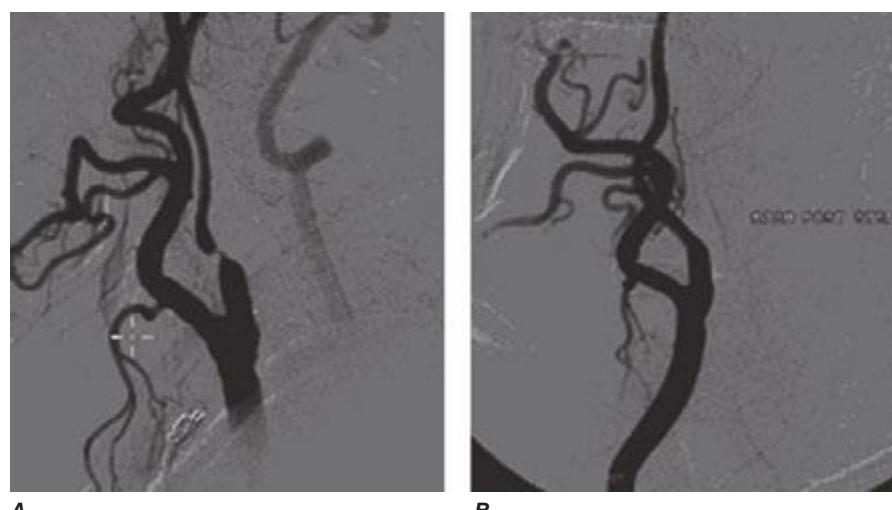


FIGURE 296e-5 An example of a high-risk patient who requires carotid revascularization, but who is not a candidate for carotid endarterectomy. Carotid artery stenting resulted in an excellent angiographic result. (From M Belkin, DL Bhatt: Circulation 119:2302, 2009; with permission.)

CIRCULATORY SUPPORT TECHNIQUES

The use of circulatory support techniques is occasionally needed in order to safely perform PCI on hemodynamically unstable patients. It also can be useful in helping to stabilize patients before surgical interventions. The most commonly used device is the percutaneous intraaortic balloon pump developed in the early 1960s. A 7- to 10-French, 25- to 50-mL balloon catheter is placed retrograde from the femoral artery into the descending aorta between the aortic arch and the abdominal aortic bifurcation. It is connected to a helium gas inflation system that synchronizes the inflation to coincide with early diastole with deflation by mid-diastole. As a result, it increases early diastolic pressure, lowers systolic pressure, and lowers late diastolic pressure through displacement of blood from the descending aorta (counterpulsation). This results in an increase in coronary blood flow and a decrease in afterload. It is contraindicated in patients with aortic regurgitation, aortic dissection, or severe peripheral artery disease. The major complications are vascular and thrombotic. Intravenous heparin is given in order to reduce thrombotic complications.

Another potentially useful tool is the Impella device (Abiomed, Danvers, Massachusetts). The catheter is placed percutaneously from the femoral artery into the left ventricle. The catheter has a small microaxial pump at its tip that can pump up to 2.5–5 L/min from the left ventricle to the aorta. Other support devices include TandemHeart (CardiacAssist, Pittsburgh, Pennsylvania), which involves placement of a large 21-French catheter from the femoral vein through the right atrium into the left atrium using the transseptal technique and a catheter in the femoral artery. A centrifugal pump can deliver 5 L of blood per minute. It may be useful in patients in shock or with STEMI or very-high-risk PCI. Patients can also be placed on peripheral extracorporeal membrane oxygenation using large cannulas placed in the femoral artery and vein.

INTERVENTIONS FOR PULMONARY EMBOLISM

The treatment of deep vein thrombosis is intravenous anticoagulation, with placement of an inferior vena cava filter if recurrent pulmonary emboli occur. Postphlebitic syndrome is a serious condition due to chronic venous obstruction that can lead to chronic leg edema and venous ulcers. Preliminary studies suggest that mechanical treatments may have a role in treatment, and a large trial is ongoing.

Pulmonary emboli (PE) should be treated with fibrinolytic agents if massive and in some cases if submassive. Surgical pulmonary embolectomy is an option for the treatment of massive PE with hemodynamic instability in patients who have contraindications for systemic fibrinolysis or those in whom it has failed. Catheter-based therapies for submassive and massive PEs are still evolving, but studies have shown

promise. The techniques employed include the use of aspiration of the clot with a large catheter (10 French), intraclot infusion of a thrombolytic agent followed by aspiration, ultrasound-assisted catheter-directed thrombolysis, and use of rheolytic thrombectomy. Success for these techniques has been reported to be 80–90%, with major complications occurring in 2–4% of patients.

INTERVENTIONS FOR REFRACTORY HYPERTENSION

The recent recognition of the importance of the renal sympathetic nerves in modulating blood pressure has led to a technique to selectively denervate renal sympathetic nerves in patients with refractory hypertension. The procedure involves applying low-power radiofrequency treatment via a catheter along the length of both renal arteries. In the randomized Symplicity HTN-2 trial, renal denervation significantly reduced blood pressure compared with medical therapy. The Symplicity device (Medtronic) is approved in Europe, though the randomized and blinded U.S. Symplicity HTN-3 trial showed no effect.

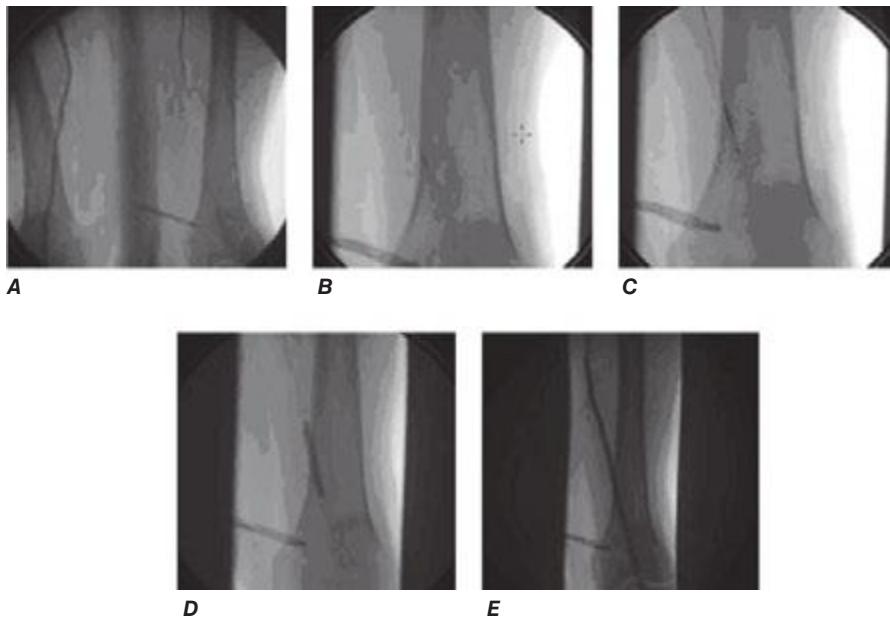


FIGURE 296e-6 Peripheral interventional procedures have become highly effective at treating anatomic lesions previously amenable only to bypass surgery. **A.** Complete occlusion of the left superficial femoral artery. **B.** Wire and catheter advanced into subintimal space. **C.** Intravascular ultrasound positioned in the subintimal space to guide retrograde wire placement through the occluded vessel. **D.** Balloon dilation of the occlusion. **E.** Stent placement with excellent angiographic result. (From A Al Mahameed, DL Bhatt: Cleve Clin J Med 73:S45, 2006; with permission.)

CONCLUSION

Interventional cardiology continues to expand its borders. Treatment for coronary artery disease, including complex anatomic subsets, continues to advance, encroaching on what has traditionally been treated by CABG. Technological advances such as drug-eluting stents, now already in their second generation, and manual thrombus aspiration devices are improving the results of PCI. In particular, PCI has been shown to prevent future ischemic events in acute coronary syndromes. For patients with stable coronary disease, PCI has an important role in symptom alleviation. Treatment of peripheral and cerebrovascular disease has also benefited from the application of percutaneous techniques. Structural heart disease is increasingly being treated with percutaneous options, with a high likelihood that interventional approaches will compete with open-heart surgery in a significant proportion of cases in years to come.

297e Atlas of Percutaneous Revascularization

Jane A. Leopold, Deepak L. Bhatt, David P. Faxon

Percutaneous coronary intervention (PCI) is the most widely employed coronary revascularization procedure worldwide (Chap. 296e). It is now applied to patients with stable angina; patients with acute coronary syndromes, including unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI); and as a primary treatment strategy in patients with ST-segment elevation myocardial infarction (STEMI). PCI is also applicable to patients with either single-vessel or multivessel disease.

In this chapter, the use of PCI will be illustrated in a variety of commonly encountered clinical and anatomic situations, such as chronic total occlusion of a coronary artery, bifurcation disease, acute STEMI, saphenous vein graft disease, left main coronary artery disease, multivessel disease, and stent thrombosis. In addition, the use of interventional techniques to treat structural heart disease will be shown, including closure of an atrial septal defect (ASD) and transcatheter aortic valve replacement (TAVR).

CASE 1: CHRONIC TOTAL OCCLUSION

(Videos 297e-1 to 297e-7)

- An 81-year-old male with angina, New York Heart Association (NYHA) class IV congestive heart failure and inferoapicoposterior ischemia on an exercise technetium-99m scan.
- Diagnostic cardiac catheterization revealed a left dominant system with a totally occluded left circumflex (LCx) artery. The distal LCx filled via collaterals from the left anterior descending (LAD) artery, indicating chronicity of the total occlusion.

VIDEO 297e-1 Baseline left coronary angiogram shows an occluded LCx with left-to-left collaterals originating from LAD septal vessels.

VIDEO 297e-2 Attempts to cross the total occlusion in the LCx using a hydrophilic wire and an antegrade approach were not successful with the wire tracking to the right of the trajectory.

VIDEO 297e-3 The LAD septal collateral is accessed with a guidewire that is directed toward the distal LCx to cross the total occlusion retrograde.

VIDEO 297e-4 The total occlusion is crossed retrograde. The wire is snared in the guide, exteriorized, and used to provide antegrade access to the LCx.

VIDEO 297e-5 Antegrade flow in the LCx is restored after balloon inflation.

VIDEO 297e-6 Following stenting of the total occlusion, blood flow in the distal vessel is improved and a second significant stenosis is seen.

VIDEO 297e-7 Final result after LCx stenting.

SUMMARY

- Approximately 15–30% of all patients referred for cardiac catheterization will have a chronic total occlusion (CTO) of a coronary artery.
- CTO often leads to a surgical referral for complete revascularization.
- Incomplete revascularization due to an untreated CTO is associated with an increased mortality rate (hazard ratio = 1.36; 95% confidence interval [CI], 1.12–1.66, $p < .05$).
- Successful PCI of a CTO leads to a 3.8–8.4% absolute reduction in mortality, symptom relief, and improved left ventricular function.
- Newer techniques, such as the retrograde approach to crossing total occlusions, are useful when the antegrade approach fails or is not feasible and there are well-developed collateral vessels.

(Case contributed with permission by Dr. Frederick G.P. Welt.)

CASE 2: BIFURCATION STENTING

(Fig. 297e-1; Videos 297e-8 to 297e-16)

- A 52-year-old male with an acute coronary syndrome and a troponin I = 0.18 (upper limit of normal, <0.04).
- Diagnostic cardiac catheterization showed single-vessel coronary artery disease with a significant stenosis in the mid-LAD and a bifurcation lesion involving a large diagonal branch.

VIDEO 297e-8 Baseline angiogram of the left coronary circulation shows the significant stenosis in the mid-LAD and the bifurcation lesion involving a large diagonal branch.

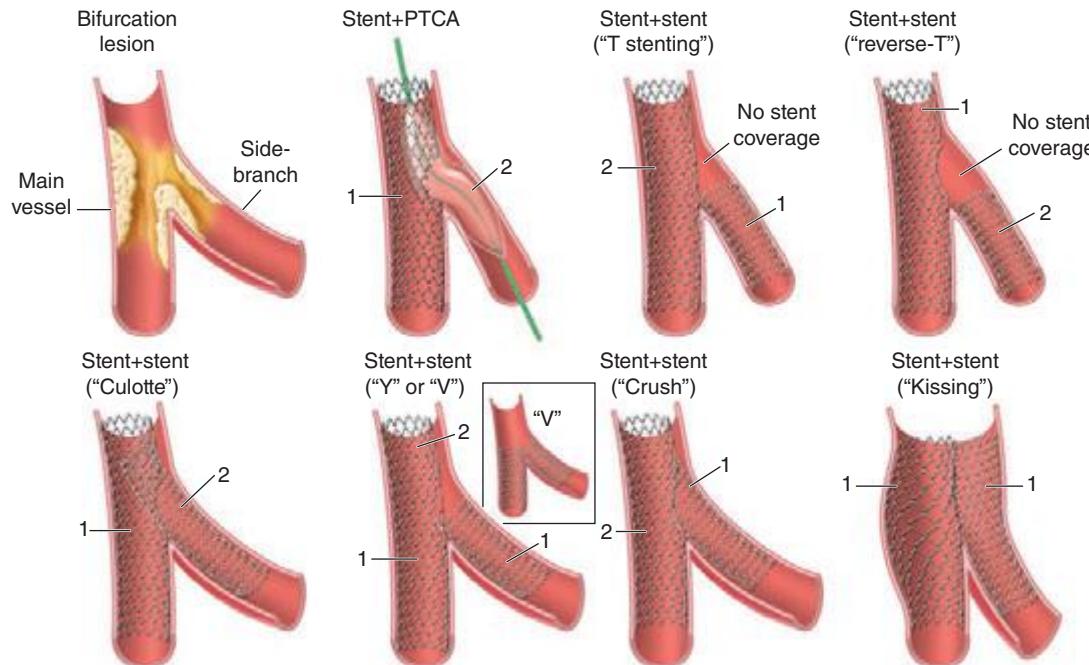


FIGURE 297e-1 Schematic representation of one-stent and two-stent techniques to treat bifurcation lesions. PTCA, percutaneous transluminal coronary angioplasty.

- 297e-2** **VIDEO 297e-9** Both vessels are accessed with guidewires and pre-treated with balloon angioplasty.
- VIDEO 297e-10** Result after balloon angioplasty.
- VIDEO 297e-11** Stent being positioned in the LAD.
- VIDEO 297e-12** LAD poststent result.
- VIDEO 297e-13** Stent deployed in the diagonal branch through the stent struts in the LAD using the “culotte” technique.
- VIDEO 297e-14** Diagonal branch poststent result.
- VIDEO 297e-15** Simultaneous inflation of two 2.5-mm “kissing” balloons.
- VIDEO 297e-16** Final postbifurcation stenting result.

SUMMARY

- Approximately 15–20% of PCIs will involve the treatment of bifurcation lesions.
- Bifurcation lesions require consideration of PCI strategies that protect side-branch patency.
- There are both one-stent and two-stent techniques to treat bifurcation lesions; the selection of technique depends on anatomic considerations, including plaque burden, angle of side-branch take-off, plaque shift during angioplasty, and side-branch distribution.
- Rates of target lesion revascularization and stent thrombosis are similar between one-stent and two-stent procedures.

CASE 3: INFERIOR MYOCARDIAL INFARCTION—THROMBUS AND MANUAL THROMBECTOMY

(Figs. 297e-2 to 297e-4; Videos 297e-17 to 297e-22)

- A 59-year-old male presented to the emergency room with 2 h of severe midsternal chest pressure.
- His systolic blood pressure was 100 mmHg, and he was tachycardic in sinus rhythm with a heart rate of 90–100 beats/min.
- His initial electrocardiogram (ECG) showed inferior ST-segment elevations with lateral ST-segment depressions.
- He was referred emergently to the cardiac catheterization laboratory for primary PCI.

VIDEO 297e-17 The right coronary artery (RCA) is totally occluded with filling defects in the vessel after contrast injection, indicating thrombus is present in the vessel.

VIDEO 297e-18 An angioplasty wire is threaded through the thrombotic lesion, but this does not restore blood flow to the distal vessel.

VIDEO 297e-19 Result after manual thrombectomy and thrombus extraction. The “culprit” ruptured plaque and residual thrombus are now apparent in the vessel.

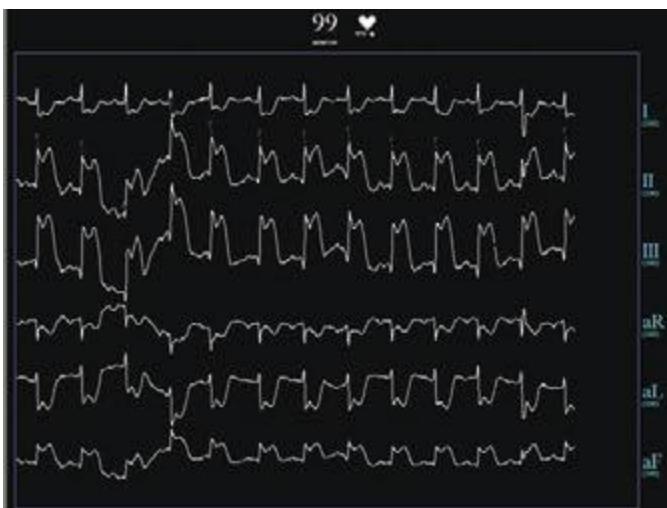


FIGURE 297e-2 Preprocedure ECG showing inferior ST-segment elevations and lateral ST-segment depressions.

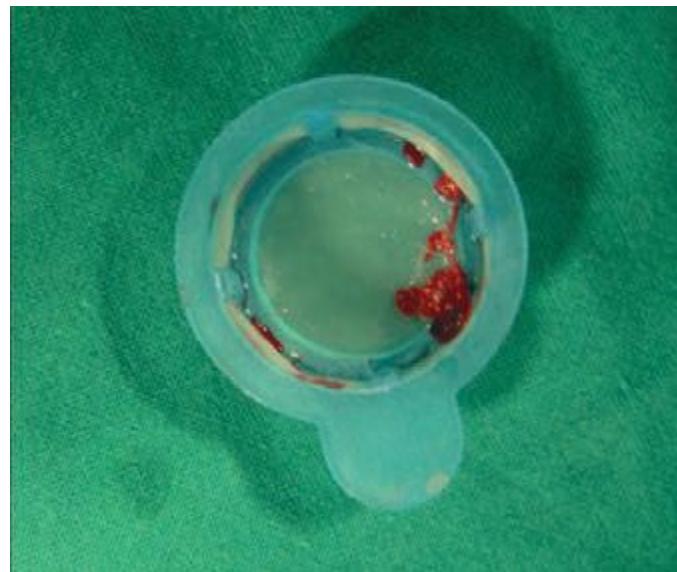


FIGURE 297e-3 Example of an organized red thrombus retrieved by manual thrombectomy.

VIDEO 297e-20 After balloon angioplasty and stenting, thrombus is still present.

VIDEO 297e-21 After repeat manual thrombectomy and expansion of the stent, the thrombus is no longer present.

VIDEO 297e-22 Final result.

SUMMARY

- An acute STEMI occurs following plaque rupture that promotes thrombotic occlusion of a coronary artery.
- Despite successful revascularization of the epicardial coronary artery, microemboli liberated during balloon angioplasty and stenting may lead to persistent microvascular dysfunction. When present, microvascular dysfunction is associated with a larger infarct size, heart failure, malignant ventricular arrhythmias, and death.
- Manual thrombectomy is used to aspirate or remove thrombus in the vessel and limit distal embolization during angioplasty and stenting.
- Manual thrombectomy in primary PCI is associated with improved myocardial perfusion and a reduction in mortality.
- Adjunctive antiplatelet and antithrombin agents are important to aid in the resolution of intracoronary thrombus.

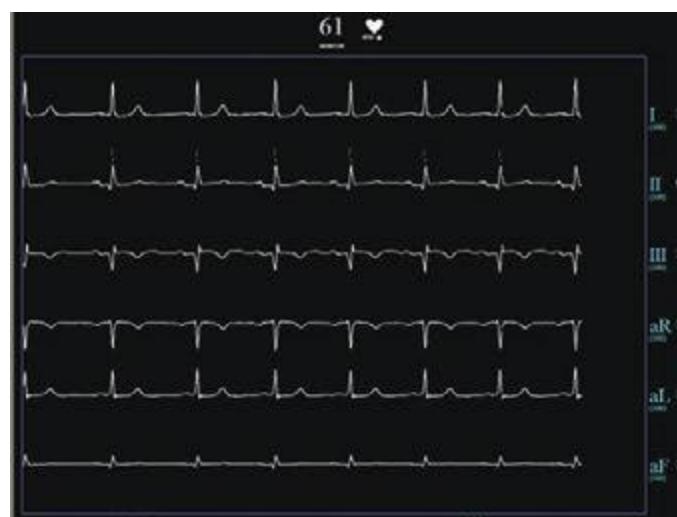


FIGURE 297e-4 Postprocedure ECG showing resolution of ST-segment elevations.

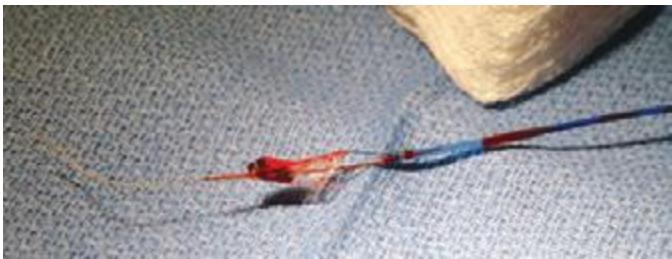


FIGURE 297e-5 Distal protection device showing captured atherosclerotic debris liberated by initial balloon dilation.

CASE 4: SAPHENOUS VEIN GRAFT INTERVENTION WITH DISTAL PROTECTION

(Fig. 297e-5; Videos 297e-23 to 297e-26)

- A 62-year-old male with a history of chronic stable angina.
- A four-vessel coronary artery bypass grafting (CABG) surgery was performed 17 years earlier with a left internal mammary artery graft to the LAD, a right internal mammary artery graft to the right coronary artery (RCA), a saphenous vein graft to the first obtuse marginal branch, and a saphenous vein graft to the first diagonal branch.
- The patient had a recent increase in angina with exertion and was found to have lateral ischemia on an exercise technetium-99m scan.
- Diagnostic cardiac catheterization revealed a significant stenosis in the body of the saphenous vein graft to the first obtuse marginal branch.

VIDEO 297e-23 Saphenous vein graft to a first obtuse marginal branch with an 80% eccentric stenosis in the midgraft.

VIDEO 297e-24 A distal protection device is deployed past the lesion.

VIDEO 297e-25 Angioplasty balloon inflation with the distal protection device in place.

VIDEO 297e-26 Final result after stent placement.

SUMMARY

- Saphenous vein grafts have a failure rate of up to 20% after 1 year and as high as 50% by 5 years.
- Graft failure (after >1 month) results from intimal hyperplasia and atherosclerosis.

- Saphenous vein graft PCI is associated with distal embolization of atherosclerotic debris and microthrombi leading to microvascular occlusion, reduced antegrade blood flow (the “no-reflow” phenomenon), and myocardial infarction.
- Embolic distal protection devices decrease the risk of distal embolization, as well as the incidence of no-reflow and myocardial infarction associated with saphenous vein graft interventions.

CASE 5: UNPROTECTED LEFT MAIN PCI IN A HIGH-RISK PATIENT

(Figs. 297e-6 and 297e-7; Videos 297e-27 to 297e-34)

- An 89-year-old woman presented with a NSTEMI associated with 5-mm ST-segment depression in the apical leads occurring 2 weeks after hospitalization for a NSTEMI that was treated conservatively.
- Chronic obstructive lung disease, elderly age, and the patient’s refusal to consider cardiac surgery restricted the choice of therapeutic options to medical and/or percutaneous interventions.
- Diagnostic catheterization revealed a left dominant circulation with a heavily calcified 80% distal left main coronary artery stenosis extending into the LAD and into the proximal LCx coronary arteries. A 70% proximal LAD lesion was also present.
- After consultation with the patient, family, and a cardiac surgeon, PCI was performed with intraaortic balloon pump support and a temporary pacemaker in the right ventricle.

VIDEO 297e-27 Baseline left coronary artery injection in right anterior oblique (RAO) cranial projection shows a high-grade calcified stenosis in the left main coronary artery and a significant stenosis in the proximal LAD.

VIDEO 297e-28 In the left anterior oblique (LAO) caudal view, the left main coronary artery lesion can be seen to extend into the ostia of both the LCx and the LAD.

VIDEO 297e-29 Guidewires were placed into both the LCx and LAD. After the left main coronary artery and LCx are dilated with balloon angioplasty, the proximal LAD is dilated, and a long drug-eluting stent is placed to cover a lesion dissection that occurred with wiring of the vessel.

VIDEO 297e-30 The bifurcation lesion in the left main coronary artery extending into the LCx and LAD ostia is treated using a “culotte” technique. First, a drug-eluting stent is placed in the left main coronary artery and into the proximal LCx.

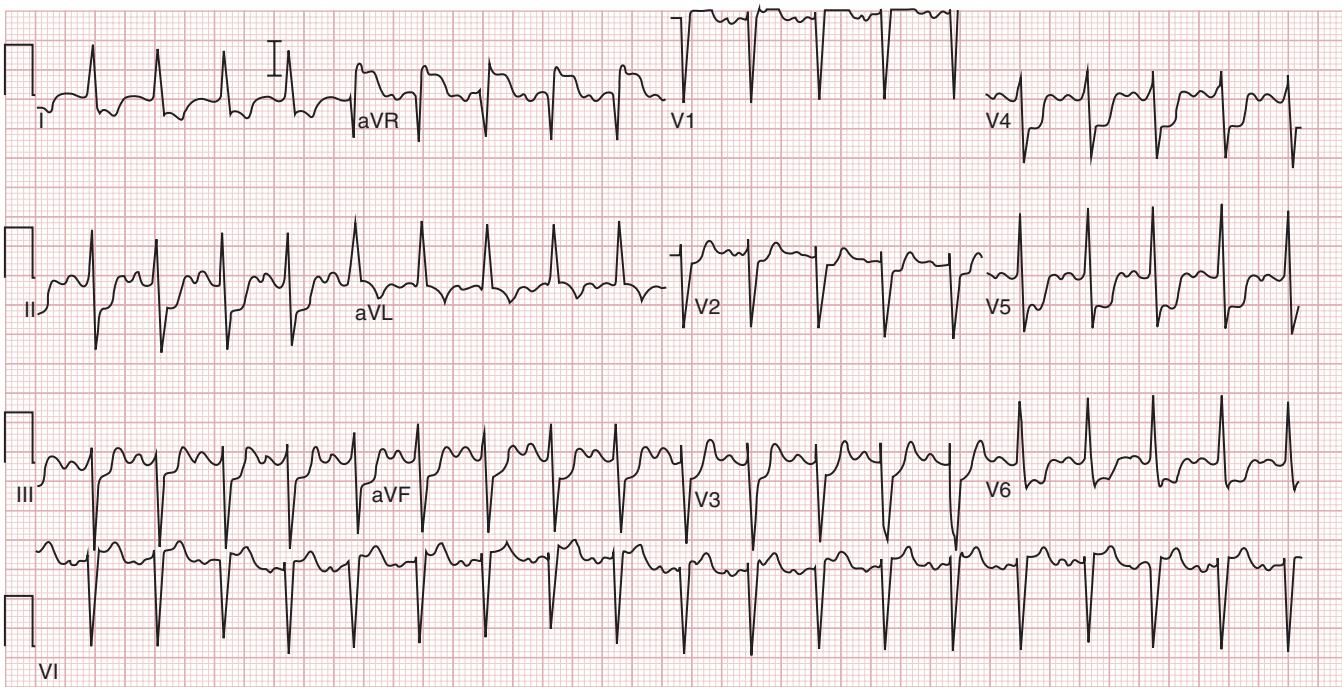


FIGURE 297e-6 During chest pain, the ECG showed diffuse ST-segment depression of up to 5 mm in the inferior and lateral leads.

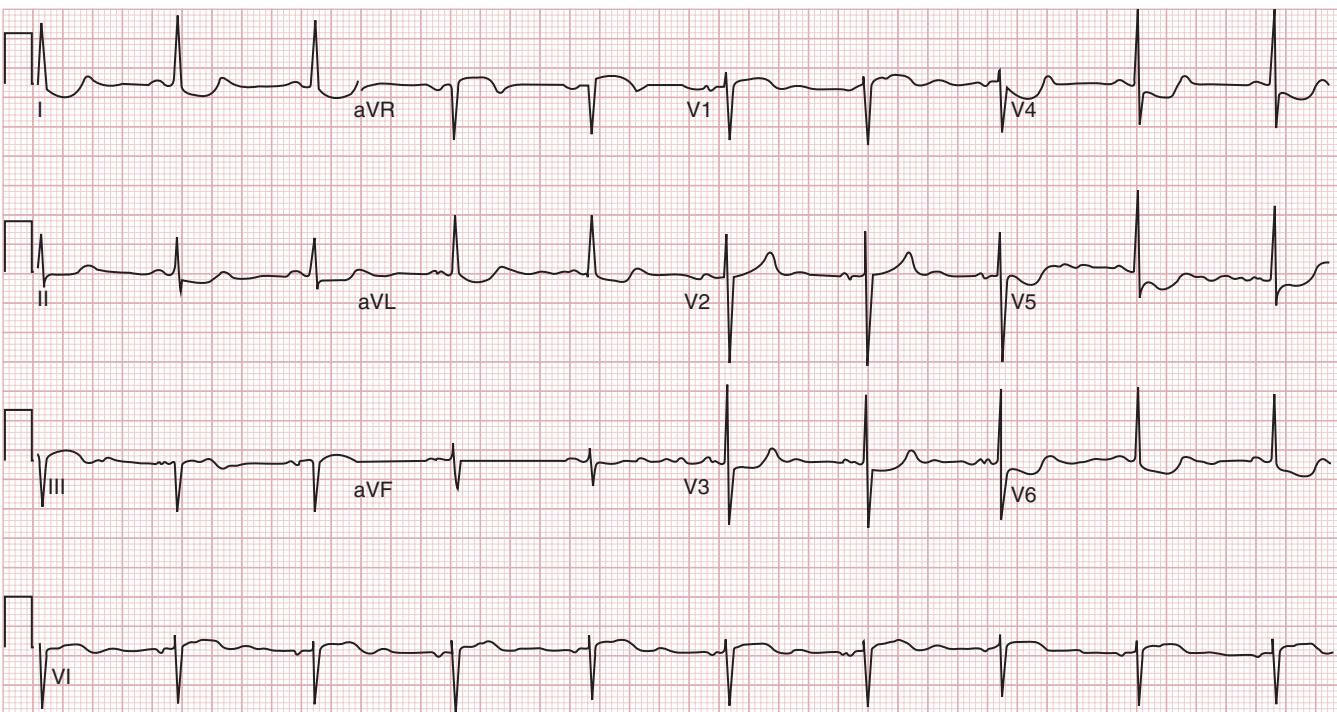


FIGURE 297e-7 Following resolution of the chest pain, the ST-segment depression is less marked.

VIDEO 297e-31 Next, the LAD wire is removed and passed through the stent into the distal LAD. A second drug-eluting stent is deployed through the struts of the left main coronary artery/LCx stent.

VIDEO 297e-32 Following rewiring of the LCx, both stents are re-dilated simultaneously ("kissing" balloons).

VIDEO 297e-33 The final result in the LAO caudal view.

VIDEO 297e-34 The final result in the RAO cranial view showing patent left main, LCx, and LAD coronary arteries.

SUMMARY

- Left main coronary artery disease occurs in 5–10% of patients with symptomatic coronary artery disease.
- In patients with left main coronary artery disease, revascularization with CABG has been shown to decrease mortality significantly over 5–10 years of follow-up.
- PCI with drug-eluting stents in selected cases has been shown to have equal in-hospital and 1-year death and myocardial infarction rates compared with CABG in the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial. Long-term outcome differences between the two treatment strategies are not known.
- Indications for PCI of left main coronary artery lesions are high-risk surgical patients and patients with protected left main coronary artery disease (i.e., prior CABG with patent bypass grafts). Patients who are good candidates for bypass surgery may also undergo a stenting procedure, but discussion with the patient, the interventional cardiologist, and the cardiac surgeon should be undertaken to determine the best treatment option in an individual case.
- Outcomes are better for patients with an isolated lesion in the ostium and body of the left main coronary artery where a single stent can be placed compared to bifurcation lesions that involve the ostium of the LAD and LCx.

CASE 6: MULTIVESSEL PCI IN A DIABETIC PATIENT

(Videos 297e-35 to 297e-42)

- A 58-year-old man presented with a NSTEMI.
- The patient has hyperlipidemia and type 2 diabetes mellitus treated with oral hypoglycemic agents.
- Diagnostic catheterization revealed two-vessel disease with a total occlusion of the second obtuse marginal branch that was felt to be

responsible for the patient's symptoms (culprit lesion). In addition, there was a high-grade stenosis in a large ramus intermedius branch, and the RCA had a significant stenosis in the midsegment of the vessel.

VIDEO 297e-35 Baseline angiogram of the left coronary circulation in the RAO view shows the total occlusion of the second obtuse marginal branch with delayed retrograde filling via collateral vessels and a high-grade stenosis in the ramus intermedius.

VIDEO 297e-36 A guidewire is passed through the total occlusion, and the lesion is pretreated with balloon angioplasty.

VIDEO 297e-37 Following placement of a drug-eluting stent in the lesion, the vessel is widely patent. A third obtuse marginal vessel, not previously seen, now fills faintly (Thrombolysis in Myocardial Infarction [TIMI] grade 1 flow) with contrast but was not treated.

VIDEO 297e-38 The ramus intermedius lesion was crossed with a guidewire and pretreated with balloon angioplasty.

VIDEO 297e-39 A drug-eluting stent is placed across the ramus lesion and deployed. The final result shows no residual stenosis in either the ramus or second obtuse marginal vessels.

VIDEO 297e-40 Baseline angiogram of the RCA shows a high-grade lesion in the midsegment of the vessel.

VIDEO 297e-41 The lesion was pretreated with balloon dilation followed by stent deployment.

VIDEO 297e-42 The final result shows no residual stenosis in the mid-RCA.

SUMMARY

- Multivessel PCI is performed commonly and may be done in one setting or staged with two or more procedures.
- Acute and long-term studies of multivessel PCI have shown comparable rates of death and myocardial infarction when compared to CABG, but a higher incidence of repeat revascularization as a result of restenosis is associated with PCI.
- In the randomized Bypass Angioplasty Revascularization Investigation (BARI) trial, diabetic patients treated with PCI had a worse long-term mortality than diabetic patients treated with CABG. However, the BARI registry found that in selected diabetic patients with favorable anatomy, PCI can result in outcomes equal to those observed with CABG.

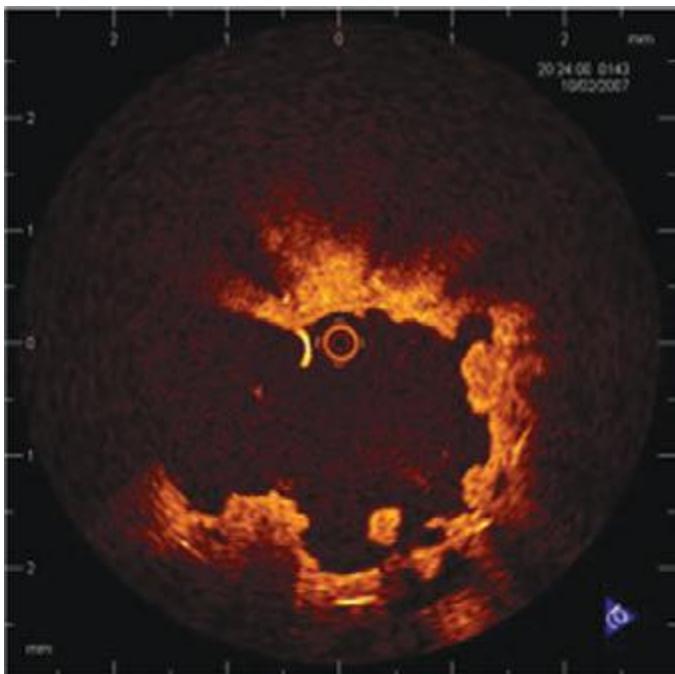


FIGURE 297e-8 Optical coherence tomography image following initial balloon dilation. Residual thrombus that is adherent to the stent struts is seen.

CASE 7: VERY LATE STENT THROMBOSIS OF A PROXIMAL LAD DRUG-ELUTING STENT

(Figs. 297e-8 and 297e-9; Videos 297e-43 to 297e-46)

- A 62-year-old male had a drug-eluting stent placed in a proximal LAD lesion to treat severe angina. He received dual antiplatelet therapy with aspirin and clopidogrel for 1 year and then discontinued clopidogrel per protocol.
- He remained asymptomatic until 15 months after the initial stent placement when he presented with severe chest pain due to an acute anterior STEMI.
- He was taken to the catheterization laboratory within 70 min of presentation, and his initial angiogram showed a total occlusion of the proximal LAD stent.

VIDEO 297e-43 Baseline angiogram showing a total occlusion of the proximal LAD within the drug-eluting stent and a significant stenosis at the origin of the LCx.

VIDEO 297e-44 The LAO view shows the LCx stenosis with a filling defect indicating that thrombus is present in the vessel lumen.

VIDEO 297e-45 The LAD lesion was crossed with a guidewire, which resulted in slow filling of the mid-LAD (TIMI 2 flow) and revealed thrombus filling the stent.

VIDEO 297e-46 The final result after LAD and LCx stenting. The LAD lesion was pretreated with balloon angioplasty, and a bare metal stent was deployed to cover the proximal lesion. The LCx ostial lesion was dilated with balloon angioplasty, and a bare metal stent was placed using a "V stenting" technique.

SUMMARY

- Stent thrombosis is an infrequent (1–2%) but serious complication of stent placement. It occurs most commonly within the first month, but rarely can occur as late as 1 year (0.2–0.6%) with bare metal stents. Very late stent thrombosis (VLST), which occurs after 1 year, is very rare with bare metal stents but can occur with drug-eluting stents.
- Premature discontinuation of dual antiplatelet therapy is the most common cause of early and late stent thrombosis; however, the etiology of VLST is not clear.
- The majority of patients with stent thrombosis present with acute coronary syndromes or STEMI; this presentation is associated with a high mortality rate (10%).
- Treatment is immediate PCI with balloon angioplasty or re-stenting.

CASE 8: TRANSCATHETER AORTIC VALVE REPLACEMENT

(Figs. 297e-10 to 297e-14; Videos 297e-47 to 297e-50)

- A 75-year-old female with symptomatic aortic stenosis and a valve area of 0.58 cm^2 by transthoracic echocardiogram.
- Chronic obstructive pulmonary disease (forced expiratory volume in 1 s [FEV_1] = 0.54) and other comorbidities contributed to an unacceptably high cardiac surgical risk (calculated logistic Euroscore = 29.57%) for aortic valve replacement.
- She was referred for transcatheter aortic valve replacement (TAVR) as part of a clinical trial.

VIDEO 297e-47 Aortogram shows patent coronary arteries and minimal aortic insufficiency.

VIDEO 297e-48 Balloon valvuloplasty is performed with rapid ventricular pacing at 180 beats/min.

VIDEO 297e-49 A 26-mm Edwards SAPIEN valve is positioned using fluoroscopic and transesophageal echo guidance and deployed.

VIDEO 297e-50 Aortogram after valve deployment shows a functional valve with mild aortic insufficiency and without impingement of the coronary ostia.

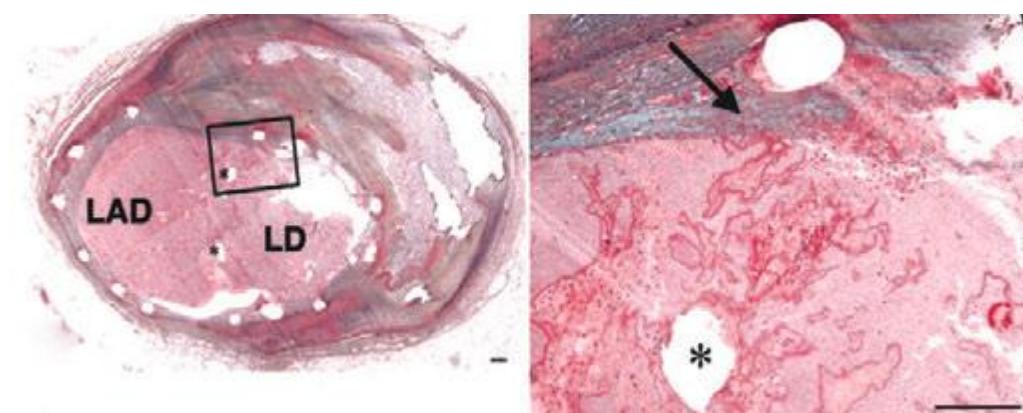


FIGURE 297e-9 Pathologic specimen of late stent thrombosis obtained at autopsy. Thrombus is seen filling the LAD vessel lumen and extending into a diagonal branch (LD). Stent struts occupied the space denoted by the asterisk (*) (left). A magnified view of the vessel reveals thrombus around the stent strut and neointima formation (arrow) (right).



FIGURE 297e-10 Transesophageal echocardiogram shows a calcified trileaflet aortic valve (left) with reduced leaflet excursion and a narrowed orifice in peak systole (right).

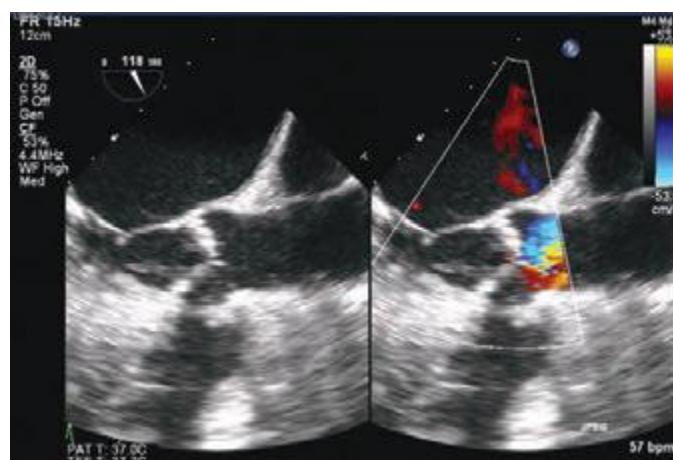


FIGURE 297e-11 Hemodynamically significant aortic (AO) stenosis. Simultaneous recording of AO and left ventricle (LV) pressures shows an 82 mmHg peak-to-peak gradient and a 63.3 mmHg mean gradient between the LV (154/9 mmHg) and AO (72/29 mmHg) pressures. This is consistent with an aortic valve area of 0.58 cm^2 .



FIGURE 297e-13 The Edwards SAPIEN transcatheter heart valve. (Reprinted with permission from A Zajarias, AG Cribier: J Am Coll Cardiol 53:1829, 2009.)

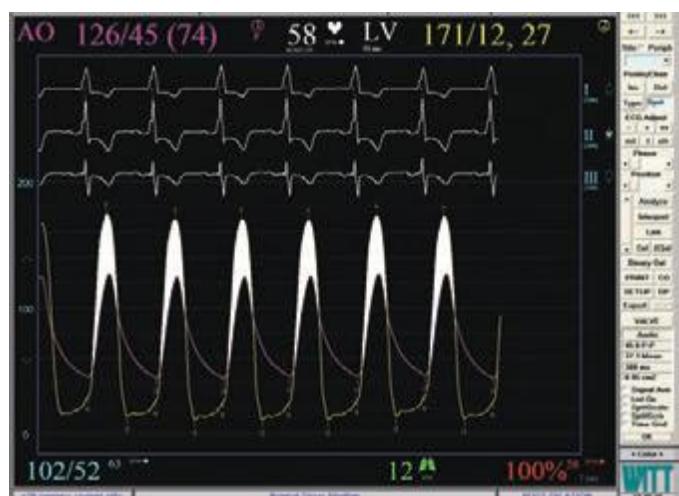


FIGURE 297e-12 After balloon valvuloplasty, the LV-AO mean pressure gradient decreased to 37.3 mmHg, indicating that the aortic valve area increased to 0.95 cm^2 .



FIGURE 297e-14 Once the valve was deployed, the pressure gradient between the LV and AO decreased to 11.6 mmHg, and the functional valve area is 1.34 cm^2 .

SUMMARY

- The prevalence of calcific aortic stenosis is 2–3% in individuals age ≥ 75 years.
- Symptomatic aortic stenosis is associated with an average survival of 2–3 years and an increased risk of sudden death; aortic valve replacement improves both symptoms and survival.
- In high-risk patients with severe aortic stenosis who are not surgical candidates, 1- and 5-year survival rates are ~62% and 38%, respectively.
- TAVR is approved in Europe and was recently approved in the United States as an alternative to surgical aortic valve replacement in high-risk patients.

(Case contributed with permission by Dr. Andrew C. Eisenhauer.)

CASE 9: ATRIAL SEPTAL DEFECT CLOSURE

(Figs. 297e-15 to 297e-21; Videos 297e-51 to 297e-53)

- A 48-year-old female with increased shortness of breath, exercise intolerance, and an 18-mm secundum ASD.
- Echocardiogram showed a dilated right atrium (RA) and right ventricle (RV) with evidence of right ventricular volume overload.

