15 - Cardiovascular Disorders

Chapter 206. Approach to the Cardiac Patient

Introduction

Symptoms or the physical examination may suggest a cardiovascular disorder. For confirmation, selected noninvasive and invasive tests are usually done (see Ch. 207).

History

A thorough history is fundamental; it cannot be replaced by testing. The history must include a thorough systems review because many symptoms apparently occurring in other systems (eg, dyspnea, indigestion) are often caused by cardiac disease. A family history is taken because many cardiac disorders (eg, coronary artery disease, systemic hypertension, bicuspid aortic valve, hypertrophic cardiomyopathy, mitral valve prolapse) have a heritable basis.

Serious cardiac symptoms include chest pain or discomfort, dyspnea (see p. 1832), weakness, fatigue, palpitations, light-headedness, sense of an impending faint, syncope, and edema. These symptoms commonly occur in more than one cardiac disorder and in noncardiac disorders.

Physical Examination

Complete examination of all systems is essential to detect peripheral and systemic effects of cardiac disorders and evidence of noncardiac disorders that might affect the heart. Examination includes the following:

• Vital sign measurement

• Pulse palpation and auscultation

• Vein observation

• Chest inspection, percussion, auscultation, and palpation

• Cardiac percussion, palpation, and auscultation

• Lung examination (see p. 1827)

• Extremity and abdomen examination

Vital Signs

BP is measured in both arms and, for suspected congenital cardiac disorders or peripheral vascular disorders, in both legs. The bladder of an appropriately sized cuff encircles 80% of the limb's circumference, and the bladder's width is 40% of the circumference. The first sound heard as the Hg column falls is systolic pressure; disappearance of the sound is diastolic pressure (5th-phase Korotkoff sound). Up to a 15 mm Hg pressure differential between the right and left arms is normal; a greater differential suggests a vascular abnormality (eg, dissecting thoracic aorta) or a peripheral vascular disorder. Leg pressure is usually 20 mm Hg higher than arm pressure. Ankle-brachial index (ratio of ankle to arm systolic BP) is normally > 1. A Doppler probe may be used to measure the ankle BP if the pedal pulses are not easily palpable.

Heart rate and rhythm are assessed by palpating the carotid or radial pulse or by cardiac auscultation if arrhythmia is suspected; some heartbeats during arrhythmias may be audible but do not generate a palpable pulse.

Respiratory rate, if abnormal, may indicate cardiac decompensation or a primary lung disorder. The rate increases in patients with heart failure or anxiety and decreases or becomes intermittent in the moribund. Shallow, rapid respirations may indicate pleuritic pain.

Temperature may be elevated by acute rheumatic fever or cardiac infection (eg, endocarditis). After MI, low grade fever is very common. Other causes are sought only if fever persists > 72 h.

Orthostatic changes: BP and heart rate are measured with the patient supine, seated, and standing; a 1-min interval is needed between each change in position. A difference of ≤ 10 mm Hg is normal; the difference tends to be a little greater in the elderly due to loss of vascular elasticity.

Pulsus paradoxus: Normally during inspiration, systolic arterial BP can decrease as much as 10 mm Hg, and pulse rate increases to compensate. A greater decrease in systolic BP or weakening of the pulse during inspiration is considered pulsus paradoxus. Pulsus paradoxus occurs in

• Cardiac tamponade (commonly)

• Constrictive pericarditis, severe asthma, and COPD (occasionally)

• Restrictive cardiomyopathy, severe pulmonary embolism, and hypovolemic shock (rarely)

BP decreases during inspiration because negative intrathoracic pressure increases venous return and hence right ventricular (RV) filling; as a result, the interventricular septum bulges slightly into the left ventricular (LV) outflow tract, decreasing cardiac output and thus BP. This mechanism (and the drop in systolic BP) is exaggerated in disorders that cause high negative intrathoracic pressure (eg, asthma) or that restrict RV filling (eg, cardiac tamponade, cardiomyopathy) or outflow (eg, pulmonary embolism).