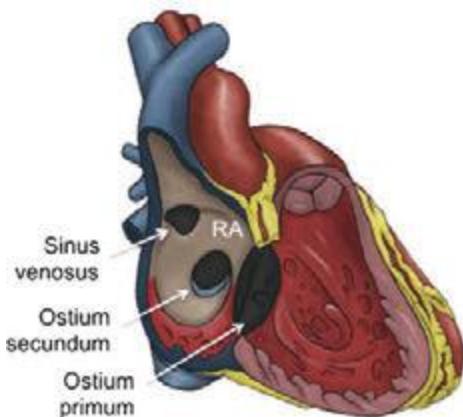


FIGURE 297e-15 Anatomic location of common atrial septal defects (ASDs). The most common ASDs are the sinus venosus, ostium secundum, and ostium primum ASDs. The sinus venosus ASD is located at the junction of the superior vena cava (SVC) and the right atrium (RA). This ASD is often associated with anomalous drainage of the right-side pulmonary veins into the RA instead of the left atrium. The secundum ASD is located at the foramen ovale and allows blood to flow between the RA and the left atrium. The primum ASD, also known as an atrioventricular septal defect, connects the RA and right ventricle with the left atrium and ventricle. (Illustration by Justin E. Tribuna.)

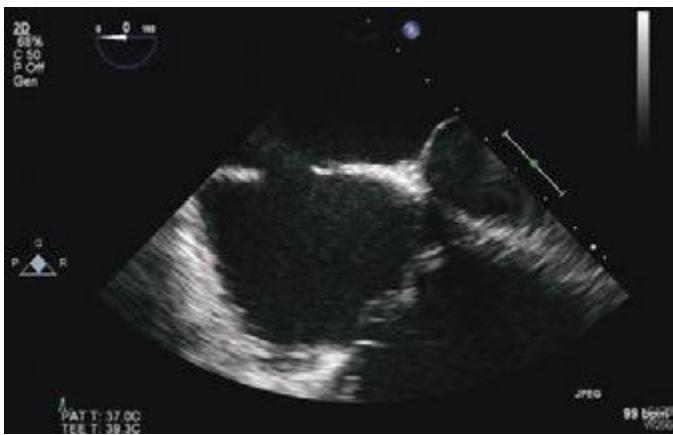


FIGURE 297e-16 Transesophageal echocardiogram of a secundum ASD. The ASD is seen as “dropout” in the interatrial septum between the left atrium (LA) and RA (left). Doppler color flow imaging shows blue in the RA consistent with left-to-right flow (right).

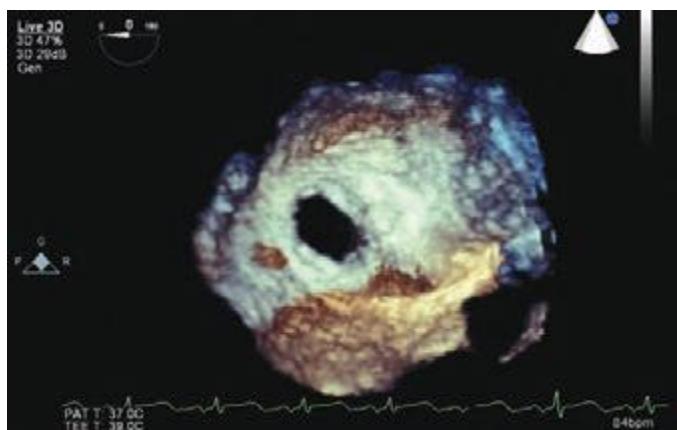


FIGURE 297e-17 Three-dimensional echocardiographic reconstruction of the secundum ASD. The ASD is round and has an acceptable margin of tissue to seat a septal occluder device.

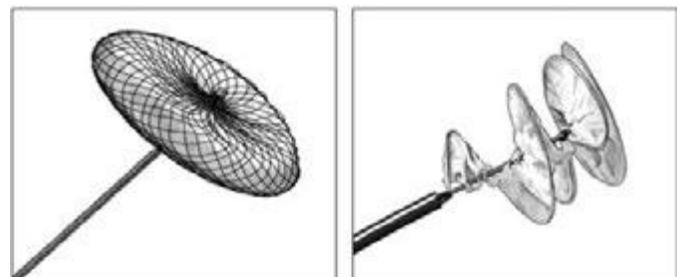
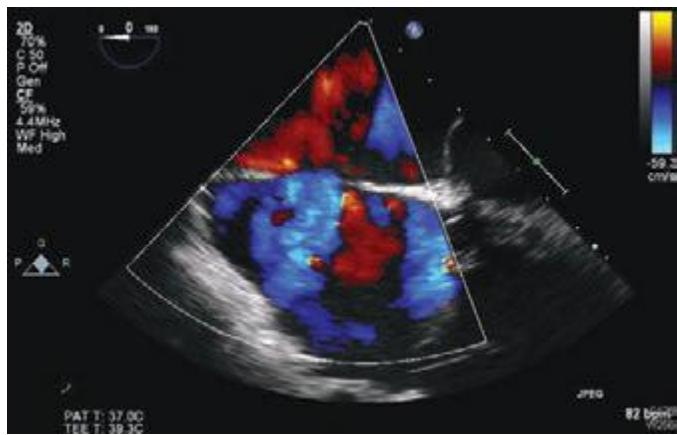


FIGURE 297e-18 ASD percutaneous closure devices. The Amplatzer® septal occluder (left) and the HELEX® septal occluder (right) are among the devices used for percutaneous closure of ASDs. The Amplatzer® septal occluder is a plug between two disks that are positioned on each side of the ASD to obstruct blood flow. The HELEX® Septal Occluder is positioned on each side of the ASD to allow circular rings covered with rapidly stretching polytetrafluoroethylene device to limit blood flow. The delivery catheters are detached and the devices are left in place. (Illustration by Justin E. Tribuna.)



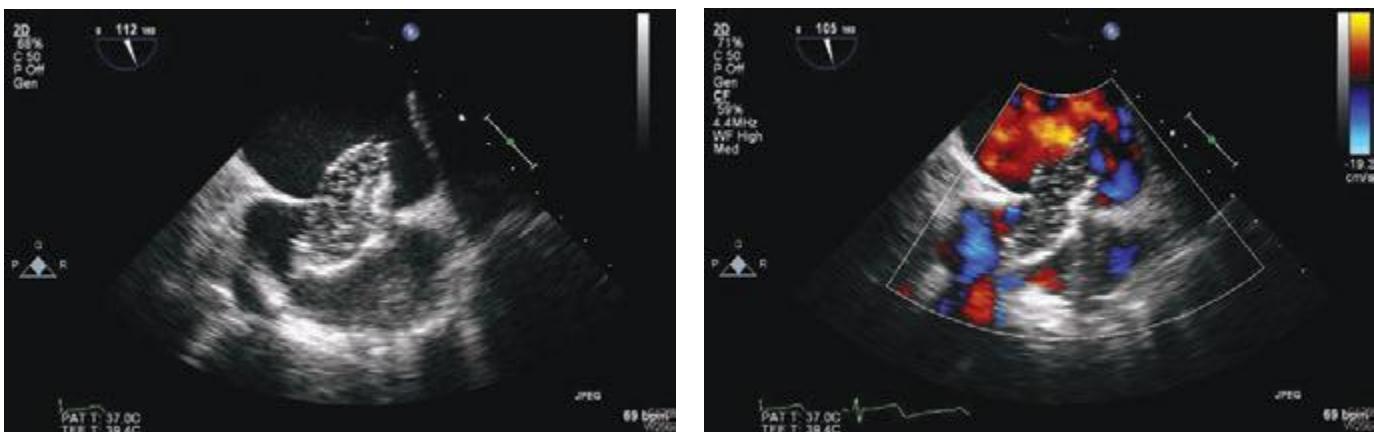


FIGURE 297e-19 Transesophageal echocardiogram showing sizing balloon (left) and no flow (right) across the atrial septal defect.

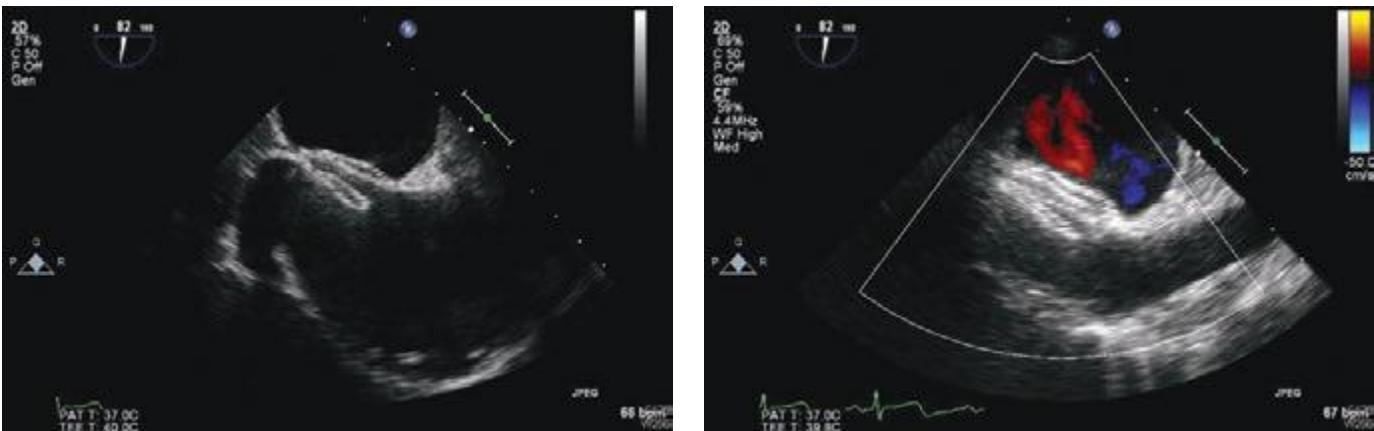


FIGURE 297e-20 Amplatzer® septal occluder in place (left). There is no blood flow across the device (right).

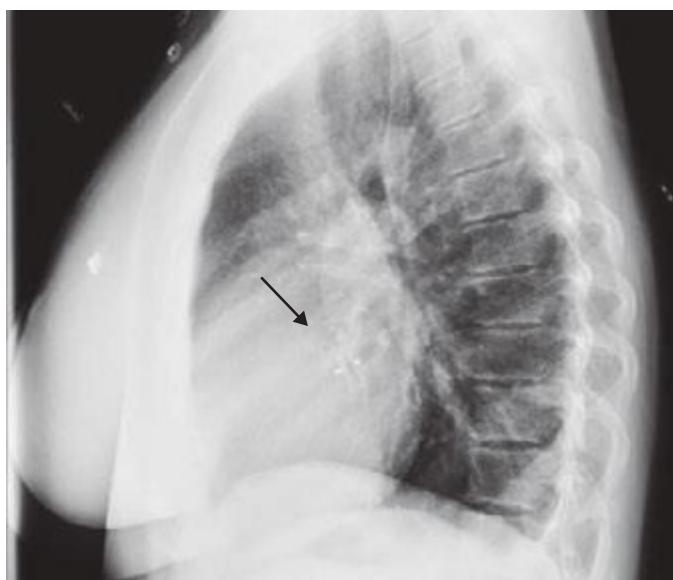


FIGURE 297e-21 Postprocedure lateral chest x-ray showing the Amplatzer® septal occluder in place.

- A shunt ratio (Qp/Qs) of 2.3:1 was determined at cardiac catheterization.
- Based on her symptoms, evidence of right-side chamber dilation, and a moderately sized ASD, the patient was referred for percutaneous closure of the ASD.

VIDEO 297e-51 A sizing balloon is placed across the ASD.

VIDEO 297e-52 An Amplatzer® septal occluder is being positioned across the ASD.

VIDEO 297e-53 The two disks of the device in place across the ASD.

SUMMARY

- Unrepaired ASDs lead to signs and symptoms of increased pulmonary blood flow and right heart failure, dyspnea, exercise intolerance, fatigue, palpitations and atrial arrhythmias, and pulmonary infections.

- Percutaneous closure of an ASD may be recommended for individuals with a secundum ASD and evidence of RA and RV enlargement with or without symptoms.
- Percutaneous closure is contraindicated in patients with irreversible pulmonary arterial hypertension and no left-to-right shunt. It is not recommended for closure of sinus venosus, coronary sinus, or primum ASDs.
- After the atrial septal occluder device is placed, patients are treated with antiplatelet agents and use antibiotic prophylaxis for certain procedures for 6 months. Follow-up echocardiograms to assess for device migration or erosion, residual shunting, thrombus, or pericardial effusion are recommended at 1 day, 1 month, 6 months, 1 year, and periodically thereafter.

(Case contributed with permission by Dr. Andrew C. Eisenhauer.)

298 Hypertensive Vascular Disease

Theodore A. Kotchen

Hypertension is one of the leading causes of the global burden of disease. Approximately 7.6 million deaths (13–15% of the total) and 92 million disability-adjusted life years worldwide were attributable to high blood pressure in 2001. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. It often is associated with additional cardiovascular disease risk factors, and the risk of cardiovascular disease increases with the total burden of risk factors. Although anti-hypertensive therapy reduces the risks of cardiovascular and renal disease, large segments of the hypertensive population are either untreated or inadequately treated.

EPIDEMIOLOGY

Blood pressure levels, the rate of age-related increases in blood pressure, and the prevalence of hypertension vary among countries and among subpopulations within a country. Hypertension is present in all populations except for a small number of individuals living in developing countries. In industrialized societies, blood pressure increases steadily during the first two decades of life. In children and adolescents, blood pressure is associated with growth and maturation. Blood pressure “tracks” over time in children and between adolescence and young adulthood. In the United States, average systolic blood pressure is higher for men than for women during early adulthood, although among older individuals the age-related rate of rise is steeper for women. Consequently, among individuals age 60 and older, systolic blood pressures of women are higher than those of men. Among adults, diastolic blood pressure also increases progressively with age until ~55 years, after which it tends to decrease. The consequence is a widening of pulse pressure (the difference between systolic and diastolic blood pressure) beyond age 60.

In the United States, based on results of the National Health and Nutrition Examination Survey (NHANES), approximately 30% (age-adjusted prevalence) of adults, or at least 65 million individuals, have hypertension (defined as any one of the following: systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, taking antihypertensive medications). Hypertension prevalence is 33.5% in non-Hispanic blacks, 28.9% in non-Hispanic whites, and 20.7% in Mexican Americans. The likelihood of hypertension increases with age, and among individuals age ≥ 60 , the prevalence is 65.4%. Recent evidence suggests that the prevalence of hypertension in the United States may be increasing, possibly as a consequence of increasing obesity. The prevalence of hypertension and stroke mortality rates are higher in the southeastern United States than in other regions. In African Americans, hypertension appears earlier, is generally more severe, and results in higher rates of morbidity and mortality from stroke, left ventricular hypertrophy, CHF, and end-stage renal disease (ESRD) than in white Americans.

Both environmental and genetic factors may contribute to regional and racial variations in hypertension prevalence. Studies of societies undergoing "acculturation" and studies of migrants from a less to a more urbanized setting indicate a profound environmental contribution to blood pressure. Obesity and weight gain are strong, independent risk factors for hypertension. It has been estimated that 60% of hypertensives are $>20\%$ overweight. Among populations, hypertension prevalence is related to dietary NaCl intake, and the age-related increase in blood pressure may be augmented by a high NaCl intake. Low dietary intakes of calcium and potassium also may contribute to the risk of hypertension. The urine sodium-to-potassium ratio (an index of both sodium and potassium intakes) is a stronger correlate of blood pressure than is either sodium or potassium alone. Alcohol consumption, psychosocial stress, and low levels of physical activity also may contribute to hypertension.

Adoption, twin, and family studies document a significant heritable component to blood pressure levels and hypertension. Family studies controlling for a common environment indicate that blood pressure heritabilities are in the range 15–35%. In twin studies, heritability estimates of blood pressure are ~60% for males and 30–40% for females. High blood pressure before age 55 occurs 3.8 times more frequently among persons with a positive family history of hypertension. However, to date, only a fraction of high heritability estimates are accounted for by specific genetic determinants.

GENETIC CONSIDERATIONS

 Although specific genetic variants have been identified in rare Mendelian forms of hypertension (Table 298-5), these variants are not applicable to the vast majority (>98%) of patients with hypertension. For most individuals, it is likely that hypertension represents a polygenic disorder in which a combination of genes acts in concert with environmental exposures to make only a modest contribution to blood pressure. Further, different subsets of genes may lead to different phenotypes associated with hypertension, e.g., obesity, dyslipidemia, insulin resistance.

Several strategies are being used in the search for specific hypertension-related genes. Animal models (including selectively bred rats and congenic rat strains) provide a powerful approach for evaluating genetic loci and genes associated with hypertension. Comparative mapping strategies allow for the identification of syntenic genomic regions between the rat and human genomes that may be involved in blood pressure regulation. In association studies, different alleles (or combinations of alleles at different loci) of specific candidate genes or chromosomal regions are compared in hypertensive patients and normotensive control subjects. Current evidence suggests that genes that encode components of the renin-angiotensin-aldosterone system, along with angiotensinogen and angiotensin-converting enzyme (ACE) polymorphisms, may be related to hypertension and to blood pressure sensitivity to dietary NaCl. The alpha-adducin gene is thought to be associated with increased renal tubular absorption of sodium, and variants of this gene may be associated with hypertension and salt sensitivity of blood pressure. Other genes possibly related to hypertension include

genes encoding the AT₁ receptor, aldosterone synthase, atrial natriuretic peptide, and the β₂ adrenoreceptor. Genomewide association studies involve rapidly scanning markers across the entire genome to identify loci (not specific genes) associated with an observable trait (e.g., blood pressure) or a particular disease. This strategy has been facilitated by the availability of dense genotyping chips and the International HapMap. Results of candidate gene studies often have not been replicated, and in contrast to several other polygenic disorders, genomewide association studies have had limited success in identifying genetic determinants of hypertension.

Preliminary evidence suggests that there may also be genetic determinants of target organ damage attributed to hypertension. Family studies indicate significant heritability of left ventricular mass, and there is considerable individual variation in the responses of the heart to hypertension. Family studies and variations in candidate genes associated with renal damage suggest that genetic factors also may contribute to hypertensive nephropathy. Specific genetic variants have been linked to CHD and stroke.

In the future, it is possible that DNA analysis will predict individual risk for hypertension and target organ damage and will identify responders to specific classes of antihypertensive agents. However, with the exception of the rare, monogenic hypertensive diseases, the genetic variants associated with hypertension remain to be confirmed, and the intermediate steps by which these variants affect blood pressure remain to be determined.

MECHANISMS OF HYPERTENSION

To provide a framework for understanding the pathogenesis of and treatment options for hypertensive disorders, it is useful to understand factors involved in the regulation of both normal and elevated arterial pressure. Cardiac output and peripheral resistance are the two determinants of arterial pressure (Fig. 298-1). Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular compartment. Peripheral resistance is determined by functional and anatomic changes in small arteries (lumen diameter 100–400 μm) and arterioles.

INTRAVASCULAR VOLUME

Sodium is predominantly an extracellular ion and is a primary determinant of the extracellular fluid volume. When NaCl intake exceeds the capacity of the kidney to excrete sodium, vascular volume may initially expand and cardiac output may increase. However, many vascular beds have the capacity to autoregulate blood flow, and if constant blood flow is to be maintained in the face of increased arterial pressure, resistance within that bed must increase, since

$$\text{Blood flow} = \frac{\text{pressure across the vascular bed}}{\text{vascular resistance}}$$

The initial elevation of blood pressure in response to vascular volume expansion may be related to an increase of cardiac output; however, over time, peripheral resistance increases and cardiac output reverts toward normal. Whether this hypothesized sequence of events occurs in the pathogenesis of hypertension is not clear. What is clear is that salt can activate a number of neural, endocrine/paracrine, and vascular mechanisms, all of which have the potential to increase arterial pressure. The effect of sodium on blood pressure is related to the provision of sodium with chloride; nonchloride salts of sodium have

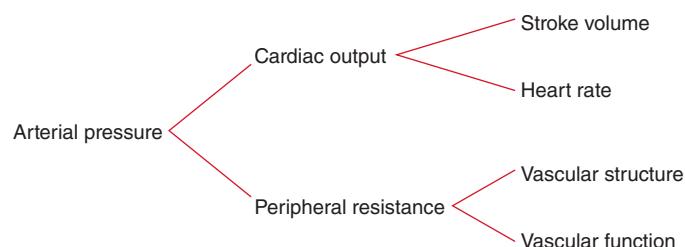


FIGURE 298-1 Determinants of arterial pressure.

little or no effect on blood pressure. As arterial pressure increases in response to a high NaCl intake, urinary sodium excretion increases and sodium balance is maintained at the expense of an increase in arterial pressure. The mechanism for this “pressure-natriuresis” phenomenon may involve a subtle increase in the glomerular filtration rate, decreased absorbing capacity of the renal tubules, and possibly hormonal factors such as atrial natriuretic factor. In individuals with an impaired capacity to excrete sodium, greater increases in arterial pressure are required to achieve natriuresis and sodium balance.

NaCl-dependent hypertension may be a consequence of a decreased capacity of the kidney to excrete sodium, due either to intrinsic renal disease or to increased production of a salt-retaining hormone (mineralocorticoid) resulting in increased renal tubular reabsorption of sodium. Renal tubular sodium reabsorption also may be augmented by increased neural activity to the kidney. In each of these situations, a higher arterial pressure may be required to achieve sodium balance. Conversely, salt-wasting disorders are associated with low blood pressure levels. ESRD is an extreme example of volume-dependent hypertension. In ~80% of these patients, vascular volume and hypertension can be controlled with adequate dialysis; in the other 20%, the mechanism of hypertension is related to increased activity of the renin-angiotensin system and is likely to be responsive to pharmacologic blockade of renin-angiotensin.

AUTONOMIC NERVOUS SYSTEM

Adrenergic reflexes modulate blood pressure over the short term, and adrenergic function, in concert with hormonal and volume-related factors, contributes to the long-term regulation of arterial pressure. Norepinephrine, epinephrine, and dopamine all play important roles in tonic and phasic cardiovascular regulation.

The activities of the adrenergic receptors are mediated by guanosine nucleotide-binding regulatory proteins (G proteins) and by intracellular concentrations of downstream second messengers. In addition to receptor affinity and density, physiologic responsiveness to catecholamines may be altered by the efficiency of receptor-effector coupling at a site “distal” to receptor binding. The receptor sites are relatively specific both for the transmitter substance and for the response that occupancy of the receptor site elicits. Based on their physiology and pharmacology, adrenergic receptors have been divided into two principal types: α and β . These types have been differentiated further into α_1 , α_2 , β_1 , and β_2 receptors. Recent molecular cloning studies have identified several additional subtypes. α_1 Receptors are occupied and activated more avidly by norepinephrine than by epinephrine, and the reverse is true for β receptors. α_1 Receptors are located on postsynaptic cells in smooth muscle and elicit vasoconstriction. α_2 Receptors are localized on presynaptic membranes of postganglionic nerve terminals that synthesize norepinephrine. When activated by catecholamines, α_2 receptors act as negative feedback controllers, inhibiting further norepinephrine release. In the kidney, activation of α_1 -adrenergic receptors increases renal tubular reabsorption of sodium. Different classes of antihypertensive agents either inhibit α_1 receptors or act as agonists of α_2 receptors and reduce systemic sympathetic outflow. Activation of myocardial β_1 receptors stimulates the rate and strength of cardiac contraction and consequently increases cardiac output. β_1 Receptor activation also stimulates renin release from the kidney. Another class of antihypertensive agents acts by inhibiting β_1 receptors. Activation of β_2 receptors by epinephrine relaxes vascular smooth muscle and results in vasodilation.

Circulating catecholamine concentrations may affect the number of adrenoceptors in various tissues. Downregulation of receptors may be a consequence of sustained high levels of catecholamines and provides an explanation for decreasing responsiveness, or tachyphylaxis, to catecholamines. For example, orthostatic hypotension frequently is observed in patients with pheochromocytoma, possibly due to the lack of norepinephrine-induced vasoconstriction with assumption of the upright posture. Conversely, with chronic reduction of neurotransmitter substances, adrenoceptors may increase in number or be upregulated, resulting in increased responsiveness to the neurotransmitter. Chronic administration of agents that block adrenergic receptors may

result in upregulation, and abrupt withdrawal of those agents may produce a condition of temporary hypersensitivity to sympathetic stimuli. For example, clonidine is an antihypertensive agent that is a centrally acting α_2 agonist that inhibits sympathetic outflow. Rebound hypertension may occur with the abrupt cessation of clonidine therapy, probably as a consequence of upregulation of α_1 receptors.

Several reflexes modulate blood pressure on a minute-to-minute basis. One arterial baroreflex is mediated by stretch-sensitive sensory nerve endings in the carotid sinuses and the aortic arch. The rate of firing of these baroreceptors increases with arterial pressure, and the net effect is a decrease in sympathetic outflow, resulting in decreases in arterial pressure and heart rate. This is a primary mechanism for rapid buffering of acute fluctuations of arterial pressure that may occur during postural changes, behavioral or physiologic stress, and changes in blood volume. However, the activity of the baroreflex declines or adapts to sustained increases in arterial pressure such that the baroreceptors are reset to higher pressures. Patients with autonomic neuropathy and impaired baroreflex function may have extremely labile blood pressures with difficult-to-control episodic blood pressure spikes associated with tachycardia.

In both normal-weight and obese individuals, hypertension often is associated with increased sympathetic outflow. Based on recordings of postganglionic muscle nerve activity (detected by a microelectrode inserted in a peroneal nerve in the leg), sympathetic outflow tends to be higher in hypertensive than in normotensive individuals. Sympathetic outflow is increased in obesity-related hypertension and in hypertension associated with obstructive sleep apnea. Baroreceptor activation via electrical stimulation of carotid sinus afferent nerves lowers blood pressure in patients with “resistant” hypertension. Drugs that block the sympathetic nervous system are potent antihypertensive agents, indicating that the sympathetic nervous system plays a permissive, although not necessarily a causative, role in the maintenance of increased arterial pressure.

Pheochromocytoma is the most blatant example of hypertension related to increased catecholamine production, in this instance by a tumor. Blood pressure can be reduced by surgical excision of the tumor or by pharmacologic treatment with an α_1 receptor antagonist or with an inhibitor of tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis.

RENIN-ANGIOTENSIN-ALDOSTERONE

The renin-angiotensin-aldosterone system contributes to the regulation of arterial pressure primarily via the vasoconstrictor properties of angiotensin II and the sodium-retaining properties of aldosterone. Renin is an aspartyl protease that is synthesized as an enzymatically inactive precursor, prorenin. Most renin in the circulation is synthesized in the renal afferent renal arteriole. Prorenin may be secreted directly into the circulation or may be activated within secretory cells and released as active renin. Although human plasma contains two to five times more prorenin than renin, there is no evidence that prorenin contributes to the physiologic activity of this system. There are three primary stimuli for renin secretion: (1) decreased NaCl transport in the distal portion of the thick ascending limb of the loop of Henle that abuts the corresponding afferent arteriole (macula densa), (2) decreased pressure or stretch within the renal afferent arteriole (baroreceptor mechanism), and (3) sympathetic nervous system stimulation of renin-secreting cells via β_1 adrenoreceptors. Conversely, renin secretion is inhibited by increased NaCl transport in the thick ascending limb of the loop of Henle, by increased stretch within the renal afferent arteriole, and by β_1 receptor blockade. In addition, angiotensin II directly inhibits renin secretion due to angiotensin II type 1 receptors on juxtaglomerular cells, and renin secretion increases in response to pharmacologic blockade of either ACE or angiotensin II receptors.

Once released into the circulation, active renin cleaves a substrate, angiotensinogen, to form an inactive decapeptide, angiotensin I (Fig. 298-2). A converting enzyme, located primarily but not exclusively in the pulmonary circulation, converts angiotensin I to the active octapeptide, angiotensin II, by releasing the C-terminal histidyl-leucine dipeptide. The same converting enzyme cleaves a number

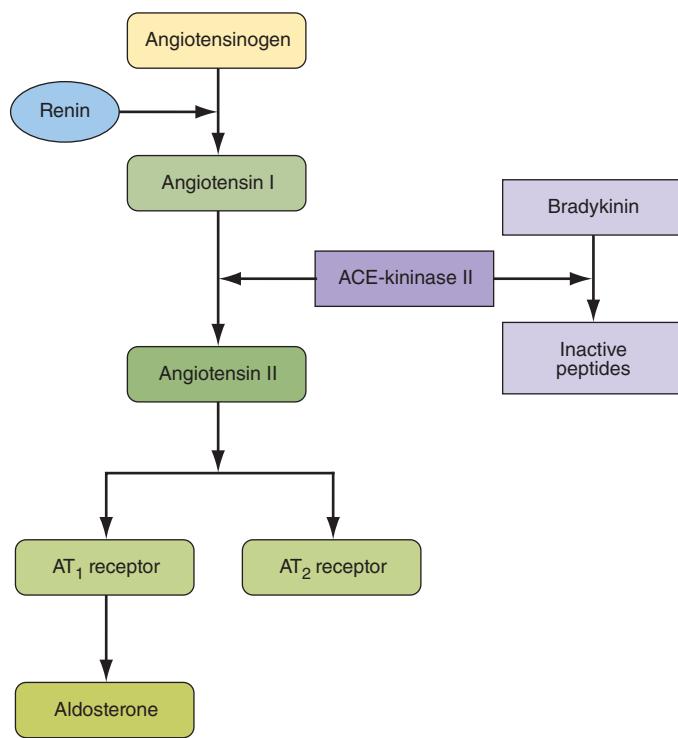


FIGURE 298-2 Renin-angiotensin-aldosterone axis. ACE, angiotensin-converting enzyme.

of other peptides, including and thereby inactivating the vasodilator bradykinin. Acting primarily through angiotensin II type 1 (AT_1) receptors on cell membranes, angiotensin II is a potent pressor substance, the primary tropic factor for the secretion of aldosterone by the adrenal zona glomerulosa, and a potent mitogen that stimulates vascular smooth muscle cell and myocyte growth. Independent of its hemodynamic effects, angiotensin II may play a role in the pathogenesis of atherosclerosis through a direct cellular action on the vessel wall. The angiotensin II type 2 (AT_2) receptor has the opposite functional effects of the AT_1 receptor. The AT_2 receptor induces vasodilation, sodium excretion, and inhibition of cell growth and matrix formation. Experimental evidence suggests that the AT_2 receptor improves vascular remodeling by stimulating smooth muscle cell apoptosis and contributes to the regulation of glomerular filtration rate. AT_1 receptor blockade induces an increase in AT_2 receptor activity.

Renin-secreting tumors are clear examples of renin-dependent hypertension. In the kidney, these tumors include benign hemangiopericytomas of the juxtaglomerular apparatus and, infrequently, renal carcinomas, including Wilms' tumors. Renin-producing carcinomas also have been described in lung, liver, pancreas, colon, and adrenals. In these instances, in addition to excision and/or ablation of the tumor, treatment of hypertension includes pharmacologic therapies targeted to inhibit angiotensin II production or action. Renovascular hypertension is another renin-mediated form of hypertension. Obstruction of the renal artery leads to decreased renal perfusion pressure, thereby stimulating renin secretion. Over time, possibly as a consequence of secondary renal damage, this form of hypertension may become less renin dependent.

Angiotensinogen, renin, and angiotensin II are also synthesized locally in many tissues, including the brain, pituitary, aorta, arteries, heart, adrenal glands, kidneys, adipocytes, leukocytes, ovaries, testes, uterus, spleen, and skin. Angiotensin II in tissues may be formed by the enzymatic activity of renin or by other proteases, e.g., tonin, chymase, and cathepsins. In addition to regulating local blood flow, tissue angiotensin II is a mitogen that stimulates growth and contributes to modeling and repair. Excess tissue angiotensin II may contribute to atherosclerosis, cardiac hypertrophy, and renal failure and consequently may be a target for pharmacologic therapy to prevent target organ damage.

Angiotensin II is the primary tropic factor regulating the synthesis and secretion of aldosterone by the zona glomerulosa of the adrenal

cortex. Aldosterone synthesis is also dependent on potassium, and aldosterone secretion may be decreased in potassium-depleted individuals. Although acute elevations of adrenocorticotrophic hormone (ACTH) levels also increase aldosterone secretion, ACTH is not an important tropic factor for the chronic regulation of aldosterone.

Aldosterone is a potent mineralocorticoid that increases sodium reabsorption by amiloride-sensitive epithelial sodium channels (ENaC) on the apical surface of the principal cells of the renal cortical collecting duct (Chap. 332e). Electric neutrality is maintained by exchanging sodium for potassium and hydrogen ions. Consequently, increased aldosterone secretion may result in hypokalemia and alkalosis.

Cortisol also binds to the mineralocorticoid receptor but normally functions as a less potent mineralocorticoid than aldosterone because cortisol is converted to cortisone by the enzyme 11β -hydroxysteroid dehydrogenase type 2. Cortisone has no affinity for the mineralocorticoid receptor. Primary aldosteronism is a compelling example of mineralocorticoid-mediated hypertension. In this disorder, adrenal aldosterone synthesis and release are independent of renin-angiotensin, and renin release is suppressed by the resulting volume expansion.

Mineralocorticoid receptors are expressed in a number of tissues in addition to the kidney, and mineralocorticoid receptor activation induces structural and functional alterations in the heart, kidney, and blood vessels, leading to myocardial fibrosis, nephrosclerosis, and vascular inflammation and remodeling, perhaps as a consequence of oxidative stress. These effects are amplified by a high salt intake. In animal models, high circulating aldosterone levels stimulate cardiac fibrosis and left ventricular hypertrophy, and spironolactone (an aldosterone antagonist) prevents aldosterone-induced myocardial fibrosis. Pathologic patterns of left ventricular geometry also have been associated with elevations of plasma aldosterone concentration in hypertensive patients. In patients with CHF, low-dose spironolactone reduces the risk of progressive heart failure and sudden death from cardiac causes by 30%. Due to a renal hemodynamic effect, in patients with primary aldosteronism, high circulating levels of aldosterone also may cause glomerular hyperfiltration and albuminuria. These renal effects are reversible after removal of the effects of excess aldosterone by adrenalectomy or spironolactone.

Increased activity of the renin-angiotensin-aldosterone axis is not invariably associated with hypertension. In response to a low-NaCl diet or to volume contraction, arterial pressure and volume homeostasis may be maintained by increased activity of the renin-angiotensin-aldosterone axis. Secondary aldosteronism (i.e., increased aldosterone secondary to increased renin-angiotensin), but not hypertension, also is observed in edematous states such as CHF and liver disease.

VASCULAR MECHANISMS

Vascular radius and compliance of resistance arteries are important determinants of arterial pressure. Resistance to flow varies inversely with the fourth power of the radius, and consequently, small decreases in lumen size significantly increase resistance. In hypertensive patients, structural, mechanical, or functional changes may reduce the lumen diameter of small arteries and arterioles. Remodeling refers to geometric alterations in the vessel wall without a change in vessel volume. Hypertrophic (increased cell size, and increased deposition of intercellular matrix) or eutrophic vascular remodeling results in decreased lumen size and, hence, increased peripheral resistance. Apoptosis, low-grade inflammation, and vascular fibrosis also contribute to remodeling. Lumen diameter also is related to elasticity of the vessel. Vessels with a high degree of elasticity can accommodate an increase of volume with relatively little change in pressure, whereas in a semirigid vascular system, a small increment in volume induces a relatively large increment of pressure.

Hypertensive patients may have stiffer arteries due to arteriosclerosis, and high systolic blood pressures and wide pulse pressures are a consequence of decreased vascular compliance. Due to arterial stiffness, central blood pressures (aortic, carotid) may not correspond to brachial artery pressures. Ejection of blood into the aorta elicits a pressure wave that is propagated at a given velocity. The forward travelling wave generates a reflected wave that travels backward toward

the ascending aorta. Although mean arterial pressure is determined by cardiac output and peripheral resistance, pulse pressure is related to the functional properties of large arteries and the amplitude and timing of the incident and reflected waves. Increased arterial stiffness results in increased pulse wave velocity of both incident and reflected waves. Due to the timing of these waves, the consequence is augmentation of aortic systolic pressure and a reduction of aortic diastolic pressure, i.e., an increase in pulse pressure. The aortic augmentation index, an index of arterial stiffening, is calculated as the ratio of central arterial pressure-to-pulse pressure. Central blood pressure may be measured directly by placing a sensor in the aorta or noninvasively by radial tonometry using commercially available devices. Central blood pressure and the aortic augmentation index are strong, independent predictors of cardiovascular disease and all-cause mortality.

Ion transport by vascular smooth muscle cells may contribute to hypertension-associated abnormalities of vascular tone and vascular growth, both of which are modulated by intracellular pH (pH_i). Three ion transport mechanisms participate in the regulation of pH_i : (1) Na^+/H^+ exchange, (2) Na^+ -dependent $\text{HCO}_3^-/\text{Cl}^-$ exchange, and (3) cation-independent $\text{HCO}_3^-/\text{Cl}^-$ exchange. Based on measurements in cell types that are more accessible than vascular smooth muscle (e.g., leukocytes, erythrocytes, platelets, skeletal muscle), activity of the Na^+/H^+ exchanger is increased in hypertension, and this may result in increased vascular tone by two mechanisms. First, increased sodium entry may lead to increased vascular tone by activating $\text{Na}^+/\text{Ca}^{2+}$ exchange and thereby increasing intracellular calcium. Second, increased pH_i enhances calcium sensitivity of the contractile apparatus, leading to an increase in contractility for a given intracellular calcium concentration. Additionally, increased Na^+/H^+ exchange may stimulate growth of vascular smooth muscle cells by enhancing sensitivity to mitogens.

Vascular endothelial function also modulates vascular tone. The vascular endothelium synthesizes and releases several vasoactive substances, including nitric oxide, a potent vasodilator. Endothelium-dependent vasodilation is impaired in hypertensive patients. This impairment often is assessed with high-resolution ultrasonography before and after the hyperemic phase of reperfusion that follows 5 minutes of forearm ischemia. Alternatively, endothelium-dependent vasodilation may be assessed in response to an intra-arterially infused endothelium-dependent vasodilator, e.g., acetylcholine. Endothelin is a vasoconstrictor peptide produced by the endothelium, and orally active endothelin antagonists may lower blood pressure in patients with resistant hypertension.

Currently, it is not known if the hypertension-related vascular abnormalities of ion transport and endothelial function are primary alterations or secondary consequences of elevated arterial pressure. Limited evidence suggests that vascular compliance and endothelium-dependent vasodilation may be improved by aerobic exercise, weight loss, and antihypertensive agents. It remains to be determined whether these interventions affect arterial structure and stiffness via a blood pressure-independent mechanism and whether different classes of antihypertensive agents preferentially affect vascular structure and function.

PATHOLOGIC CONSEQUENCES OF HYPERTENSION

Hypertension is an independent predisposing factor for heart failure, coronary artery disease, stroke, renal disease, and peripheral arterial disease (PAD).

HEART

Heart disease is the most common cause of death in hypertensive patients. Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and microvascular disease, and cardiac arrhythmias.

Individuals with left ventricular hypertrophy are at increased risk for CHD, stroke, CHF, and sudden death. Aggressive control of hypertension can regress or reverse left ventricular hypertrophy and reduce

the risk of cardiovascular disease. It is not clear whether different classes of antihypertensive agents have an added impact on reducing left ventricular mass, independent of their blood pressure-lowering effect.

CHF may be related to systolic dysfunction, diastolic dysfunction, or a combination of the two. Abnormalities of diastolic function that range from asymptomatic heart disease to overt heart failure are common in hypertensive patients. Approximately one-third of patients with CHF have normal systolic function but abnormal diastolic function. Diastolic dysfunction is an early consequence of hypertension-related heart disease and is exacerbated by left ventricular hypertrophy and ischemia. Cardiac catheterization provides the most accurate assessment of diastolic function. Alternatively, diastolic function can be evaluated by several noninvasive methods, including echocardiography and radionuclide angiography.

BRAIN

Stroke is the second most frequent cause of death in the world; it accounts for 5 million deaths each year, with an additional 15 million persons having nonfatal strokes. Elevated blood pressure is the strongest risk factor for stroke. Approximately 85% of strokes are due to infarction, and the remainder are due to either intracerebral or subarachnoid hemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals >65 years. Treatment of hypertension decreases the incidence of both ischemic and hemorrhagic strokes.

Hypertension also is associated with impaired cognition in an aging population, and longitudinal studies support an association between midlife hypertension and late-life cognitive decline. Hypertension-related cognitive impairment and dementia may be a consequence of a single infarct due to occlusion of a "strategic" larger vessel or multiple lacunar infarcts due to occlusive small vessel disease resulting in subcortical white matter ischemia. Several clinical trials suggest that antihypertensive therapy has a beneficial effect on cognitive function, although this remains an active area of investigation.

Cerebral blood flow remains unchanged over a wide range of arterial pressures (mean arterial pressure of 50–150 mmHg) through a process termed *autoregulation* of blood flow. In patients with the clinical syndrome of malignant hypertension, encephalopathy is related to failure of autoregulation of cerebral blood flow at the upper pressure limit, resulting in vasodilation and hyperperfusion. Signs and symptoms of hypertensive encephalopathy may include severe headache, nausea and vomiting (often of a projectile nature), focal neurologic signs, and alterations in mental status. Untreated, hypertensive encephalopathy may progress to stupor, coma, seizures, and death within hours. It is important to distinguish hypertensive encephalopathy from other neurologic syndromes that may be associated with hypertension, e.g., cerebral ischemia, hemorrhagic or thrombotic stroke, seizure disorder, mass lesions, pseudotumor cerebri, delirium tremens, meningitis, acute intermittent porphyria, traumatic or chemical injury to the brain, and uremic encephalopathy.

KIDNEY

The kidney is both a target and a cause of hypertension. Primary renal disease is the most common etiology of secondary hypertension. Mechanisms of kidney-related hypertension include a diminished capacity to excrete sodium, excessive renin secretion in relation to volume status, and sympathetic nervous system overactivity. Conversely, hypertension is a risk factor for renal injury and ESRD. The increased risk associated with high blood pressure is graded, continuous, and present throughout the distribution of blood pressure above optimal pressure. Renal risk appears to be more closely related to systolic than to diastolic blood pressure, and black men are at greater risk than white men for developing ESRD at every level of blood pressure.

Atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect preglomerular arterioles, resulting in ischemic changes in the glomeruli and postglomerular structures. Glomerular injury also may be a consequence of direct damage to the glomerular capillaries due to glomerular hyperperfusion. Studies of hypertension-related

renal damage, primarily in experimental animals, suggest that loss of autoregulation of renal blood flow at the afferent arteriole results in transmission of elevated pressures to an unprotected glomerulus with ensuing hyperfiltration, hypertrophy, and eventual focal segmental glomerular sclerosis. With progressive renal injury there is a loss of autoregulation of renal blood flow and glomerular filtration rate, resulting in a lower blood pressure threshold for renal damage and a steeper slope between blood pressure and renal damage. The result may be a vicious cycle of renal damage and nephron loss leading to more severe hypertension, glomerular hyperfiltration, and further renal damage. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic. The renal lesion associated with malignant hypertension consists of fibrinoid necrosis of the afferent arterioles, sometimes extending into the glomerulus, and may result in focal necrosis of the glomerular tuft.

Clinically, macroalbuminuria (a random urine albumin/creatinine ratio >300 mg/g) or microalbuminuria (a random urine albumin/creatinine ratio 30–300 mg/g) are early markers of renal injury. These are also risk factors for renal disease progression and cardiovascular disease.

PERIPHERAL ARTERIES

In addition to contributing to the pathogenesis of hypertension, blood vessels are a target organ for atherosclerotic disease secondary to long-standing elevated blood pressure. In hypertensive patients, vascular disease is a major contributor to stroke, heart disease, and renal failure. Further, hypertensive patients with arterial disease of the lower extremities are at increased risk for future cardiovascular disease. Although patients with stenotic lesions of the lower extremities may be asymptomatic, intermittent claudication is the classic symptom of PAD. The ankle-brachial index is a useful approach for evaluating PAD and is defined as the ratio of noninvasively assessed ankle to brachial (arm) systolic blood pressure. An ankle-brachial index <0.90 is considered diagnostic of PAD and is associated with >50% stenosis in at least one major lower limb vessel. An ankle-brachial index <0.80 is associated with elevated blood pressure, particularly systolic blood pressure.

DEFINING HYPERTENSION

From an epidemiologic perspective, there is no obvious level of blood pressure that defines hypertension. In adults, there is a continuous, incremental risk of cardiovascular disease, stroke, and renal disease across levels of both systolic and diastolic blood pressure. The Multiple Risk Factor Intervention Trial (MRFIT), which included >350,000 male participants, demonstrated a continuous and graded influence of both systolic and diastolic blood pressure on CHD mortality, extending down to systolic blood pressures of 120 mmHg. Similarly, results of a meta-analysis involving almost 1 million participants indicate that ischemic heart disease mortality, stroke mortality, and mortality from other vascular causes are directly related to the height of the blood pressure, beginning at 115/75 mmHg, without evidence of a threshold. Cardiovascular disease risk doubles for every 20-mmHg increase in systolic and 10-mmHg increase in diastolic pressure. Among older individuals, systolic blood pressure and pulse pressure are more powerful predictors of cardiovascular disease than is diastolic blood pressure.

Clinically, hypertension may be defined as that level of blood pressure at which the institution of therapy reduces blood pressure-related morbidity and mortality. Current clinical criteria for defining hypertension generally are based on the average of two or more seated blood pressure readings during each of two or more outpatient visits. A recent classification recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II), and isolated systolic hypertension, which is frequent among the elderly ([Table 298-1](#)). In children and adolescents, hypertension generally is defined as systolic and/or diastolic blood pressure consistently >95th percentile for age, sex, and height. Blood pressures between the 90th

TABLE 298-1 BLOOD PRESSURE CLASSIFICATION

Blood Pressure Classification	Systolic, mmHg	Diastolic, mmHg
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	≥160	or ≥100
Isolated systolic hypertension	≥140	and <90

Source: Adapted from AV Chobanian et al: JAMA 289:2560, 2003.

and 95th percentiles are considered prehypertensive and are an indication for lifestyle interventions.

Home blood pressure and average 24-h ambulatory blood pressure measurements are generally lower than clinic blood pressures. Because ambulatory blood pressure recordings yield multiple readings throughout the day and night, they provide a more comprehensive assessment of the vascular burden of hypertension than do a limited number of office readings. Increasing evidence suggests that home blood pressures, including 24-h blood pressure recordings, more reliably predict target organ damage than do office blood pressures. Blood pressure tends to be higher in the early morning hours, soon after waking, than at other times of day. Myocardial infarction and stroke are more common in the early morning hours. Nighttime blood pressures are generally 10–20% lower than daytime blood pressures, and an attenuated nighttime blood pressure “dip” may be associated with increased cardiovascular disease risk. Recommended criteria for a diagnosis of hypertension, based on 24-h blood pressure monitoring, are average awake blood pressure ≥135/85 mmHg and asleep blood pressure ≥120/75 mmHg. These levels approximate a clinic blood pressure of 140/90 mmHg.

Approximately 15–20% of patients with stage 1 hypertension (as defined in [Table 298-1](#)) based on office blood pressures have average ambulatory readings <135/85 mmHg. This phenomenon, so-called white coat hypertension, also may be associated with an increased risk of target organ damage, although to a lesser extent than in individuals with elevated office and ambulatory readings. Individuals with white coat hypertension are also at increased risk for developing sustained hypertension.

CLINICAL DISORDERS OF HYPERTENSION

Depending on methods of patient ascertainment, ~80–95% of hypertensive patients are diagnosed as having primary, or “essential,” hypertension. In the remaining 5–20% of hypertensive patients, a specific underlying disorder causing the elevation of blood pressure can be identified ([Tables 298-2 and 298-3](#)). In individuals with “secondary” hypertension, a specific mechanism for the blood pressure elevation is often more apparent.

PRIMARY HYPERTENSION

Primary hypertension tends to be familial and is likely to be the consequence of an interaction between environmental and genetic factors. The prevalence of primary hypertension increases with age, and individuals with relatively high blood pressures at younger ages are at increased risk for the subsequent development of hypertension. It is

TABLE 298-2 SYSTOLIC HYPERTENSION WITH WIDE PULSE PRESSURE

1. Decreased vascular compliance (arteriosclerosis)
2. Increased cardiac output
 - a. Aortic regurgitation
 - b. Thyrotoxicosis
 - c. Hyperkinetic heart syndrome
 - d. Fever
 - e. Arteriovenous fistula
 - f. Patent ductus arteriosus

TABLE 298-3 SECONDARY CAUSES OF SYSTOLIC AND DIASTOLIC HYPERTENSION

Renal	Parenchymal diseases, renal cysts (including polycystic kidney disease), renal tumors (including renin-secreting tumors), obstructive uropathy
Renovascular	Arteriosclerotic, fibromuscular dysplasia
Adrenal	Primary aldosteronism, Cushing's syndrome, 17 α -hydroxylase deficiency, 11 β -hydroxylase deficiency, 11-hydroxysteroid dehydrogenase deficiency (licorice), pheochromocytoma
Aortic coarctation	
Obstructive sleep apnea	
Preeclampsia/eclampsia	
Neurogenic	Psychogenic, diencephalic syndrome, familial dysautonomia, polyneuritis (acute porphyria, lead poisoning), acute increased intracranial pressure, acute spinal cord section
Miscellaneous endocrine	Hypothyroidism, hyperthyroidism, hypercalcemia, acromegaly
Medications	High-dose estrogens, adrenal steroids, decongestants, appetite suppressants, cyclosporine, tricyclic antidepressants, monoamine oxidase inhibitors, erythropoietin, nonsteroidal anti-inflammatory agents, cocaine
Mendelian forms of hypertension	See Table 298-4

likely that primary hypertension represents a spectrum of disorders with different underlying pathophysiologies. In the majority of patients with established hypertension, peripheral resistance is increased and cardiac output is normal or decreased; however, in younger patients with mild or labile hypertension, cardiac output may be increased and peripheral resistance may be normal.

When plasma renin activity (PRA) is plotted against 24-h sodium excretion, ~10–15% of hypertensive patients have high PRA and 25% have low PRA. High-renin patients may have a vasoconstrictor form of hypertension, whereas low-renin patients may have volume-dependent hypertension. Inconsistent associations between plasma aldosterone and blood pressure have been described in patients with primary hypertension. The association between aldosterone and blood pressure is more striking in African Americans, and PRA tends to be low in hypertensive African Americans. This raises the possibility that subtle increases in aldosterone may contribute to hypertension in at least some groups of patients who do not have overt primary aldosteronism. Furthermore, spironolactone, an aldosterone antagonist, may be a particularly effective antihypertensive agent for some patients with primary hypertension, including some patients with “drug-resistant” hypertension.

OBESITY AND THE METABOLIC SYNDROME

(See also Chap. 422) There is a well-documented association between obesity (body mass index >30 kg/m²) and hypertension. Further, cross-sectional studies indicate a direct linear correlation between body weight (or body mass index) and blood pressure. Centrally located body fat is a more important determinant of blood pressure elevation than is peripheral body fat. In longitudinal studies, a direct correlation exists between change in weight and change in blood pressure over time. Sixty percent of hypertensive adults are more than 20% overweight. It has been established that 60–70% of hypertension in adults may be directly attributable to adiposity.

Hypertension and dyslipidemia frequently occur together and in association with resistance to insulin-stimulated glucose uptake. This clustering of risk factors is often, but not invariably, associated with obesity, particularly abdominal obesity. Insulin resistance also is associated with an unfavorable imbalance in the endothelial production of mediators that regulate platelet aggregation, coagulation, fibrinolysis, and vessel tone. When these risk factors cluster, the risks for CHD, stroke, diabetes, and cardiovascular disease mortality are increased further.

Depending on the populations studied and the methodologies for defining insulin resistance, ~25–50% of nonobese, nondiabetic hypertensive persons are insulin resistant. The constellation of insulin resistance, abdominal obesity, hypertension, and dyslipidemia has been designated as the *metabolic syndrome*. As a group, first-degree relatives of patients with primary hypertension are also insulin resistant, and hyperinsulinemia (a surrogate marker of insulin resistance) may predict the eventual development of hypertension and cardiovascular disease. Although the metabolic syndrome may in part be heritable as a polygenic condition, the expression of the syndrome is modified by environmental factors, such as degree of physical activity and diet. Insulin sensitivity increases and blood pressure decreases in response to weight loss. The recognition that cardiovascular disease risk factors tend to cluster within individuals has important implications for the evaluation and treatment of hypertension. Evaluation of both hypertensive patients and individuals at risk for developing hypertension should include assessment of overall cardiovascular disease risk. Similarly, introduction of lifestyle modification strategies and drug therapies should address overall risk and not focus exclusively on hypertension.

RENAL PARENCHYMAL DISEASES

Virtually all disorders of the kidney may cause hypertension (Table 298-3), and renal disease is the most common cause of secondary hypertension. Hypertension is present in >80% of patients with chronic renal failure. In general, hypertension is more severe in glomerular diseases than in interstitial diseases such as chronic pyelonephritis. Conversely, hypertension may cause nephrosclerosis, and in some instances it may be difficult to determine whether hypertension or renal disease was the initial disorder. Proteinuria >1000 mg/d and an active urine sediment are indicative of primary renal disease. In either instance, the goals are to control blood pressure and retard the rate of progression of renal dysfunction.

RENOVASCULAR HYPERTENSION

Hypertension due to an occlusive lesion of a renal artery, renovascular hypertension, is a potentially curable form of hypertension. In the initial stages, the mechanism of hypertension generally is related to activation of the renin-angiotensin system. However, renin activity and other components of the renin-angiotensin system may be elevated only transiently; over time, recruitment of other pressure mechanisms may contribute to elevated arterial pressure. Two groups of patients are at risk for this disorder: older arteriosclerotic patients who have a plaque obstructing the renal artery, frequently at its origin, and patients with fibromuscular dysplasia. Atherosclerosis accounts for the large majority of patients with renovascular hypertension. Although fibromuscular dysplasia may occur at any age, it has a strong predilection for young white women. The prevalence in females is eightfold that in males. There are several histologic variants of fibromuscular dysplasia, including medial fibroplasia, perimedial fibroplasia, medial hyperplasia, and intimal fibroplasia. Medial fibroplasia is the most common variant and accounts for approximately two-thirds of patients. The lesions of fibromuscular dysplasia are frequently bilateral and, in contrast to atherosclerotic renovascular disease, tend to affect more distal portions of the renal artery.

Several clues from the history and physical examination may suggest renovascular hypertension. The diagnosis should be considered in patients with other evidence of atherosclerotic vascular disease. Although response to antihypertensive therapy does not exclude the diagnosis, severe or refractory hypertension, recent loss of hypertension control or recent onset of moderately severe hypertension, and unexplained deterioration of renal function or deterioration of renal function associated with an ACE inhibitor should raise the possibility of renovascular hypertension. Approximately 50% of patients with renovascular hypertension have an abdominal or flank bruit, and the bruit is more likely to be hemodynamically significant if it lateralizes or extends throughout systole into diastole.

If blood pressure is adequately controlled with a simple antihypertensive regimen and renal function remains stable, there may be little

1618 impetus to pursue an evaluation for renal artery stenosis, particularly in an older patient with atherosclerotic disease and comorbid conditions. Patients with long-standing hypertension, advanced renal insufficiency, or diabetes mellitus are less likely to benefit from renal vascular repair. The most effective medical therapies include an ACE inhibitor or an angiotensin II receptor blocker; however, these agents decrease glomerular filtration rate in a stenotic kidney owing to efferent renal arteriolar dilation. In the presence of bilateral renal artery stenosis or renal artery stenosis to a solitary kidney, progressive renal insufficiency may result from the use of these agents. Importantly, the renal insufficiency is generally reversible after discontinuation of the offending drug.

If renal artery stenosis is suspected and if the clinical condition warrants an intervention such as percutaneous transluminal renal angioplasty (PTRA), placement of a vascular endoprosthesis (stent), or surgical renal revascularization, imaging studies should be the next step in the evaluation. As a screening test, renal blood flow may be evaluated with a radionuclide [¹³¹I]-orthoiodohippurate (OIH) scan, or glomerular filtration rate may be evaluated with a [^{99m}Tc]-diethylenetriamine pentaacetic acid (DTPA) scan before and after a single dose of captopril (or another ACE inhibitor). The following are consistent with a positive study: (1) decreased relative uptake by the involved kidney, which contributes <40% of total renal function, (2) delayed uptake on the affected side, and (3) delayed washout on the affected side. In patients with normal, or nearly normal, renal function, a normal captopril renogram essentially excludes functionally significant renal artery stenosis; however, its usefulness is limited in patients with renal insufficiency (creatinine clearance <20 mL/min) or bilateral renal artery stenosis. Additional imaging studies are indicated if the scan is positive. Doppler ultrasound of the renal arteries produces reliable estimates of renal blood flow velocity and offers the opportunity to track a lesion over time. Positive studies usually are confirmed at angiography, whereas false-negative results occur frequently, particularly in obese patients. Gadolinium-contrast magnetic resonance angiography offers clear images of the proximal renal artery but may miss distal lesions. An advantage is the opportunity to image the renal arteries with an agent that is not nephrotoxic. Contrast arteriography remains the “gold standard” for evaluation and identification of renal artery lesions. Potential risks include nephrotoxicity, particularly in patients with diabetes mellitus or preexisting renal insufficiency.

Some degree of renal artery obstruction may be observed in almost 50% of patients with atherosclerotic disease, and there are several approaches for evaluating the functional significance of such a lesion to predict the effect of vascular repair on blood pressure control and renal function. Each approach has varying degrees of sensitivity and specificity, and no single test is sufficiently reliable to determine a causal relationship between a renal artery lesion and hypertension. Functionally significant lesions generally occlude more than 70% of the lumen of the affected renal artery. On angiography, the presence of collateral vessels to the ischemic kidney suggests a functionally significant lesion. A lateralizing renal vein renin ratio (ratio >1.5 of affected side/contralateral side) has a 90% predictive value for a lesion that would respond to vascular repair; however, the false-negative rate for blood pressure control is 50–60%. Measurement of the pressure gradient across a renal artery lesion does not reliably predict the response to vascular repair.

In the final analysis, a decision concerning vascular repair vs. medical therapy and the type of repair procedure should be individualized. Patients with fibromuscular disease have more favorable outcomes than do patients with atherosclerotic lesions, presumably owing to their younger age, shorter duration of hypertension, and less systemic disease. Because of its low risk-versus-benefit ratio and high success rate (improvement or cure of hypertension in 90% of patients and restenosis rate of 10%), PTRA is the initial treatment of choice for these patients. Surgical revascularization may be undertaken if PTRA is unsuccessful or if a branch lesion is present. In atherosclerotic patients, vascular repair should be considered if blood pressure cannot be controlled adequately despite optimal medical therapy or if renal function deteriorates. Surgery may be the preferred initial approach

for younger atherosclerotic patients without comorbid conditions; however, for most atherosclerotic patients, depending on the location of the lesion, the initial approach may be PTRA and/or stenting. Surgical revascularization may be indicated if these approaches are unsuccessful, the vascular lesion is not amenable to PTRA or stenting, or concomitant aortic surgery is required, e.g., to repair an aneurysm. A National Institutes of Health-sponsored prospective, randomized clinical trial is in progress comparing medical therapy alone with medical therapy plus renal artery stenting regarding Cardiovascular Outcomes for Renal Atherosclerotic Lesions (CORAL).

PRIMARY ALDOSTERONISM

Excess aldosterone production due to primary aldosteronism is a potentially curable form of hypertension. In patients with primary aldosteronism, increased aldosterone production is independent of the renin-angiotensin system, and the consequences are sodium retention, hypertension, hypokalemia, and low PRA. The reported prevalence of this disorder varies from <2% to ~15% of hypertensive individuals. In part, this variation is related to the intensity of screening and the criteria for establishing the diagnosis.

History and physical examination provide little information about the diagnosis. The age at the time of diagnosis is generally the third through fifth decade. Hypertension is usually mild to moderate but occasionally may be severe; primary aldosteronism should be considered in all patients with refractory hypertension. Hypertension in these patients may be associated with glucose intolerance. Most patients are asymptomatic; however, infrequently, polyuria, polydipsia, paresthesias, or muscle weakness may be present as a consequence of hypokalemic alkalosis. Although aldosterone is a salt-retaining hormone, patients with primary aldosteronism rarely have edema. Renal dysfunction and cardiovascular disease are strikingly increased in patients with primary aldosteronism compared to those with primary hypertension.

In a hypertensive patient with unprovoked hypokalemia (i.e., unrelated to diuretics, vomiting, or diarrhea), the prevalence of primary aldosteronism approaches 40–50%. In patients on diuretics, serum potassium <3.1 mmol/L (<3.1 meq/L) also raises the possibility of primary aldosteronism; however, serum potassium is an insensitive and nonspecific screening test. Serum potassium is normal in ~25% of patients subsequently found to have an aldosterone-producing adenoma, and higher percentages of patients with other etiologies of primary aldosteronism are not hypokalemic. Additionally, hypokalemic hypertension may be a consequence of secondary aldosteronism, other mineralocorticoid- and glucocorticoid-induced hypertensive disorders, and pheochromocytoma.

The ratio of plasma aldosterone to plasma renin activity (PA/PRA) is a useful screening test. These measurements preferably are obtained in ambulatory patients in the morning. A ratio >30:1 in conjunction with a plasma aldosterone concentration >555 pmol/L (>20 ng/dL) reportedly has a sensitivity of 90% and a specificity of 91% for an aldosterone-producing adenoma. In a Mayo Clinic series, an aldosterone-producing adenoma subsequently was confirmed surgically in >90% of hypertensive patients with a PA/PRA ratio ≥20 and a plasma aldosterone concentration ≥415 pmol/L (≥15 ng/dL). There are, however, several caveats to interpreting the ratio. The cutoff for a “high” ratio is laboratory- and assay-dependent. Some antihypertensive agents may affect the ratio (e.g., aldosterone antagonists, angiotensin receptor antagonists, and ACE inhibitors may increase renin; aldosterone antagonists may increase aldosterone). Current recommendations are to withdraw aldosterone antagonists for at least 4–6 weeks before obtaining these measurements. Because aldosterone biosynthesis is potassium-dependent, hypokalemia should be corrected with oral potassium supplements prior to screening. With these caveats, the ratio has been reported to be useful as a screening test in measurements obtained with patients taking their usual antihypertensive medications. A high ratio in the absence of an elevated plasma aldosterone level is considerably less specific for primary aldosteronism since many patients with primary hypertension have low renin levels in this setting, particularly African Americans and elderly patients.

In patients with renal insufficiency, the ratio may also be elevated because of decreased aldosterone clearance. In patients with an elevated PA/PRA ratio, the diagnosis of primary aldosteronism can be confirmed by demonstrating failure to suppress plasma aldosterone to <277 pmol/L (<10 ng/dL) after IV infusion of 2 L of isotonic saline over 4 h; post-saline infusion plasma aldosterone values between 138 and 277 pmol/L (5–10 ng/dL) are not determinant. Alternative confirmatory tests include failure to suppress aldosterone (based on test specific criteria) in response to an oral NaCl load, fludrocortisone, or captopril.

Several sporadic and familial adrenal abnormalities may culminate in the syndrome of primary aldosteronism, and appropriate therapy depends on the specific etiology. The two most common causes of sporadic primary aldosteronism are an aldosterone-producing adenoma and bilateral adrenal hyperplasia. Together, they account for >90% of all patients with primary aldosteronism. The tumor is almost always unilateral, and most often measures <3 cm in diameter. Most of the remainder of these patients have bilateral adrenocortical hyperplasia (idiopathic hyperaldosteronism). Rarely, primary aldosteronism may be caused by an adrenal carcinoma or an ectopic malignancy, e.g., ovarian arrhenoblastoma. Most aldosterone-producing carcinomas, in contrast to adrenal adenomas and hyperplasia, produce excessive amounts of other adrenal steroids in addition to aldosterone. Functional differences in hormone secretion may assist in the diagnosis of adenoma vs. hyperplasia. Aldosterone biosynthesis is more responsive to ACTH in patients with adenoma and more responsive to angiotensin in patients with hyperplasia. Consequently, patients with adenoma tend to have higher plasma aldosterone in the early morning that decreases during the day, reflecting the diurnal rhythm of ACTH, whereas plasma aldosterone tends to increase with upright posture in patients with hyperplasia, reflecting the normal postural response of the renin-angiotensin-aldosterone axis. However, there is overlap in the ability of these measurements to discriminate between adenoma and hyperplasia. Rare familial forms of primary aldosteronism include glucocorticoid-remediable primary aldosteronism and familial aldosteronism types II and III. Genetic testing may assist in the diagnosis of these familial disorders.

Adrenal computed tomography (CT) should be carried out in all patients diagnosed with primary aldosteronism. High-resolution CT may identify tumors as small as 0.3 cm and is positive for an adrenal tumor 90% of the time. If the CT is not diagnostic, an adenoma may be detected by adrenal scintigraphy with 6β -[I¹³¹] iodomethyl-19-norcholesterol after dexamethasone suppression (0.5 mg every 6 h for 7 days); however, this technique has decreased sensitivity for adenomas <1.5 cm.

When carried out by an experienced radiologist, bilateral adrenal venous sampling for measurement of plasma aldosterone is the most accurate means of differentiating unilateral from bilateral forms of primary aldosteronism. The sensitivity and specificity of adrenal venous sampling (95% and 100%, respectively) for detecting unilateral aldosterone hypersecretion are superior to those of adrenal CT; success rates are 90–96%, and complication rates are <2.5%. One frequently used protocol involves sampling for aldosterone and cortisol levels in response to ACTH stimulation. An ipsilateral/contralateral aldosterone ratio >4, with symmetric ACTH-stimulated cortisol levels, is indicative of unilateral aldosterone production.

Hypertension generally is responsive to surgery in patients with adenoma but not in patients with bilateral adrenal hyperplasia. Unilateral adrenalectomy, often done via a laparoscopic approach, is curative in 40–70% of patients with an adenoma. Transient hypoadosteronism may occur up to 3 months postoperatively, resulting in hyperkalemia. Potassium should be monitored during this time, and hyperkalemia should be treated with potassium-wasting diuretics and with fludrocortisone, if needed. Patients with bilateral hyperplasia should be treated medically. The drug regimen for these patients, as well as for patients with an adenoma who are poor surgical candidates, should include an aldosterone antagonist and, if necessary, other potassium-sparing diuretics.

Glucocorticoid-remediable hyperaldosteronism is a rare, monogenic autosomal dominant disorder characterized by moderate to

severe hypertension, often occurring at an early age. These patients may have a family history of hemorrhagic stroke at a young age. Hypokalemia is usually mild or absent. Normally, angiotensin II stimulates aldosterone production by the adrenal zona glomerulosa, whereas ACTH stimulates cortisol production in the zona fasciculata. Owing to a chimeric gene on chromosome 8, ACTH also regulates aldosterone secretion by the zona fasciculata in patients with glucocorticoid-remediable hyperaldosteronism. The consequence is overproduction in the zona fasciculata of both aldosterone and hybrid steroids (18-hydroxycortisol and 18-oxocortisol) due to oxidation of cortisol. The diagnosis may be established by urine excretion rates of these hybrid steroids that are 20 to 30 times normal or by direct genetic testing. Therapeutically, suppression of ACTH with low-dose glucocorticoids corrects the hyperaldosteronism, hypertension, and hypokalemia. Aldosterone antagonists are also therapeutic options. Patients with familial aldosteronism types II and III are treated with aldosterone antagonists or adrenalectomy.

CUSHING'S SYNDROME

(See also Chap. 406) Cushing's syndrome is related to excess cortisol production due either to excess ACTH secretion (from a pituitary tumor or an ectopic tumor) or to ACTH-independent adrenal production of cortisol. Hypertension occurs in 75–80% of patients with Cushing's syndrome. The mechanism of hypertension may be related to stimulation of mineralocorticoid receptors by cortisol and increased secretion of other adrenal steroids. If clinically suspected based on phenotypic characteristics, in patients not taking exogenous glucocorticoids, laboratory screening may be carried out with measurement of 24-h excretion rates of urine free cortisol or an overnight dexamethasone-suppression test. Late night salivary cortisol is also a sensitive and convenient screening test. Further evaluation is required to confirm the diagnosis and identify the specific etiology of Cushing's syndrome. Appropriate therapy depends on the etiology.

PHEOCHROMOCYTOMA

(See also Chap. 407) Catecholamine-secreting tumors are located in the adrenal medulla (pheochromocytoma) or in extra-adrenal paraganglion tissue (paraganglioma) and account for hypertension in ~0.05% of patients. If unrecognized, pheochromocytoma may result in lethal cardiovascular consequences. Clinical manifestations, including hypertension, are primarily related to increased circulating catecholamines, although some of these tumors may secrete a number of other vasoactive substances. In a small percentage of patients, epinephrine is the predominant catecholamine secreted by the tumor, and these patients may present with hypotension rather than hypertension. The initial suspicion of the diagnosis is based on symptoms and/or the association of pheochromocytoma with other disorders (Table 298-4). Approximately 20% of pheochromocytomas are familial with autosomal dominant inheritance. Inherited pheochromocytomas may be associated with multiple endocrine neoplasia (MEN) type 2A and type 2B, von Hippel-Lindau disease, and neurofibromatosis (Table 298-4). Each of these syndromes is related to specific, identifiable germ-line mutations. Additionally, mutations of succinate dehydrogenase genes are associated with paraganglioma syndromes, generally characterized by head and neck paragangliomas. Laboratory testing consists of measuring catecholamines in either urine or plasma, e.g., 24-h urine metanephrine excretion or fractionated plasma free metanephrines. The urine measurement is less sensitive but more specific. Genetic screening is available for evaluating patients and relatives suspected of harboring a pheochromocytoma associated with a familial syndrome. Surgical excision is the definitive treatment of pheochromocytoma and results in cure in ~90% of patients.

MISCELLANEOUS CAUSES OF HYPERTENSION

Independent of obesity, hypertension occurs in >50% of individuals with *obstructive sleep apnea*. The severity of hypertension correlates with the severity of sleep apnea. Approximately 70% of patients with obstructive sleep apnea are obese. Hypertension related to obstructive sleep apnea also should be considered in patients with drug-resistant

TABLE 298-4 RARE MENDELIAN FORMS OF HYPERTENSION

Disease	Phenotype	Genetic Cause
Glucocorticoid-remediable hyperaldosteronism	Autosomal dominant Absent or mild hypokalemia	Chimeric 11 β -hydroxylase/aldosterone gene on chromosome 8
17 α -hydroxylase deficiency	Autosomal recessive Males: pseudohermaphroditism Females: primary amenorrhea, absent secondary sexual characteristics	Random mutations of the CYP17 gene on chromosome 10
11 β -hydroxylase deficiency	Autosomal recessive Masculinization	Mutations of the CYP11B1 gene on chromosome 8q21-q22
11 β -hydroxysteroid dehydrogenase deficiency (apparent mineralocorticoid excess syndrome)	Autosomal recessive Hypokalemia, low renin, low aldosterone	Mutations in the 11 β -hydroxysteroid dehydrogenase gene
Liddle's syndrome	Autosomal dominant Hypokalemia, low renin, low aldosterone	Mutation subunits of the epithelial sodium channel SCNN1B and SCNN1C genes
Pseudohypoaldosteronism type II (Gordon's syndrome)	Autosomal dominant Hyperkalemia, normal glomerular filtration rate	Linkage to chromosomes 1q31-q42 and 17p11-q21
Hypertension exacerbated in pregnancy	Autosomal dominant Severe hypertension in early pregnancy	Missense mutation with substitution of leucine for serine at codon 810 (MR _{L810})
Polycystic kidney disease	Autosomal dominant Large cystic kidneys, renal failure, liver cysts, cerebral aneurysms, valvular heart disease	Mutations in the PKD1 gene on chromosome 16 and PKD2 gene on chromosome 4
Pheochromocytoma	Autosomal dominant (a) Multiple endocrine neoplasia, type 2A Medullary thyroid carcinoma, hyperparathyroidism (b) Multiple endocrine neoplasia, type 2B Medullary thyroid carcinoma, mucosal neuromas, thickened corneal nerves, alimentary ganglioneuromatoses, marfanoid habitus (c) von Hippel-Lindau disease Retinal angiomas, hemangioblastomas of the cerebellum and spinal cord, renal cell carcinoma (d) Neurofibromatosis type 1 Multiple neurofibromas, café-au-lait spots	(a) Mutations in the RET protooncogene (b) Mutations in the RET protooncogene (c) Mutations in the VHL tumor-suppressor gene (d) Mutations in the NF1 tumor-suppressor gene

hypertension and patients with a history of snoring. The diagnosis can be confirmed by polysomnography. In obese patients, weight loss may alleviate or cure sleep apnea and related hypertension. Continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) administered during sleep is an effective therapy for obstructive sleep apnea. With CPAP or BiPAP, patients with apparently drug-resistant hypertension may be more responsive to antihypertensive agents.

Coarctation of the aorta is the most common congenital cardiovascular cause of hypertension (*Chap. 282*). The incidence is 1–8 per 1000 live births. It is usually sporadic but occurs in 35% of children with Turner's syndrome. Even when the anatomic lesion is surgically corrected in infancy, up to 30% of patients develop subsequent hypertension and are at risk of accelerated coronary artery disease and cerebrovascular events. Patients with less severe lesions may not be diagnosed until young adulthood. Physical findings include diminished and delayed femoral pulses and a systolic pressure gradient between the right arm and the legs and, depending on the location of the coarctation, between the right and left arms. A blowing systolic murmur may be heard in the posterior left interscapular areas. The diagnosis may be confirmed by chest x-ray and transesophageal echocardiography. Therapeutic options include surgical repair and balloon angioplasty, with or without placement of an intravascular stent. Subsequently, many patients do not have a normal life expectancy but may have persistent hypertension, with death due to ischemic heart disease, cerebral hemorrhage, or aortic aneurysm.

Several additional endocrine disorders, including *thyroid diseases* and *acromegaly*, cause hypertension. Mild diastolic hypertension may be a consequence of hypothyroidism, whereas hyperthyroidism may result in systolic hypertension. *Hypercalcemia* of any etiology, the most

common being primary hyperparathyroidism, may result in hypertension. Hypertension also may be related to a number of prescribed or over-the-counter medications.

MONOGENIC HYPERTENSION

In addition to glucocorticoid-remediable primary aldosteronism, a number of rare forms of monogenic hypertension have been identified (Table 298-4). These disorders may be recognized by their characteristic phenotypes, and in many instances the diagnosis may be confirmed by genetic analysis. Several inherited defects in adrenal steroid biosynthesis and metabolism result in mineralocorticoid-induced hypertension and hypokalemia. In patients with a 17 α -hydroxylase deficiency, synthesis of sex hormones and cortisol is decreased (*Fig. 298-3*). Consequently, these individuals do not mature sexually; males may present with pseudohermaphroditism and females with primary amenorrhea and absent secondary sexual characteristics. Because cortisol-induced negative feedback on pituitary ACTH production is diminished, ACTH-stimulated adrenal steroid synthesis proximal to the enzymatic block is increased. Hypertension and hypokalemia are consequences of increased synthesis of mineralocorticoids proximal to the enzymatic block, particularly desoxycorticosterone. Increased steroid production and, hence, hypertension may be treated with low-dose glucocorticoids. An 11 β -hydroxylase deficiency results in a salt-retaining adrenogenital syndrome that occurs in 1 in 100,000 live births. This enzymatic defect results in decreased cortisol synthesis, increased synthesis of mineralocorticoids (e.g., desoxycorticosterone), and shunting of steroid biosynthesis into the androgen pathway. In the severe form, the syndrome may present early in life, including the

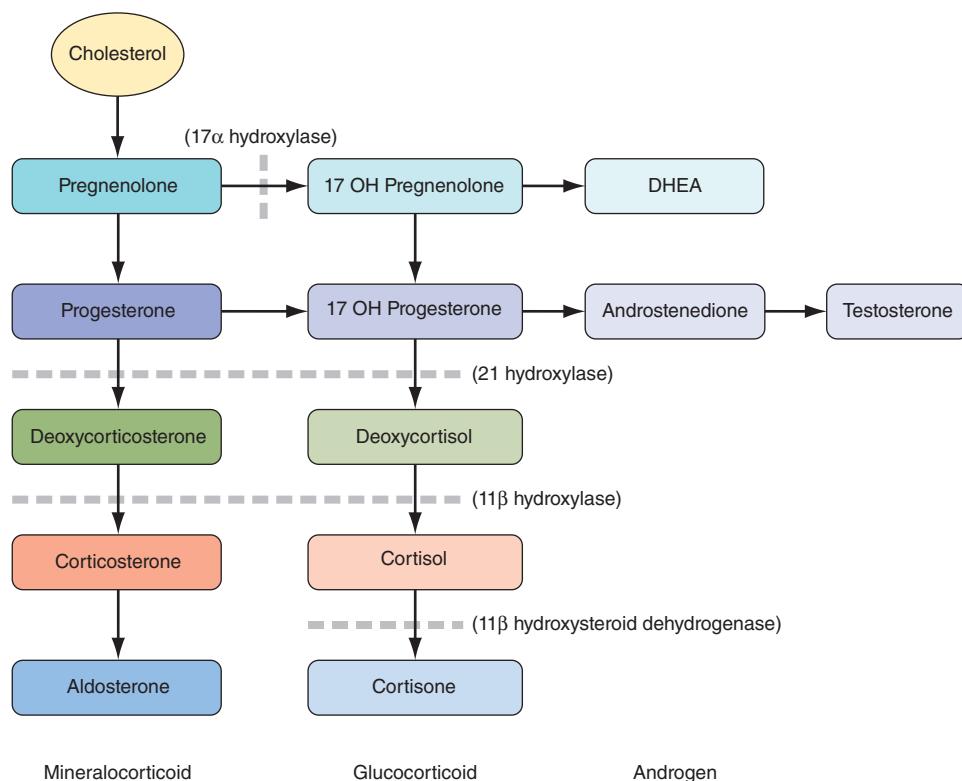


FIGURE 298-3 Adrenal enzymatic defects. DHEA, dehydroepiandrosterone.

newborn period, with virilization and ambiguous genitalia in females and penile enlargement in males, or in older children as precocious puberty and short stature. Acne, hirsutism, and menstrual irregularities may be the presenting features when the disorder is first recognized in adolescence or early adulthood. Hypertension is less common in the late-onset forms. Patients with an 11 β -hydroxysteroid dehydrogenase deficiency have an impaired capacity to metabolize cortisol to its inactive metabolite, cortisone, and hypertension is related to activation of mineralocorticoid receptors by cortisol. This defect may be inherited or acquired, due to licorice-containing glycyrrhizin acid. The same substance is present in the paste of several brands of chewing tobacco. The defect in Liddle's syndrome (Chaps. 63 and 406) results from constitutive activation of amiloride-sensitive epithelial sodium channels on the distal renal tubule, resulting in excess sodium reabsorption; the syndrome is ameliorated by amiloride. Hypertension exacerbated in pregnancy (Chap. 8) may be due to activation of the mineralocorticoid receptor by progesterone.

APPROACH TO THE PATIENT: Hypertension

HISTORY

The initial assessment of a hypertensive patient should include a complete history and physical examination to confirm a diagnosis of hypertension, screen for other cardiovascular disease risk factors, screen for secondary causes of hypertension, identify cardiovascular consequences of hypertension and other comorbidities, assess blood pressure-related lifestyles, and determine the potential for intervention.

Most patients with hypertension have no specific symptoms referable to their blood pressure elevation. Although popularly considered a symptom of elevated arterial pressure, headache generally occurs only in patients with severe hypertension. Characteristically, a "hypertensive headache" occurs in the morning and is localized to the occipital region. Other nonspecific symptoms that may be related to elevated blood pressure include

dizziness, palpitations, easy fatigability, and impotence. When symptoms are present, they are generally related to hypertensive cardiovascular disease or to manifestations of secondary hypertension. Table 298-5 lists salient features that should be addressed in obtaining a history from a hypertensive patient.

MEASUREMENT OF BLOOD PRESSURE

Reliable measurements of blood pressure depend on attention to the details of the technique and conditions of the measurement. Proper training of observers, positioning of the patient, and selection of cuff size are essential. Owing to recent regulations preventing the use of mercury because of concerns about its potential toxicity, most office measurements are made with aneroid sphygmomanometers or with oscillometric devices. These instruments should be calibrated periodically, and their accuracy confirmed. Before the blood pressure measurement is taken, the individual should be seated quietly in a chair (not the exam table) with feet on the floor for 5 min in a private, quiet setting with a comfortable room temperature. At least two measurements should be made. The center of the cuff should be at heart level, and the width of the bladder cuff

TABLE 298-5 PATIENT'S RELEVANT HISTORY

Duration of hypertension
Previous therapies: responses and side effects
Family history of hypertension and cardiovascular disease
Dietary and psychosocial history
Other risk factors: weight change, dyslipidemia, smoking, diabetes, physical inactivity
Evidence of secondary hypertension: history of renal disease; change in appearance; muscle weakness; spells of sweating, palpitations, tremor; erratic sleep, snoring, daytime somnolence; symptoms of hypo- or hyperthyroidism; use of agents that may increase blood pressure
Evidence of target organ damage: history of TIA, stroke, transient blindness; angina, myocardial infarction, congestive heart failure; sexual function
Other comorbidities

Abbreviation: TIA, transient ischemic attack.

should equal at least 40% of the arm circumference; the length of the cuff bladder should encircle at least 80% of the arm circumference. It is important to pay attention to cuff placement, stethoscope placement, and the rate of deflation of the cuff (2 mmHg/s). Systolic blood pressure is the first of at least two regular “tapping” Korotkoff sounds, and diastolic blood pressure is the point at which the last regular Korotkoff sound is heard. In current practice, a diagnosis of hypertension generally is based on seated, office measurements.

Currently available ambulatory monitors are fully automated, use the oscillometric technique, and typically are programmed to take readings every 15–30 min. Twenty-four-hour ambulatory blood pressure monitoring more reliably predicts cardiovascular disease risk than do office measurements. However, ambulatory monitoring is not used routinely in clinical practice and generally is reserved for patients in whom white coat hypertension is suspected. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has also recommended ambulatory monitoring for treatment resistance, symptomatic hypotension, autonomic failure, and episodic hypertension.

PHYSICAL EXAMINATION

Body habitus, including weight and height, should be noted. At the initial examination, blood pressure should be measured in both arms and preferably in the supine, sitting, and standing positions to evaluate for postural hypotension. Even if the femoral pulse is normal to palpation, arterial pressure should be measured at least once in the lower extremity in patients in whom hypertension is discovered before age 30. Heart rate also should be recorded. Hypertensive individuals have an increased prevalence of atrial fibrillation. The neck should be palpated for an enlarged thyroid gland, and patients should be assessed for signs of hypo- and hyperthyroidism. Examination of blood vessels may provide clues about underlying vascular disease and should include funduscopic examination, auscultation for bruits over the carotid and femoral arteries, and palpation of femoral and pedal pulses. The retina is the only tissue in which arteries and arterioles can be examined directly. With increasing severity of hypertension and atherosclerotic disease, progressive funduscopic changes include increased arteriolar light reflex, arteriovenous crossing defects, hemorrhages and exudates, and, in patients with malignant hypertension, papilledema. Examination of the heart may reveal a loud second heart sound due to closure of the aortic valve and an S_4 gallop attributed to atrial contraction against a noncompliant left ventricle. Left ventricular hypertrophy may be detected by an enlarged, sustained, and laterally displaced apical impulse. An abdominal bruit, particularly a bruit that lateralizes and extends throughout systole into diastole, raises the possibility of renovascular hypertension. Kidneys of patients with polycystic kidney disease may be palpable in the abdomen. The physical examination also should include evaluation for signs of CHF and a neurologic examination.

LABORATORY TESTING

Table 298-6 lists recommended laboratory tests in the initial evaluation of hypertensive patients. Repeat measurements of renal function, serum electrolytes, fasting glucose, and lipids may be obtained

after the introduction of a new antihypertensive agent and then annually or more frequently if clinically indicated. More extensive laboratory testing is appropriate for patients with apparent drug-resistant hypertension or when the clinical evaluation suggests a secondary form of hypertension.

TREATMENT HYPERTENSION

LIFESTYLE INTERVENTIONS

Implementation of lifestyles that favorably affect blood pressure has implications for both the prevention and the treatment of hypertension. Health-promoting lifestyle modifications are recommended for individuals with prehypertension and as an adjunct to drug therapy in hypertensive individuals. These interventions should address overall cardiovascular disease risk. Although the impact of lifestyle interventions on blood pressure is more pronounced in persons with hypertension, in short-term trials, weight loss and reduction of dietary NaCl have been shown to prevent the development of hypertension. In hypertensive individuals, even if these interventions do not produce a sufficient reduction in blood pressure to avoid drug therapy, the number of medications or doses required for blood pressure control may be reduced. Dietary modifications that effectively lower blood pressure are weight loss, reduced NaCl intake, increased potassium intake, moderation of alcohol consumption, and an overall healthy dietary pattern (**Table 298-7**).

Prevention and treatment of obesity are important for reducing blood pressure and cardiovascular disease risk. In short-term trials, even modest weight loss can lead to a reduction of blood pressure and an increase in insulin sensitivity. Average blood pressure reductions of 6.3/3.1 mmHg have been observed with a reduction in mean body weight of 9.2 kg. Regular physical activity facilitates weight loss, decreases blood pressure, and reduces the overall risk of cardiovascular disease. Blood pressure may be lowered by 30 min of moderately intense physical activity, such as brisk walking, 6–7 days a week, or by more intense, less frequent workouts.

There is individual variability in the sensitivity of blood pressure to NaCl, and this variability may have a genetic basis. Based on results of meta-analyses, lowering of blood pressure by limiting daily NaCl intake to 4.4–7.4 g (75–125 meq) results in blood pressure reductions of 3.7–4.9/0.9–2.9 mmHg in hypertensive individuals and lesser reductions in normotensive individuals. Several long-term, prospective, randomized clinical trials have reported that a reduced salt intake results in a decreased incidence of cardiovascular events. Although reduced salt intakes are generally recommended for both the prevention and treatment of hypertension, overly rigorous salt restriction may have adverse cardiovascular outcomes in diabetic patients and in patients with CHF aggressively treated with diuretics. Potassium and calcium supplementation have inconsistent, modest antihypertensive effects, and, independent of blood pressure, potassium supplementation may be associated with reduced stroke mortality. Consuming three or more alcoholic drinks per day (a standard drink contains ~14 g ethanol) is associated with higher blood pressures, and a reduction of alcohol consumption is associated with a

TABLE 298-7 LIFESTYLE MODIFICATIONS TO MANAGE HYPERTENSION

Weight reduction	Attain and maintain BMI <25 kg/m ²
Dietary salt reduction	<6 g NaCl/d
Adapt DASH-type dietary plan	Diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat
Moderation of alcohol consumption	For those who drink alcohol, consume ≤2 drinks/day in men and ≤1 drink/day in women
Physical activity	Regular aerobic activity, e.g., brisk walking for 30 min/d

Abbreviations: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension (trial).

TABLE 298-6 BASIC LABORATORY TESTS FOR INITIAL EVALUATION

System	Test
Renal	Microscopic urinalysis, albumin excretion, serum BUN and/or creatinine
Endocrine	Serum sodium, potassium, calcium, ?TSH
Metabolic	Fasting blood glucose, total cholesterol, HDL and LDL (often computed) cholesterol, triglycerides
Other	Hematocrit, electrocardiogram

Abbreviations: BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.

reduction of blood pressure. In patients with advanced renal disease, dietary protein restriction may have a modest effect in mitigating renal damage by reducing the intrarenal transmission of systemic arterial pressure.

The DASH (Dietary Approaches to Stop Hypertension) trial convincingly demonstrated that over an 8-week period a diet high in fruits, vegetables, and low-fat dairy products lowers blood pressure in individuals with high-normal blood pressures or mild hypertension. Reduction of daily NaCl intake to <6 g (100 meq) augmented the effect of this diet on blood pressure. Fruits and vegetables are enriched sources of potassium, magnesium, and fiber, and dairy products are an important source of calcium.

PHARMACOLOGIC THERAPY

Drug therapy is recommended for individuals with blood pressures $\geq 140/90$ mmHg. The degree of benefit derived from antihypertensive agents is related to the magnitude of the blood pressure reduction. Lowering systolic blood pressure by 10–12 mmHg and diastolic blood pressure by 5–6 mmHg confers relative risk reductions of 35–40% for stroke and 12–16% for CHD within 5 years of the initiation of treatment. Risk of heart failure is reduced by >50%. Hypertension control is the single most effective intervention for slowing the rate of progression of hypertension-related kidney disease.

There is considerable variation in individual responses to different classes of antihypertensive agents, and the magnitude of response to any single agent may be limited by activation of counter-regulatory mechanisms. Most available agents reduce systolic blood pressure by 7–13 mmHg and diastolic blood pressure by 4–8 mmHg when corrected for placebo effect. More often than not, combinations of agents, with complementary antihypertensive mechanisms, are required to achieve goal blood pressure reductions. Selection of antihypertensive agents and combinations of agents should be individualized, taking into account age, severity of hypertension, other cardiovascular disease risk factors, comorbid conditions, and practical considerations related to cost, side effects, and frequency of dosing (**Table 298-8**).

Diuretics Low-dose thiazide diuretics may be used alone or in combination with other antihypertensive drugs. Thiazides inhibit the Na^+/Cl^- pump in the distal convoluted tubule and hence increase sodium excretion. In the long term, they also may act as vasodilators. Thiazides are safe, efficacious, inexpensive, and reduce clinical events. They provide additive blood pressure-lowering effects when combined with beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs). In contrast, addition of a diuretic to a calcium channel blocker is less effective. Usual doses of hydrochlorothiazide range from 6.25–50 mg/d. Owing to an increased incidence of metabolic side effects (hypokalemia, insulin resistance, increased cholesterol), higher doses generally are not recommended. Chlorthalidone is a diuretic structurally similar to hydrochlorothiazide, and like hydrochlorothiazide, it blocks sodium-chloride cotransport in the early distal tubule. However, chlorthalidone has a longer half-life (40–60 h vs. 9–15 h) and an antihypertensive potency ~1.5–2.0 times that of hydrochlorothiazide. Potassium loss is also greater with chlorthalidone. Two potassium-sparing diuretics, amiloride and triamterene, act by inhibiting epithelial sodium channels in the distal nephron. These agents are weak antihypertensive agents but may be used in combination with a thiazide to protect against hypokalemia. The main pharmacologic target for loop diuretics is the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter in the thick ascending limb of the loop of Henle. Loop diuretics generally are reserved for hypertensive patients with reduced glomerular filtration rates (reflected in serum creatinine $>220 \mu\text{mol/L}$ [$>2.5 \text{ mg/dL}$]), CHF, or sodium retention and edema for some other reason, such as treatment with a potent vasodilator, e.g., minoxidil.

Blockers of the Renin–Angiotensin System ACEIs decrease the production of angiotensin II, increase bradykinin levels, and reduce sympathetic nervous system activity. ARBs provide selective blockade of AT₁

receptors, and the effect of angiotensin II on unblocked AT₂ receptors may augment their hypotensive effect. Both classes of agents are effective antihypertensive agents that may be used as monotherapy or in combination with diuretics, calcium antagonists, and alpha blocking agents. ACEIs and ARBs improve insulin action and ameliorate the adverse effects of diuretics on glucose metabolism. Although the overall impact on the incidence of diabetes is modest, compared with amlodipine (a calcium antagonist), valsartan (an ARB) has been shown to reduce the risk of developing diabetes in high-risk hypertensive patients. ACEI/ARB combinations are less effective in lowering blood pressure than is the case when either class of these agents is used in combination with other classes of agents. In patients with vascular disease or a high risk of diabetes, combination ACEI/ARB therapy has been associated with more adverse events (e.g., cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure) without increases in benefit.

Side effects of ACEIs and ARBs include functional renal insufficiency due to efferent renal arteriolar dilation in a kidney with a stenotic lesion of the renal artery. Additional predisposing conditions to renal insufficiency induced by these agents include dehydration, CHF, and use of nonsteroidal anti-inflammatory drugs. Dry cough occurs in ~15% of patients, and angioedema occurs in <1% of patients taking ACEIs. Angioedema occurs most commonly in individuals of Asian origin and more commonly in African Americans than in whites. Hyperkalemia due to hypoaldosteronism is an occasional side effect of both ACEIs and ARBs.

An alternative approach to blocking the renin-angiotensin system has recently been introduced into clinical practice for the treatment of hypertension: direct renin inhibitors. Blockade of the renin-angiotensin system is more complete with renin inhibitors than with ACEIs or ARBs. Aliskiren is the first of a class of oral, nonpeptide competitive inhibitors of the enzymatic activity of renin. Monotherapy with aliskiren seems to be as effective as an ACEI or ARB for lowering blood pressure, but not more effective. Further blood reductions may be achieved when aliskiren is used in combination with a thiazide diuretic or a calcium antagonist. Currently, aliskiren is not considered a first-line antihypertensive agent.

Aldosterone Antagonists Spironolactone is a nonselective aldosterone antagonist that may be used alone or in combination with a thiazide diuretic. It may be a particularly effective agent in patients with low-renin primary hypertension, resistant hypertension, and primary aldosteronism. In patients with CHF, low-dose spironolactone reduces mortality and hospitalizations for heart failure when given in addition to conventional therapy with ACEIs, digoxin, and loop diuretics. Because spironolactone binds to progesterone and androgen receptors, side effects may include gynecomastia, impotence, and menstrual abnormalities. These side effects are circumvented by a newer agent, eplerenone, which is a selective aldosterone antagonist.

Beta Blockers β -Adrenergic receptor blockers lower blood pressure by decreasing cardiac output, due to a reduction of heart rate and contractility. Other proposed mechanisms by which beta blockers lower blood pressure include a central nervous system effect and inhibition of renin release. Beta blockers are particularly effective in hypertensive patients with tachycardia, and their hypotensive potency is enhanced by coadministration with a diuretic. In lower doses, some beta blockers selectively inhibit cardiac β_1 receptors and have less influence on β_2 receptors on bronchial and vascular smooth muscle cells; however, there seems to be no difference in the antihypertensive potencies of cardioselective and nonselective beta blockers. Some beta blockers have intrinsic sympathomimetic activity, although it is uncertain whether this constitutes an overall advantage or disadvantage in cardiac therapy. Beta blockers without intrinsic sympathomimetic activity decrease the rate of sudden death, overall mortality, and recurrent myocardial infarction. In patients with CHF, beta blockers have been shown to reduce the risks of hospitalization and mortality. Overall, beta blockers

TABLE 298-8 EXAMPLES OF ORAL DRUGS USED IN TREATMENT OF HYPERTENSION

Drug Class	Examples	Usual Total Daily Dose ^a (Dosing Frequency/Day)	Other Indications	Contraindications/Cautions
Diuretics				
Thiazides	Hydrochlorothiazide Chlorthalidone	6.25–50 mg (1–2) 25–50 mg (1)		Diabetes, dyslipidemia, hyperuricemia, gout, hypokalemia
Loop diuretics	Furosemide Ethacrynic acid	40–80 mg (2–3) 50–100 mg (2–3)	CHF due to systolic dysfunction, renal failure	Diabetes, dyslipidemia, hyperuricemia, gout, hypokalemia
Aldosterone antagonists	Spironolactone Eplerenone	25–100 mg (1–2) 50–100 mg (1–2)	CHF due to systolic dysfunction, primary aldosteronism	Renal failure, hyperkalemia
K ⁺ retaining	Amiloride Triamterene	5–10 mg (1–2) 50–100 mg (1–2)		Renal failure, hyperkalemia
Beta blockers				
Cardioselective	Atenolol	25–100 mg (1)	Angina, CHF due to systolic dysfunction, post-MI, sinus tachycardia, ventricular tachyarrhythmias	Asthma, COPD, 2nd- or 3rd-degree heart block, sick-sinus syndrome
Nonselective	Metoprolol Propranolol Propranolol LA	25–100 mg (1–2) 40–160 mg (2) 60–180 (1)		
Combined alpha/beta	Labetalol Carvedilol	200–800 mg (2) 12.5–50 mg (2)	?Post-MI, CHF	
Alpha antagonists				
Selective	Prazosin Doxazosin Terazosin	2–20 mg (2–3) 1–16 mg (1) 1–10 mg (1–2)	Prostatism	
Nonselective	Phenoxybenzamine	20–120 mg (2–3)	Pheochromocytoma	
Sympatholytics				
Central	Clonidine Clonidine patch Methyldopa Reserpine Guanfacine	0.1–0.6 mg (2) 0.1–0.3 mg (1/week) 250–1000 mg (2) 0.05–0.25 mg (1) 0.5–2 mg (1)		
ACE inhibitors	Captopril Lisinopril Ramipril	25–200 mg (2) 10–40 mg (1) 2.5–20 mg (1–2)	Post-MI, coronary syndromes, CHF with low ejection fraction, nephropathy	Acute renal failure, bilateral renal artery stenosis, pregnancy, hyperkalemia
Angiotensin II antagonists	Losartan Valsartan Candesartan	25–100 mg (1–2) 80–320 mg (1) 2–32 mg (1–2)	CHF with low ejection fraction, nephropathy, ACE inhibitor cough	Renal failure, bilateral renal artery stenosis, pregnancy, hyperkalemia
Renin inhibitors	A lisinopril	150–300 mg (1)	Diabetic nephropathy	Pregnancy
Calcium antagonists				
Dihydropyridines	Nifedipine (long-acting)	30–60 mg (1)		
Nondihydropyridines	Verapamil (long-acting) Diltiazem (long-acting)	120–360 mg (1–2) 180–420 mg (1)	Post-MI, supraventricular tachycardias, angina	2nd- or 3rd-degree heart block
Direct vasodilators	Hydralazine Minoxidil	25–100 mg (2) 2.5–80 mg (1–2)		Severe coronary artery disease

^aAt the initiation of therapy, lower doses may be preferable for elderly patients and for select combinations of antihypertensive agents.

Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

may be less protective against cardiovascular and cerebrovascular endpoints, and some beta blockers may have less effect on central aortic pressure than other classes of antihypertensive agents. However, beta blockers remain appropriate therapy for hypertensive patients with concomitant heart disease and related comorbidities. Carvedilol and labetalol block both β receptors and peripheral α -adrenergic receptors. The potential advantages of combined β - and α -adrenergic blockade in treating hypertension remain to be determined. Nebivolol represents another class of cardioselective beta blockers that has additional vasodilator actions related to enhancement of nitric oxide activity. Whether this confers greater clinical effectiveness remains to be determined.

α -Adrenergic Blockers Postsynaptic, selective α -adrenoreceptor antagonists lower blood pressure by decreasing peripheral vascular resistance. They are effective antihypertensive agents used either as monotherapy or in combination with other agents. However, in clinical trials of hypertensive patients, alpha blockade has not been shown to reduce cardiovascular morbidity and mortality or to provide as much protection against CHF as other classes of antihypertensive agents. These agents are also effective in treating lower urinary tract symptoms in men with prostatic hypertrophy. Nonselective α -adrenoreceptor antagonists bind to postsynaptic and presynaptic receptors and are used primarily for the management of patients with pheochromocytoma.

Sympatholytic Agents Centrally acting α_2 sympathetic agonists decrease peripheral resistance by inhibiting sympathetic outflow. They may be particularly useful in patients with autonomic neuropathy who have wide variations in blood pressure due to baroreceptor denervation. Drawbacks include somnolence, dry mouth, and rebound hypertension on withdrawal. Peripheral sympatholytics decrease peripheral resistance and venous constriction by depleting nerve terminal norepinephrine. Although they are potentially effective antihypertensive agents, their usefulness is limited by orthostatic hypotension, sexual dysfunction, and numerous drug-drug interactions. Rebound hypertension is another concern with abrupt cessation of drugs with a short half-life.

Calcium Channel Blockers Calcium antagonists reduce vascular resistance through L-channel blockade, which reduces intracellular calcium and blunts vasoconstriction. This is a heterogeneous group of agents that includes drugs in the following three classes: phenylalkylamines (verapamil), benzothiazepines (diltiazem), and 1,4-dihydropyridines (nifedipine-like). Used alone and in combination with other agents (ACEIs, beta blockers, α_1 -adrenergic blockers), calcium antagonists effectively lower blood pressure; however, it is unclear if adding a diuretic to a calcium blocker results in a further lowering of blood pressure. Side effects of flushing, headache, and edema with dihydropyridine use are related to their potencies as arteriolar dilators; edema is due to an increase in transcapillary pressure gradients, not to net salt and water retention.

Direct Vasodilators Direct vasodilators decrease peripheral resistance and concomitantly activate mechanisms that defend arterial pressure, notably the sympathetic nervous system, the renin-angiotensin-aldosterone system, and sodium retention. Usually, they are not considered first-line agents but are most effective when added to a combination that includes a diuretic and a beta blocker. Hydralazine is a potent direct vasodilator that has antioxidant and nitric oxide-enhancing actions, and minoxidil is a particularly potent agent and is used most frequently in patients with renal insufficiency who are refractory to all other drugs. Hydralazine may induce a lupus-like syndrome, and side effects of minoxidil include hypertrichosis and pericardial effusion. Intravenous nitroprusside can be used to treat malignant hypertension and life-threatening left ventricular heart failure associated with elevated arterial pressure.

COMPARISONS OF ANTIHYPERTENSIVES

Based on pooling results from clinical trials, meta-analyses of the efficacy of different classes of antihypertensive agents suggest essentially equivalent blood pressure-lowering effects of the following six major classes of antihypertensive agents when used as monotherapy: thiazide diuretics, beta blockers, ACEIs, ARBs, calcium antagonists, and α_1 blockers. On average, standard doses of most antihypertensive agents reduce blood pressure by 8–10/4–7 mmHg; however, there may be subgroup differences in responsiveness. Younger patients may be more responsive to beta blockers and ACEIs, whereas patients over age 50 may be more responsive to diuretics and calcium antagonists. There is a limited relationship between plasma renin and blood pressure response. Patients with high-renin hypertension may be more responsive to ACEIs and ARBs than to other classes of agents, whereas patients with low-renin hypertension are more responsive to diuretics and calcium antagonists. Hypertensive African Americans tend to have low renin and may require higher doses of ACEIs and ARBs than whites for optimal blood pressure control, although this difference is abolished when these agents are combined with a diuretic. Beta blockers also appear to be less effective than thiazide diuretics in African Americans than in non-African Americans. Early pharmacogenetic studies, utilizing either a candidate gene approach or genome-wide scans, have shown associations of gene polymorphisms with blood pressure responsiveness to specific antihypertensive drugs. However, the reported effects have generally been too small to affect clinical decisions, and associated polymorphisms remain to be confirmed.

Currently, in practical terms, the presence of comorbidities often influences the selection of antihypertensive agents.

A meta-analysis of more than 30 randomized trials of blood pressure-lowering therapy indicates that for a given reduction in blood pressure, the major drug classes seem to produce similar overall net effects on total cardiovascular events. In both non-diabetic and diabetic hypertensive patients, most trials have failed to show significant differences in cardiovascular outcomes with different drug regimens as long as equivalent decreases in blood pressure were achieved. For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that the occurrence of CHD and nonfatal myocardial infarction, as well as overall mortality, was virtually identical in hypertensive patients treated with either an ACEI (lisinopril), a diuretic (chlorthalidone), or a calcium antagonist (amlodipine).

However, in specific patient groups, ACEIs may have particular advantages, beyond that of blood pressure control, in reducing cardiovascular and renal outcomes. ACEIs and ARBs decrease intraglomerular pressure and proteinuria and may retard the rate of progression of renal insufficiency, not totally accounted for by their hypotensive effects, in both diabetic and nondiabetic renal diseases. In patients with type 2 diabetes, treatment with an ACEI, an ARB, or aliskiren decreases proteinuria and delays the progression of renal disease. In experimental models of hypertension and diabetes, renal protection with aliskiren is comparable to that with ACEIs and ARBs. However, in patients with type 2 diabetes, addition of aliskiren to an ACEI provides no additional protection against cardiovascular or renal disease and may be associated with more adverse outcomes. Among African Americans with hypertension-related renal disease, ACEIs appear to be more effective than beta blockers or dihydropyridine calcium channel blockers in slowing, although not preventing, the decline of glomerular filtration rate. The renoprotective effect of these renin-angiotensin blockers, compared with other antihypertensive drugs, is less obvious at lower blood pressures. In most patients with hypertension and heart failure due to systolic and/or diastolic dysfunction, the use of diuretics, ACEIs or ARBs, and beta blockers is recommended to improve survival. Independent of blood pressure, in both hypertensive and normotensive individuals, ACEIs attenuate the development of left ventricular hypertrophy, improve symptomatology and risk of death from CHF, and reduce morbidity and mortality rates in post-myocardial infarction patients. Similar benefits in cardiovascular morbidity and mortality rates in patients with CHF have been observed with the use of ARBs. ACEIs provide better coronary protection than do calcium channel blockers, whereas calcium channel blockers provide more stroke protection than do either ACEIs or beta blockers. Results of a large, double-blind, prospective clinical trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension [ACCOMPLISH Trial]) indicated that combination treatment with an ACEI (benazepril) plus a calcium antagonist (amlodipine) was superior to treatment with the ACEI plus a diuretic (hydrochlorothiazide) in reducing the risk of cardiovascular events and death among high-risk patients with hypertension. However, the combination of an ACEI and a diuretic has recently been shown to produce major reductions in morbidity and mortality in the very elderly.

After a stroke, combination therapy with an ACEI and a diuretic, but not with an ARB, has been reported to reduce the rate of recurrent stroke. Some of these apparent differences may reflect differences in trial design and/or patient groups.

There is a recent resurgence of interest in two nonpharmacologic, antihypertensive therapies that interrupt sympathetic outflow: (1) device-based carotid baroreflex activation by electrical stimulation of the carotid sinus; and (2) endovascular radiofrequency ablation of the renal sympathetic nerves. Whereas renal denervation is a minimally invasive procedure, carotid baroreceptor stimulation is a surgical procedure, usually performed under general anesthesia, that currently involves implanting electrodes on both the right and left carotid arteries. Both interventions inhibit sympathetic drive and

1626 decrease blood pressure by increasing the capacity of the kidney to excrete sodium and by decreasing renin release. Sustained activation of the baroreflex most likely lowers blood pressure by other mechanisms as well. Clinical experience with these interventions is limited. In the short term, blood pressure is lowered in 75–80% of patients, and the magnitude of the blood pressure reduction is similar for both procedures. To date, the most impressive results have been observed in patients with “resistant” hypertension and patients with obesity-related hypertension. Awaiting the results of long-term, multicenter clinical trials to evaluate their efficacy and safety, it remains to be seen whether these interventions will be adopted into clinical practice.

PART 10

Disorders of the Cardiovascular System

BLOOD PRESSURE GOALS OF ANTIHYPERTENSIVE THERAPY

Based on clinical trial data, the maximum protection against combined cardiovascular endpoints is achieved with pressures <135–140 mmHg for systolic blood pressure and <80–85 mmHg for diastolic blood pressure; however, treatment has not reduced cardiovascular disease risk to the level in nonhypertensive individuals. In diabetic patients, effective blood pressure control reduces the risk of cardiovascular events and death as well as the risk for microvascular disease (nephropathy, retinopathy). Although guidelines for hypertension control have recommended more aggressive blood pressure targets (e.g., office or clinic blood pressure <130/80 mmHg) for patients with diabetes, CHD, chronic kidney disease, or additional cardiovascular disease risk factors, recent evidence suggests that overly aggressive targets for blood pressure control may not be advantageous, particularly in high-risk patients. For example, among hypertensive patients with diabetes and coronary heart disease, “tight control” of systolic blood pressure (<130 mmHg) is not associated with improved cardiovascular outcomes. The concept of a “J-curve” suggests that the risk of cardiovascular events increases at blood pressures that are either too high or too low. Theoretically blood pressures that are too low may exceed the autoregulatory capacity of cerebral, coronary, and renal blood flows. There is some suggestive evidence from recent randomized clinical trials for a J-shaped relationship between blood pressure and cardiovascular outcomes (including all-cause mortality) in high-risk patients. Consequently, caution should be exercised in lowering blood pressure <130/80 mmHg in patients with diabetes, CHD, and other high-risk patients. In patients with chronic renal insufficiency, a small, nonprogressive increase in the serum creatinine concentration may occur. This generally reflects a hemodynamic response, not structural renal injury, indicating that intraglomerular pressure has been reduced. Blood pressure control should not be allowed to deteriorate in order to prevent the modest creatinine rise. Among older patients with isolated systolic hypertension, further lowering of diastolic blood pressure does not result in harm. However, relatively little information is available concerning the risk-versus-benefit ratio of antihypertensive therapy in individuals >80 years of age, and in this population, gradual blood pressure reduction to a less aggressive target level of control may be appropriate.

To achieve recommended blood pressure goals, the majority of individuals with hypertension will require treatment with more than one drug. Three or more drugs frequently are needed in patients with diabetes and renal insufficiency. For most agents, reduction of blood pressure at half-standard doses is only ~20% less than at standard doses. Appropriate combinations of agents at these lower doses may have additive or almost additive effects on blood pressure with a lower incidence of side effects.

The term *resistant hypertension* refers to patients with blood pressures persistently >140/90 mmHg despite taking three or more antihypertensive agents, including a diuretic. Resistant or difficult-to-control hypertension is more common in patients >60 years than in younger patients. Resistant hypertension may be related to “pseudoresistance” (high office blood pressures and lower home blood pressures), nonadherence to therapy, identifiable causes of hypertension (including obesity and excessive alcohol intake), and the use of any of a number of nonprescription and prescription

drugs (Table 298-3). Rarely, in older patients, pseudohypertension may be related to the inability to measure blood pressure accurately in severely sclerotic arteries. This condition is suggested if the radial pulse remains palpable despite occlusion of the brachial artery by the cuff (Osler maneuver). The actual blood pressure can be determined by direct intra-arterial measurement. Evaluation of patients with resistant hypertension might include home blood pressure monitoring to determine if office blood pressures are representative of the usual blood pressure. A more extensive evaluation for a secondary form of hypertension should be undertaken if no other explanation for hypertension resistance becomes apparent.

HYPERTENSIVE EMERGENCIES

Probably due to the widespread availability of antihypertensive therapy, in the United States there has been a decline in the numbers of patients presenting with “crisis levels” of blood pressure. Most patients who present with severe hypertension are chronically hypertensive, and in the absence of acute end organ damage, precipitous lowering of blood pressure may result in significant morbidity and should be avoided. The key to successful management of severe hypertension is to differentiate hypertensive crises from hypertensive urgencies. The degree of target organ damage, rather than the level of blood pressure alone, determines the rapidity with which blood pressure should be lowered. **Tables 298-9 and 298-10** list a number of hypertension-related emergencies and recommended therapies.

Malignant hypertension is a syndrome associated with an abrupt increase of blood pressure in a patient with underlying hypertension or related to the sudden onset of hypertension in a previously normotensive individual. The absolute level of blood pressure is not as important as its rate of rise. Pathologically, the syndrome is associated with diffuse necrotizing vasculitis, arteriolar thrombi, and fibrin deposition in arteriolar walls. Fibrinoid necrosis has been observed in arterioles of kidney, brain, retina, and other organs. Clinically, the syndrome is recognized by progressive retinopathy (arteriolar spasm, hemorrhages, exudates, and papilledema), deteriorating renal function with proteinuria, microangiopathic hemolytic anemia, and encephalopathy. Historic inquiry should include questions about the use of monoamine oxidase inhibitors and recreational drugs (e.g., cocaine, amphetamines).

Although blood pressure should be lowered rapidly in patients with hypertensive encephalopathy, there are inherent risks of overly aggressive therapy. In hypertensive individuals, the upper and lower limits of autoregulation of cerebral blood flow are shifted to higher levels of arterial pressure, and rapid lowering of blood pressure to below the lower limit of autoregulation may precipitate cerebral ischemia or infarction as a consequence of decreased cerebral blood flow. Renal and coronary blood flows also may decrease with overly aggressive acute therapy. The initial goal of therapy is to reduce

TABLE 298-9 PREFERRED PARENTERAL DRUGS FOR SELECTED HYPERTENSIVE EMERGENCIES

Hypertensive encephalopathy	Nitroprusside, nicardipine, labetalol
Malignant hypertension (when IV therapy is indicated)	Labetalol, nicardipine, nitroprusside, enalaprilat
Stroke	Nicardipine, labetalol, nitroprusside
Myocardial infarction/unstable angina	Nitroglycerin, nicardipine, labetalol, esmolol
Acute left ventricular failure	Nitroglycerin, enalaprilat, loop diuretics
Aortic dissection	Nitroprusside, esmolol, labetalol
Adrenergic crisis	Phentolamine, nitroprusside
Postoperative hypertension	Nitroglycerin, nitroprusside, labetalol, nicardipine
Preeclampsia/eclampsia of pregnancy	Hydralazine, labetalol, nicardipine

Source: Adapted from DG Vidy, in S Oparil, MA Weber (eds): *Hypertension*, 2nd ed. Philadelphia, Elsevier Saunders, 2005.

TABLE 298-10 USUAL INTRAVENOUS DOSES OF ANTIHYPERTENSIVE AGENTS USED IN HYPERTENSIVE EMERGENCIES^a

Antihypertensive Agent	Intravenous Dose
Nitroprusside	Initial 0.3 ($\mu\text{g}/\text{kg}$)/min; usual 2–4 ($\mu\text{g}/\text{kg}$)/min; maximum 10 ($\mu\text{g}/\text{kg}$)/min for 10 min
Nicardipine	Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h
Labetalol	2 mg/min up to 300 mg or 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total
Enalaprilat	Usual 0.625–1.25 mg over 5 min every 6–8 h; maximum 5 mg/dose
Esmolol	Initial 80–500 $\mu\text{g}/\text{kg}$ over 1 min, then 50–300 ($\mu\text{g}/\text{kg}$)/min
Phentolamine	5–15 mg bolus
Nitroglycerin	Initial 5 $\mu\text{g}/\text{min}$, then titrate by 5 $\mu\text{g}/\text{min}$ at 3–5-min intervals; if no response is seen at 20 $\mu\text{g}/\text{min}$, incremental increases of 10–20 $\mu\text{g}/\text{min}$ may be used
Hydralazine	10–50 mg at 30-min intervals

^aConstant blood pressure monitoring is required. Start with the lowest dose. Subsequent doses and intervals of administration should be adjusted according to the blood pressure response and duration of action of the specific agent.

mean arterial blood pressure by no more than 25% within minutes to 2 h or to a blood pressure in the range of 160/100–110 mmHg. This may be accomplished with IV nitroprusside, a short-acting vasodilator with a rapid onset of action that allows for minute-to-minute control of blood pressure. Parenteral labetalol and nicardipine are also effective agents for the treatment of hypertensive encephalopathy.

In patients with malignant hypertension without encephalopathy or another catastrophic event, it is preferable to reduce blood pressure over hours or longer rather than minutes. This goal may effectively be achieved initially with frequent dosing of short-acting oral agents such as captopril, clonidine, and labetalol.

Acute, transient blood pressure elevations that last days to weeks frequently occur after thrombotic and hemorrhagic strokes. Autoregulation of cerebral blood flow is impaired in ischemic cerebral tissue, and higher arterial pressures may be required to maintain cerebral blood flow. Although specific blood pressure targets have not been defined for patients with acute cerebrovascular events, aggressive reductions of blood pressure are to be avoided. With the increasing availability of improved methods for measuring cerebral blood flow (using CT technology), studies are in progress to evaluate the effects of different classes of antihypertensive agents on both blood pressure and cerebral blood flow after an acute stroke. Currently, in the absence of other indications for acute therapy, for patients with cerebral infarction who are not candidates for thrombolytic therapy, one recommended guideline is to institute antihypertensive therapy only for patients with a systolic blood pressure >220 mmHg or a diastolic blood pressure >130 mmHg. If thrombolytic therapy is to be used, the recommended goal blood pressure is <185 mmHg systolic pressure and <110 mmHg diastolic pressure. In patients with hemorrhagic stroke, suggested guidelines for initiating antihypertensive therapy are systolic >180 mmHg or diastolic pressure >130 mmHg. The management of hypertension after subarachnoid hemorrhage is controversial. Cautious reduction of blood pressure is indicated if mean arterial pressure is >130 mmHg.

In addition to pheochromocytoma, an adrenergic crisis due to catecholamine excess may be related to cocaine or amphetamine overdose, clonidine withdrawal, acute spinal cord injuries, and an interaction of tyramine-containing compounds with monoamine oxidase inhibitors. These patients may be treated with phentolamine or nitroprusside.

Treatment of hypertension in patients with acute aortic dissection is discussed in Chap. 301, and treatment of hypertension in pregnancy is discussed in Chap. 8.

299

Renovascular Disease

Stephen C. Texor

The renal vasculature is unusually complex with rich arteriolar flow to the cortex in excess of metabolic requirements, consistent with its primary function as a filtering organ. After delivering blood to cortical glomeruli, the postglomerular circulation supplies deeper medullary segments that support energy-dependent solute transport at multiple levels of the renal tubule. These postglomerular vessels carry less blood, and high oxygen consumption leaves the deeper medullary regions at the margin of hypoxemia. Vascular disorders that commonly threaten the blood supply of the kidney include large-vessel atherosclerosis, fibromuscular diseases, and embolic disorders. **Microvascular injury, including inflammatory and primary hematologic disorders, is described in Chap. 341.**

The glomerular capillary endothelium shares susceptibility to oxidative stress, pressure injury, and inflammation with other vascular territories. Rates of urinary albumin excretion (UAE) are predictive of systemic atherosclerotic disease events. Increased UAE may develop years before cardiovascular events. UAE and the risk of cardiovascular events are both reduced with pharmacologic therapy such as statins. Experimental studies demonstrate functional changes and rarefaction of renal microvessels under conditions of accelerated atherosclerosis and/or compromise of proximal perfusion pressures with large-vessel disease (Fig. 299-1).

MACROVASCULAR DISEASE

Large-vessel renal artery occlusive disease can result from extrinsic compression of the vessel, fibromuscular dysplasia, or, most commonly, atherosclerotic disease. Any disorder that reduces perfusion pressure to the kidney can activate mechanisms that tend to restore renal pressures at the expense of developing systemic hypertension. Because restoration of perfusion pressures can reverse these pathways, renal artery stenosis is considered a specifically treatable “secondary” cause of hypertension.

Renal artery stenosis is common and often has only minor hemodynamic effects. Fibromuscular dysplasia (FMD) is reported in 3–5% of normal subjects presenting as potential kidney donors without hypertension. It may present clinically with hypertension in younger individuals (between age 15 and 50), most often women. FMD does not often threaten kidney function, but sometimes produces total occlusion and can be associated with renal artery aneurysms. Atherosclerotic renal artery stenosis (ARAS) is common in the general population (6.8% of a community-based sample above age 65), and the prevalence increases with age and for patients with other vascular conditions such as coronary artery disease (18–23%) and/or peripheral aortic or lower extremity disease (>30%). If untreated, ARAS progresses in nearly 50% of cases over a 5-year period, sometimes to total occlusion. Intensive treatment of arterial blood pressure and statin therapy appear to slow these rates and improve clinical outcomes.

Critical levels of stenosis lead to a reduction in perfusion pressure that activates the renin-angiotensin system, reduces sodium excretion, and activates sympathetic adrenergic pathways. These events lead to systemic hypertension characterized by angiotensin dependence in the early stages, widely varying pressures, loss of circadian blood pressure (BP) rhythms, and accelerated target organ injury, including left ventricular hypertrophy and renal fibrosis. Renovascular hypertension can be treated with agents that block the renin-angiotensin system and other drugs that modify these pressor pathways. It can also be treated with restoration of renal blood flow by either endovascular or surgical revascularization. Most patients require continued antihypertensive drug therapy because revascularization alone rarely lowers BP to normal.

ARAS and systemic hypertension tend to affect both the post-stenotic and contralateral kidneys, reducing overall glomerular filtration rate (GFR) in ARAS. When kidney function is threatened by

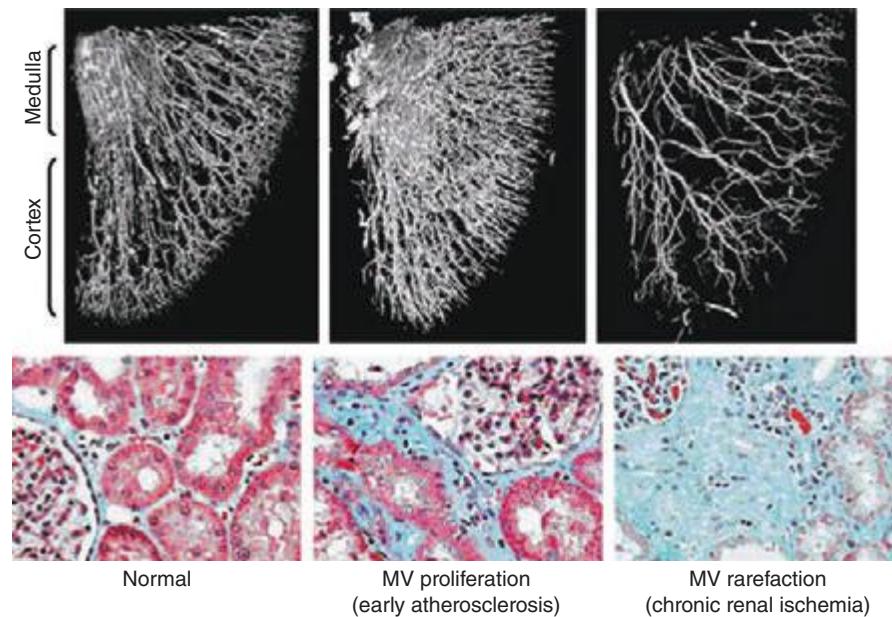


FIGURE 299-1 Examples of micro-CT images from vessels defined by radiopaque casts injected into the renal vasculature. These illustrate the complex, dense cortical capillary network supplying the kidney cortex that can either proliferate or succumb to rarefaction under the influence of atherosclerosis and/or occlusive disease. Changes in blood supply are followed by tubulointerstitial fibrosis and loss of kidney function. MV, microvascular. (From LO Lerman, AR Chade: *Curr Opin Nephrol Hyper* 18:160, 2009, with permission.)

large-vessel disease primarily, it has been labeled ischemic nephropathy. Moderately reduced blood flow that develops gradually is associated with reduced GFR and limited oxygen consumption with preserved tissue oxygenation. Hence, kidney function can remain stable during medical therapy, sometimes for years. With more advanced disease, reductions in cortical perfusion and frank tissue hypoxia develop. Unlike FMD, ARAS develops in patients with other risk factors for atherosclerosis and is commonly superimposed upon preexisting small-vessel disease in the kidney resulting from hypertension, aging, and diabetes. Nearly 85% of patients considered for renal revascularization have stage 3–5 chronic kidney disease (CKD) with GFR below 60 mL/min per 1.73 m². The presence of ARAS is a strong predictor of morbidity- and mortality-related cardiovascular events, independent of whether renal revascularization is undertaken.

Diagnostic approaches to renal artery stenosis depend partly on the specific issues to be addressed. Noninvasive characterization of the renal vasculature may be achieved by several techniques, summarized in Table 299-1. Although activation of the renin-angiotensin system is a key step in developing renovascular hypertension, it is transient. Levels of renin activity are therefore subject to timing, the effects of

drugs, and sodium intake, and do not reliably predict the response to vascular therapy. Renal artery velocities by Doppler ultrasound above 200 cm/s generally predict hemodynamically important lesions (above 60% vessel lumen occlusion), although treatment trials require velocity above 300 cm/s to avoid false positives. The renal resistive index has predictive value regarding the viability of the kidney. It remains operator- and institution-dependent, however. Captopril-enhanced renography has a strong negative predictive value when entirely normal. Magnetic resonance angiography (MRA) is now less often used, as gadolinium contrast has been associated with nephrogenic systemic fibrosis. Contrast-enhanced computed tomography (CT) with vascular reconstruction provides excellent vascular images and functional assessment, but carries a small risk of contrast toxicity.

TREATMENT RENAL ARTERY STENOSIS

While restoring renal blood flow and perfusion seems intuitively beneficial for high-grade occlusive lesions, revascularization procedures also pose hazards and expense. Patients with FMD are commonly younger females with otherwise normal vessels and a

TABLE 299-1 SUMMARY OF IMAGING MODALITIES FOR EVALUATING THE KIDNEY VASCULATURE

Perfusion Studies to Assess Differential Renal Blood Flow			
Captopril renography with technetium- ^{99m} Tc mertiatide (^{99m} Tc MAG3)	Captopril-mediated fall in filtration pressure amplifies differences in renal perfusion	Normal study excludes renovascular hypertension	Multiple limitations in patients with advanced atherosclerosis or creatinine >2.0 mg/dL (177 μmol/L)
Vascular Studies to Evaluate the Renal Arteries			
Duplex ultrasonography	Shows the renal arteries and measures flow velocity as a means of assessing the severity of stenosis	Inexpensive; widely available	Heavily dependent on operator's experience; less useful than invasive angiography for the diagnosis of fibromuscular dysplasia and abnormalities in accessory renal arteries
Magnetic resonance angiography	Shows the renal arteries and perirenal aorta	Not nephrotoxic, but concerns for gadolinium toxicity exclude use in GFR <30 mL/min/1.73 m ² ; provides excellent images	Expensive; gadolinium excluded in renal failure, unable to visualize stented vessels
Computed tomographic angiography	Shows the renal arteries and perirenal aorta	Provides excellent images; stents do not cause artifacts	Expensive, moderate volume of contrast required, potentially nephrotoxic
Intraarterial angiography	Shows location and severity of vascular lesion	Considered "gold standard" for diagnosis of large-vessel disease, usually performed simultaneous with planned intervention	Expensive, associated hazard of atheroemboli, contrast toxicity, procedure-related complications, e.g., dissection

Abbreviation: GFR, glomerular filtration rate.

long life expectancy. These patients often respond well to percutaneous renal artery angioplasty. If BP can be controlled to goal levels and kidney function remains stable in patients with ARAS, it may be argued that medical therapy with follow-up for disease progression is equally effective. Prospective trials up to now have failed to identify compelling benefits for interventional procedures regarding short-term results of BP and renal function, and long-term studies regarding cardiovascular outcomes, such as stroke, congestive heart failure, myocardial infarction, and end-stage renal failure, are not yet complete. Medical therapy should include blockade of the renin-angiotensin system, attainment of goal BPs, cessation of tobacco, statins, and aspirin. Renal revascularization is now often reserved for patients failing medical therapy or developing additional complications.

Techniques of renal revascularization are improving. With experienced operators, major complications occur in about 9% of cases, including renal artery dissection, capsular perforation, hemorrhage, and occasional atheroembolic disease. Although not common, atheroembolic disease can be catastrophic and accelerate both hypertension and kidney failure, precisely the events that revascularization is intended to prevent. Although renal blood flow usually can be restored by endovascular stenting, recovery of renal function is limited to about 25% of cases, with no change in 50% and some deterioration evident in others. Patients with rapid loss of kidney function, sometimes associated with antihypertensive drug therapy, or with vascular disease affecting the entire functioning kidney mass are more likely to recover function after restoring blood flow. When hypertension is refractory to effective therapy, revascularization offers real benefits. **Table 299-2** summarizes currently accepted guidelines for considering renal revascularization.

ATHEROEMBOLIC RENAL DISEASE

Emboli to the kidneys arise most frequently as a result of cholesterol crystals breaking free of atherosclerotic vascular plaque and lodging in downstream microvessels. Most clinical atheroembolic events follow angiographic procedures, often of the coronary vessels. It has been argued that nearly all vascular interventional procedures lead to plaque fracture and release of microemboli, but clinical manifestations develop only in a fraction of these. The incidence of clinical atheroemboli has been increasing with more vascular procedures and

longer life spans. Atheroembolic renal disease is suspected in more than 3% of elderly subjects with end-stage renal disease (ESRD) and is likely underdiagnosed. It is more frequent in males with a history of diabetes, hypertension, and ischemic cardiac disease. Atheroemboli in the kidney are strongly associated with aortic aneurysmal disease and renal artery stenosis. Most clinical cases can be linked to precipitating events, such as angiography, vascular surgery, anticoagulation with heparin, thrombolytic therapy, or trauma. Clinical manifestations of this syndrome commonly develop between 1 and 14 days after an inciting event and may continue to develop for weeks thereafter. Systemic embolic disease manifestations, such as fever, abdominal pain, and weight loss, are present in less than half of patients, although cutaneous manifestations including livedo reticularis and localized toe gangrene may be more common. Worsening hypertension and deteriorating kidney function are common, sometimes reaching a malignant phase. Progressive renal failure can occur and require dialytic support. These cases often develop after a stuttering onset over many weeks and have an ominous prognosis. Mortality rate after 1 year reaches 38%, and although some may eventually recover sufficiently to no longer require dialysis, many do not.

Beyond the clinical manifestations above, laboratory findings include rising creatinine, transient eosinophilia (60–80%), elevated sedimentation rate, and hypocomplementemia (15%). Establishing this diagnosis can be difficult and is often by exclusion. Definitive diagnosis depends on kidney biopsy demonstrating microvessel occlusion with cholesterol crystals that leave a “cleft” in the vessel. Biopsies obtained from patients undergoing surgical revascularization of the kidney indicate that silent cholesterol emboli are frequently present before any further manipulation is performed.

No effective therapy is available for atheroembolic disease once it has developed. Withdrawal of anticoagulation is recommended. Late recovery of kidney function after supportive measures sometimes occurs, and statin therapy may improve outcome. The role of embolic protection devices in the renal circulation is unclear, but a few prospective trials have failed to demonstrate major benefits. These devices are limited to distal protection during the endovascular procedure and offer no protection from embolic debris after removal.

THROMBOEMBOLIC RENAL DISEASE

Thrombotic occlusion of renal vessels or branch arteries can lead to declining renal function and hypertension. It is difficult to diagnose and is often overlooked, especially in elderly patients. Thrombosis can develop as a result of local vessel abnormalities, such as local dissection, trauma, or inflammatory vasculitis. Local microdissections sometimes lead to patchy, transient areas of infarctions labeled “segmental arteriolar mediolysis.” Although hypercoagulability conditions sometimes present as renal artery thrombosis, this is rare. It can also derive from distant embolic events, e.g., the left atrium in patients with atrial fibrillation or from fat emboli originating from traumatized tissue, most commonly large bone fractures. Cardiac sources include vegetations from subacute bacterial endocarditis. Systemic emboli to the kidneys may also arise from the venous circulation if right-to-left shunting occurs, e.g., through a patent foramen ovale.

Clinical manifestations vary depending on the rapidity of onset and extent of occlusion. Acute arterial thrombosis may produce flank pain, fever, leukocytosis, nausea, and vomiting. If kidney infarction results, enzymes such as lactate dehydrogenase (LDH) rise to extreme levels. If both kidneys are affected, renal function will decline precipitously with a drop in urine output. If a single kidney is involved, renal functional changes may be minor. Hypertension related to sudden release of renin from ischemic tissue can develop rapidly, as long as some viable tissue in the “peri-infarct” border zone remains. If the infarct zone demarcates precisely, the rise in BP and renin activity may resolve. Diagnosis of renal infarction may be established by vascular imaging with MRI, CT angiography, or arteriography (**Fig. 299-2**).

MANAGEMENT OF ARTERIAL THROMBOSIS OF THE KIDNEY

Options for interventions of newly detected arterial occlusion include surgical reconstruction, anticoagulation, thrombolytic therapy,

TABLE 299-2 CLINICAL FACTORS FAVORING MEDICAL THERAPY AND REVASCULARIZATION OR SURVEILLANCE FOR RENAL ARTERY STENOSIS

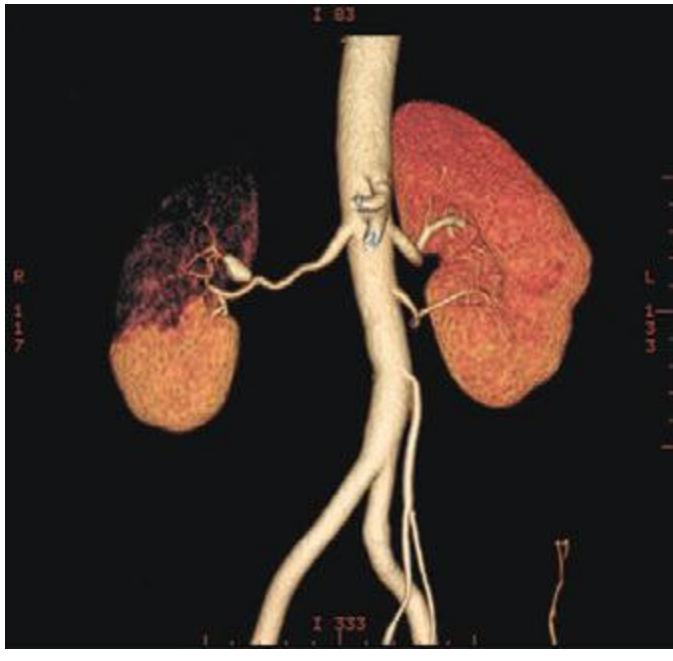
Factors Favoring Medical Therapy and Revascularization for Renal Artery Stenosis

- Progressive decline in GFR during treatment of systemic hypertension
- Failure to achieve adequate blood pressure control with optimal medical therapy (medical failure)
- Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure
- Decline in the GFR during therapy with ACE inhibitors or ARBs
- Recurrent congestive heart failure in a patient in whom the adequacy of left ventricular function does not explain a cause

Factors Favoring Medical Therapy and Surveillance of Renal Artery Disease

- Controlled blood pressure with stable renal function (e.g., stable renal insufficiency)
- Stable renal artery stenosis without progression on surveillance studies (e.g., serial duplex ultrasound)
- Very advanced age and/or limited life expectancy
- Extensive comorbidity that make revascularization too risky
- High risk for or previous experience with atheroembolic disease
- Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g., interstitial nephritis, diabetic nephropathy)

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate.



A



B

FIGURE 299-2 **A.** CT angiogram illustrating loss of circulation to the upper pole of the right kidney in a patient with fibromuscular disease and a renal artery aneurysm. Activation of the renin-angiotensin system produced rapidly developing hypertension. **B.** Angiogram illustrating high-grade renal artery stenosis affecting the left kidney. This lesion is often part of widespread atherosclerosis and sometimes is an extension of aortic plaque. This lesion develops in older individuals with preexisting atherosclerotic risk factors.

endovascular procedures, and supportive care, particularly antihypertensive drug therapy. Application of these methods depends on the patient's overall condition, the precipitating factors (e.g., local trauma or systemic illness), the magnitude of renal tissue and function at risk, and the likelihood of recurrent events in the future. For unilateral disease, e.g., arterial dissection with thrombosis, supportive care with anticoagulation may suffice. Acute, bilateral occlusion is potentially catastrophic, producing anuric renal failure. Depending on the precipitating event, surgical or thrombolytic therapies can sometimes restore kidney viability.

MICROVASCULAR INJURY ASSOCIATED WITH HYPERTENSION

ARTERIOLONEPHROSCLEROSIS

"Malignant" Hypertension Although BP rises with age, it has long been recognized that some individuals develop rapidly progressive BP elevations with target organ injury including retinal hemorrhages, encephalopathy, and declining kidney function. Placebo arms during the controlled trials of hypertension therapy identified progression to severe levels in 20% of subjects over 5 years. If untreated, patients with target organ injury including papilledema and declining kidney function suffered mortality rates in excess of 50% over 6–12 months, hence the designation "malignant." Postmortem studies of such patients identified vascular lesions, designated "fibrinoid necrosis," with breakdown of the vessel wall, deposition of eosinophilic material including fibrin, and a perivascular cellular infiltrate. A separate lesion was identified in the larger interlobular arteries in many patients with hyperplastic proliferation of the vascular wall cellular elements, deposition of collagen, and separation of layers, designated the "onionskin" lesion. For many of these patients, fibrinoid necrosis led to obliteration of glomeruli and loss of tubular structures. Progressive kidney failure ensued and, without dialysis support, led to early mortality in untreated malignant-phase hypertension. These vascular changes could develop with pressure-related injury from a variety of hypertensive pathways, including but not limited to activation of the renin-angiotensin system and severe vasospasm associated with catecholamine release. Occasionally, endothelial injury is sufficient to induce microangiopathic hemolysis, as discussed below.

Antihypertensive therapy is the mainstay of therapy for malignant hypertension. With effective BP reduction, manifestations of vascular

injury including microangiopathic hemolysis and renal dysfunction can improve over time. Whereas series reported before the era of drug therapy suggested that 1-year mortality rates exceeded 90%, current survival over 5 years exceeds 50%.

Malignant hypertension is less common in Western countries, although it persists in parts of the world where medical care and antihypertensive drug therapy are less available. It most commonly develops in patients with treated hypertension who neglect to take medications or who may use vasospastic drugs, such as cocaine. Renal abnormalities typically include rising serum creatinine and occasionally hematuria and proteinuria. Biochemical findings may include evidence of hemolysis (anemia, schistocytes, and reticulocytosis) and changes associated with kidney failure. African-American males are more likely to develop rapidly progressive hypertension and kidney failure than are whites in the United States. Genetic polymorphisms (first identified as *MYH9*, but now thought to be *APOL1*) that are common in the African-American population predispose to subtle focal sclerosing glomerular disease, with severe hypertension developing at younger ages secondary to renal disease in this instance.

Hypertensive Nephrosclerosis Based on experience with malignant hypertension and epidemiologic evidence linking BP with long-term risks of kidney failure, it has long been assumed that lesser degrees of hypertension induce less severe, but prevalent, changes in kidney vessels and loss of kidney function. As a result, a large portion of patients reaching ESRD without a specific etiologic diagnosis are assigned the designation "hypertensive nephrosclerosis." Pathologic examination commonly identifies afferent arteriolar thickening with deposition of homogeneous eosinophilic material (hyaline arteriolosclerosis) associated with narrowing of vascular lumina. Clinical manifestations include retinal vessel changes associated with hypertension (arteriolar narrowing, crossing changes), left ventricular hypertrophy, and elevated BP. The role of these vascular changes in kidney function is unclear. Postmortem and biopsy samples from normotensive kidney donors demonstrate similar vessel changes associated with aging, dyslipidemia, and glucose intolerance. Although BP reduction does slow progression of proteinuric kidney diseases and is warranted to reduce the excessive cardiovascular risks associated with CKD, antihypertensive therapy does not alter the course of kidney dysfunction identified specifically as hypertensive nephrosclerosis.

300 Deep Venous Thrombosis and Pulmonary Thromboembolism

Samuel Z. Goldhaber

EPIDEMIOLOGY

Venous thromboembolism (VTE) encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE) and causes cardiovascular death and disability. In the United States, the Surgeon General estimates there are 100,000 to 180,000 deaths annually from PE and has declared that PE is the most common preventable cause of death among hospitalized patients. Survivors may succumb to the disabilities of chronic thromboembolic pulmonary hypertension or postthrombotic syndrome. Chronic thromboembolic pulmonary hypertension causes breathlessness, especially with exertion. Postthrombotic syndrome (also known as *chronic venous insufficiency*) damages the venous valves of the leg and causes ankle or calf swelling and leg aching, especially after prolonged standing. In its most severe form, postthrombotic syndrome causes skin ulceration (Fig. 300-1).

PATOPHYSIOLOGY

Inflammation and Platelet Activation Virchow's triad of inflammation, hypercoagulability, and endothelial injury leads to recruitment of activated platelets, which release microparticles. These microparticles contain proinflammatory mediators that bind neutrophils, stimulating them to release their nuclear material and form web-like extracellular networks called neutrophil extracellular traps. These prothrombotic networks contain histones that stimulate platelet aggregation and promote platelet-dependent thrombin generation. Venous thrombi form and flourish in an environment of stasis, low oxygen tension, and upregulation of proinflammatory genes.

Prothrombotic States The two most common autosomal dominant genetic mutations are factor V Leiden, which causes resistance to the



FIGURE 300-1 Skin ulceration in the lateral malleolus from post-thrombotic syndrome of the leg.



FIGURE 300-2 Deep venous thrombosis at autopsy.

endogenous anticoagulant, activated protein C (which inactivates clotting factors V and VIII), and the prothrombin gene mutation, which increases the plasma prothrombin concentration (Chaps. 78 and 142). Antithrombin, protein C, and protein S are naturally occurring coagulation inhibitors. Deficiencies of these inhibitors are associated with VTE but are rare. Antiphospholipid antibody syndrome is the most common acquired cause of thrombophilia and is associated with venous or arterial thrombosis. Other common predisposing factors include cancer, obesity, cigarette smoking, systemic arterial hypertension, chronic obstructive pulmonary disease, chronic kidney disease, blood transfusion, long-haul air travel, air pollution, oral contraceptives, pregnancy, postmenopausal hormone replacement, surgery, and trauma.

Embolization When deep venous thrombi (Fig. 300-2) detach from their site of formation, they embolize to the vena cava, right atrium, and right ventricle, and lodge in the pulmonary arterial circulation, thereby causing acute PE. Paradoxically, these thrombi occasionally embolize to the arterial circulation through a patent foramen ovale or atrial septal defect. Many patients with PE have no evidence of DVT because the clot has already embolized to the lungs.

Physiology The most common gas exchange abnormalities are arterial hypoxemia and an increased alveolar-arterial O₂ tension gradient, which represents the inefficiency of O₂ transfer across the lungs. Anatomic dead space increases because breathed gas does not enter gas exchange units of the lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries.

Other pathophysiologic abnormalities include:

1. *Increased pulmonary vascular resistance* due to vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents such as serotonin. Release of vasoactive mediators can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for discordance between a small PE and a large alveolar-arterial O₂ gradient.
2. *Impaired gas exchange* due to increased alveolar dead space from vascular obstruction, hypoxemia from alveolar hypoventilation relative to perfusion in the nonobstructed lung, right-to-left shunting, or impaired carbon monoxide transfer due to loss of gas exchange surface.
3. *Alveolar hyperventilation* due to reflex stimulation of irritant receptors.
4. *Increased airway resistance* due to constriction of airways distal to the bronchi.
5. *Decreased pulmonary compliance* due to lung edema, lung hemorrhage, or loss of surfactant.

Pulmonary Hypertension, Right Ventricular (RV) Dysfunction, and RV Microinfarction Pulmonary artery obstruction causes a rise in pulmonary

artery pressure and in pulmonary vascular resistance. When RV wall tension rises, RV dilation and dysfunction ensue, with release of the cardiac biomarker, brain natriuretic peptide. The interventricular septum bulges into and compresses an intrinsically normal left ventricle (LV). Diastolic LV dysfunction reduces LV distensibility and impairs LV filling. Increased RV wall tension also compresses the right coronary artery, limits myocardial oxygen supply, and precipitates right coronary artery ischemia and RV microinfarction, with release of cardiac biomarkers such as troponin. Underfilling of the LV may lead to a fall in LV cardiac output and systemic arterial pressure, with consequent circulatory collapse and death.

CLASSIFICATION OF PULMONARY EMBOLISM AND DEEP VENOUS THROMBOSIS

Pulmonary Embolism Massive PE accounts for 5–10% of cases, and is characterized by extensive thrombosis affecting at least half of the pulmonary vasculature. Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE. Patients with massive PE may present in cardiogenic shock and can die from multisystem organ failure. Submassive PE accounts for 20–25% of patients, and is characterized by RV dysfunction despite normal systemic arterial pressure. The combination of right heart failure and release of cardiac biomarkers indicates an increased likelihood of clinical deterioration. Low-risk PE constitutes about 70–75% of cases. These patients have an excellent prognosis.

Deep Venous Thrombosis Lower extremity DVT usually begins in the calf and propagates proximally to the popliteal vein, femoral vein, and iliac veins. Leg DVT is about 10 times more common than **upper extremity DVT**, which is often precipitated by placement of pacemakers, internal cardiac defibrillators, or indwelling central venous catheters. The likelihood of upper extremity DVT increases as the catheter diameter and number of lumens increase. **Superficial venous thrombosis** usually presents with erythema, tenderness, and a “palpable cord.” Patients are at risk for extension of the thrombosis to the deep venous system.

DIAGNOSIS

Clinical Evaluation PE is known as “the Great Masquerader.” Diagnosis is difficult because symptoms and signs are nonspecific. The most common symptom is unexplained breathlessness. When occult PE occurs concomitantly with overt congestive heart failure or pneumonia, clinical improvement often fails to occur despite standard medical treatment of the concomitant illness. This scenario presents a clinical clue to the possible coexistence of PE.

With DVT, the most common symptom is a cramp or “charley horse” in the lower calf that persists and intensifies over several days. Point score criteria help estimate the clinical likelihood of DVT and PE (**Table 300-1**). Patients with a low-to-moderate likelihood of DVT or PE should undergo initial diagnostic evaluation with d-dimer testing alone (see “Blood Tests”) without obligatory imaging tests (**Fig. 300-3**). However, patients with a high clinical likelihood of VTE should skip d-dimer testing and undergo imaging as the next step in the diagnostic algorithm.

Clinical Pearls Not all leg pain is due to DVT, and not all dyspnea is due to PE (**Table 300-2**). Sudden, severe calf discomfort suggests a ruptured Baker’s cyst. Fever and chills usually herald cellulitis rather than DVT. Physical findings, if present, may consist only of mild palpation discomfort in the lower calf. However, massive DVT often presents with marked thigh swelling, tenderness, and erythema. If the leg is diffusely edematous, DVT is unlikely. More probable is an acute exacerbation of venous insufficiency due to postthrombotic syndrome. Upper extremity venous thrombosis may present with asymmetry in the supraclavicular fossa or in the circumference of the upper arms.

Pulmonary infarction usually indicates a small PE. This condition is exquisitely painful because the thrombus lodges peripherally, near the innervation of pleural nerves. *Nonthrombotic PE* etiologies include fat embolism after pelvic or long bone fracture, tumor embolism, bone marrow, and air embolism. Cement embolism and bony fragment embolism

TABLE 300-1 CLINICAL DECISION RULES

Low Clinical Likelihood of DVT if Point Score Is Zero or Less; Moderate Likelihood if Score Is 1 to 2; High Likelihood if Score Is 3 or Greater

Clinical Variable	DVT Score
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery <12 weeks	1
Tenderness along distribution of deep veins	1
Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	-2
High Clinical Likelihood of PE if Point Score Exceeds 4	
Clinical Variable	PE Score
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

can occur after total hip or knee replacement. Intravenous drug users may inject themselves with a wide array of substances that can embolize such as hair, talc, and cotton. *Amniotic fluid embolism* occurs when fetal membranes leak or tear at the placental margin.

Nonimaging Diagnostic Modalities • BLOOD TESTS The quantitative plasma d-dimer enzyme-linked immunosorbent assay (ELISA) rises in the presence of DVT or PE because of the breakdown of fibrin by plasmin. Elevation of d-dimer indicates endogenous although often clinically ineffective thrombolysis. The sensitivity of the d-dimer is >80% for DVT (including isolated calf DVT) and >95% for PE. The d-dimer is less sensitive for DVT than for PE because the DVT thrombus size is smaller. A normal d-dimer is a useful “rule out” test. However, the d-dimer assay is not specific. Levels increase in patients with myocardial infarction, pneumonia, sepsis, cancer, and the postoperative state and those in the second or third trimester of pregnancy. Therefore, d-dimer rarely has a useful role among hospitalized patients, because levels are frequently elevated due to systemic illness.

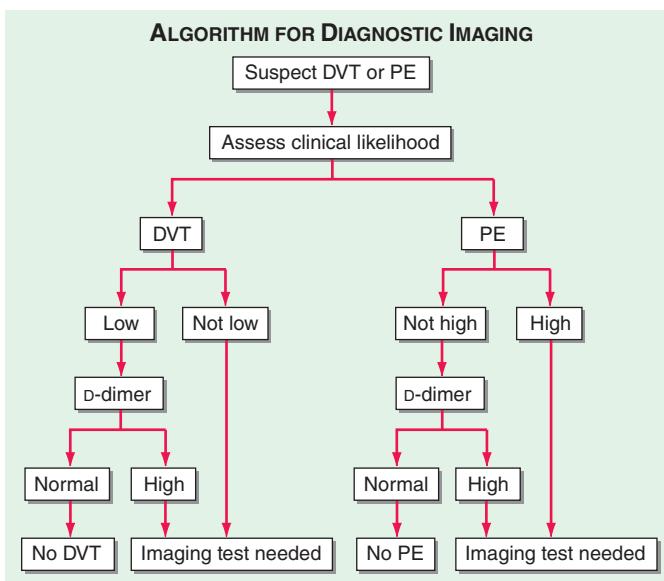


FIGURE 300-3 How to decide whether diagnostic imaging is needed. For assessment of clinical likelihood, see Table 300-1.

TABLE 300-2 DIFFERENTIAL DIAGNOSIS

DVT
Ruptured Baker's cyst
Cellulitis
Postphlebitic syndrome/venous insufficiency
PE
Pneumonia, asthma, chronic obstructive pulmonary disease
Congestive heart failure
Pericarditis
Pleurisy: "viral syndrome," costochondritis, musculoskeletal discomfort
Rib fracture, pneumothorax
Acute coronary syndrome
Anxiety

ELEVATED CARDIAC BIOMARKERS Serum troponin and plasma heart-type fatty acid-binding protein levels increase because of RV microinfarction. Myocardial stretch causes release of brain natriuretic peptide or NT-pro-brain natriuretic peptide.

ELECTROCARDIOGRAM The most frequently cited abnormality, in addition to sinus tachycardia, is the S1Q3T3 sign: an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III (*Chap. 268*). This finding is relatively specific but insensitive. RV strain and ischemia cause the most common abnormality, T-wave inversion in leads V₁ to V₄.

Noninvasive Imaging Modalities • VENOUS ULTRASONOGRAPHY Ultrasonography of the deep venous system relies on loss of vein compressibility as the primary criterion for DVT. When a normal vein is imaged in cross-section, it readily collapses with gentle manual pressure from the ultrasound transducer. This creates the illusion of a "wink." With acute DVT, the vein loses its compressibility because of passive distention by acute thrombus. The diagnosis of acute DVT is even more secure when thrombus is directly visualized. It appears homogeneous and has low echogenicity (*Fig. 300-4*). The vein itself often appears mildly dilated, and collateral channels may be absent.

Venous flow dynamics can be examined with Doppler imaging. Normally, manual calf compression causes augmentation of the Doppler flow pattern. Loss of normal respiratory variation is caused by an obstructing DVT or by any obstructive process within the pelvis. For patients with a technically poor or nondiagnostic venous ultrasound, one should consider alternative imaging modalities for DVT, such as computed tomography (CT) and magnetic resonance imaging.

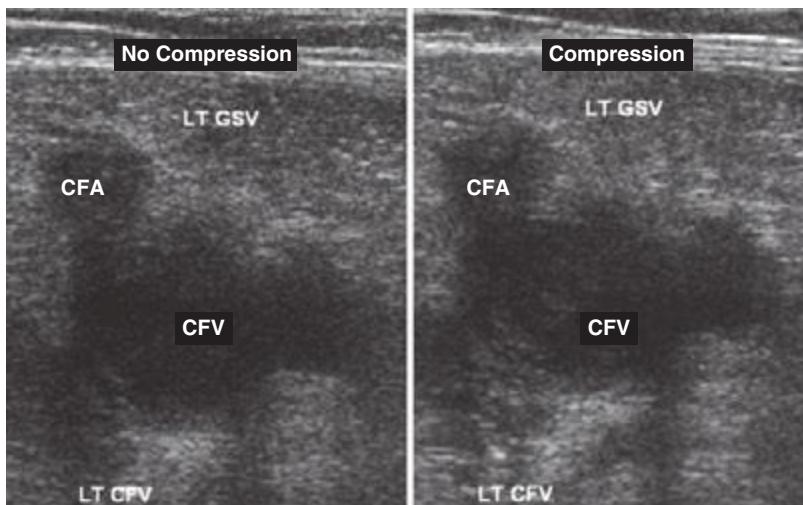


FIGURE 300-4 Venous ultrasound, with and without compression of the leg veins. CFA, common femoral artery; CFV, common femoral vein; GSV, great saphenous vein; LT, left.

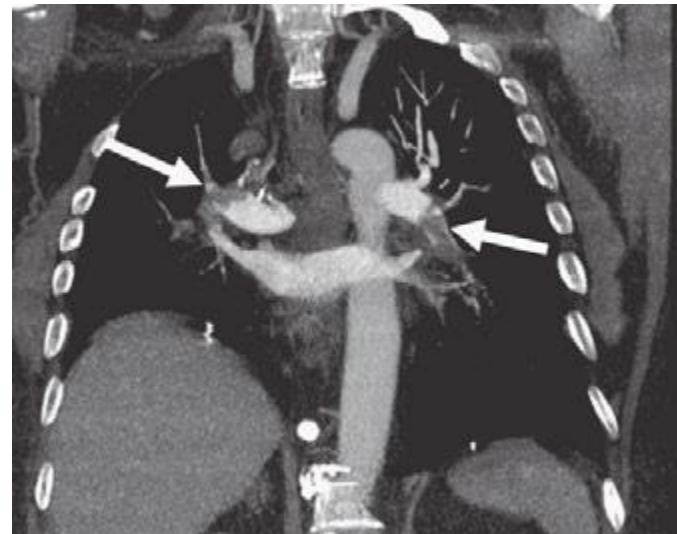


FIGURE 300-5 Large bilateral proximal PE on a coronal chest CT image in a 54-year-old man with lung cancer and brain metastases. He had developed sudden onset of chest heaviness and shortness of breath while at home. There are filling defects in the main and segmental pulmonary arteries bilaterally (white arrows). Only the left upper lobe segmental artery is free of thrombus.

CHEST ROENTGENOGRAPHY A normal or nearly normal chest x-ray often occurs in PE. Well-established abnormalities include focal oligemia (Westermark's sign), a peripheral wedged-shaped density above the diaphragm (Hampton's hump), and an enlarged right descending pulmonary artery (Palla's sign).

CHEST CT CT of the chest with intravenous contrast is the principal imaging test for the diagnosis of PE (*Fig. 300-5*). Multidetector-row spiral CT acquires all chest images with ≤ 1 mm of resolution during a short breath hold. Sixth-order branches can be visualized with resolution superior to that of conventional invasive contrast pulmonary angiography. The CT scan also provides an excellent four-chamber view of the heart. RV enlargement on chest CT indicates an increased likelihood of death within the next 30 days compared with PE patients who have normal RV size. When imaging is continued below the chest to the knee, pelvic and proximal leg DVT also can be diagnosed by CT scanning. In patients without PE, the lung parenchymal images may establish alternative diagnoses not apparent on chest x-ray that explain the presenting symptoms and signs such as pneumonia, emphysema, pulmonary fibrosis, pulmonary mass, and aortic pathology. Sometimes asymptomatic early-stage lung cancer is diagnosed incidentally.

LUNG SCANNING Lung scanning has become a second-line diagnostic test for PE, used mostly for patients who cannot tolerate intravenous contrast. Small particulate aggregates of albumin labeled with a gamma-emitting radionuclide are injected intravenously and are trapped in the pulmonary capillary bed. The perfusion scan defect indicates absent or decreased blood flow, possibly due to PE. Ventilation scans, obtained with a radiolabeled inhaled gas such as xenon or krypton, improve the specificity of the perfusion scan. Abnormal ventilation scans indicate abnormal nonventilated lung, thereby providing possible explanations for perfusion defects other than acute PE, such as asthma and chronic obstructive pulmonary disease. A high-probability scan for PE is defined as two or more segmental perfusion defects in the presence of normal ventilation.

The diagnosis of PE is very unlikely in patients with normal and nearly normal scans and is about 90% certain in patients with high-probability scans. Unfortunately, most

1634 patients have nondiagnostic scans, and fewer than one-half of patients with angiographically confirmed PE have a high probability scan. As many as 40% of patients with high clinical suspicion for PE but “low-probability” scans do, in fact, have PE at angiography.

MAGNETIC RESONANCE (MR) (CONTRAST-ENHANCED) IMAGING When ultrasound is equivocal, MR venography with gadolinium contrast is an excellent imaging modality to diagnose DVT. MR pulmonary angiography may detect large proximal PE but is not reliable for smaller segmental and subsegmental PE.

ECHOCARDIOGRAPHY Echocardiography is *not* a reliable diagnostic imaging tool for acute PE because most patients with PE have normal echocardiograms. However, echocardiography is a very useful diagnostic tool for detecting conditions that may mimic PE, such as acute myocardial infarction, pericardial tamponade, and aortic dissection. Transthoracic echocardiography rarely images thrombus directly. The best-known indirect sign of PE on transthoracic echocardiography is McConnell's sign: hypokinesis of the RV free wall with normal or hyperkinetic motion of the RV apex. One should consider transesophageal echocardiography when CT scanning facilities are not available or when a patient has renal failure or severe contrast allergy that precludes administration of contrast despite premedication with high-dose steroids. This imaging modality can identify saddle, right main, or left main PE.

Invasive Diagnostic Modalities • PULMONARY ANGIOGRAPHY Chest CT with contrast (see above) has virtually replaced invasive pulmonary angiography as a diagnostic test. Invasive catheter-based diagnostic testing is reserved for patients with technically unsatisfactory chest CTs and for those in whom an interventional procedure such as catheter-directed thrombolysis is planned. A definitive diagnosis of PE depends on visualization of an intraluminal filling defect in more than one projection. Secondary signs of PE include abrupt occlusion (“cut-off”) of vessels, segmental oligemia or avascularity, a prolonged arterial phase with slow filling, and tortuous, tapering peripheral vessels.

CONTRAST PHLEBOGRAPHY Venous ultrasonography has virtually replaced contrast phlebography as the diagnostic test for suspected DVT.

Integrated Diagnostic Approach An integrated diagnostic approach (Fig. 300-3) streamlines the workup of suspected DVT and PE (Fig. 300-6).

TREATMENT DEEP VENOUS THROMBOSIS

PRIMARY THERAPY

Primary therapy consists of clot dissolution with pharmacomechanical therapy that usually includes low-dose catheter-directed thrombolysis. This approach is reserved for patients with extensive femoral, iliofemoral, or upper extremity DVT. The open vein hypothesis postulates that patients who receive primary therapy will sustain less long-term damage to venous valves, with consequent lower rates of postthrombotic syndrome. A National Heart, Lung, and Blood Institute-sponsored randomized controlled trial called ATTRACT (NCT00790335) is testing this hypothesis.

SECONDARY PREVENTION

Anticoagulation or placement of an inferior vena caval filter constitutes *secondary prevention* of VTE. To lessen the severity of post-thrombotic syndrome of the legs, below-knee graduated compression stockings may be prescribed, 30–40 mmHg, for 2 years after the DVT episode. They should be replaced every 3 months because they lose their elasticity.

TREATMENT PULMONARY EMBOLISM

RISK STRATIFICATION

Hemodynamic instability, RV dysfunction on echocardiography, RV enlargement on chest CT, or elevation of the troponin level

ALGORITHM FOR DVT AND PE DIAGNOSIS

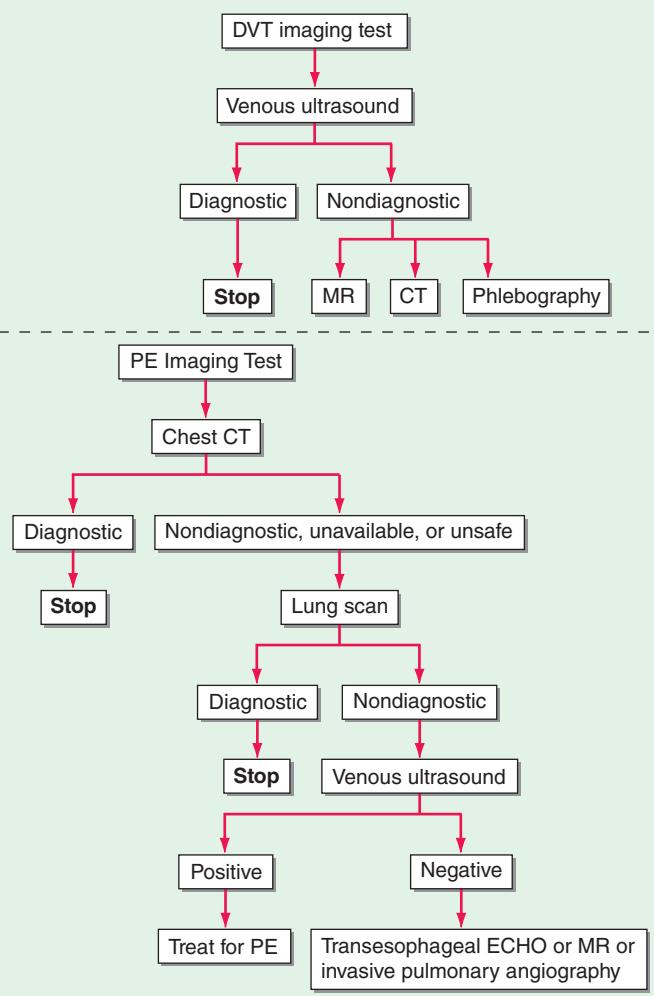


FIGURE 300-6 Imaging tests to diagnose DVT and PE. ECHO, echocardiography.

due to RV microinfarction portend a high risk of an adverse clinical outcome. When RV function remains normal in a hemodynamically stable patient, a good clinical outcome is highly likely with anticoagulation alone (Fig. 300-7).

ANTICOAGULATION

Effective anticoagulation is the foundation for successful treatment of DVT and PE. There are three options: (1) the conventional strategy

ALGORITHM FOR PE MANAGEMENT

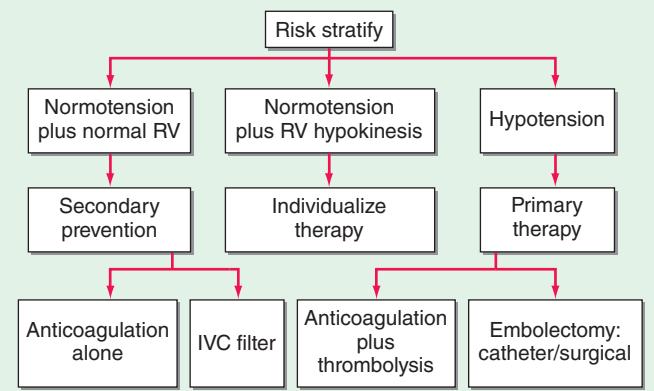


FIGURE 300-7 Acute management of pulmonary thromboembolism. RV, right ventricular; IVC, inferior vena cava.

TABLE 300-3 ANTICOAGULATION OF VTE**Immediate Anticoagulation**

Unfractionated heparin, bolus and continuous infusion, to achieve aPTT 2–3 times the upper limit of the laboratory normal, or
 Enoxaparin 1 mg/kg twice daily with normal renal function, or
 Dalteparin 200 U/kg once daily or 100 U/kg twice daily, with normal renal function, or
 Tinzaparin 175 U/kg once daily with normal renal function, or
 Fondaparinux weight-based once daily; adjust for impaired renal function
 Direct thrombin inhibitors: argatroban or bivalirudin
 Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily with the dinner meal thereafter
 Apixaban (not yet licensed)

Warfarin Anticoagulation

Requires 5–10 days of administration to achieve effectiveness as monotherapy
 (Unfractionated heparin, low-molecular-weight heparin, and fondaparinux are the usual immediately effective “bridging agents” used when initiating warfarin)
 Usual start dose is 5 mg
 Titrate to INR, target 2.0–3.0
 Continue parenteral anticoagulation for a minimum of 5 days and until two sequential INR values, at least 1 day apart, achieve the target INR range

Novel Oral Anticoagulants for Extended-Duration Anticoagulation following Initial Parenteral Anticoagulation

Edoxaban (not yet licensed)
 Dabigatran (not yet licensed)

of parenteral therapy “bridged” to warfarin, (2) parenteral therapy “bridged” to a novel oral anticoagulant such as dabigatran (a direct thrombin inhibitor) or edoxaban (an anti-Xa agent), or (3) oral anticoagulation with rivaroxaban or apixaban (both are anti-Xa agents) with a loading dose followed by a maintenance dose as monotherapy without parenteral anticoagulation.

The three heparin-based parenteral anticoagulants are (1) unfractionated heparin (UFH), (2) low-molecular-weight heparin (LMWH), and (3) fondaparinux. For patients with suspected or proven heparin-induced thrombocytopenia, there are two parenteral direct thrombin inhibitors: argatroban and bivalirudin (**Table 300-3**).

Unfractionated Heparin UFH anticoagulates by binding to and accelerating the activity of antithrombin, thus preventing additional thrombus formation. UFH is dosed to achieve a target activated partial thromboplastin time (aPTT) of 60–80 s. The most popular nomogram uses an initial bolus of 80 U/kg, followed by an initial infusion rate of 18 U/kg per h.

The major advantage of UFH is its short half-life, which is especially useful in patients in whom hour-to-hour control of the intensity of anticoagulation is desired.

Low-Molecular-Weight Heparins These fragments of UFH exhibit less binding to plasma proteins and endothelial cells and consequently have greater bioavailability, a more predictable dose response, and a longer half-life than does UFH. No monitoring or dose adjustment is needed unless the patient is markedly obese or has chronic kidney disease.

Fondaparinux Fondaparinux, an anti-Xa pentasaccharide, is administered as a weight-based once-daily subcutaneous injection in a pre-filled syringe. No laboratory monitoring is required. Fondaparinux is synthesized in a laboratory and, unlike LMWH or UFH, is not derived from animal products. It does not cause heparin-induced thrombocytopenia. The dose must be adjusted downward for patients with renal dysfunction.

Warfarin This vitamin K antagonist prevents carboxylation activation of coagulation factors II, VII, IX, and X. The full effect of warfarin requires at least 5 days, even if the prothrombin time,

used for monitoring, becomes elevated more rapidly. If warfarin is initiated as monotherapy during an acute thrombotic illness, a paradoxical exacerbation of hypercoagulability increases the likelihood of thrombosis. Overlapping UFH, LMWH, fondaparinux, or parenteral direct thrombin inhibitors with warfarin for at least 5 days will nullify the early procoagulant effect of warfarin.

WARFARIN DOSING In an average-size adult, warfarin is often initiated in a dose of 5 mg. The prothrombin time is standardized by calculating the international normalized ratio (INR), which assesses the anticoagulant effect of warfarin (**Chap. 78**). The target INR is usually 2.5, with a range of 2.0–3.0.

The warfarin dose is usually titrated empirically to achieve the target INR. Proper dosing is difficult because hundreds of drug-drug and drug-food interactions affect warfarin metabolism. Increasing age and systemic illness reduce the required warfarin dose. Pharmacogenomics may provide more precise initial dosing of warfarin. CYP2C9 variant alleles impair the hydroxylation of S-warfarin, thereby lowering the dose requirement. Variants in the gene encoding the vitamin K epoxide reductase complex 1 (VKORC1) can predict whether patients require low, moderate, or high warfarin doses.

Centralized anticoagulation clinics have improved the efficacy and safety of warfarin dosing. Patients can self-monitor their INR with a home point-of-care fingerstick machine and can occasionally be taught to self-dose their warfarin.

Novel Oral Anticoagulants Novel oral anticoagulants are administered in a fixed dose, establish effective anticoagulation within hours of ingestion, require no laboratory coagulation monitoring, and have few of the drug-drug or drug-food interactions that make warfarin so difficult to dose. Rivaroxaban, a factor Xa inhibitor, is approved for treatment of acute DVT and acute PE as monotherapy, without a parenteral “bridging” anticoagulant. Apixaban is likely to receive similar approval for oral monotherapy. Dabigatran, a direct thrombin inhibitor, and edoxaban, a factor Xa inhibitor, are likely to be approved for treatment of VTE after an initial course of parenteral anticoagulation.

Complications of Anticoagulants The most serious adverse effect of anticoagulation is hemorrhage. For life-threatening or intracranial hemorrhage due to heparin or LMWH, protamine sulfate can be administered. Heparin-induced thrombocytopenia is less common with LMWH than with UFH. There is no specific reversal agent for bleeding caused by fondaparinux, direct thrombin inhibitors, or factor Xa inhibitors.

Major bleeding from warfarin is best managed with prothrombin complex concentrate. With serious but non-life-threatening bleeding, fresh-frozen plasma or intravenous vitamin K can be used. Recombinant human coagulation factor VIIa (rFVIIa) is an off-label option to manage catastrophic bleeding from warfarin, but prothrombin complex concentrate is a better choice. Oral vitamin K is effective for managing minor bleeding or an excessively high INR in the absence of bleeding.

Duration of Anticoagulation For DVT isolated to an upper extremity or calf that has been provoked by surgery, trauma, estrogen, or an indwelling central venous catheter or pacemaker, 3 months of anticoagulation usually suffice. For an initial episode of provoked proximal leg DVT or PE, 3 to 6 months of anticoagulation are considered sufficient. For patients with cancer and VTE, prescribe LMWH as monotherapy without warfarin and continue anticoagulation indefinitely unless the patient is rendered cancer-free.

Among patients with idiopathic, unprovoked VTE, the recurrence rate is high after cessation of anticoagulation. VTE that occurs during long-haul air travel is considered unprovoked. Unprovoked VTE may be caused by an exacerbation of an underlying inflammatory state and can be conceptualized as a chronic illness, with latent periods between flares of recurrent episodes. American College of Chest Physicians (ACCP) guidelines recommend considering

1636 anticoagulation for an indefinite duration with a target INR between 2 and 3 for patients with idiopathic VTE. An alternative approach after the first 6 months of anticoagulation is to reduce the intensity of anticoagulation and to lower the target INR range to between 1.5 and 2.

Counterintuitively, the presence of genetic mutations such as heterozygous factor V Leiden and prothrombin gene mutation does not appear to increase the risk of recurrent VTE. However, patients with antiphospholipid antibody syndrome may warrant indefinite-duration anticoagulation, even if the initial VTE was provoked by trauma or surgery.

INFERIOR VENA CAVAL (IVC) FILTERS

The two principal indications for insertion of an IVC filter are (1) active bleeding that precludes anticoagulation and (2) recurrent venous thrombosis despite intensive anticoagulation. Prevention of recurrent PE in patients with right heart failure who are not candidates for fibrinolysis and prophylaxis of extremely high-risk patients are “softer” indications for filter placement. The filter itself may fail by permitting the passage of small-to medium-size clots. Large thrombi may embolize to the pulmonary arteries via collateral veins that develop. A more common complication is caval thrombosis with marked bilateral leg swelling.

Paradoxically, by providing a nidus for clot formation, filters increase the DVT rate, even though they usually prevent PE (over the short term). Retrievable filters can now be placed for patients with an anticipated temporary bleeding disorder or for patients at temporary high risk of PE, such as individuals undergoing bariatric surgery who have a prior history of perioperative PE. The filters can be retrieved up to several months after insertion unless thrombus forms and is trapped within the filter. The retrievable filter becomes permanent if it remains in place or if, for technical reasons such as rapid endothelialization, it cannot be removed.

MANAGEMENT OF MASSIVE PE

For patients with massive PE and hypotension, replete volume with 500 mL of normal saline. Additional fluid should be infused with extreme caution because excessive fluid administration exacerbates RV wall stress, causes more profound RV ischemia, and worsens LV compliance and filling by causing further interventricular septal shift toward the LV. Dopamine and dobutamine are first-line inotropic agents for treatment of PE-related shock. Maintain a low threshold for initiating these pressors. Often, a “trial-and-error” approach works best; other agents that may be effective include norepinephrine, vasopressin, or phenylephrine.

FIBRINOLYSIS

Successful fibrinolytic therapy rapidly reverses right heart failure and may result in a lower rate of death and recurrent PE by (1) dissolving much of the anatomically obstructing pulmonary arterial thrombus, (2) preventing the continued release of serotonin and other neurohumoral factors that exacerbate pulmonary hypertension, and (3) lysing much of the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent PE.

The preferred fibrinolytic regimen is 100 mg of recombinant tissue plasminogen activator (tPA) administered as a continuous peripheral intravenous infusion over 2 h. The sooner thrombolysis is administered, the more effective it is. However, this approach can be used for at least 14 days after the PE has occurred.

Contraindications to fibrinolysis include intracranial disease, recent surgery, and trauma. The overall major bleeding rate is about 10%, including a 1–3% risk of intracranial hemorrhage. Careful screening of patients for contraindications to fibrinolytic therapy ([Chap. 295](#)) is the best way to minimize bleeding risk.

The only Food and Drug Administration-approved indication for PE fibrinolysis is massive PE. For patients with submassive PE, who have preserved systolic blood pressure but moderate or severe RV dysfunction, use of fibrinolysis remains controversial. Results of a 1006-patient European multicentered randomized trial of submassive

PE, using the thrombolytic agent tenecteplase, were published in 2014. Death or hemodynamic collapse within 7 days of randomization was reduced by 56% in the tenecteplase group. However, hemorrhagic stroke occurred in 2% of tenecteplase patients versus 0.2% in patients who only received heparin.

PHARMACOMECHANICAL CATHETER-DIRECTED THERAPY

Many patients have relative contraindications to full-dose thrombolysis. Pharmacomechanical catheter-directed therapy usually combines physical fragmentation or pulverization of thrombus with catheter-directed low-dose thrombolysis. Mechanical techniques include catheter maceration and intentional embolization of clot more distally, suction thrombectomy, rheolytic hydrolysis, and low-energy ultrasound-facilitated thrombolysis. The dose of alteplase can be markedly reduced, usually to a range of 20 to 25 mg instead of the peripheral intravenous systemic dose of 100 mg.

PULMONARY EMBOLECTOMY

The risk of major hemorrhage with systemically administered fibrinolysis has prompted a renaissance of interest in surgical embolectomy, an operation that had almost become extinct. More rapid referral before the onset of irreversible multisystem organ failure and improved surgical technique have resulted in a high survival rate.

PULMONARY THROMBOENDARTERECTOMY

Chronic thromboembolic pulmonary hypertension develops in 2–4% of acute PE patients. Therefore, PE patients who have initial pulmonary hypertension (usually diagnosed with Doppler echocardiography) should be followed up at about 6 weeks with a repeat echocardiogram to determine whether pulmonary arterial pressure has normalized. Patients impaired by dyspnea due to chronic thromboembolic pulmonary hypertension should be considered for pulmonary thromboendarterectomy, which, if successful, can markedly reduce, and sometimes even cure, pulmonary hypertension ([Chap. 304](#)). The operation requires median sternotomy, cardiopulmonary bypass, deep hypothermia, and periods of hypothermic circulatory arrest. The mortality rate at experienced centers is approximately 5%. Inoperable patients should be managed with pulmonary vasodilator therapy.

EMOTIONAL SUPPORT

Patients with VTE may feel overwhelmed when they learn that they are suffering from PE or DVT. Some have never previously encountered serious cardiovascular illness. They wonder whether they will be able to adapt to the new limitations imposed by anticoagulation. They worry about the health of their families and the genetic implications of their illness. Those who are advised to discontinue anticoagulation may feel especially vulnerable about the potential for suffering recurrent VTE. At Brigham and Woman’s Hospital, a physician-nurse-facilitated PE support group was initiated to address these concerns and has met monthly for more than 20 years.

PREVENTION OF VTE

Prevention of DVT and PE ([Table 300-4](#)) is of paramount importance because VTE is difficult to detect and poses a profound medical and economic burden. Low-dose UFH or LMWH is the most common form of in-hospital prophylaxis. Computerized reminder systems can increase the use of preventive measures and, at Brigham and Women’s Hospital, have reduced the symptomatic VTE rate by more than 40%. Audits of hospitals to ensure that prophylaxis protocols are being used will also increase utilization of preventive measures. Duration of prophylaxis is an important consideration. Extended-duration prophylaxis has not been shown to be both effective and safe in medically ill patients after hospital discharge in separate large trials that have tested enoxaparin, apixaban, and rivaroxaban. There is an ongoing trial of a novel oral anticoagulant, betrixaban, for extended-duration VTE prophylaxis in medically ill patients.

TABLE 300-4 PREVENTION OF VENOUS THROMBOEMBOLISM AMONG HOSPITALIZED PATIENTS

Condition	Prophylaxis Strategy
High-risk nonorthopedic surgery	Unfractionated heparin 5000 units SC bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily
Cancer surgery, including gynecologic cancer surgery	Enoxaparin 40 mg daily, consider 1 month of prophylaxis
Major orthopedic surgery	Warfarin (target INR 2.0–3.0) Enoxaparin 40 mg daily Enoxaparin 30 mg bid Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily Rivaroxaban 10 mg daily Aspirin 81–325 mg daily Dabigatran 220 mg daily (not in the United States) Apixaban 2.5 mg bid (not in the United States)
Medically ill patients, especially if immobilized, with a history of prior VTE, with an indwelling central venous catheter, or with cancer (but without active gastroduodenal ulcer, major bleeding within 3 months, or platelet count <50,000)	Intermittent pneumatic compression (with or without pharmacologic prophylaxis) Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily
Anticoagulation contraindicated	Intermittent pneumatic compression devices (but whether graduated compression stockings are effective in medical patients is controversial)

Patients who have undergone total hip or knee replacement or cancer surgery will benefit from extended pharmacologic VTE prophylaxis after hospital discharge. For hip replacement or extensive cancer surgery, the duration of prophylaxis is usually at least 1 month.

double aortic arch, origin of the right subclavian artery distal to the left subclavian artery, and right-sided aortic arch with an aberrant left subclavian artery. A Kommerell's diverticulum is an anatomic remnant of a right aortic arch. Most congenital anomalies of the aorta do not cause symptoms and are detected during catheter-based procedures. The diagnosis of suspected congenital anomalies of the aorta typically is confirmed by computed tomographic (CT) or magnetic resonance (MR) angiography. Surgery is used to treat symptomatic anomalies.

301 Diseases of the Aorta

Mark A. Creager, Joseph Loscalzo

The aorta is the conduit through which blood ejected from the left ventricle is delivered to the systemic arterial bed. In adults, its diameter is approximately 3 cm at the origin and in the ascending portion, 2.5 cm in the descending portion in the thorax, and 1.8–2 cm in the abdomen. The aortic wall consists of a thin intima composed of endothelium, subendothelial connective tissue, and an internal elastic lamina; a thick tunica media composed of smooth muscle cells and extracellular matrix; and an adventitia composed primarily of connective tissue enclosing the vasa vasorum and nervi vascularis. In addition to the conduit function of the aorta, its viscoelastic and compliant properties serve a buffering function. The aorta is distended during systole to allow a portion of the stroke volume and elastic energy to be stored, and it recoils during diastole so that blood continues to flow to the periphery. Owing to its continuous exposure to high pulsatile pressure and shear stress, the aorta is particularly prone to injury and disease resulting from mechanical trauma. The aorta is also more prone to rupture than is any other vessel, especially with the development of aneurysmal dilation, since its wall tension, as governed by Laplace's law (i.e., proportional to the product of pressure and radius), will be increased.

CONGENITAL ANOMALIES OF THE AORTA

Congenital anomalies of the aorta usually involve the aortic arch and its branches. Symptoms such as dysphagia, stridor, and cough may occur if an anomaly causes a ring around or otherwise compresses the esophagus or trachea. Anomalies associated with symptoms include

AORTIC ANEURYSM

An *aneurysm* is defined as a pathologic dilation of a segment of a blood vessel. A *true aneurysm* involves all three layers of the vessel wall and is distinguished from a *pseudoaneurysm*, in which the intimal and medial layers are disrupted and the dilated segment of the aorta is lined by adventitia only and, at times, by perivascular clot. Aneurysms also may be classified according to their gross appearance. A *fusiform aneurysm* affects the entire circumference of a segment of the vessel, resulting in a diffusely dilated artery. In contrast, a *saccular aneurysm* involves only a portion of the circumference, resulting in an outpouching of the vessel wall. Aortic aneurysms also are classified according to location, i.e., abdominal versus thoracic. Aneurysms of the descending thoracic aorta are usually contiguous with infradiaphragmatic aneurysms and are referred to as *thoracoabdominal aortic aneurysms*.

ETIOLOGY

Aortic aneurysms result from conditions that cause degradation or abnormal production of the structural components of the aortic wall: elastin and collagen. The causes of aortic aneurysms may be broadly categorized as degenerative disorders, genetic or developmental diseases, vasculitis, infections, and trauma (Table 301-1). Inflammation, oxidative stress, proteolysis, and biomechanical wall stress contribute to the degenerative processes that characterize most aneurysms of the abdominal and descending thoracic aorta. These are mediated by B cell and T cell lymphocytes, macrophages, inflammatory cytokines, and matrix metalloproteinases that degrade elastin and collagen and alter the tensile strength and ability of the aorta to accommodate pulsatile stretch. The associated histopathology demonstrates destruction of elastin and collagen, decreased vascular smooth muscle, in-growth of new blood vessels, and inflammation. Factors associated with degenerative aortic aneurysms include aging, cigarette smoking, hypercholesterolemia, hypertension, and male sex.

TABLE 301-1 DISEASES OF THE AORTA: ETIOLOGY AND ASSOCIATED FACTORS

Aortic aneurysm
Degenerative
Aging
Cigarette smoking
Hypercholesterolemia
Hypertension
Atherosclerosis
Genetic or developmental
Marfan's syndrome
Loeys-Dietz syndrome
Ehlers-Danlos syndrome type IV
Turner's syndrome
Familial
Bicuspid aortic valve
Chronic aortic dissection
Aortitis (see below)
Infective (see below)
Trauma
Acute aortic syndromes (aortic dissection, acute intramural hematoma, penetrating atherosclerotic ulcer)
Degenerative disorders (see above)
Genetic/developmental disorders (see above)
Hypertension
Aortitis (see below)
Pregnancy
Trauma
Aortic occlusion
Atherosclerosis
Thromboembolism
Aortitis
Vasculitis
Takayasu's arteritis
Giant cell arteritis
Rheumatic
HLA-B27-associated spondyloarthropathies
Behçet's syndrome
Cogan's syndrome
Idiopathic aortitis
Infective
Syphilis
Tuberculosis
Mycotic (<i>Salmonella</i> , staphylococcal, streptococcal, fungal)

The most common pathologic condition associated with degenerative aortic aneurysms is *atherosclerosis*. Many patients with aortic aneurysms have coexisting risk factors for atherosclerosis (Chap. 291e), as well as atherosclerosis in other blood vessels.

Medial degeneration, previously designated *cystic medial necrosis*, is the histopathologic term used to describe the degeneration of collagen and elastic fibers in the tunica media of the aorta as well as the loss of medial cells that are replaced by multiple clefts of mucoid material, such as proteoglycans. Medial degeneration characteristically affects the proximal aorta, results in circumferential weakness and dilation, and leads to the development of fusiform aneurysms involving the ascending aorta and the sinuses of Valsalva. This condition is particularly prevalent in patients with Marfan's syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome type IV (Chap. 427), hypertension, congenital bicuspid aortic valves, and familial thoracic aortic aneurysm syndromes; sometimes it appears as an isolated condition in patients without any other apparent disease.

Familial clusterings of aortic aneurysms occur in 20% of patients, suggesting a hereditary basis for the disease. Mutations of the gene that encodes fibrillin-1 are present in patients with Marfan's syndrome. Fibrillin-1 is an important component of extracellular microfibrils, which support the architecture of elastic fibers and other connective tissue. Deficiency of fibrillin-1 in the extracellular matrix leads to excessive signaling by transforming growth factor β (TGF- β). Loeys-Dietz syndrome is caused by mutations in the genes that encode TGF- β receptors 1 (*TGFB1*) and 2 (*TGFB2*). Increased signaling by TGF- β and mutations of *TGFB1* and *TGFB2* may cause thoracic aortic aneurysms. Mutations of type III procollagen have been implicated in Ehlers-Danlos type IV syndrome. Mutations of *SMAD3*, which encodes a downstream signaling protein involved with TGF binding to its receptors, have been described in a syndrome of thoracic aortic aneurysm; craniofacial, skeletal, and cutaneous anomalies; and osteoarthritis. Mutations of the genes encoding the smooth muscle-specific alpha-actin (*ACTA2*), smooth muscle cell-specific myosin heavy chain 11 (*MHC11*), and myosin light chain kinase (*MYLK*) and mutations of *TGFB2* and *SMAD3* have been reported in some patients with non-syndromic familial thoracic aortic aneurysms.

The infectious causes of aortic aneurysms include syphilis, tuberculosis, and other bacterial infections. *Syphilis* (Chap. 206) is a relatively uncommon cause of aortic aneurysm. Syphilitic periaortitis and meso-aortitis damage elastic fibers, resulting in thickening and weakening of the aortic wall. Approximately 90% of syphilitic aneurysms are located in the ascending aorta or aortic arch. *Tuberculous aneurysms* (Chap. 202) typically affect the thoracic aorta and result from direct extension of infection from hilar lymph nodes or contiguous abscesses as well as from bacterial seeding. Loss of aortic wall elasticity results from granulomatous destruction of the medial layer. A *mycotic aneurysm* is a rare condition that develops as a result of staphylococcal, streptococcal, *Salmonella*, or other bacterial or fungal infections of the aorta, usually at an atherosclerotic plaque. These aneurysms are usually saccular. Blood cultures are often positive and reveal the nature of the infective agent.

Vasculitides associated with aortic aneurysm include Takayasu's arteritis and giant cell arteritis, which may cause aneurysms of the aortic arch and descending thoracic aorta. Spondyloarthropathies such as ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, relapsing polychondritis, and reactive arthritis (formerly known as Reiter's syndrome) are associated with dilation of the ascending aorta. Aortic aneurysms occur in patients with Behçet's syndrome (Chap. 387), Cogan's syndrome, and IgG4-related systemic disease. Aortic aneurysms also result from idiopathic aortitis. *Traumatic aneurysms* may occur after penetrating or nonpenetrating chest trauma and most commonly affect the descending thoracic aorta just beyond the site of insertion of the ligamentum arteriosum. Chronic aortic dissections are associated with weakening of the aortic wall that may lead to the development of aneurysmal dilatation.

THORACIC AORTIC ANEURYSMS

The clinical manifestations and natural history of thoracic aortic aneurysms depend on their location. Medial degeneration is the most common pathology associated with ascending aortic aneurysms, whereas atherosclerosis is the condition most frequently associated with aneurysms of the descending thoracic aorta. The average growth rate of thoracic aneurysms is 0.1–0.2 cm per year. Thoracic aortic aneurysms associated with Marfan's syndrome or aortic dissection may expand at a greater rate. The risk of rupture is related to the size of the aneurysm and the presence of symptoms, ranging approximately from 2–3% per year for thoracic aortic aneurysms <4.0 cm in diameter to 7% per year for those >6 cm in diameter. Most thoracic aortic aneurysms are asymptomatic; however, compression or erosion of adjacent tissue by aneurysms may cause symptoms such as chest pain, shortness of breath, cough, hoarseness, and dysphagia. Aneurysmal dilation of the ascending aorta may cause congestive heart failure as a consequence of aortic regurgitation, and compression of the superior vena cava may produce congestion of the head, neck, and upper extremities.

A chest x-ray may be the first test that suggests the diagnosis of a thoracic aortic aneurysm (Fig. 301-1). Findings include widening



FIGURE 301-1 A chest x-ray of a patient with a thoracic aortic aneurysm.

of the mediastinal shadow and displacement or compression of the trachea or left main stem bronchus. Echocardiography, particularly transesophageal echocardiography, can be used to assess the proximal ascending aorta and descending thoracic aorta. Contrast-enhanced CT, magnetic resonance imaging (MRI), and conventional invasive aortography are sensitive and specific tests for assessment of aneurysms of the thoracic aorta and involvement of branch vessels (Fig. 301-2). In asymptomatic patients whose aneurysms are too small to justify surgery, noninvasive testing with either contrast-enhanced CT or MRI should be performed at least every 6–12 months to monitor expansion.



FIGURE 301-2 A magnetic resonance angiogram demonstrating a fusiform aneurysm of the ascending thoracic aorta. (Courtesy of Dr. Michael Steigner, Brigham and Women's Hospital, Boston, MA, with permission.)

TREATMENT

THORACIC AORTIC ANEURYSMS

β -Adrenergic blockers currently are recommended for patients with thoracic aortic aneurysms, particularly those with Marfan's syndrome, who have evidence of aortic root dilatation to reduce the rate of further expansion. Additional medical therapy should be given as necessary to control hypertension. Recent studies indicate that angiotensin receptor antagonists and angiotensin-converting enzyme inhibitors reduce the rate of aortic dilation in patients with Marfan's syndrome by blocking TGF- β signaling; clinical outcome trials of this treatment approach are in progress. Operative repair with placement of a prosthetic graft is indicated in patients with symptomatic ascending thoracic aortic aneurysms and for most asymptomatic aneurysms when the ascending aortic diameter is >5.5 cm. In patients with Marfan's syndrome or bicuspid aortic valve, ascending thoracic aortic aneurysms of 4–5 cm should be considered for surgery. Operative repair is indicated for patients with descending thoracic aortic aneurysms when the diameter is >6 cm, and endovascular repair should be considered if feasible when the diameter is >5.5 cm. Repair is also recommended when the diameter of an aneurysm has increased >1 cm per year.

ABDOMINAL AORTIC ANEURYSMS

Abdominal aortic aneurysms occur more frequently in males than in females, and the incidence increases with age. Abdominal aortic aneurysms ≥ 4.0 cm may affect 1–2% of men older than 50 years. At least 90% of all abdominal aortic aneurysms >4.0 cm are related to atherosclerotic disease, and most of these aneurysms are below the level of the renal arteries. Prognosis is related to both the size of the aneurysm and the severity of coexisting coronary artery and cerebrovascular disease. The risk of rupture increases with the size of the aneurysm: the 5-year risk for aneurysms <5 cm is 1–2%, whereas it is 20–40% for aneurysms >5 cm in diameter. The formation of mural thrombi within aneurysms may predispose to peripheral embolization.

An abdominal aortic aneurysm commonly produces no symptoms. It usually is detected on routine examination as a palpable, pulsatile, expansile, and nontender mass, or it is an incidental finding observed on an abdominal imaging study performed for other reasons. As abdominal aortic aneurysms expand, however, they may become painful. Some patients complain of strong pulsations in the abdomen; others experience pain in the chest, lower back, or scrotum. Aneurysmal pain is usually a harbinger of rupture and represents a medical emergency. More often, acute rupture occurs without any prior warning, and this complication is always life-threatening. Rarely, there is leakage of the aneurysm with severe pain and tenderness. Acute pain and hypotension occur with rupture of the aneurysm, which requires an emergency operation.

Abdominal radiography may demonstrate the calcified outline of the aneurysm; however, about 25% of aneurysms are not calcified and cannot be visualized by x-ray imaging. An abdominal ultrasound can delineate the transverse and longitudinal dimensions of an abdominal aortic aneurysm and may detect mural thrombus. Abdominal ultrasound is useful for serial documentation of aneurysm size and can be used to screen patients at risk for developing an aortic aneurysm. In one large study, ultrasound screening of men age 65–74 years was associated with a risk reduction in aneurysm-related death of 42%. For this reason, screening by ultrasonography is recommended for men age 65–75 years who have ever smoked. In addition, siblings or offspring of persons with abdominal aortic aneurysms, as well as individuals with thoracic aortic or peripheral arterial aneurysms, should be considered for screening for abdominal aortic aneurysms. CT with contrast and MRI are accurate noninvasive tests to determine the location and size of abdominal aortic aneurysms and to plan endovascular or open surgical repair (Fig. 301-3). Contrast aortography may be used for the evaluation of patients with aneurysms, but the procedure carries a small risk of complications such as bleeding, allergic reactions, and atheroembolism. Since the presence of mural thrombi may reduce the luminal size, aortography may underestimate the diameter of an aneurysm.



FIGURE 301-3 A computed tomographic angiogram depicting a fusiform abdominal aortic aneurysm before (left) and after (right) treatment with a bifurcated stent graft. (Courtesy of Drs. Elizabeth George and Frank Rybicki, Brigham and Women's Hospital, Boston, MA, with permission.)

TREATMENT ABDOMINAL AORTIC ANEURYSMS

Operative repair of the aneurysm with insertion of a prosthetic graft or endovascular placement of an aortic stent graft (Fig. 301-3) is indicated for abdominal aortic aneurysms of any size that are expanding rapidly or are associated with symptoms. For asymptomatic aneurysms, abdominal aortic aneurysm repair is indicated if the diameter is >5.5 cm. In randomized trials of patients with abdominal aortic aneurysms <5.5 cm, there was no difference in the long-term (5- to 8-year) mortality rate between those followed with ultrasound surveillance and those undergoing elective surgical repair. Thus, serial noninvasive follow-up of smaller aneurysms (<5 cm) is an alternative to immediate repair. The decision to perform an open surgical operation or endovascular repair is based in part on the vascular anatomy and comorbid conditions. Endovascular repair of abdominal aortic aneurysms has a lower short-term morbidity rate but a comparable long-term mortality rate with open surgical reconstruction. Long-term surveillance with CT or MR aortography is indicated after endovascular repair to detect leaks and possible aneurysm expansion.

In surgical candidates, careful preoperative cardiac and general medical evaluations (followed by appropriate therapy for complicating conditions) are essential. Preexisting coronary artery disease, congestive heart failure, pulmonary disease, diabetes mellitus, and advanced age add to the risk of surgery. β -Adrenergic blockers decrease perioperative cardiovascular morbidity and mortality. With careful preoperative cardiac evaluation and postoperative care, the operative mortality rate approximates 1–2%. After acute rupture, the mortality rate of emergent operation is 45–50%. Endovascular repair with stent placement is an alternative approach to treat ruptured aneurysms and may be associated with a lower mortality rate.

ACUTE AORTIC SYNDROMES

The four major acute aortic syndromes are aortic rupture (discussed earlier), aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcer. Aortic dissection is caused by a circumferential or, less frequently, transverse tear of the intima. It often occurs along the right lateral wall of the ascending aorta where the hydraulic shear

stress is high. Another common site is the descending thoracic aorta just below the ligamentum arteriosum. The initiating event is either a primary intimal tear with secondary dissection into the media or a medial hemorrhage that dissects into and disrupts the intima. The pulsatile aortic flow then dissects along the elastic lamellar plates of the aorta and creates a false lumen. The dissection usually propagates distally down the descending aorta and into its major branches, but it may propagate proximally. Distal propagation may be limited by atherosclerotic plaque. In some cases, a secondary distal intimal disruption occurs, resulting in the reentry of blood from the false to the true lumen.

There are at least two important pathologic and radiologic variants of aortic dissection: intramural hematoma without an intimal flap and penetrating atherosclerotic ulcer. Acute intramural hematoma is thought to result from rupture of the vasa vasorum with hemorrhage into the wall of the aorta. Most of these hematomas occur in the descending thoracic aorta. Acute intramural hematomas may progress to dissection and rupture. Penetrating atherosclerotic ulcers are caused by erosion of a plaque into the aortic media, are usually localized, and are not associated with extensive propagation. They are found primarily in the middle and distal portions of the descending thoracic aorta and are associated with extensive atherosclerotic disease. The ulcer can erode beyond the internal elastic lamina, leading to medial hematoma, and may progress to false aneurysm formation or rupture.

Several classification schemes have been developed for thoracic aortic dissections. DeBakey and colleagues initially classified aortic dissections as type I, in which an intimal tear occurs in the ascending aorta but involves the descending aorta as well; type II, in which the dissection is limited to the ascending aorta; and type III, in which the intimal tear is located in the descending aorta with distal propagation of the dissection (Fig. 301-4). Another classification (Stanford) is that of type A, in which the dissection involves the ascending aorta (proximal dissection), and type B, in which it is limited to the arch and/or descending aorta (distal dissection). From a management standpoint, classification of aortic dissections and intramural hematomas into type A or B is more practical and useful, since DeBakey types I and II are managed in a similar manner.

The factors that predispose to aortic dissection include those associated with medial degeneration and others that increase aortic wall stress (Table 301-1). Systemic hypertension is a coexisting condition in

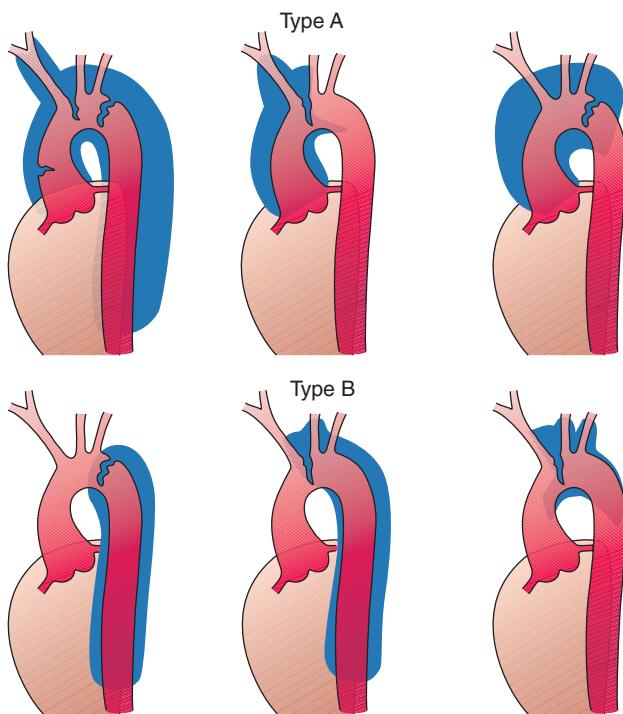


FIGURE 301-4 Classification of aortic dissections. Stanford classification: Type A dissections (top) involve the ascending aorta independent of site of tear and distal extension; type B dissections (bottom) involve transverse and/or descending aorta without involvement of the ascending aorta. DeBakey classification: Type I dissection involves ascending to descending aorta (top left); type II dissection is limited to ascending or transverse aorta, without descending aorta (top center + top right); type III dissection involves descending aorta only (bottom left). (From DC Miller, In RM Doroghazi, EE Slater [eds]: *Aortic Dissection*. New York, McGraw-Hill, 1983, with permission.)

70% of patients. Aortic dissection is the major cause of morbidity and mortality in patients with Marfan's syndrome (Chap. 427) or Loeys-Dietz syndrome, and similarly may affect patients with Ehlers-Danlos syndrome. The incidence also is increased in patients with inflammatory aortitis (i.e., Takayasu's arteritis, giant cell arteritis), congenital aortic valve anomalies (e.g., bicuspid valve), coarctation of the aorta, and a history of aortic trauma. In addition, the risk of dissection is increased in otherwise normal women during the third trimester of pregnancy. Aortic dissection also may occur as a consequence of weight lifting, cocaine use, or deceleration injury.

CLINICAL MANIFESTATIONS

The peak incidence of aortic dissection is in the sixth and seventh decades. Men are more affected than women by a ratio of 2:1. The presentations of aortic dissection and its variants are the consequences of intimal tear, dissecting hematoma, occlusion of involved arteries, and compression of adjacent tissues. Acute aortic dissection presents with the sudden onset of pain (Chap. 19), which often is described as very severe and tearing and is associated with diaphoresis. The pain may be localized to the front or back of the chest, often the interscapular region, and typically migrates with propagation of the dissection. Other symptoms include syncope, dyspnea, and weakness. Physical findings may include hypertension or hypotension, loss of pulses, aortic regurgitation, pulmonary edema, and neurologic findings due to carotid artery obstruction (hemiplegia, hemianesthesia) or spinal cord ischemia (paraplegia). Bowel ischemia, hematuria, and myocardial ischemia have all been observed. These clinical manifestations reflect complications resulting from the dissection occluding the major arteries. Furthermore, clinical manifestations may result from the compression of adjacent structures (e.g., superior cervical ganglia, superior vena cava, bronchus, esophagus) by the expanding dissection, causing aneurysmal dilation, and include Horner's syndrome, superior

vena cava syndrome, hoarseness, dysphagia, and airway compromise. Hemopericardium and cardiac tamponade may complicate a type A lesion with retrograde dissection. Acute aortic regurgitation is an important and common (>50%) complication of proximal dissection. It is the outcome of either a circumferential tear that widens the aortic root or a disruption of the annulus by a dissecting hematoma that tears a leaflet(s) or displaces it, inferior to the line of closure. Signs of aortic regurgitation include bounding pulses, a wide pulse pressure, a diastolic murmur often radiating along the right sternal border, and evidence of congestive heart failure. The clinical manifestations depend on the severity of the regurgitation.

In dissections involving the ascending aorta, the chest x-ray often reveals a widened superior mediastinum. A pleural effusion (usually left-sided) also may be present. This effusion is typically serosanguineous and not indicative of rupture unless accompanied by hypotension and falling hematocrit. In dissections of the descending thoracic aorta, a widened mediastinum may be observed on chest x-ray. In addition, the descending aorta may appear to be wider than the ascending portion. An electrocardiogram that shows no evidence of myocardial ischemia is helpful in distinguishing aortic dissection from myocardial infarction. Rarely, the dissection involves the right or, less commonly, left coronary ostium and causes acute myocardial infarction.

The diagnosis of aortic dissection can be established by noninvasive techniques such as echocardiography, CT, and MRI. Aortography is used less commonly because of the accuracy of these noninvasive techniques. Transthoracic echocardiography can be performed simply and rapidly and has an overall sensitivity of 60–85% for aortic dissection. For diagnosing proximal ascending aortic dissections, its sensitivity exceeds 80%; it is less useful for detecting dissection of the arch and descending thoracic aorta. Transesophageal echocardiography requires greater skill and patient cooperation but is very accurate in identifying dissections of the ascending and descending thoracic aorta but not the arch, achieving 98% sensitivity and approximately 90% specificity. Echocardiography also provides important information regarding the presence and severity of aortic regurgitation and pericardial effusion. CT and MRI are both highly accurate in identifying the intimal flap and the extent of the dissection and involvement of major arteries; each has a sensitivity and specificity >90%. They are useful in recognizing intramural hemorrhage and penetrating ulcers. The relative utility of transesophageal echocardiography, CT, and MRI depends on the availability and expertise in individual institutions as well as on the hemodynamic stability of the patient, with CT and MRI obviously less suitable for unstable patients.

TREATMENT AORTIC DISSECTION

Medical therapy should be initiated as soon as the diagnosis is considered. The patient should be admitted to an intensive care unit for hemodynamic monitoring. Unless hypotension is present, therapy should be aimed at reducing cardiac contractility and systemic arterial pressure, and thus shear stress. For acute dissection, unless contraindicated, β -adrenergic blockers should be administered parenterally, using intravenous propranolol, metoprolol, or the short-acting esmolol to achieve a heart rate of approximately 60 beats/min. This should be accompanied by sodium nitroprusside infusion to lower systolic blood pressure to ≤ 120 mmHg. Labetalol (Chap. 298), a drug with both β - and α -adrenergic blocking properties, also may be used as a parenteral agent in acute therapy for dissection.

The calcium channel antagonists verapamil and diltiazem may be used intravenously if nitroprusside or β -adrenergic blockers cannot be employed. The addition of a parenteral angiotensin-converting enzyme (ACE) inhibitor such as enalaprilat to a β -adrenergic blocker also may be considered. Isolated use of a direct vasodilator such as hydralazine is contraindicated because these agents can increase hydraulic shear and may propagate the dissection.

Emergent or urgent surgical correction is the preferred treatment for acute ascending aortic dissections and intramural hematomas (type A) and for complicated type B dissections, including

- PART 10**
- Disorders of the Cardiovascular System**
- 1642** those characterized by propagation, compromise of major aortic branches, impending rupture, or continued pain. Surgery involves excision of the intimal flap, obliteration of the false lumen, and placement of an interposition graft. A composite valve-graft conduit is used if the aortic valve is disrupted. The overall in-hospital mortality rate after surgical treatment of patients with aortic dissection is reported to be 15–25%. The major causes of perioperative mortality and morbidity include myocardial infarction, paraplegia, renal failure, tamponade, hemorrhage, and sepsis. Endoluminal stent grafts may be considered in selected patients. Other transcatheter techniques, such as fenestration of the intimal flaps and stenting of narrowed branch vessels to increase flow to compromised organs, are used in selected patients. For uncomplicated and stable distal dissections and intramural hematomas (type B), medical therapy is the preferred treatment. The in-hospital mortality rate of medically treated patients with type B dissection is 10–20%. Long-term therapy for patients with aortic dissection and intramural hematomas (with or without surgery) consists of control of hypertension and reduction of cardiac contractility with the use of beta blockers plus other antihypertensive agents, such as ACE inhibitors or calcium antagonists. Patients with chronic type B dissection and intramural hematomas should be followed on an outpatient basis every 6–12 months with contrast-enhanced CT or MRI to detect propagation or expansion. Patients with Marfan's syndrome are at high risk for postdissection complications. The long-term prognosis for patients with treated dissections is generally good with careful follow-up; the 10-year survival rate is approximately 60%.

CHRONIC ATHEROSCLEROTIC OCCLUSIVE DISEASE

Atherosclerosis may affect the thoracic and abdominal aorta. Occlusive aortic disease caused by atherosclerosis usually is confined to the distal abdominal aorta below the renal arteries. Frequently the disease extends to the iliac arteries (**Chap. 302**). Claudication characteristically involves the buttocks, thighs, and calves and may be associated with impotence in males (Leriche's syndrome). The severity of the symptoms depends on the adequacy of collaterals. With sufficient collateral blood flow, a complete occlusion of the abdominal aorta may occur without the development of ischemic symptoms. The physical findings include the absence of femoral and other distal pulses bilaterally and the detection of an audible bruit over the abdomen (usually at or below the umbilicus) and the common femoral arteries. Atrophic skin, loss of hair, and coolness of the lower extremities usually are observed. In advanced ischemia, rubor on dependency and pallor on elevation can be seen.

The diagnosis usually is established by physical examination and noninvasive testing, including leg pressure measurements, Doppler velocity analysis, pulse volume recordings, and duplex ultrasonography. The anatomy may be defined by MRI, CT, or conventional aortography, typically performed when one is considering revascularization. Catheter-based endovascular or operative treatment is indicated in patients with lifestyle-limiting or debilitating symptoms of claudication and patients with critical limb ischemia.

ACUTE AORTIC OCCLUSION

Acute occlusion in the distal abdominal aorta constitutes a medical emergency because it threatens the viability of the lower extremities; it usually results from an occlusive (saddle) embolus that almost always originates from the heart. Rarely, acute occlusion may occur as the result of *in situ* thrombosis in a preexisting severely narrowed segment of the aorta.

The clinical picture is one of acute ischemia of the lower extremities. Severe rest pain, coolness, and pallor of the lower extremities and the absence of distal pulses bilaterally are the usual manifestations. Diagnosis should be established rapidly by MRI, CT, or aortography. Emergency thrombectomy or revascularization is indicated.

AORTITIS

Aortitis, a term referring to inflammatory disease of the aorta, may be caused by large vessel vasculitides such as Takayasu's arteritis and

giant cell arteritis, rheumatic and HLA-B27-associated spondyloarthropathies, Behcet's syndrome, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, Cogan's syndrome, IgG4-related systemic disease, and infections such as syphilis, tuberculosis, and *Salmonella*, or may be associated with retroperitoneal fibrosis. Aortitis may result in aneurysmal dilation and aortic regurgitation, occlusion of the aorta and its branch vessels, or acute aortic syndromes.

TAKAYASU'S ARTERITIS

This inflammatory disease often affects the ascending aorta and aortic arch, causing obstruction of the aorta and its major arteries. Takayasu's arteritis is also termed *pulseless disease* because of the frequent occlusion of the large arteries originating from the aorta. It also may involve the descending thoracic and abdominal aorta and occlude large branches such as the renal arteries. Aortic aneurysms also may occur. The pathology is a panarteritis characterized by mononuclear cells and occasionally giant cells, with marked intimal hyperplasia, medial and adventitial thickening, and, in the chronic form, fibrotic occlusion. The disease is most prevalent in young females of Asian descent but does occur in women of other geographic and ethnic origins and also in young men. During the acute stage, fever, malaise, weight loss, and other systemic symptoms may be evident. Elevations of the erythrocyte sedimentation rate and C-reactive protein are common. The chronic stages of the disease, which is intermittently active, present with symptoms related to large artery occlusion, such as upper extremity claudication, cerebral ischemia, and syncope. The process is progressive, and there is no definitive therapy. Glucocorticoids and immunosuppressive agents are effective in some patients during the acute phase. Surgical bypass or endovascular intervention of a critically stenotic artery may be necessary.

GIANT CELL ARTERITIS

(See also **Chap. 385**) This vasculitis occurs in older individuals and affects women more often than men. Primarily large and medium-size arteries are affected. The pathology is that of focal granulomatous lesions involving the entire arterial wall; it may be associated with polymyalgia rheumatica. Obstruction of medium-size arteries (e.g., temporal and ophthalmic arteries) and major branches of the aorta and the development of aortitis and aortic regurgitation are important complications of the disease. High-dose glucocorticoid therapy may be effective when given early.

RHEUMATIC AORTITIS

Rheumatoid arthritis (**Chap. 380**), ankylosing spondylitis (**Chap. 384**), psoriatic arthritis (**Chap. 384**), reactive arthritis (formerly known as Reiter's syndrome) (**Chap. 384**), relapsing polychondritis, and inflammatory bowel disorders may all be associated with aortitis involving the ascending aorta. The inflammatory lesions usually involve the ascending aorta and may extend to the sinuses of Valsalva, the mitral valve leaflets, and adjacent myocardium. The clinical manifestations are aneurysm, aortic regurgitation, and involvement of the cardiac conduction system.

IDIOPATHIC AORTITIS

Idiopathic abdominal aortitis is characterized by adventitial and periaortic inflammation with thickening of the aortic wall. It is associated with abdominal aortic aneurysms and idiopathic retroperitoneal fibrosis. Affected individuals may present with vague constitutional symptoms, fever, and abdominal pain. Retroperitoneal fibrosis can cause ureteral obstruction and hydronephrosis. Glucocorticoids and immunosuppressive agents may reduce the inflammation.

INFECTIVE AORTITIS

Infective aortitis may result from direct invasion of the aortic wall by bacterial pathogens such as *Staphylococcus*, *Streptococcus*, and *Salmonella* or by fungi. These bacteria cause aortitis by infecting the aorta at sites of atherosclerotic plaque. Bacterial proteases lead to degradation of collagen, and the ensuing destruction of the aortic wall leads to the formation of a saccular aneurysm referred to as a mycotic

aneurysm. Mycotic aneurysms have a predilection for the suprarenal abdominal aorta. The pathologic characteristics of the aortic wall include acute and chronic inflammation, abscesses, hemorrhage, and necrosis. Mycotic aneurysms typically affect the elderly and occur in men three times more frequently than in women. Patients may present with fever, sepsis, and chest, back, or abdominal pain; there may have been a preceding diarrheal illness. Blood cultures are positive in the majority of patients. Both CT and MRI are useful to diagnose mycotic aneurysms. Treatment includes antibiotic therapy and surgical removal of the affected part of the aorta and revascularization of the lower extremities with grafts placed in uninjected tissue.

Syphilitic aortitis is a late manifestation of luetic infection (Chap. 206) that usually affects the proximal ascending aorta, particularly the aortic root, resulting in aortic dilation and aneurysm formation. Syphilitic aortitis occasionally may involve the aortic arch or the descending aorta. The aneurysms may be saccular or fusiform and are usually asymptomatic, but compression of and erosion into adjacent structures may result in symptoms; rupture also may occur.

The initial lesion is an obliterative endarteritis of the vasa vasorum, especially in the adventitia. This is an inflammatory response to the invasion of the adventitia by the spirochetes. Destruction of the aortic media occurs as the spirochetes spread into this layer, usually via the lymphatics accompanying the vasa vasorum. Destruction of collagen and elastic tissues leads to dilation of the aorta, scar formation, and calcification. These changes account for the characteristic radiographic appearance of linear calcification of the ascending aorta.

The disease typically presents as an incidental chest radiographic finding 15–30 years after initial infection. Symptoms may result from aortic regurgitation, narrowing of coronary ostia due to syphilitic aortitis, compression of adjacent structures (e.g., esophagus), or rupture. Diagnosis is established by a positive serologic test, i.e., rapid plasmin reagin (RPR) or fluorescent treponemal antibody. Treatment includes penicillin and surgical excision and repair.

Clinical Evaluation Fewer than 50% of patients with PAD are symptomatic, although many have a slow or impaired gait. The most common symptom is intermittent claudication, which is defined as a pain, ache, cramp, numbness, or a sense of fatigue in the muscles; it occurs during exercise and is relieved by rest. The site of claudication is distal to the location of the occlusive lesion. For example, buttock, hip, thigh, and calf discomfort occurs in patients with aortoiliac disease, whereas calf claudication develops in patients with femoral-popliteal disease. Symptoms are far more common in the lower than in the upper extremities because of the higher incidence of obstructive lesions in the former region. In patients with severe arterial occlusive disease in whom resting blood flow cannot accommodate basal nutritional needs of the tissues, critical limb ischemia may develop. Patients complain of rest pain or a feeling of cold or numbness in the foot and toes. Frequently, these symptoms occur at night when the legs are horizontal and improve when the legs are in a dependent position. With severe ischemia, rest pain may be persistent.

Important physical findings of PAD include decreased or absent pulses distal to the obstruction, the presence of bruits over the narrowed artery, and muscle atrophy. With more severe disease, hair loss, thickened nails, smooth and shiny skin, reduced skin temperature, and pallor or cyanosis are common physical signs. In patients with critical limb ischemia, ulcers or gangrene may occur. Elevation of the legs and repeated flexing of the calf muscles produce pallor of the soles of the feet, whereas rubor, secondary to reactive hyperemia, may develop when the legs are dependent. The time required for rubor to develop or for the veins in the foot to fill when the patient's legs are transferred from an elevated to a dependent position is related to the severity of the ischemia and the presence of collateral vessels. Patients with severe ischemia may develop peripheral edema because they keep their legs in a dependent position much of the time. Ischemic neuropathy can result in numbness and hyporeflexia.

Noninvasive Testing The history and physical examination are often sufficient to establish the diagnosis of PAD. An objective assessment of the presence and severity of disease is obtained by noninvasive techniques. Arterial pressure can be recorded noninvasively in the legs by placement of sphygmomanometric cuffs at the ankles and the use of a Doppler device to auscultate or record blood flow from the dorsalis pedis and posterior tibial arteries. Normally, systolic blood pressure in the legs and arms is similar. Indeed, ankle pressure may be slightly higher than arm pressure due to pulse-wave amplification. In the presence of hemodynamically significant stenoses, the systolic blood pressure in the leg is decreased. Thus, the ratio of the ankle and brachial artery pressures (termed the *ankle:brachial index*, or ABI) is 1.00–1.40 in normal individuals. ABI values of 0.91–0.99 are considered "borderline," and those <0.90 are abnormal and diagnostic of PAD. ABIs >1.40 indicate noncompressible arteries secondary to vascular calcification.

Other noninvasive tests include segmental pressure measurements, segmental pulse volume recordings, duplex ultrasonography (which combines B-mode imaging and Doppler flow velocity waveform analysis examination), transcutaneous oximetry, and stress testing (usually using a treadmill). Placement of pneumatic cuffs enables assessment of systolic pressure along the legs. The presence of pressure gradients between sequential cuffs provides evidence of the presence and location of hemodynamically significant stenoses. In addition, the amplitude of the pulse volume contour becomes blunted in the presence of significant PAD. Duplex ultrasonography is used to image and detect stenotic lesions in native arteries and bypass grafts.

Treadmill testing allows the physician to assess functional limitations objectively. Decline of the ABI immediately after exercise provides further support for the diagnosis of PAD in patients with equivocal symptoms and findings on examination.

Magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and conventional catheter-based angiography should not be used for routine diagnostic testing but are performed before potential revascularization (Fig. 302-1). Each test is useful in defining the anatomy to assist planning for endovascular and surgical revascularization procedures.

302 Arterial Diseases of the Extremities

Mark A. Creager, Joseph Loscalzo

PERIPHERAL ARTERY DISEASE

Peripheral artery disease (PAD) is defined as a clinical disorder in which there is a stenosis or occlusion in the aorta or the arteries of the limbs. Atherosclerosis is the leading cause of PAD in patients >40 years old. Other causes include thrombosis, embolism, vasculitis, fibromuscular dysplasia, entrapment, cystic adventitial disease, and trauma. The highest prevalence of atherosclerotic PAD occurs in the sixth and seventh decades of life. As in patients with atherosclerosis of the coronary and cerebral vasculature, there is an increased risk of developing PAD in cigarette smokers and in persons with diabetes mellitus, hypercholesterolemia, hypertension, or renal insufficiency.

Pathology (See also Chap. 291) Segmental lesions that cause stenosis or occlusion are usually localized to large and medium-size vessels. The pathology of the lesions includes atherosclerotic plaques with calcium deposition, thinning of the media, patchy destruction of muscle and elastic fibers, fragmentation of the internal elastic lamina, and thrombi composed of platelets and fibrin. The primary sites of involvement are the abdominal aorta and iliac arteries (30% of symptomatic patients), the femoral and popliteal arteries (80–90% of patients), and the more distal vessels, including the tibial and peroneal arteries (40–50% of patients). Atherosclerotic lesions occur preferentially at arterial branch points, which are sites of increased turbulence, altered shear stress, and intimal injury. Involvement of the distal vasculature is most common in elderly individuals and patients with diabetes mellitus.

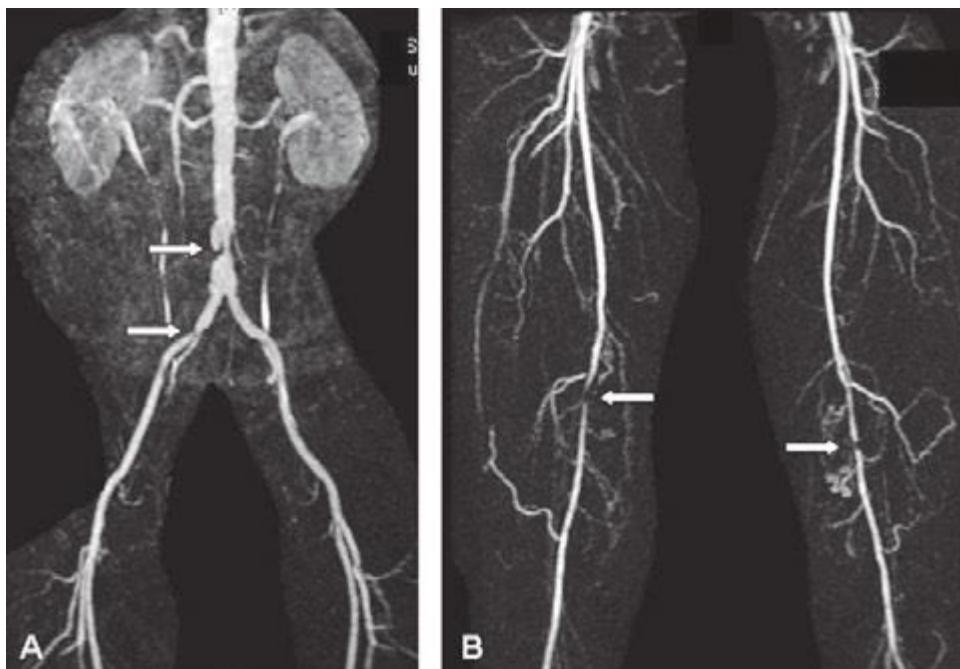


FIGURE 302-1 Magnetic resonance angiography of a patient with intermittent claudication, showing stenoses of the distal abdominal aorta and right iliac common iliac artery (**A**) and stenoses of the right and left superficial femoral arteries (**B**). (Courtesy of Dr. Edwin Gravereaux, with permission.)

Prognosis The natural history of patients with PAD is influenced primarily by the extent of coexisting coronary artery and cerebrovascular disease. Approximately one-third to one-half of patients with symptomatic PAD have evidence of coronary artery disease (CAD) based on clinical presentation and electrocardiogram, and over one-half have significant CAD by coronary angiography. Patients with PAD have a 15–30% 5-year mortality rate and a two- to sixfold increased risk of death from coronary heart disease. Mortality rates are highest in those with the most severe PAD. Measurement of ABI is useful for detecting PAD and identifying persons at risk for future atherothrombotic events. The likelihood of symptomatic progression of PAD is lower than the chance of succumbing to CAD. Approximately 75–80% of nondiabetic patients who present with mild to moderate claudication remain symptomatically stable. Deterioration is likely to occur in the remainder, with approximately 1–2% of the group ultimately developing critical limb ischemia each year. Approximately 25–30% of patients with critical limb ischemia undergo amputation within 1 year. The prognosis is worse in patients who continue to smoke cigarettes or have diabetes mellitus.

TREATMENT PERIPHERAL ARTERY DISEASE

Patients with PAD should receive therapies to reduce the risk of associated cardiovascular events, such as myocardial infarction and death, and to improve limb symptoms, prevent progression to critical limb ischemia, and preserve limb viability. Risk factor modification and antiplatelet therapy should be initiated to improve cardiovascular outcomes. The importance of discontinuing cigarette smoking cannot be overemphasized. The physician must assume a major role in this lifestyle modification. Counseling and adjunctive drug therapy with the nicotine patch, bupropion, or varenicline increase smoking cessation rates and reduce recidivism. It is important to control blood pressure in hypertensive patients. Angiotensin-converting enzyme inhibitors may reduce the risk of cardiovascular events in patients with symptomatic PAD. β -Adrenergic blockers do not worsen claudication and may be used to treat hypertension, especially in patients with coexistent CAD. Treatment of hypercholesterolemia with statins is advocated to reduce the risk of myocardial infarction, stroke, and death. The 2013 ACC/AHA Guideline on the Treatment

of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recommends high intensity statin treatment in patients with atherosclerotic disorders, including peripheral artery disease. Platelet inhibitors, including aspirin and clopidogrel, reduce the risk of adverse cardiovascular events in patients with atherosclerosis and are recommended for patients with symptomatic PAD, including those with intermittent claudication or critical limb ischemia or prior lower extremity revascularization. Dual antiplatelet therapy with both aspirin and clopidogrel is not more effective than aspirin alone in reducing cardiovascular morbidity and mortality rates in patients with PAD. The anticoagulant warfarin is as effective as antiplatelet therapy in preventing adverse cardiovascular events but causes more major bleeding; therefore, it is not indicated to improve outcomes in patients with chronic PAD.

Therapies for intermittent claudication and critical limb ischemia include supportive measures, medications, nonoperative interventions, and surgery. Supportive measures include meticulous care of the feet, which should be kept clean and protected against excessive drying with moisturizing creams. Well-fitting and protective shoes are advised to reduce trauma. Elastic support hose should be avoided, as it reduces blood flow to the skin. In patients with critical limb ischemia, shock blocks under the head of the bed together with a canopy over the feet may improve perfusion pressure and ameliorate some of the rest pain.

Patients with claudication should be encouraged to exercise regularly and at progressively more strenuous levels. Supervised exercise training programs for 30- to 45-min sessions, three to five times per week for at least 12 weeks, prolong walking distance. Patients also should be advised to walk until nearly maximum claudication discomfort occurs and then rest until the symptoms resolve before resuming ambulation. The beneficial effect of supervised exercise training on walking performance in patients with claudication often is similar to or greater than that realized after a revascularization procedure. Pharmacologic treatment of PAD has not been as successful as the medical treatment of CAD (Chap. 293). In particular, vasodilators as a class have not proved to be beneficial. During exercise, peripheral vasodilation occurs distal to sites of significant arterial stenoses. As a result, perfusion pressure falls, often to levels lower than that generated in the interstitial tissue by the exercising muscle. Drugs such as α -adrenergic blocking agents, calcium

channel antagonists, and other vasodilators have not been shown to be effective in patients with PAD.

Cilostazol, a phosphodiesterase inhibitor with vasodilator and antiplatelet properties, increases claudication distance by 40–60% and improves measures of quality of life. The mechanism of action accounting for its beneficial effects is not known. Pentoxyphylline, a substituted xanthine derivative, increases blood flow to the microcirculation and enhances tissue oxygenation. Although several placebo-controlled studies have found that pentoxyphylline increases the duration of exercise in patients with claudication, its efficacy has not been confirmed in all clinical trials. Statins and angiotensin-converting enzyme inhibitors appear promising for treatment of intermittent claudication in initial clinical trials, but more studies are needed to confirm the efficacy of each class of drugs. There is no definitive medical therapy for critical limb ischemia, although several studies have suggested that long-term parenteral administration of vasodilator prostaglandins decreases pain and facilitates healing of ulcers. Enthusiasm for therapy with angiogenic growth factors abated when clinical trials of intramuscular gene transfer of DNA encoding vascular endothelial growth factor, fibroblast growth factor, hepatocyte growth factor, or hypoxia-inducible factor 1a failed to demonstrate improvement in symptoms or outcomes in patients with intermittent claudication or critical limb ischemia. Clinical trials assessing the ability of bone marrow-derived vascular progenitor cells to promote angiogenesis and preserve limb viability in patients with critical limb ischemia are ongoing.

REVASCULARIZATION

Revascularization procedures, including catheter-based and surgical interventions, are usually indicated for patients with disabling, progressive, or severe symptoms of intermittent claudication despite medical therapy and for those with critical limb ischemia. MRA, CTA, or conventional angiography should be performed to assess vascular anatomy in patients who are being considered for revascularization. Nonoperative interventions include percutaneous transluminal angiography (PTA) and stent placement (Chap. 296e). PTA and stenting of the iliac artery are associated with higher success rates than are PTA and stenting of the femoral and popliteal arteries. Approximately 90–95% of iliac PTAs are initially successful, and the 3-year patency rate is >75%. Patency rates may be higher if a stent is placed in the iliac artery. The initial success rates for femoral-popliteal PTA and stenting are approximately 80%, with 60% 3-year patency rates. Patency rates are influenced by the severity of pre-treatment stenoses; the prognosis of occlusive lesions is worse than that of nonocclusive stenotic lesions. The role of drug-eluting stents and drug-coated balloons in PAD is under investigation.

Several operative procedures are available for treating patients with aortoiliac and femoral-popliteal artery disease. The preferred operative procedure depends on the location and extent of the obstruction(s) and the general medical condition of the patient. Operative procedures for aortoiliac disease include aortobifemoral bypass, axillofemoral bypass, femoro-femoral bypass, and aortoiliac endarterectomy. The most frequently used procedure is the aortobifemoral bypass using knitted Dacron grafts. Immediate graft patency approaches 99%, and 5- and 10-year graft patency rates in survivors are >90% and 80%, respectively. Operative complications include myocardial infarction and stroke, infection of the graft, peripheral embolization, and sexual dysfunction from interruption of autonomic nerves in the pelvis. The operative mortality rate ranges from 1–3%, mostly due to ischemic heart disease.

Operative therapy for femoral-popliteal artery disease includes in situ and reverse autogenous saphenous vein bypass grafts, placement of polytetrafluoroethylene (PTFE) or other synthetic grafts, and thromboendarterectomy. The operative mortality rate ranges from 1–3%. The long-term patency rate depends on the type of graft used, the location of the distal anastomosis, and the patency of runoff vessels beyond the anastomosis. Patency rates of femoral-popliteal saphenous vein bypass grafts approach 90% at 1 year and 70–80% at 5 years. Five-year patency rates of infrapopliteal saphenous vein

bypass grafts are 60–70%. In contrast, 5-year patency rates of infrapopliteal PTFE grafts are <30%.

Preoperative cardiac risk assessment may identify individuals who are especially likely to experience an adverse cardiac event during the perioperative period. Patients with angina, prior myocardial infarction, ventricular ectopy, heart failure, or diabetes are among those at increased risk. Stress testing with treadmill exercise (if feasible), radionuclide myocardial perfusion imaging, or echocardiography permits further stratification of risk in these patients (Chap. 296e). Patients with abnormal test results require close supervision and adjunctive management with anti-ischemic medications. β -Adrenergic blockers and statins reduce the risk of postoperative cardiovascular complications. Coronary angiography and coronary artery revascularization compared with optimal medical therapy do not improve outcomes in most patients undergoing peripheral vascular surgery, but cardiac catheterization should be considered in patients with unstable angina and angina refractory to medical therapy as well as those suspected of having left main or three-vessel CAD.

FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia is a hyperplastic disorder that affects medium-size and small arteries. It occurs predominantly in females and usually involves the renal and carotid arteries but can affect extremity vessels such as the iliac and subclavian arteries. The histologic classification includes intimal fibroplasia (also classified as focal), medial dysplasia (multifocal), and adventitial hyperplasia. Medial dysplasia is subdivided into medial fibroplasia, perimedial fibroplasia, and medial hyperplasia. Medial fibroplasia is the most common type and is characterized by alternating areas of thinned media and fibromuscular ridges. The internal elastic lamina usually is preserved. The iliac arteries are the limb arteries most likely to be affected by fibromuscular dysplasia. It is identified angiographically by a “string of beads” appearance caused by thickened fibromuscular ridges contiguous with thin, less-involved portions of the arterial wall, which is typical of medial fibroplasia. When limb vessels are involved, clinical manifestations are similar to those for atherosclerosis, including claudication and rest pain. PTA and surgical reconstruction have been beneficial in patients with debilitating symptoms or threatened limbs.

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans (Buerger’s disease) is an inflammatory occlusive vascular disorder involving small and medium-size arteries and veins in the distal upper and lower extremities. Cerebral, visceral, and coronary vessels may be affected rarely. This disorder develops most frequently in men <40 years of age. The prevalence is higher in Asians and individuals of Eastern European descent. Although the cause of thromboangiitis obliterans is not known, there is a definite relationship to cigarette smoking in patients with this disorder.

In the initial stages of thromboangiitis obliterans, polymorphonuclear leukocytes infiltrate the walls of the small and medium-size arteries and veins. The internal elastic lamina is preserved, and a cellular, inflammatory thrombus develops in the vascular lumen. As the disease progresses, mononuclear cells, fibroblasts, and giant cells replace the neutrophils. Later stages are characterized by perivascular fibrosis, organized thrombus, and recanalization.

The clinical features of thromboangiitis obliterans often include a triad of claudication of the affected extremity, Raynaud’s phenomenon, and migratory superficial vein thrombophlebitis. Claudication usually is confined to the calves and feet or the forearms and hands because this disorder primarily affects distal vessels. In the presence of severe digital ischemia, trophic nail changes, painful ulcerations, and gangrene may develop at the tips of the fingers or toes. The physical examination shows normal brachial and popliteal pulses but reduced or absent radial, ulnar, and/or tibial pulses. MRA, CTA, and conventional arteriography are helpful in making the diagnosis. Smooth, tapering segmental lesions in the distal vessels are characteristic, as are

collateral vessels at sites of vascular occlusion. Proximal atherosclerotic disease is usually absent. The diagnosis can be confirmed by excisional biopsy and pathologic examination of an involved vessel.

There is no specific treatment except abstention from tobacco. The prognosis is worse in individuals who continue to smoke, but results are discouraging even in those who stop smoking. Arterial bypass of the larger vessels may be used in selected instances, as well as local debridement, depending on the symptoms and severity of ischemia. Antibiotics may be useful; anticoagulants and glucocorticoids are not helpful. If these measures fail, amputation may be required.

TREATMENT

ACUTE LIMB ISCHEMIA

Once the diagnosis is made, the patient should be anticoagulated with intravenous heparin to prevent propagation of the clot. In cases of severe ischemia of recent onset, particularly when limb viability is jeopardized, immediate intervention to ensure reperfusion is indicated. Catheter-directed thrombolysis/thrombectomy, surgical thromboembolectomy, and arterial bypass procedures are used to restore blood flow to the ischemic extremity promptly, particularly when a large proximal vessel is occluded.

Intraarterial thrombolytic therapy with recombinant tissue plasminogen activator, reteplase, or tenecteplase is most effective when acute arterial occlusion is recent (<2 weeks) and caused by a thrombus in an atherosclerotic vessel, arterial bypass graft, or occluded stent. Thrombolytic therapy is also indicated when the patient's overall condition contraindicates surgical intervention or when smaller distal vessels are occluded, thus preventing surgical access. Meticulous observation for hemorrhagic complications is required during intraarterial thrombolytic therapy. Another endovascular approach to thrombus removal is percutaneous mechanical thrombectomy using devices that employ hydrodynamic forces or rotating baskets to fragment and remove the clot. These treatments may be used alone but usually are used in conjunction with pharmacologic thrombolysis. Surgical revascularization is preferred when restoration of blood flow must occur within 24 h to prevent limb loss or when symptoms of occlusion have been present for more than 2 weeks. Amputation is performed when the limb is not viable, as characterized by loss of sensation, paralysis, and the absence of Doppler-detected blood flow in both arteries and veins.

If the limb is not in jeopardy, a more conservative approach that includes observation and administration of anticoagulants may be taken. Anticoagulation prevents recurrent embolism and reduces the likelihood of thrombus propagation; it can be initiated with intravenous heparin and followed by oral warfarin. Recommended doses are the same as those used for deep vein thrombosis (*Chap. 300*). Emboli resulting from infective endocarditis, the presence of prosthetic heart valves, or atrial myxoma often require surgical intervention to remove the cause.

ATHEROEMBOLISM

Atheroembolism is another cause of limb ischemia. In this condition, multiple small deposits of fibrin, platelets, and cholesterol debris embolize from proximal atherosclerotic lesions or aneurysmal sites. Large protruding aortic atheromas are a source of emboli that may lead to limb ischemia, as well as stroke and renal insufficiency. Atheroembolism may occur after intraarterial procedures. Since atheroemboli to limbs tend to lodge in the small vessels of the muscle and skin and may not occlude the large vessels, distal pulses usually remain palpable. Patients complain of acute pain and tenderness at the site of embolization. Digital vascular occlusion may result in ischemia and the "blue toe" syndrome; digital necrosis and gangrene may develop (*Fig. 302-2*). Localized areas of tenderness, pallor, and livedo reticularis (see below) occur at sites of emboli. Skin or muscle biopsy may demonstrate cholesterol crystals.

Ischemia resulting from atheroemboli is notoriously difficult to treat. Usually neither surgical revascularization procedures nor thrombolytic therapy is helpful because of the multiplicity, composition, and distal location of the emboli. There is limited evidence that anti-thrombotic therapy with platelet inhibitors or anticoagulants prevents atheroembolism. Statins may stabilize plaque and potentially reduce the risk of atheroembolism. Surgical intervention to remove or bypass the atherosclerotic vessel or aneurysm that causes the recurrent atheroemboli may be necessary.

THORACIC OUTLET COMPRESSION SYNDROME

This is a symptom complex resulting from compression of the neurovascular bundle (artery, vein, or nerves) at the thoracic outlet as it courses through the neck and shoulder. Cervical ribs, abnormalities of

VASCULITIS

Other vasculitides may affect the arteries that supply the upper and lower extremities. **Takayasu's arteritis and giant cell (temporal) arteritis are discussed in Chap. 385.**

ACUTE LIMB ISCHEMIA

Acute limb ischemia occurs when arterial occlusion results in the sudden cessation of blood flow to an extremity. The severity of ischemia and the viability of the extremity depend on the location and extent of the occlusion and the presence and subsequent development of collateral blood vessels. Principal causes of acute arterial occlusion include embolism, thrombus *in situ*, arterial dissection, and trauma.

The most common sources of arterial emboli are the heart, aorta, and large arteries. Cardiac disorders that cause thromboembolism include atrial fibrillation, both chronic and paroxysmal; acute myocardial infarction; ventricular aneurysm; cardiomyopathy; infectious and marantic endocarditis; thrombi associated with prosthetic heart valves; and atrial myxoma. Emboli to the distal vessels may also originate from proximal sites of atherosclerosis and aneurysms of the aorta and large vessels. Less frequently, an arterial occlusion results paradoxically from a venous thrombus that has entered the systemic circulation via a patent foramen ovale or another septal defect. Arterial emboli tend to lodge at vessel bifurcations because the vessel caliber decreases at those sites; in the lower extremities, emboli lodge most frequently in the femoral artery, followed by the iliac artery, aorta, and popliteal and tibiofemoral arteries.

Acute arterial thrombosis *in situ* occurs most frequently in atherosclerotic vessels at the site of an atherosclerotic plaque or aneurysm and in arterial bypass grafts. Trauma to an artery may disrupt continuity of blood flow and cause acute limb ischemia via formation of an acute arterial thrombus or by disruption of an artery's integrity and extravasation of blood. Arterial occlusion may complicate arterial punctures and placement of catheters; it also may result from arterial dissection if the intimal flap obstructs the artery. Less common causes include thoracic outlet compression syndrome, which causes subclavian artery occlusion, and entrapment of the popliteal artery by abnormal placement of the medial head of the gastrocnemius muscle. Polycythemia and hypercoagulable disorders (*Chaps. 131 and 141*) are also associated with acute arterial thrombosis.

CLINICAL FEATURES

The symptoms of an acute arterial occlusion depend on the location, duration, and severity of the obstruction. Often, severe pain, paresthesia, numbness, and coldness develop in the involved extremity within 1 hour. Paralysis may occur with severe and persistent ischemia. Physical findings include loss of pulses distal to the occlusion, cyanosis or pallor, mottling, decreased skin temperature, muscle stiffening, loss of sensation, weakness, and/or absent deep tendon reflexes. If acute arterial occlusion occurs in the presence of an adequate collateral circulation, as is often the case in acute graft occlusion, the symptoms and findings may be less impressive. In this situation, the patient complains about an abrupt decrease in the distance walked before claudication occurs or of modest pain and paresthesia. Pallor and coolness are evident, but sensory and motor functions generally are preserved. The diagnosis of acute limb ischemia is usually apparent from the clinical presentation. In most circumstances, MRA, CTA, or catheter-based arteriography is used to confirm the diagnosis and demonstrate the location and extent of arterial occlusion.



FIGURE 302-2 Atheroembolism causing cyanotic discoloration and impending necrosis of the toes ("blue toe" syndrome).

the scalenus anticus muscle, proximity of the clavicle to the first rib, or abnormal insertion of the pectoralis minor muscle may compress the subclavian artery, subclavian vein, and brachial plexus as these structures pass from the thorax to the arm. Depending on the structures affected, thoracic outlet compression syndrome is divided into arterial, venous, and neurogenic forms. Patients with neurogenic thoracic outlet compression may develop shoulder and arm pain, weakness, and paresthesias. Patients with arterial compression may experience claudication, Raynaud's phenomenon, and even ischemic tissue loss and gangrene. Venous compression may cause thrombosis of the subclavian and axillary veins; this is often associated with effort and is referred to as *Paget-Schroetter syndrome*.

APPROACH TO THE PATIENT

Thoracic Outlet Compression Syndrome

Examination of a patient with arterial thoracic outlet compression syndrome is often normal unless provocative maneuvers are performed. Occasionally, distal pulses are decreased or absent and digital cyanosis and ischemia may be evident.

Several maneuvers that support the diagnosis of arterial thoracic outlet compression syndrome may be used to precipitate symptoms, cause a subclavian artery bruit, and diminish arm pulses. These maneuvers include the abduction and external rotation test, in which the affected arm is abducted by 90° and the shoulder is externally rotated; the scalene maneuver (extension of the neck and rotation of the head to the side of the symptoms); the costoclavicular maneuver (posterior rotation of shoulders); and the hyperabduction maneuver (raising the arm 180°). A chest x-ray will indicate the presence of cervical ribs. Duplex ultrasonography, MRA, and contrast angiography can be performed during provocative maneuvers to demonstrate thoracic outlet compression of the subclavian artery. Neurophysiologic tests such as the electromyogram, nerve conduction studies, and somatosensory evoked potentials may be abnormal if the brachial plexus is involved, but the diagnosis of neurogenic thoracic outlet syndrome is not necessarily excluded if these tests are normal owing to their low sensitivity.

Most patients can be managed conservatively. They should be advised to avoid the positions that cause symptoms. Many patients benefit from shoulder girdle exercises. Surgical procedures such as removal of the first rib and resection of the scalenus anticus muscle are necessary occasionally for relief of symptoms or treatment of ischemia.

POPLITEAL ARTERY ENTRAPMENT

Popliteal artery entrapment typically affects young athletic men and women when the gastrocnemius or popliteus muscle compresses the

popliteal artery and causes intermittent claudication. Thrombosis, embolism, or popliteal artery aneurysm may occur. The pulse examination may be normal unless provocative maneuvers such as ankle dorsiflexion and plantar flexion are performed. The diagnosis is confirmed by duplex ultrasound, CTA, MRA, or conventional angiography. Treatment involves surgical release of the popliteal artery or vascular reconstruction.

POPLITEAL ARTERY ANEURYSM

Popliteal artery aneurysms are the most common peripheral artery aneurysms. Approximately 50% are bilateral. Patients with popliteal artery aneurysms often have aneurysms of other arteries, especially the aorta. The most common clinical presentation is limb ischemia secondary to thrombosis or embolism. Rupture occurs less frequently. Other complications include compression of the adjacent popliteal vein or peroneal nerve. Popliteal artery aneurysm can be detected by palpation and confirmed by duplex ultrasonography. Repair is indicated for symptomatic aneurysms or when the diameter exceeds 2–3 cm, owing to the risk of thrombosis, embolism, or rupture.

ARTERIOVENOUS FISTULA

Abnormal communications between an artery and a vein, bypassing the capillary bed, may be congenital or acquired. Congenital arteriovenous fistulas are a result of persistent embryonic vessels that fail to differentiate into arteries and veins; they may be associated with birthmarks, can be located in almost any organ of the body, and frequently occur in the extremities. Acquired arteriovenous fistulas either are created to provide vascular access for hemodialysis or occur as a result of a penetrating injury such as a gunshot or knife wound or as complications of arterial catheterization or surgical dissection. An uncommon cause of arteriovenous fistula is rupture of an arterial aneurysm into a vein.

The clinical features depend on the location and size of the fistula. Frequently, a pulsatile mass is palpable, and a thrill and a bruit lasting throughout systole and diastole are present over the fistula. With long-standing fistulas, clinical manifestations of chronic venous insufficiency, including peripheral edema; large, tortuous varicose veins; and stasis pigmentation become apparent because of the high venous pressure. Evidence of ischemia may occur in the distal portion of the extremity. Skin temperature is higher over the arteriovenous fistula. Large arteriovenous fistulas may result in an increased cardiac output with consequent cardiomegaly and high-output heart failure ([Chap. 279](#)).

The diagnosis is often evident from the physical examination. Compression of a large arteriovenous fistula may cause reflex slowing of the heart rate (Nicoladoni-Branham sign). Duplex ultrasonography may detect an arteriovenous fistula, especially one that affects the femoral artery and vein at the site of catheter access. CTA and conventional angiography can confirm the diagnosis and are useful in demonstrating the site and size of the arteriovenous fistula.

Management of arteriovenous fistulas may involve surgery, radiotherapy, or embolization. Congenital arteriovenous fistulas are often difficult to treat because the communications may be numerous and extensive, and new communications frequently develop after ligation of the most obvious ones. Many of these lesions are best treated conservatively using elastic support hose to reduce the consequences of venous hypertension. Occasionally, embolization with autologous material, such as fat or muscle, or with hemostatic agents, such as gelatin sponges or silicon spheres, is used to obliterate the fistula. Acquired arteriovenous fistulas are usually amenable to surgical treatment that involves division or excision of the fistula. Occasionally, autogenous or synthetic grafting is necessary to reestablish continuity of the artery and vein.

RAYNAUD'S PHENOMENON

Raynaud's phenomenon is characterized by episodic digital ischemia, manifested clinically by the sequential development of digital blanching, cyanosis, and rubor of the fingers or toes after cold exposure



FIGURE 302-3 Vascular diseases associated with temperature: (A) Raynaud's phenomenon; (B) acrocytosis; (C) livedo reticularis; (D) pernio; (E) erythromelalgia; and (F) frostbite.

and subsequent rewarming. Emotional stress may also precipitate Raynaud's phenomenon. The color changes are usually well demarcated and are confined to the fingers or toes. Typically, one or more digits will appear white when the patient is exposed to a cold environment or touches a cold object (Fig. 302-3A). The blanching, or pallor, represents the ischemic phase of the phenomenon and results from vasospasm of digital arteries. During the ischemic phase, capillaries and venules dilate, and cyanosis results from the deoxygenated blood that is present in these vessels. A sensation of cold or numbness or paresthesia of the digits often accompanies the phases of pallor and cyanosis.

With rewarming, the digital vasospasm resolves, and blood flow into the dilated arterioles and capillaries increases dramatically. This “reactive hyperemia” imparts a bright red color to the digits. In addition to rubor and warmth, patients often experience a throbbing, painful sensation during the hyperemic phase. Although the triphasic color response is typical of Raynaud's phenomenon, some patients may develop only pallor and cyanosis; others may experience only cyanosis.

Raynaud's phenomenon is broadly separated into two categories: idiopathic, termed primary Raynaud's phenomenon, and secondary Raynaud's phenomenon, which is associated with other disease states or known causes of vasospasm (Table 302-1).

Primary Raynaud's Phenomenon This appellation is applied when the secondary causes of Raynaud's phenomenon have been excluded. Over 50% of patients with Raynaud's phenomenon have the primary form. Women are affected about five times more often than men, and the age of presentation is usually between 20 and 40 years. The fingers are involved more frequently than the toes. Initial episodes may involve only one or two fingertips, but subsequent attacks may involve

the entire finger and may include all the fingers. The toes are affected in 40% of patients. Although vasospasm of the toes usually occurs in patients with symptoms in the fingers, it may happen alone. Rarely, the earlobes, the tip of the nose, and the penis are involved. Raynaud's phenomenon occurs frequently in patients who also have migraine headaches or variant angina. These associations suggest that there may be a common predisposing cause for the vasospasm.

Results of physical examination are often entirely normal; the radial, ulnar, and pedal pulses are normal. The fingers and toes may

TABLE 302-1 CLASSIFICATION OF RAYNAUD'S PHENOMENON

Primary or idiopathic Raynaud's phenomenon
Secondary Raynaud's phenomenon
Collagen vascular diseases: scleroderma, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polymyositis, mixed connective tissue disease, Sjögren's syndrome
Arterial occlusive diseases: atherosclerosis of the extremities, thromboangiitis obliterans, acute arterial occlusion, thoracic outlet syndrome
Pulmonary hypertension
Neurologic disorders: intervertebral disk disease, syringomyelia, spinal cord tumors, stroke, poliomyelitis, carpal tunnel syndrome, complex regional pain syndrome
Blood dyscrasias: cold agglutinins, cryoglobulinemia, cryofibrinogenemia, myeloproliferative disorders, lymphoplasmacytic lymphoma
Trauma: vibration injury, hammer hand syndrome, electric shock, cold injury, typing, piano playing
Drugs and toxins: ergot derivatives, methysergide, β -adrenergic receptor blockers, bleomycin, vinblastine, cisplatin, gemcitabine, vinyl chloride

be cool between attacks and may perspire excessively. Thickening and tightening of the digital subcutaneous tissue (*sclerodactyly*) develop in 10% of patients. Angiography of the digits for diagnostic purposes is not indicated.

In general, patients with primary Raynaud's disease have milder clinical manifestations. Fewer than 1% of these patients lose a part of a digit. After the diagnosis is made, the disease improves spontaneously in approximately 15% of patients and progresses in about 30%.

Secondary Causes of Raynaud's Phenomenon Raynaud's phenomenon occurs in 80–90% of patients with systemic sclerosis (scleroderma) and is the presenting symptom in 30% (Chap. 382). It may be the only symptom of scleroderma for many years. Abnormalities of the digital vessels may contribute to the development of Raynaud's phenomenon in this disorder. Ischemic fingertip ulcers may develop and progress to gangrene and autoamputation. About 20% of patients with systemic lupus erythematosus (SLE) have Raynaud's phenomenon (Chap. 378). Occasionally, persistent digital ischemia develops and may result in ulcers or gangrene. In most severe cases, the small vessels are occluded by a proliferative endarteritis. Raynaud's phenomenon occurs in about 30% of patients with dermatomyositis or polymyositis (Chap. 388). It frequently develops in patients with rheumatoid arthritis and may be related to the intimal proliferation that occurs in the digital arteries.

Atherosclerosis of the extremities is a common cause of Raynaud's phenomenon in men >50 years. Thromboangiitis obliterans is an uncommon cause of Raynaud's phenomenon but should be considered in young men, particularly those who are cigarette smokers. The development of cold-induced pallor in these disorders may be confined to one or two digits of the involved extremity. Occasionally, Raynaud's phenomenon may follow acute occlusion of large and medium-size arteries by a thrombus or embolus. Embolization of atheroembolic debris may cause digital ischemia. The latter situation often involves one or two digits and should not be confused with Raynaud's phenomenon. In patients with thoracic outlet compression syndrome, Raynaud's phenomenon may result from diminished intravascular pressure, stimulation of sympathetic fibers in the brachial plexus, or a combination of both. Raynaud's phenomenon occurs in patients with primary pulmonary hypertension (Chap. 304); this is more than coincidental and may reflect a neurohumoral abnormality that affects both the pulmonary and digital circulations.

A variety of blood dyscrasias may be associated with Raynaud's phenomenon. Cold-induced precipitation of plasma proteins, hyperviscosity, and aggregation of red cells and platelets may occur in patients with cold agglutinins, cryoglobulinemia, or cryofibrinogenemia. Hyperviscosity syndromes that accompany myeloproliferative disorders and lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia) should also be considered in the initial evaluation of patients with Raynaud's phenomenon.

Raynaud's phenomenon occurs often in patients whose vocations require the use of vibrating hand tools, such as chain saws or jackhammers. The frequency of Raynaud's phenomenon also seems to be increased in pianists and keyboard operators. Electric shock injury to the hands or frostbite may lead to the later development of Raynaud's phenomenon.

Several drugs have been causally implicated in Raynaud's phenomenon. They include ergot preparations, methysergide, β -adrenergic receptor antagonists, and the chemotherapeutic agents bleomycin, vinblastine, cisplatin, and gemcitabine.

TREATMENT

RAYNAUD'S PHENOMENON

Most patients with Raynaud's phenomenon experience only mild and infrequent episodes. These patients need reassurance and should be instructed to dress warmly and avoid unnecessary cold exposure. In addition to gloves and mittens, patients should protect the trunk, head, and feet with warm clothing to prevent cold-induced reflex vasoconstriction. Tobacco use is contraindicated.

Drug treatment should be reserved for severe cases. 1649 Dihydropyridine calcium channel antagonists such as nifedipine, isradipine, felodipine, and amlodipine decrease the frequency and severity of Raynaud's phenomenon. Diltiazem may be considered but is less effective. The postsynaptic α_1 -adrenergic antagonist prazosin has been used with favorable responses; doxazosin and terazosin may also be effective. Phosphodiesterase type 5 inhibitors such as sildenafil and tadalafil may improve symptoms in patients with secondary Raynaud's phenomenon, as occurs with systemic sclerosis. Digital sympathectomy is helpful in some patients who are unresponsive to medical therapy.

ACROCYANOSIS

In this condition, there is arterial vasoconstriction and secondary dilation of the capillaries and venules with resulting persistent cyanosis of the hands and, less frequently, the feet. Cyanosis may be intensified by exposure to a cold environment. Acrocyanosis may be categorized as primary or secondary to an underlying condition. In primary acrocyanosis, women are affected much more frequently than men, and the age of onset is usually <30 years. Generally, patients are asymptomatic but seek medical attention because of the discoloration. The prognosis is favorable, and pain, ulcers, and gangrene do not occur. Examination reveals normal pulses, peripheral cyanosis, and moist palms (Fig. 302-3B). Trophic skin changes and ulcerations do *not* occur. The disorder can be distinguished from Raynaud's phenomenon because it is persistent and not episodic, the discoloration extends proximally from the digits, and blanching does not occur. Ischemia secondary to arterial occlusive disease can usually be excluded by the presence of normal pulses. Central cyanosis and decreased arterial oxygen saturation are not present. Patients should be reassured and advised to dress warmly and avoid cold exposure. Pharmacologic intervention is not indicated.

Secondary acrocyanosis may result from hypoxemia, vasopressor medications, connective tissue diseases, atheroembolism, antiphospholipid antibodies, cold agglutinins, or cryoglobulins and is associated with anorexia nervosa and postural orthostatic tachycardia syndrome. Treatment should be directed at the underlying disorder.

LIVEDO RETICULARIS

In this condition, localized areas of the extremities develop a mottled or rete (netlike) appearance of reddish to blue discoloration (Fig. 302-3C). The mottled appearance may be more prominent after cold exposure. There are primary and secondary forms of livedo reticularis. The primary, or idiopathic, form of this disorder may be benign or associated with ulcerations. The benign form occurs more frequently in women than in men, and the most common age of onset is the third decade. Patients with the benign form are usually asymptomatic and seek attention for cosmetic reasons. These patients should be reassured and advised to avoid cold environments. No drug treatment is indicated. Primary livedo reticularis with ulceration is also called *atrophie blanche en plaque*. The ulcers are painful and may take months to heal. Secondary livedo reticularis can occur with atheroembolism (see above), SLE and other vasculitides, anticardiolipin antibodies, hyperviscosity, cryoglobulinemia, and Sneddon's syndrome (ischemic stroke and livedo reticularis). Rarely, skin ulcerations develop.

PERNIO (CHILBLAINS)

Pernio is a vasculitic disorder associated with exposure to cold; acute forms have been described. Raised erythematous lesions develop on the lower part of the legs and feet in cold weather (Fig. 302-3D). They are associated with pruritus and a burning sensation, and they may blister and ulcerate. Pathologic examination demonstrates angiitis characterized by intimal proliferation and perivascular infiltration of mononuclear and polymorphonuclear leukocytes. Giant cells may be present in the subcutaneous tissue. Patients should avoid exposure to cold, and ulcers should be kept clean and protected with sterile dressings. Sympatholytic drugs and dihydropyridine calcium channel antagonists may be effective in some patients.

This disorder is characterized by burning pain and erythema of the extremities (Fig. 302-3E). The feet are involved more frequently than the hands, and males are affected more frequently than females. Erythromelalgia may occur at any age but is most common in middle age. It may be primary (also termed erythermalgia) or secondary. Mutations in the SCN9A gene, which encodes the Nav1.7 voltage-gated sodium channel expressed in sensory and sympathetic nerves, has been described in inherited forms of erythromelalgia. The most common causes of secondary erythromelalgia are myeloproliferative disorders such as polycythemia vera and essential thrombocythosis. Less common causes include drugs, such as calcium channel blockers, bromocriptine, and pergolide; neuropathies; connective tissue diseases such as SLE; and paraneoplastic syndromes. Patients complain of burning in the extremities that is precipitated by exposure to a warm environment and aggravated by a dependent position. The symptoms are relieved by exposing the affected area to cool air or water or by elevation. Erythromelalgia can be distinguished from ischemia secondary to peripheral arterial disorders because the peripheral pulses are present. There is no specific treatment; aspirin may produce relief in patients with erythromelalgia secondary to myeloproliferative disease. Treatment of associated disorders in secondary erythromelalgia may be helpful.

FROSTBITE

In this condition, tissue damage results from severe environmental cold exposure or from direct contact with a very cold object. Tissue injury results from both freezing and vasoconstriction. Frostbite usually affects the distal aspects of the extremities or exposed parts of the face, such as the ears, nose, chin, and cheeks. Superficial frostbite involves the skin and subcutaneous tissue. Patients experience pain or paresthesia, and the skin appears white and waxy. After rewarming, there is cyanosis and erythema, wheal-and-flare formation, edema, and superficial blisters. Deep frostbite involves muscle, nerves, and deeper blood vessels. It may result in edema of the hand or foot, vesicles and bullae, tissue necrosis, and gangrene (Fig. 302-3F).

Initial treatment is rewarming, performed in an environment where reexposure to freezing conditions will not occur. Rewarming is accomplished by immersion of the affected part in a water bath at temperatures of 40°–44°C (104°–111°F). Massage, application of ice water, and extreme heat are contraindicated. The injured area should be cleansed with soap or antiseptic, and sterile dressings should be applied. Analgesics are often required during rewarming. Antibiotics are used if there is evidence of infection. The efficacy of sympathetic blocking drugs is not established. After recovery, the affected extremity may exhibit increased sensitivity to cold.

VENOUS ANATOMY

Veins in the extremities can be broadly classified as either superficial or deep. The superficial veins are located between the skin and deep fascia. In the legs, these include the great and small saphenous veins and their tributaries. The great saphenous vein is the longest vein in the body. It originates on the medial side of the foot and ascends anterior to the medial malleolus and then along the medial side of the calf and thigh, and drains into the common femoral vein. The small saphenous vein originates on the dorsolateral aspect of the foot, ascends posterior to the lateral malleolus and along the posterolateral aspect of the calf, and drains into the popliteal vein. The deep veins of the leg accompany the major arteries. There are usually paired peroneal, anterior tibial, and posterior tibial veins in the calf, which converge to form the popliteal vein. Soleal tributary veins drain into the posterior tibial or peroneal veins, and gastrocnemius tributary veins drain into the popliteal vein. The popliteal vein ascends in the thigh as the femoral vein. The confluence of the femoral vein and deep femoral vein form the common femoral vein, which ascends in the pelvis as the external iliac and then common iliac vein, which converges with the contralateral common iliac vein at the inferior vena cava. Perforating veins connect the superficial and deep systems in the legs at multiple locations, normally allowing blood to flow from the superficial to deep veins. In the arms, the superficial veins include the basilic, cephalic, and median cubital veins and their tributaries. The basilic and cephalic veins course along the medial and lateral aspects of the arm, respectively, and these are connected via the median cubital vein in the antecubital fossa. The deep veins of the arms accompany the major arteries and include the radial, ulnar, brachial, axillary, and subclavian veins. The subclavian vein converges with the internal jugular vein to form the brachiocephalic vein, which joins the contralateral brachiocephalic vein to form the superior vena cava. Bicuspid valves are present throughout the venous system to direct the flow of venous blood centrally.

Pathophysiology of Chronic Venous Disease Varicose veins are dilated, bulging, tortuous superficial veins, measuring at least 3 mm in diameter. The smaller and less tortuous reticular veins are dilated intradermal veins, which appear blue-green, measure 1 to 3 mm in diameter, and do not protrude from the skin surface. Telangiectasias, or spider veins, are small, dilated veins, less than 1 mm in diameter, located near the skin surface, and form blue, purple, or red linear, branching, or spider-web patterns.

Varicose veins can be categorized as primary or secondary. Primary varicose veins originate in the superficial system and result from defective structure and function of the valves of the saphenous veins, intrinsic weakness of the vein wall, and high intraluminal pressure. Approximately one-half of these patients have a family history of varicose veins. Other factors associated with primary varicose veins include aging, pregnancy, hormonal therapy, obesity, and prolonged standing. Secondary varicose veins result from venous hypertension, associated with deep venous insufficiency or deep venous obstruction, and incompetent perforating veins that cause enlargement of superficial veins. Arteriovenous fistulas also cause varicose veins in the affected limb.

Chronic venous insufficiency is a consequence of incompetent veins in which there is venous hypertension and extravasation of fluid and blood elements into the tissue of the limb. It may occur in patients with varicose veins but usually is caused by disease in the deep veins. It also is categorized as primary or secondary. Primary deep venous insufficiency is a consequence of an intrinsic structural or functional abnormality in the vein wall or venous valves leading to valvular reflux. Secondary deep venous insufficiency is caused by obstruction and/or valvular incompetence from previous deep vein thrombosis (Chap. 300). Deep venous insufficiency occurs following deep vein thrombosis, as the delicate valve leaflets become thickened and contracted and can no longer prevent retrograde flow of blood and the vein itself becomes rigid and thick walled. Although most veins recanalize after an episode of thrombosis, the large proximal veins may remain occluded. Secondary incompetence develops in distal valves because high pressures distend the vein and separate the leaflets. Other

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CHRONIC VENOUS DISEASE

Chronic venous diseases range from telangiectasias and reticular veins, to varicose veins, to chronic venous insufficiency with edema, skin changes, and ulceration. This section of the chapter will focus on identification and treatment of varicose veins and chronic venous insufficiency, since these problems are encountered frequently by the internist. The estimated prevalence of varicose veins in the United States is approximately 15% in men and 30% in women. Chronic venous insufficiency with edema affects approximately 7.5% of men and 5% of women, and the prevalence increases with age ranging from 2% among those less than 50 years of age to 10% of those 70 years of age. Approximately 20% of patients with chronic venous insufficiency develop venous ulcers.

causes of secondary deep venous insufficiency include May-Thurner syndrome, where the left iliac vein is occluded or stenosed by extrinsic compression from the overlapping right common iliac artery; arteriovenous fistulas resulting in increased venous pressure; congenital deep vein agenesis or hypoplasia; and venous malformations as may occur in Klippel-Trénaunay-Weber and Parkes-Weber syndromes.

Clinical Presentation Patients with venous varicosities are often asymptomatic but still concerned about the cosmetic appearance of their legs. Superficial venous thrombosis may be a recurring problem, and, rarely, a varicosity ruptures and bleeds. Symptoms in patients with varicose veins or venous insufficiency, when they occur, include a dull ache, throbbing or heaviness, or pressure sensation in the legs typically after prolonged standing; these symptoms usually are relieved with leg elevation. Additional symptoms may include cramping, burning, pruritus, leg swelling, and skin ulceration.

The legs are examined in both the supine and standing positions. Visual inspection and palpation of the legs in the standing position confirm the presence of varicose veins. The location and extent of the varicose veins should be noted. Edema, stasis dermatitis, and skin ulceration near the ankle may be present if there is superficial venous insufficiency and venous hypertension. Findings of deep venous insufficiency include increased leg circumference, venous varicosities, edema, and skin changes. The edema, which is usually pitting, may be confined to the ankles, extend above the ankles to the knees, or involve the thighs in severe cases. Over time, the edema may become less pitting and more indurated. Dermatologic findings associated with venous stasis include hyperpigmentation, erythema, eczema, lipodermatosclerosis, *atrophie blanche*, and a phlebectasia corona. Lipodermatosclerosis is the combination of induration, hemosiderin deposition, and inflammation, and typically occurs in the lower part of the leg just above the ankle. Atrophie blanche is a white patch of scar tissue, often with focal telangiectasias and a hyperpigmented border; it usually develops near the medial malleolus. A phlebectasia corona is a fan-shaped pattern of intradermal veins near the ankle or on the foot. Skin ulceration may occur near the medial and lateral malleoli. A venous ulcer is often shallow and characterized by an irregular border, a base of granulation tissue, and the presence of exudate (Fig. 303-1).

Bedside maneuvers can be used to distinguish primary varicose veins from secondary varicose veins caused by deep venous insufficiency. With the contemporary use of venous ultrasound (see below), however, these maneuvers are employed infrequently. The Brodie-Trendelenburg

test is used to determine whether varicose veins are secondary to deep venous insufficiency. As the patient is lying supine, the leg is elevated and the veins allowed to empty. Then, a tourniquet is placed on the proximal part of the thigh and the patient is asked to stand. Filling of the varicose veins within 30 s indicates that the varicose veins are caused by deep venous insufficiency and incompetent perforating veins. Primary varicose veins with superficial venous insufficiency are the likely diagnosis if venous refilling occurs promptly after tourniquet removal. The Perthes test assesses the possibility of deep venous obstruction. A tourniquet is placed on the midthigh after the patient has stood, and the varicose veins are filled. The patient is then instructed to walk for 5 min. A patent deep venous system and competent perforating veins enable the superficial veins below the tourniquet to collapse. Deep venous obstruction is likely to be present if the superficial veins distend further with walking.

Differential Diagnosis The duration of leg edema helps to distinguish chronic venous insufficiency from acute deep vein thrombosis. Lymphedema, as discussed later in this chapter, is often confused with chronic venous insufficiency, and both may occur together. Other disorders that cause leg swelling should be considered and excluded when evaluating a patient with presumed venous insufficiency. Bilateral leg swelling occurs in patients with congestive heart failure, hypoalbuminemia secondary to nephrotic syndrome or severe hepatic disease, myxedema caused by hypothyroidism or pretibial myxedema associated with Graves' disease, and with drugs such as dihydropyridine calcium channel blockers and thiazolidinediones. Unilateral causes of leg swelling also include ruptured leg muscles, hematomas secondary to trauma, and popliteal cysts. Cellulitis may cause erythema and swelling of the affected limb. Leg ulcers may be caused by severe peripheral artery disease and critical limb ischemia; neuropathies, particularly those associated with diabetes; and less commonly, skin cancer, vasculitis, or rarely as a complication of hydroxyurea. The location and characteristics of venous ulcers help to differentiate these from other causes.

Classification of Chronic Venous Disease The CEAP (clinical, etiologic, anatomic, pathophysiologic) classification schema incorporates the range of symptoms and signs of chronic venous disease to characterize its severity. It also broadly categorizes the etiology as congenital, primary, or secondary; identifies the affected veins as superficial, deep, or perforating; and characterizes the pathophysiology as reflux, obstruction, both, or neither (Table 303-1).

Diagnostic Testing The principal diagnostic test to evaluate patients with chronic venous disease is venous duplex ultrasonography. A venous duplex ultrasound examination uses a combination of B-mode imaging and spectral Doppler to detect the presence of venous obstruction and venous reflux in superficial and deep veins. Color-assisted Doppler ultrasound is useful to visualize venous flow patterns. Obstruction may be diagnosed by absence of flow, the presence of an echogenic thrombus within the vein, or failure of the vein to collapse when a compression maneuver is applied by the sonographer, the last implicating the presence of an intraluminal thrombus. Venous reflux is detected by prolonged reversal of venous flow direction during a Valsalva maneuver, particularly for the common femoral vein or saphenofemoral junction, or after compression and release of a cuff placed on the limb distal to the area being interrogated.

Some vascular laboratories use air or strange gauge plethysmography to assess the severity of venous reflux and complement findings from the venous ultrasound examination. Venous volume and venous refilling time are measured when the legs are placed in a dependent position and after calf exercise to quantify the severity of venous reflux and the efficiency of the calf muscle pump to affect venous return.

Magnetic resonance, computed tomographic, and conventional venography are rarely required to determine the cause and plan treatment for chronic venous insufficiency unless there is suspicion for pathology that might warrant intervention. These modalities are used to identify obstruction or stenosis of the inferior vena cava and iliofemoral veins, as may occur in patients with previous proximal



FIGURE 303-1 Venous insufficiency with active venous ulcer near the medial malleolus. (Courtesy of Dr. Steven Dean, with permission.)

TABLE 303-1 CEAP (CLINICAL, ETIOLOGIC, ANATOMIC, PATHOPHYSIOLOGIC) CLASSIFICATION**Clinical Classification**

- C0 No visible or palpable signs of venous disease
- C1 Telangiectasias, reticular veins
- C2 Varicose veins
- C3 Edema without skin changes
- C4 Skin changes, including pigmentation, eczema, lipodermatosclerosis, and atrophie blanche
- C5 Healed venous ulcer
- C6 Active venous ulcer

Etiologic Classification

- Ec Congenital
- Ep Primary
- Es Secondary (postthrombotic)
- En No venous etiology identified

Anatomic Classification

- As Superficial veins
- Ap Perforator veins
- Ad Deep veins
- An No venous location identified

Pathophysiologic Classification

- Pr Reflux
- Po Obstruction
- Pr,o Reflux and obstruction
- Pn No venous pathophysiology identifiable

Source: B Eklöf et al: J Vasc Surg 40:1248, 2004.

deep vein thrombosis; occlusion of inferior vena cava filters; extrinsic compression from tumors; and May-Thurner syndrome.

TREATMENT CHRONIC VENOUS DISEASE**SUPPORTIVE MEASURES**

Varicose veins usually are treated with conservative measures. Symptoms often decrease when the legs are elevated periodically, prolonged standing is avoided, and elastic support hose are worn. External compression with elastic stockings or stretch bandages provides a counterbalance to the hydrostatic pressure in the veins. Although compression garments may improve symptoms, they do not prevent progression of varicose veins. Graduated compression stockings with pressures of 20–30 mmHg are suitable for most patients with simple varicose veins, although pressures of 30–40 mmHg may be required for patients with manifestations of venous insufficiency such as edema and ulcers.

Patients with chronic venous insufficiency also should be advised to avoid prolonged standing or sitting; frequent leg elevation is helpful. Graded compression therapy consisting of stockings or multilayered compression bandages is the standard of care for advanced chronic venous insufficiency characterized by edema, skin changes, or venous ulcers defined as CEAP clinical class C3–C6. Graduated compression stockings of 30–40 mmHg are more effective than lesser grades for healing venous ulcers. The length of stocking depends on the distribution of edema. Calf-length stockings are tolerated better by most patients, particularly elderly patients; for patients with varicose veins or edema extending to the thigh, thigh-length stockings or panty hose should be considered. Overweight and obese patients should be advised to lose weight via caloric restriction and exercise.

In addition to a compression bandage or stocking, patients with venous ulcers also may be treated with low adherent absorbent dressings that take up exudates while maintaining a moist environment. Other types of dressings include hydrocolloid (an adhesive dressing comprised of polymers such as carboxymethylcellulose that absorbs exudates by forming a gel), hydrogel (a nonabsorbent

dressing comprising over 80% water or glycerin that moisturizes wounds), foam (an absorbent dressing made with polymers such as polyurethane), and alginate (an absorbent, biodegradable dressing that is derived from seaweed), but there is little evidence that these are more effective than low adherent absorbent dressings. The choice of specific dressing depends on the amount of drainage, presence of infection, and integrity of the skin surrounding the ulcer. Antibiotics are not indicated unless the ulcer is infected. The multilayered compression bandage or graduated compression garment is then put over the dressing.

MEDICAL THERAPIES

There are no drugs approved by the U.S. Food and Drug Administration for the treatment of chronic venous insufficiency. Diuretics may reduce edema, but at the risk of volume depletion and compromise in renal function. Topical steroids may be used for a short period of time to treat inflammation associated with stasis dermatitis. Several herbal supplements, such as horse chestnut seed extract (aescin); flavonoids including diosmin, hesperidin, or the two combined as micronized purified flavonoid fraction; and French maritime pine bark extract, are touted to have venoconstrictive and anti-inflammatory properties. Although meta-analyses have suggested that aescin reduces edema, pruritus, and pain and that micronized purified flavonoid fraction in conjunction with compression therapy facilitates venous ulcer healing, there is insufficient evidence to recommend the general use of these substances in patients with chronic venous insufficiency.

INTERVENTIONAL AND SURGICAL THERAPIES

Ablative procedures, including endovenous thermal ablation, sclerotherapy, and surgery, are used to treat varicose veins in selected patients who have persistent symptoms, great saphenous vein incompetency, and complications of venous insufficiency including dermatitis, edema, and ulcers. Ablative therapy may also be indicated for cosmetic reasons.

Endovenous thermal ablation procedures of the saphenous veins include endovenous laser therapy and radiofrequency ablation. To ablate the great saphenous vein, a catheter is placed percutaneously and advanced from the level of the knee to just below the saphenofemoral junction via ultrasound guidance. Thermal energy is then delivered as the catheter is pulled back. The heat injures the endothelium and media and promotes thrombosis and fibrosis, resulting in venous occlusion. Average 1- and 5-year occlusion rates exceed 90% following endovenous laser therapy and are slightly less after radiofrequency ablation. Deep vein thrombosis of the common femoral vein adjacent to the saphenofemoral junction is an uncommon but potential complication of endovenous thermal ablation. Other adverse effects of thermal ablation procedures include pain, paresthesias, bruising, hematoma, and hyperpigmentation.

Sclerotherapy involves the injection of a chemical into a vein to cause fibrosis and obstruction. Sclerosing agents approved by the U.S. Food and Drug Administration include sodium tetradecyl sulfate, polidocanol, sodium morrhuate, and glycerin. The sclerosing agent is administered as a liquid or mixed with air or CO₂/O₂ to create a foam. It first is injected into the great saphenous vein or its affected tributaries, often with ultrasound guidance. Thereafter, smaller more distal veins and incompetent perforating veins are injected. Following completion of the procedure, elastic bandages are applied, or 30–40 mmHg compression stockings are worn for 1–2 weeks. Average 1- and 5-year occlusion rates are 81% and 74%, respectively, following sclerotherapy. Complications are uncommon and include deep vein thrombosis, hematomas, damage to adjacent saphenous or sural nerves, and infection. Anaphylaxis is a very rare but severe complication.

Surgical therapy usually involves ligation and stripping of the great and small saphenous veins. The procedure is performed under general anesthesia. Incisions are made at the groin and the upper calf. The great saphenous vein is ligated below the saphenofemoral junction, and a wire is inserted into the great saphenous vein and

advanced distally. The proximal part of the great saphenous vein is secured to the wire and retrieved, i.e., stripped, via the calf incision. Stripping of the great saphenous vein below the knee and stripping of the small saphenous vein usually are not performed because of the respective risks of saphenous and sural nerve injury. Complications of great saphenous vein ligation and stripping include deep vein thrombosis, bleeding, hematoma, infection, and nerve injury. Recurrent varicose veins occur in up to 50% patients by 5 years, due to technical failures, deep venous insufficiency, and incompetent perforating veins.

Stab phlebectomy is another surgical treatment for varicose veins. A small incision is made alongside the varicose vein, and it is avulsed by means of a forceps or hook. This procedure may be performed in conjunction with saphenous vein ligation and stripping or thermal ablation. Subfascial endoscopic perforator surgery (SEPS) uses endoscopy to identify and occlude incompetent perforating veins. It also may be performed along with other ablative procedures.

Endovascular interventions, surgical bypass, and reconstruction of the valves of the deep veins are performed when feasible to treat patients with advanced chronic venous insufficiency who have not responded to other therapies. Catheter-based interventions, usually involving placement of endovenous stents, may be considered to treat some patients with chronic occlusions of the iliac veins. Technical success rates exceed 85% in most series, and long-term patency is achieved in approximately 75% of these patients. Iliocaval bypass, femoroiliac venous bypass, and femorofemoral crossover venous bypass are procedures used occasionally to treat iliofemoral vein occlusion; saphenopopliteal vein bypass can be used to treat chronic femoropopliteal vein obstruction. Long-term patency rates for venous bypass procedures generally exceed 60% and are associated with improvement in symptoms. Surgical reconstruction of the valves of the deep veins and valve transfer procedures are used to treat valvular incompetence. Valvuloplasty involves tightening the valve by commissural apposition. With valve transfer procedures, a segment of vein with a competent valve, such as a brachial or axillary vein, or adjacent saphenous or deep femoral vein, is inserted as an interposition graft in the incompetent vein. Both valvuloplasty and vein transfer operations result in ulcer healing in the majority of patients, although success rates are somewhat better with valvuloplasty.

Lymphedema Lymphedema is a chronic condition caused by impaired transport of lymph and characterized by swelling of one or more limbs and occasionally the trunk and genitalia. Fluid accumulates in interstitial tissues when there is an imbalance between lymph production and lymph absorption, a process governed in large part by Starling forces. Deficiency, reflux, or obstruction of lymph vessels perturbs the ability of the lymphatic system to reabsorb proteins that had been filtered by blood vessels, and the tissue osmotic load promotes interstitial accumulation of water. Persistent lymphedema leads to inflammatory and immune responses characterized by infiltration of mononuclear cells, fibroblasts, and adipocytes, leading to adipose and collagen deposition in the skin and subcutaneous tissues.

Lymphatic Anatomy Lymphatic capillaries are blind-ended tubes formed by a single layer of endothelial cells. The absent or widely fenestrated basement membrane of lymphatic capillaries allows access to interstitial proteins and particles. Lymphatic capillaries merge to form microlymphatic precollector vessels, which contain few smooth muscle cells. The precollector vessels drain into collecting lymphatic vessels, which comprise endothelial cells, a basement membrane, smooth muscle, and bafflelet valves. The collecting lymphatic vessels in turn merge to form larger lymphatic conduits. Analogous to venous anatomy, there are superficial and deep lymphatic vessels in the legs, which communicate at the popliteal and inguinal lymph nodes. Pelvic lymphatic vessels drain into the thoracic duct, which ascends from the abdomen to the thorax and connects with the left brachiocephalic

vein. Lymph is propelled centrally by the phasic contractile activity of lymphatic smooth muscle and facilitated by the contractions of contiguous skeletal muscle. The presence of lymphatic valves ensures unidirectional flow.

Etiology Lymphedema may be categorized as primary or secondary (Table 303-2). The prevalence of primary lymphedema is approximately 1.15 per 100,000 persons less than 20 years of age. Females are affected more frequently than males. Primary lymphedema may be caused by agenesis, hypoplasia, hyperplasia, or obstruction of the lymphatic vessels. There are three clinical subtypes: congenital lymphedema, which appears shortly after birth; lymphedema praecox, which has its onset at the time of puberty; and lymphedema tarda, which usually begins after age 35. Familial forms of congenital lymphedema (Milroy's disease) and lymphedema praecox (Meige's disease) may be inherited in an autosomal dominant manner with variable penetrance; autosomal or sex-linked recessive forms are less common. Mutations in genes expressing vascular endothelial growth factor receptor 3 (VEGFR3), which is a determinant of lymphangiogenesis, have been described in patients with Milroy's disease. A mutation on chromosome 15q is associated with the cholestasis-lymphedema syndrome. A mutation in the FOXC2 gene, which encodes a transcription factor

TABLE 303-2 CAUSES OF LYMPHEDEMA

Primary	
	Sporadic (no identified cause)
Genetic disorders	
	Milroy's disease
	Meige's disease
	Lymphedema-distichiasis syndrome
	Cholestasis-lymphedema
	Hypotrichosis-lymphedema-telangiectasia
	Turner's syndrome
	Klinefelter's syndrome
	Trisomy 13, 18, or 21
	Noonan's syndrome
	Klippel-Trénaunay syndrome
	Parkes-Weber syndrome
	Hennekam's syndrome
	Yellow nail syndrome
	Intestinal lymphangiectasia syndrome
	Lymphangiomyomatosis
	Neurofibromatosis type 1
Secondary	
Infection	
	Bacterial lymphangitis (<i>Streptococcus pyogenes</i> , <i>Staphylococcus aureus</i>)
	Lymphogranuloma venereum (<i>Chlamydia trachomatis</i>)
	Filariasis (<i>Wuchereria bancrofti</i> , <i>Brugia malayi</i> , <i>B. timori</i>)
	Tuberculosis
Neoplastic infiltration of lymph nodes	
Lymphoma	
Prostate	
Others	
Surgery or irradiation of axillary or inguinal lymph nodes for treatment of cancer	
Iatrogenic	
	Lymphatic division (during peripheral bypass surgery, varicose vein surgery, or harvesting of saphenous veins)
Miscellaneous	
Contact dermatitis	
Rheumatoid arthritis	
Pregnancy	
Factitious	

that interacts with a signaling pathway involved in the development of lymphatic vessels, has been reported in patients with the lymphedema-distichiasis syndrome, in which lymphedema praecox occurs in patients who also have a double row of eyelashes. A mutation of SOX18, a transcription factor upstream of lymphatic endothelial cell differentiation, has been described in patients with lymphedema, alopecia, and telangiectasias (hypotrichosis, lymphedema, telangiectasia syndrome). Patients with a chromosomal aneuploidy, such as Turner's syndrome, Klinefelter's syndrome, or trisomy 18, 13, or 21, may develop lymphedema. Syndromic vascular anomalies associated with lymphedema include Klippel-Trénaunay syndrome, Parkes-Weber syndrome, and Hennekam's syndrome. Other disorders associated with lymphedema include Noonan's syndrome, yellow nail syndrome, intestinal lymphangiectasia syndrome, lymphangiomatosis, and neurofibromatosis type 1.

Secondary lymphedema is an acquired condition that results from damage to or obstruction of previously normal lymphatic channels. Recurrent episodes of bacterial lymphangitis, usually caused by streptococci, are a very common cause of lymphedema. The most common cause of secondary lymphedema worldwide is lymphatic filariasis, affecting approximately 129 million children and adults worldwide and causing lymphedema and elephantiasis in 14 million of these affected individuals (Chap. 258). Recurrent bacterial lymphangitis by *Streptococcus* may result in chronic lymphedema. Other infectious causes include lymphogranuloma venereum and tuberculosis. In developed countries, the most common secondary cause of lymphedema is surgical excision or irradiation of axillary and inguinal lymph nodes for treatment of cancers, such as breast, cervical, endometrial, and prostate cancer, sarcomas, and malignant melanoma. Lymphedema of the arm occurs in 13% of breast cancer patients after axillary node dissection and in 22% after both surgery and radiotherapy. Lymphedema of the leg affects approximately 15% of patients with cancer after inguinal lymph node dissection. Tumors, such as prostate cancer and lymphoma, also can infiltrate and obstruct lymphatic vessels. Less common causes include contact dermatitis, rheumatoid arthritis, pregnancy, and self-induced or factitious lymphedema after application of tourniquets.

Clinical Presentation Lymphedema is generally a painless condition, but patients may experience a chronic dull, heavy sensation in the leg, and most often they are concerned about the appearance of the leg. Lymphedema of the lower extremity initially involves the foot and gradually progresses up the leg so that the entire limb becomes edematous (Fig. 303-2). In the early stages, the edema is soft and pits easily with pressure. Over time, subcutaneous adipose tissue accumulates, the limb enlarges further and loses its normal contour, and the toes appear square. Thickening of the skin is detected by Stemmer's sign, which is the inability to tent the skin at the base of the toes. Peau d'orange is a term used to describe dimpling of the skin, resembling that of an orange peel, caused by lymphedema. In the chronic stages, the edema no longer pits and the limb acquires a woody texture as the tissues become indurated and fibrotic. The International Society of Lymphology describes four clinical stages of lymphedema (Table 303-3).

Differential Diagnosis Lymphedema should be distinguished from other disorders that cause unilateral leg swelling, such as deep vein thrombosis and chronic venous insufficiency. In the latter condition, the edema is softer, and there is often evidence of a stasis dermatitis, hyperpigmentation, and superficial venous varicosities, as described earlier. Other causes of leg swelling that resemble lymphedema are myxedema and lipedema. Lipedema usually occurs in women and is caused by accumulation of adipose tissue in the leg from the thigh to the ankle with sparing of the feet.

Diagnostic Testing The evaluation of patients with lymphedema should include diagnostic studies to clarify the cause. Abdominal and pelvic ultrasound and computed tomography (CT) can be used to detect obstructing lesions such as neoplasms. Magnetic resonance imaging (MRI) of the affected limb may reveal a honeycomb pattern



A

B

FIGURE 303-2 **A.** Lymphedema characterized by swelling of the leg, nonpitting edema, and squaring of the toes. (Courtesy of Dr. Marie Gerhard-Herman, with permission.) **B.** Advanced chronic stage of lymphedema illustrating the woody appearance of the leg with acanthosis and verrucous overgrowths. (Courtesy of Dr. Jeffrey Olin, with permission.)

characteristic of lymphedema in the epifascial compartment and identify enlarged lymphatic channels and lymph nodes. MRI also is useful to distinguish lymphedema from lipedema. Lymphoscintigraphy and lymphangiography are rarely indicated, but either can be used to confirm the diagnosis or differentiate primary from secondary lymphedema. Lymphoscintigraphy involves the injection of radioactively labeled technetium-containing colloid into the distal subcutaneous tissue of the affected extremity, which is imaged with a scintigraphic camera to visualize lymphatic vessels and lymph nodes. Findings indicative of primary lymphedema include absent or delayed filling of the lymphatic vessels or dermal back flow caused by lymphatic reflux. Findings of secondary lymphedema include dilated lymphatic vessels distal to an area of obstruction. In lymphangiography, iodinated radio-contrast material is injected into a distal lymphatic vessel that has been isolated and cannulated. In primary lymphedema, lymphatic channels are absent, hypoplastic, or ectatic. In secondary lymphedema, lymphatic channels often appear dilated beneath the level of obstruction.

TABLE 303-3 STAGES OF LYMPHEDEMA

Stage 0 (or Ia)

A latent or subclinical condition where swelling is not evident despite impaired lymph transport. It may exist for months or years before overt edema occurs.

Stage I

Early accumulation of fluid relatively high in protein content that subsides with limb elevation. Pitting may occur. An increase in proliferating cells may also be seen.

Stage II

Limb elevation alone rarely reduces tissue swelling, and pitting is manifest. Late in stage II, the limb may or may not pit as excess fat and fibrosis supervene.

Stage III

Lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed.

Source: Adapted from The 2013 Consensus Document of the International Society of Lymphology: Lymphology 46:1, 2013.

The complexities of lymphatic cannulation and the risk of lymphangitis associated with the contrast agent limit the utility of lymphangiography. A novel technique of optical imaging with a near-infrared fluorescence dye may enable quantitative imaging of lymph flow.

TREATMENT LYMPHEDEMA

Patients with lymphedema of the lower extremities must be instructed to take meticulous care of their feet to prevent recurrent lymphangitis. Skin hygiene is important, and emollients can be used to prevent drying. Prophylactic antibiotics are often helpful, and fungal infection should be treated aggressively. Patients should be encouraged to participate in physical activity; frequent leg elevation can reduce the amount of edema. Psychosocial support is indicated to assist patients cope with anxiety or depression related to body image, self-esteem, functional disability, and fear of limb loss.

Physical therapy, including massage to facilitate lymphatic drainage, may be helpful. The type of massage used in decongestive physiotherapy for lymphedema involves mild compression of the skin of the affected extremity to dilate the lymphatic channels and enhance lymphatic motility. Multilayered, compressive bandages are applied after each massage session to reduce recurrent edema. After optimal reduction in limb volume by decongestive physiotherapy, patients can be fitted with graduated compression hose. Occasionally, intermittent pneumatic compression devices can be applied at home to facilitate reduction of the edema. Diuretics are contraindicated and may cause depletion of intravascular volume and metabolic abnormalities.

Liposuction in conjunction with decongestive physiotherapy may be considered to treat lymphedema, particularly postmastectomy lymphedema. Other surgical interventions are rarely used and often not successful in ameliorating lymphedema. Microsurgical lymphaticovenous anastomotic procedures have been performed to rechannel lymph flow from obstructed lymphatic vessels into the venous system. Limb reduction procedures to resect subcutaneous tissue and excessive skin are performed occasionally in severe cases of lymphedema to improve mobility.

Therapeutic lymphangiogenesis has been studied in rodent models of lymphedema, but not as yet in humans. Overexpression of vascular endothelial growth factor (VEGF) C generates new lymphatic vessels and improves lymphedema in a murine model of primary lymphedema, and administration of recombinant VEGF-C or VEGF-D stimulated lymphatic growth in preclinical models of post-surgical lymphedema. Clinical trials in patients with lymphedema are required to determine efficacy of gene transfer (cell-based) therapies for lymphedema.

common diseases such as asthma or chronic obstructive pulmonary disease. The availability of newer drugs has resulted in a radical change in the management of this disease with significant improvement in both quality of life and mortality. A delay in diagnosis results in an obvious delay in the initiation of appropriate treatment. Clinicians should be able to recognize the signs and symptoms of PH and to complete a systematic workup in patients suspected of having it. In this way, early diagnosis, prompt treatment, and improved outcomes for patients become achievable.

PATHOBIOLOGY

Vasoconstriction, vascular proliferation, thrombosis, and inflammation appear to underlie the development of PAH (Fig. 304-1). In long-standing PH, intimal proliferation and fibrosis, medial hypertrophy, and *in situ* thrombosis characterize the pathologic findings in the pulmonary vasculature. Vascular remodeling at earlier stages may be confined to the small pulmonary arteries. As the disease advances, intimal proliferation and pathologic remodeling progress, resulting in decreased compliance and increased elastance of the pulmonary vasculature. The outcome is a progressive increase in the right ventricular afterload or total pulmonary vascular resistance (PVR) and, thus, right ventricular work. In subjects with moderate to severe pulmonary vascular disease with significantly increased PVR, as the resting PVR increases, there will be a corresponding increase in mean pulmonary artery pressure (PAP) until the cardiac output (CO) is compromised and starts to fall. With a decline in CO, the PAP will fall. As CO declines as a result of increased afterload and decreased contractility, tachycardia is a compensatory response. Tachycardia decreases filling time and, thus, preload, and results in a reduced fraction of stroke volume available to distend the pulmonary vascular tree.

Abnormalities in multiple molecular pathways and genes that regulate the pulmonary vascular endothelial and smooth muscle cells have been identified (Table 304-1). These abnormalities include decreased expression of the voltage-regulated potassium channel, mutations in the bone morphogenetic protein receptor-2, increased tissue factor expression, overactivation of the serotonin transporter, hypoxia-induced activation of hypoxia-inducible factor-1 α , and activation of nuclear factor of activated T cells. As a result, there is a decrease in apoptosis of the smooth muscle cells and the emergence of apoptosis-resistant endothelial cells that promote their accumulation and can obliterate the vascular lumen. In addition, thrombin deposition in the pulmonary vasculature from the prothrombotic state that develops as an independent abnormality or as a result of endothelial dysfunction may amplify vascular cell proliferation and the obliterative arteriopathy.

DIAGNOSIS AND CLASSIFICATION

The diagnosis of PH can be missed without a reasonable index of suspicion. Dyspnea is the most common presenting symptom, but this complaint is far from specific for the diagnosis of PH. PH symptoms are insidious and overlap considerably with many common conditions, including asthma and other lung disease and cardiac disease. The symptoms of PH are often nonspecific and variable. Most patients will present with dyspnea and/or fatigue, whereas edema, chest pain, presyncope, and frank syncope are less common and associated with more advanced disease. On examination, there may be evidence of right ventricular failure with elevated jugular venous pressure, lower extremity edema, and ascites. Additionally, the cardiovascular examination may reveal an accentuated P₂ component of the second heart sound, a right-sided S₃ or S₄, and a holosystolic tricuspid regurgitant murmur. It is also important to seek signs of the diseases that are often concurrent with PH: clubbing may be seen in some chronic lung diseases, sclerodactyly and telangiectasia may signify scleroderma, and crackles and systemic hypertension may be clues to left-sided systolic or diastolic heart failure.

Once clinical suspicion is raised, a systematic approach to diagnosis and assessment is essential. An echocardiogram with (if indicated) a *bubble study* is the most important screening test. Echocardiography is important for the diagnosis of PH and often essential for determining the cause. All forms of PH may demonstrate a hypertrophied and

304 Pulmonary Hypertension

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Pulmonary hypertension (PH) is a spectrum of diseases involving the pulmonary vasculature, and is defined as an elevation in pulmonary arterial pressures (mean pulmonary artery pressure >22 mmHg). Pulmonary arterial hypertension (PAH) is a relatively rare form of PH and is characterized by symptoms of dyspnea, chest pain, and syncope. If left untreated, the disease carries a high mortality rate, with the most common cause of death being decompensated right heart failure. There have been significant advances in this field in regard to understanding the pathogenesis, diagnosis, and classification of PAH. Despite these significant advances, there is still a substantial delay in diagnosis of up to 2 years. In many cases, patients whose primary complaint is dyspnea on exertion are frequently misdiagnosed with more

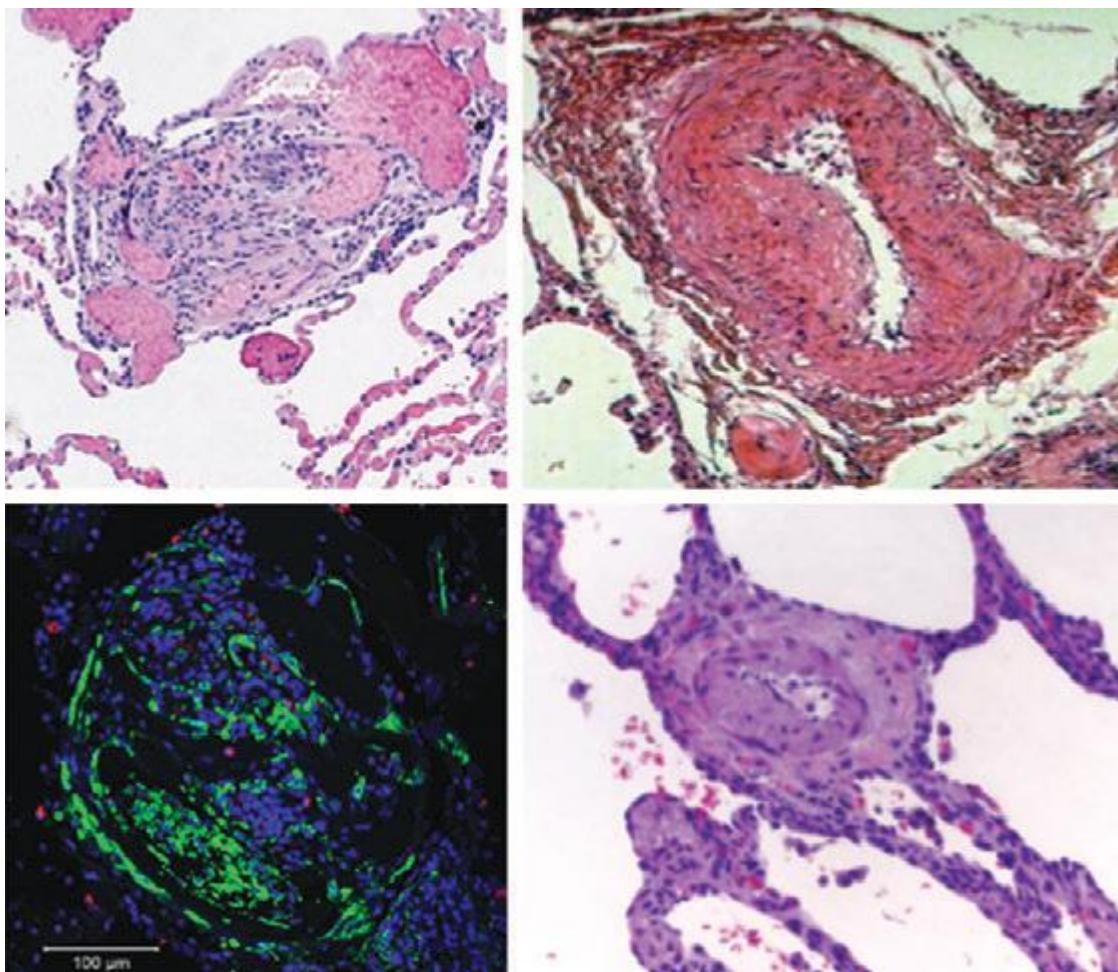


FIGURE 304-1 The left panels show examples of plexogenic pulmonary arteriopathy. These are obstructive and proliferative lesions of the small muscular pulmonary arteries, composed primarily of endothelial cells with intermixed inflammatory cells, myofibroblasts, and connective tissue components. The lower left panel demonstrates proliferating cells (red PCNA stained cells). Panels on the right demonstrate medial hypertrophy of muscular pulmonary arteries. (Photographs on the left are courtesy of Dr. Stephen Archer, Queen's University School of Medicine, Kingston, Ontario, Canada.)

dilated right ventricle (Fig. 304-2) with elevated estimated pulmonary artery systolic pressure. Important additional information can be gleaned about specific etiologies of PH such as valvular disease, left ventricular systolic and diastolic function, intracardiac shunts, and other cardiac diseases.

Although the accuracy of Doppler echocardiography is often debated, a high-quality echocardiogram that is absolutely normal may obviate the need for further evaluation for PH. An echocardiogram is a screening test, whereas invasive hemodynamic monitoring is the gold standard for diagnosis and assessment of disease severity. With a normal echocardiogram, there may still be some concern for PH; this is particularly true if there is unexplained dyspnea or hypoxemia. In this setting, it is reasonable to proceed to right heart catheterization for definitive diagnosis. Alternatively, if the patient has a reasonable functional capacity, a cardiopulmonary exercise test may help to identify a true physiologic limitation as well as differentiate between cardiac and pulmonary causes of dyspnea. If this test is normal, there is no indication for a right heart catheterization. If a cardiovascular limitation to exercise is found, a right heart catheterization should be pursued.

If the echocardiogram or cardiopulmonary exercise test (CPET) suggests PH and the diagnosis is confirmed by catheterization, a reasonable effort must be made to establish the etiology because this will largely determine the therapeutic approach. A stepwise approach to evaluation is outlined below.

Chest imaging and lung function tests are essential because lung disease is an important cause of PH. A sign of PH that may be evident on chest x-ray include enlargement of the central pulmonary arteries

associated with “vascular pruning,” a relative paucity of peripheral vessels (Fig. 304-3). Cardiomegaly, with specific evidence of right atrial and ventricular enlargement, can often be observed. The chest x-ray may also demonstrate significant interstitial lung disease or suggest hyperinflation from obstructive lung disease, which may be the underlying cause or contributor to the development of PH. High-resolution computed tomography (CT) may provide additional useful information. Classic findings of PH on CT include those found on chest x-ray: enlarged pulmonary arteries (Fig. 304-4), peripheral pruning of the small vessels, and enlarged right ventricle and atrium. However, high-resolution CT may also reveal signs of venous congestion including centrilobular ground-glass infiltrate and thickened septal lines. In the absence of left heart disease, these findings suggest pulmonary veno-occlusive disease, a rare cause of PAH that can be quite challenging to diagnose.

CT angiograms are commonly used to evaluate acute thromboembolic disease and have demonstrated excellent sensitivity and specificity for that purpose. Ventilation-perfusion (V/Q) scanning has traditionally been used for screening because of its high sensitivity and its role in qualifying patients for surgical intervention. The role of CT angiograms in the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) remains controversial, even with the advent of spiral CT. Although a negative V/Q virtually rules out CTEPH, some cases may be missed through the use of CT angiograms.

Pulmonary function tests are an important component of the evaluation. Although an isolated reduction in DL_{CO} is the classic finding in PAH, results of pulmonary function tests may also suggest restrictive or obstructive lung diseases as the cause of dyspnea or PH. The 6-minute walk test

TABLE 304-1 COMPONENTS OF THE PATHOGENESIS OF PULMONARY ARTERIAL HYPERTENSION

Alterations in regulators of proliferation

- Growth factors
- Platelet-derived growth factor
- Fibroblast growth factor
- Vascular endothelial growth factor
- Epidermal growth factor
- Transforming growth factor β (TGF- β)
- Bone morphogenetic protein
- Transcription factors
- Matrix metalloproteinases
- Cytokines
- Chemokines
- Mitochondria

Alterations in inflammatory mediators

- Altered T cell subsets
- Monocytes and macrophages
- Interleukin (IL) 1 β
- IL-6
- MCP-1
- RANTES
- Fractalkine

Alterations in vascular tone

- Endothelin
- Nitric oxide
- Serotonin
- Prostaglandin
- K⁺ channels
- Ca²⁺ channels

Hypoxia-induced remodeling

- HIF-1 α
- ROS
- Mitochondria

TGF- β signaling

- BMPR2
- ALK1
- Endoglin
- Smad9
- TGF- β 1

Abbreviations: PDGF, platelet-derived growth factor; EGF, epidermal-derived growth factor; FGF, fetal-derived growth factor; VEGF, vascular endothelial-derived growth factor; MCP-1, monocyte chemoattractant protein-1; IL, interleukin.

is also important to evaluate the degree of exertional hypoxemia and limitation and to monitor progression and response to therapy.

Sleep-disordered breathing is another important cause of PH, but a sleep study is generally necessary only when indicated by the patient's history. Nocturnal desaturation is a common finding in PH, even in the absence of sleep-disordered breathing. Thus, all patients should undergo nocturnal oximetry screening, regardless of whether classic symptoms of obstructive sleep apnea or obesity-hypoventilation syndrome are observed. Laboratory tests that are important for screening include an HIV test when clinically indicated. In addition, all patients should have antinuclear antibodies, rheumatoid factor, and scl-70 antibodies assessed to screen for the most common rheumatologic diseases associated with PH if clinically indicated. Liver function and hepatitis serology tests are important to screen for underlying liver disease. Finally, there is an increasing role for brain natriuretic peptide (BNP) testing in the diagnosis and management of PH. BNP and the N-terminus of its propeptide (NT-proBNP) correlate with right ventricular function, hemodynamic severity, and functional status in PAH.

Right heart catheterization with pulmonary vasodilator testing remains the gold standard both to establish the diagnosis of PH and to enable selection of appropriate medical therapy. The definition of precapillary PH or PAH requires (1) an increased mean pulmonary artery pressure (mPAP ≥ 25 mmHg); (2) a pulmonary capillary wedge pressure (PCWP), left atrial pressure, or left ventricular end-diastolic pressure ≤ 15 mmHg; and (3) PVR > 3 Wood units. Postcapillary PH is differentiated from precapillary PH by a PCWP of ≥ 15 mmHg; this is further differentiated into passive, based on a transpulmonary gradient < 12 mmHg, or reactive, based on a transpulmonary gradient > 12 mmHg and an increased PVR. In either case, the CO may be normal or reduced.

Vasodilators with a short duration of action, such as inhaled nitric oxide, inhaled epoprostenol, or intravenous adenosine, are preferred for vasodilator testing. A decrease in mPAP by ≥ 10 mmHg to an absolute level of ≤ 40 mmHg without a decrease in CO is defined as a positive pulmonary vasodilator response, and responders are considered for long-term treatment with calcium channel blockers (CCBs). Less than 12% of patients are deemed vasoreactive during testing, and even fewer exhibit long-term responsiveness to CCBs. Acute vasodilator-induced reductions in PVR and mPAP predict better long-term survival even among patients not treated with CCBs. The need for invasive hemodynamic measurements to diagnose PH accurately poses an additional problem when evaluating older patients. Physicians are often reluctant to refer older patients for invasive procedures. However, the diagnosis of PH is increasing in the older population, at least in part because of increased awareness of this disease in the elderly and increased use of screening echocardiograms. Furthermore, the increased availability of oral and less complicated therapeutic options has encouraged the referral of older patients for evaluation and treatment.

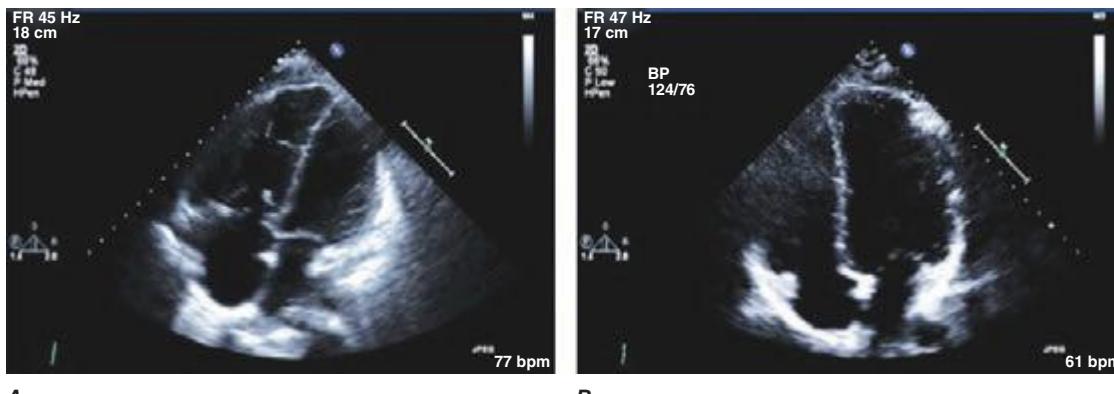


FIGURE 304-2 **A.** Representative echocardiogram showing the apical four-chamber view from a patient with pulmonary hypertension demonstrating an enlarged right atrium and ventricle with some compression of the left side of the heart. **B.** Same echocardiographic view showing a normal echocardiogram.

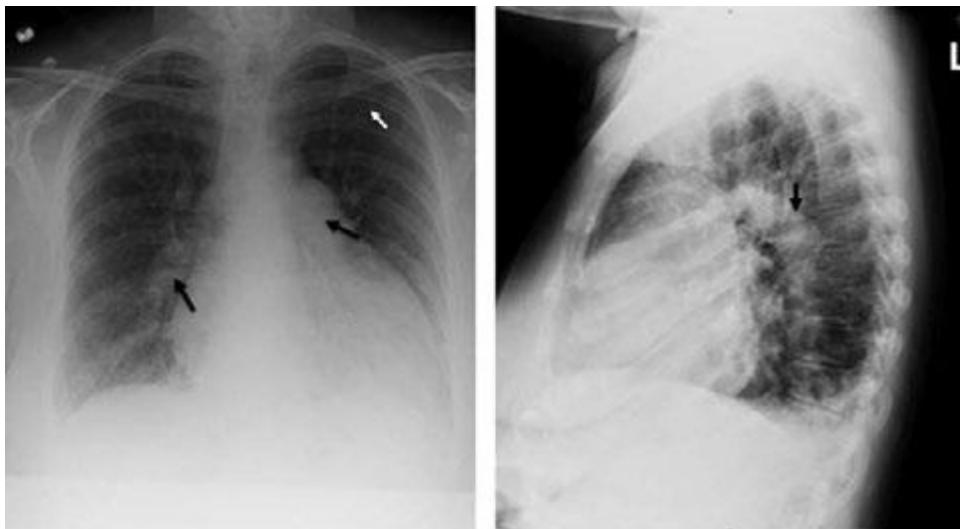


FIGURE 304-3 Posteroanterior (left) and lateral (right) chest radiograph showing enlarged pulmonary arteries (black arrows) and pruning of the distal pulmonary vasculature (white arrow) commonly seen with advanced pulmonary arterial hypertension.

PULMONARY HYPERTENSION AS A COMORBID DISEASE

PAH is just one of a number of disease classifications that affect the pulmonary vascular bed. PH was previously classified as primary or secondary, but as understanding of the various contributing diseases has increased, classification systems have attempted to group these diseases by clinical features to aid in diagnosis. The World Health Organization (WHO) formulated a clinical classification of the various manifestations of PH, of which PAH is a subgroup, according to similarities in pathophysiologic mechanisms and clinical presentation. PH is a diverse mix of pathologies in which the only unifying theme is elevated PAP relative to left atrial pressure. The categorization of PH was designed by convenience for the purpose of facilitating novel treatments to be tested across different presentations and is not based on a molecular understanding of the pathology and is not a guide for management decisions.



FIGURE 304-4 Representative computed tomography scan of the chest demonstrating enlarged main pulmonary arteries. There is also a mosaic pattern evident in both lungs.

The current classification system, last revised in 2013 during the Fifth World Symposium on Pulmonary Hypertension, recognizes five categories of PH, including PAH, PH due to left heart disease, PH due to chronic lung disease, PH associated with chronic thromboemboli, and a group of miscellaneous diseases that only rarely cause PH.

Pulmonary Arterial Hypertension WHO Group I PH, pulmonary arterial hypertension (PAH), is a relatively rare cause of PH. PAH includes a group of diseases that result in pulmonary arterial pre-capillary remodeling marked by intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion, and classic plexiform lesions. PAH is defined as a sustained elevation in resting mPAP ≥ 25 mmHg, PVR > 240 dyne·s/cm⁵, and PCWP or left ventricle end-diastolic pressure of ≤ 15 mmHg based on a right

heart catheterization. With a normal PCWP and an elevated mPAP, these diseases demonstrate an increased transpulmonary gradient (mPAP – PCWP); in addition, the PVR is elevated.

Idiopathic pulmonary arterial hypertension (IPAH) is a progressive disease that leads to right heart failure and death. It is typically seen in young women. The National Institutes of Health registry, the first large registry of patients with PAH, reported that the average age at diagnosis was 36 years, with only 9% of patients with IPAH over the age of 60 at diagnosis. However, the more current clinical data suggest that the patient demographics are changing. The Pulmonary Hypertension Connection registry found that the average age of diagnosis for IPAH was 45 years, with 8.5% of patients older than 70 years at diagnosis. This finding is supported by data from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), the largest cohort of PAH to date, which reported that the average age at diagnosis of IPAH was 44.9 ± 0.6 years.

Other forms of PAH that deserve specific consideration in patients are those associated with HIV, connective tissue disease, and portal hypertension. Although HIV is a rare cause of PAH, this form of PAH is indistinguishable from IPAH and is an important cause of mortality in the HIV-infected population. Importantly, there is no correlation between the stage of HIV infection and the development of PAH.

Among connective tissue diseases, the prevalence of PAH has been established only for systemic sclerosis, especially in those with limited cutaneous scleroderma. Although the average age of scleroderma onset is 30 to 50 years old, patients who eventually develop scleroderma-associated PAH tend to be older at the time of scleroderma diagnosis. Outcomes of scleroderma are closely linked to the development of PAH and are associated with a poor prognosis, although modern therapies have improved outcomes.

Portopulmonary hypertension occurs in 2–10% of patients with established portal hypertension. Its occurrence appears to be independent of the cause of liver disease and is observed in patients with nonhepatic causes of portal hypertension. A hyperdynamic circulatory state is common, as in most patients with advanced liver disease; however, the same pulmonary vascular remodeling observed in other forms of PAH is seen in the pulmonary vascular bed in portopulmonary hypertension. It is important to distinguish this process from hepatopulmonary syndrome, which can also manifest with dyspnea and hypoxemia but is pathophysiologically distinct from portopulmonary hypertension in that abnormal vasodilation of the pulmonary vasculature leads to intrapulmonary shunting.

Pulmonary Hypertension Associated with Left Heart Disease WHO Group II PH includes patients with left heart systolic failure, aortic and

mitral valve disease, and heart failure with preserved ejection fraction (HFpEF). PH can develop as a result of all of these conditions. The hallmark of Group II PH (i.e., PH due to left heart disease) is elevated left atrial pressure with resulting pulmonary venous hypertension. In general, the transpulmonary gradient and PVR remain normal. Although this phenomenon is well described in both left-sided valvular disease and left-sided systolic heart failure, studies suggest that HFpEF may carry a higher overall risk of PH.

Whatever the cause of elevated left atrial pressure (i.e., systolic or diastolic heart failure or valvular disease), the increased pulmonary venous pressure indirectly leads to a rise in pulmonary arterial pressure. The presence of PH portends a poor prognosis in all forms of heart failure. In particular, chronic pulmonary venous hypertension may lead to a reactive pulmonary arterial vasculopathy, seen as an elevated transpulmonary gradient (>12 mmHg) and elevated PVR (>3 Wood units). Pathologically, this process is marked by pulmonary arteriolar remodeling with intimal fibrosis and medial hyperplasia akin to that seen in PAH.

Pulmonary Hypertension Associated with Lung Disease Intrinsic lung disease is the second most common cause of PH, although its actual prevalence is difficult to ascertain. PH has been observed in both chronic obstructive lung disease and interstitial lung disease. It can also be seen in diseases with mixed obstructive/restrictive physiology: bronchiectasis, cystic fibrosis, mixed obstructive restrictive disease marked by fibrosis in the lower lung zones, and emphysema predominantly in the upper lung zones. As in patients with left heart disease, PH associated with chronic lung disease is usually modest; however, some of these patients appear to have PH “out of proportion” to their parenchymal lung disease, suggesting intrinsic pulmonary arterial disease. These patients typically have more severe PH, with results of pulmonary function tests demonstrating a very low DL_{CO} .

Although PH is described in most forms of interstitial lung disease, it has been most extensively studied in idiopathic pulmonary fibrosis; however, the individual studies have been small. Early echocardiographic data suggested that the prevalence of PH in interstitial lung diseases was high, but invasive hemodynamic monitoring suggests that the incidence is considerably lower than originally believed. The diagnosis of PH portends poor outcome in pulmonary fibrosis.

Also included in Group III PH is sleep-disordered breathing. Sleep apnea has long been associated with PH. However, PH associated with sleep-disordered breathing is generally mild.

Pulmonary Hypertension Associated with Chronic Thromboembolic Disease The development of PH after chronic thromboembolic obstruction of the pulmonary arteries is well described, but its incidence is not known. The incidence of PH after a single pulmonary embolic event is thought to be quite low and likely increases following recurrent embolism. The risk factors for developing CTEPH are unclear. Many patients have no history of clinical venous thromboembolism. The pathogenesis of CTEPH is poorly understood. Obstruction of the proximal pulmonary vasculature is important and often the dominant factor; however, additional pulmonary vascular remodeling occurs. Approximately 10–15% of patients will develop a disease very similar clinically and pathologically to PAH after resection of the proximal thrombus.

OTHER DISORDERS AFFECTING THE PULMONARY VASCULATURE

Sarcoidosis Patients with sarcoidosis can develop PH as a result of lung involvement. Consequently, patients with sarcoidosis who present with progressive dyspnea and PH require a thorough evaluation. Although the majority of sarcoidosis patients with PH generally do not respond to therapy for PAH, a subset of patients with sarcoidosis and severe PH do have a beneficial response to therapy.

Sickle Cell Disease Cardiovascular system abnormalities are prominent in the clinical spectrum of sickle cell disease, including PH. The etiology is multifactorial, including hemolysis, hypoxemia, thromboembolism, chronic high CO, and chronic liver disease. The presence of PH in patients with sickle cell disease is rare.

Schistosomiasis Globally, schistosomiasis is one of the most common causes of PH. The development of PH occurs in the setting of hepatosplenic disease and portal hypertension. Studies suggest that inflammation from the infection triggers the pulmonary vascular changes that occur. The diagnosis is confirmed by finding the parasite ova in the urine or stool of patients with symptoms, which can be difficult. The efficacy of therapies directed toward PH in these patients is unknown.

PHARMACOLOGIC TREATMENT OF PAH

PH was a consistently fatal condition with no effective medical treatment options before 1996; however, since that time, there has been an upsurge in the development of novel therapeutic agents for PAH. There are several approved agents for PAH, including prostacyclin and prostacyclin analogues, phosphodiesterase-5 inhibitors, a soluble guanylyl cyclase stimulator, and endothelin receptor antagonists, that have improved the outlook dramatically. Although there is no cure for PAH, current pharmacologic therapies improve morbidity and, in some cases, mortality.

PROSTANOID

In PAH, endothelial dysfunction and platelet activation cause an imbalance of arachidonic acid metabolites with reduced prostacyclin levels and increased thromboxane A₂ production. Prostacyclin (PGI₂) activates cyclic adenosine monophosphate (cAMP)-dependent pathways that mediate vasodilation. PGI₂ also has antiproliferative effects on vascular smooth muscle and inhibits platelet aggregation. Protein levels of prostacyclin synthase are decreased in pulmonary arteries of patients with PAH. This imbalance of mediators is addressed by the exogenous administration of prostanoids as therapy in advanced PAH.

Epoprostenol was the first prostanoid available for the management of PAH. Epoprostenol delivered as a continuous intravenous infusion improves functional capacity and survival in PAH. The efficacy of epoprostenol in WHO functional class 3 and 4 PAH patients was demonstrated in a clinical trial that showed improved quality of life, mPAP, PVR, 6-minute walk distance (6MWD), and mortality. Treprostinil has a longer half-life than epoprostenol (~4 h vs ~6 min), which allows for continuous subcutaneous and intravenous administration. Treprostinil has been shown to improve pulmonary hemodynamics, symptoms, exercise capacity, and survival in PAH.

Inhaled prostacyclins provide the beneficial effects of infused prostacyclin therapy without the inconvenience and side effects (risk of infection and infusion site reactions) of infusion catheters. Both inhaled iloprost and treprostinil have been approved for patients with WHO class 3 and 4 PAH. The main advantage of treprostinil is less frequent administration. Inhaled formulations can be efficacious in moderately symptomatic patients with PAH and may be appropriate when used in combination with an oral medication. Phosphodiesterase-5 (PDE5) inhibitors (e.g., sildenafil) increase cyclic guanosine monophosphate (cGMP) levels and activate cGMP-dependent signaling pathways that also mediate vasodilation and platelet inhibition. Thus, the addition of a PDE5 inhibitor augments the pulmonary hemodynamic and functional capacity benefits of prostanoids in PAH.

Endothelin Receptor Antagonists Endothelin receptor antagonists (ERAs) target endothelin-1 (ET-1), a potent endogenous vasoconstrictor and vascular smooth muscle mitogen that is elevated in PAH patients. Endothelin levels are increased coincident with increased PVR and mPAP and decreased CO and 6MWD.

ERAs block the binding of ET-1 to either endothelin receptor A (ET-A) and/or B (ET-B). ET-A receptors found on pulmonary artery smooth muscle cells mediate vasoconstriction. In the normal pulmonary vasculature, ET-B receptors are found on endothelial cells and mediate vasodilation via production of prostacyclin and nitric oxide as well as ET-1 clearance. Three ERAs approved for use in the United States are bosentan and macitentan both, nonselective receptor antagonists, and ambrisentan, a selective ET-A receptor antagonist.

Studies have shown that both bosentan and macitentan improve hemodynamics and exercise capacity and delay clinical worsening.

Generic Name	Route of Administration	Drug Class	Indication
Epoprostenol	IV	Prostacyclin derivative	Treatment of PAH to improve exercise capacity
Iloprost	Inhaled	Prostacyclin derivative	Treatment of PAH to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration
Treprostinil	IV or SC	Prostacyclin derivative	Treatment of PAH to diminish symptoms associated with exercise
Treprostinil	Inhaled	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Treprostinil	Oral	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Bosentan	Oral	Non-selective endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and to decrease clinical worsening
Ambrisentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and delay clinical worsening
Macitentan	Oral	Non-selective endothelin antagonist	Treatment of PAH to improve exercise capacity and delay clinical worsening
Sildenafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise capacity and delay clinical worsening
Tadalafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise ability
Riociguat	Oral	Soluble guanylyl cyclase stimulator	Treatment of PAH to improve exercise capacity and delay clinical worsening

Abbreviations: FDA, U.S. Food and Drug Administration; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDES, phosphodiesterase-5.

The randomized, placebo-controlled, phase III Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-1 comparing bosentan with placebo demonstrated improved symptoms, 6MWD, and WHO functional class. The Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients (EARLY) comparing bosentan with placebo demonstrated improved PVR and 6MWD.

Several studies, including the phase III, placebo-controlled Ambrisentan in Pulmonary Arterial Hypertension-1 (ARIES-1) trial, suggest that ambrisentan improves exercise tolerance, WHO functional class, hemodynamics, and quality of life in patients with PAH. There are no trial data to evaluate whether the selective ET-A receptor antagonism of ambrisentan has any advantage over the nonselective ET receptor antagonism of bosentan.

Phosphodiesterase Type-5 Inhibitors Nitric oxide derived from endothelial cells activates guanylyl cyclase, which, in turn, generates cGMP in vascular smooth muscle cells and platelets. cGMP is a second messenger that induces vasodilation through relaxation of the arterial smooth muscle cells and inhibits platelet activation. PDE5 enzymes metabolize cGMP. Therefore, cGMP PDE5 inhibitors prolong the vasodilatory effect of nitric oxide, especially within the pulmonary arterial bed where high concentrations of cGMP are found. There

are currently two PDE5 inhibitors used for the treatment of PAH, sildenafil and tadalafil. Both agents have been shown to improve hemodynamics and 6MWD. Recently, the oral soluble guanylyl cyclase stimulator, riociguat, was approved for the treatment of both PAH and CTEPH.

Unmet and Future Research Needs in Pulmonary Hypertension Presently there are only three classes of therapy for patients with PAH, and even with therapy, the median survival for a person with PAH is only 5–6 years (Table 304-2). Although there are five subtypes of PH, current approved therapies only address one subtype. Not only do we need to expand the treatment options for patients with PAH, we also need to develop effective therapies for all patients with PH. Limited survival is, in part, a result of delay in diagnosis. Improved awareness among clinicians and patients could lead to more timely diagnosis that will affect the response to therapy and survival. PH needs to be diagnosed in a timely manner so that therapy can be initiated as soon as possible. Patients should also have the option of referral to a specialty center that focuses on treatment of patients with pulmonary vascular disease, which will ensure their access to state-of-the-art care and a multidisciplinary approach to care. Finally, there need to be continued efforts at developing new therapies that target the increasingly complex and overlapping pathways involved in the various forms of PH.