Pulsus paradoxus is quantified by inflating a BP cuff to just above systolic BP and deflating it very slowly (eg, ≤ 2 mm Hg/heartbeat). The pressure is noted when Korotkoff sounds are first heard (at first, only during expiration) and when Korotkoff sounds are heard continuously. The difference between the pressures is the "amount" of pulsus paradoxus.

Pulses

Peripheral pulses: Major peripheral pulses in the arms and legs are palpated for symmetry and volume (intensity); elasticity of the arterial wall is noted. Absence of pulses may suggest an arterial disorder (eg, atherosclerosis) or systemic embolism. Peripheral pulses may be difficult to feel in obese or muscular people. The pulse has a rapid upstroke, then collapses in disorders with a rapid runoff of arterial blood (eg, arteriovenous communication, aortic regurgitation). The pulse is rapid and bounding in thyrotoxicosis and hypermetabolic states; it is slow and sluggish in myxedema. If pulses are asymmetric, auscultation over peripheral vessels may detect a bruit due to stenosis.

Carotid pulses: Observation, palpation, and auscultation of both carotid pulses may suggest a specific disorder (see
Table 206-1).

[**Table 206-1.** Carotid Pulse Amplitude and Associated Disorders]

Aging and arteriosclerosis lead to vessel rigidity, which tends to eliminate the characteristic findings. In very young children, the carotid pulse may be normal, even when severe aortic stenosis is present.

Auscultation over the carotid arteries can distinguish murmurs from bruits. Murmurs originate in the heart or great vessels and are usually louder over the upper precordium and diminish toward the neck. Bruits are higher-pitched, are heard only over the arteries, and seem more superficial. An arterial bruit must be distinguished from a venous hum. Unlike an arterial bruit, a venous hum is usually continuous, heard best with the patient sitting or standing, and is eliminated by compression of the ipsilateral internal jugular vein.

Veins

Peripheral veins: The peripheral veins are observed for varicosities, arteriovenous malformations (AVMs) and shunts, and overlying inflammation and tenderness due to thrombophlebitis. An AVM or a shunt produces a continuous murmur (heard on auscultation) and often a palpable thrill (because resistance is always lower in the vein than in the artery during systole and diastole).

Neck veins: The neck veins are examined to estimate venous wave height and waveform. Height is proportional to right atrial pressure, and waveform reflects events in the cardiac cycle; both are best observed in the internal jugular vein.

The jugular veins are usually examined with the patient reclining at 45°. The top of the venous column is normally just below the clavicles (upper limit of normal: 4 cm above the sternal notch in a vertical plane). The venous column is elevated in heart failure, volume overload, cardiac tamponade, constrictive pericarditis, tricuspid stenosis, superior vena cava obstruction, or reduced compliance of the RV. If such conditions are severe, the venous column can extend to jaw level, and its top can be detected only when the patient sits upright or stands. The venous column is low in hypovolemia.

Normally, the venous column can be briefly elevated by firm hand pressure on the abdomen (hepatojugular or abdominojugular reflux); the column falls back in a few seconds (maximum 3 respiratory cycles or 15 sec) despite continued abdominal pressure (because a compliant RV increases its stroke volume via the Frank-Starling mechanism). However, the column remains elevated (> 3 cm) during abdominal pressure in disorders that cause a dilated and poorly compliant RV or in obstruction of RV filling by tricuspid stenosis or right atrial tumor.

Normally, the venous column falls slightly during inspiration as lowered intrathoracic pressure draws blood from the periphery into the vena cava. A rise in the venous column during inspiration (Kussmaul's sign) occurs typically in chronic constrictive pericarditis, right ventricular MI, and COPD, and usually in heart failure and tricuspid stenosis.

Jugular vein waves (see
Fig. 206-1) can usually be discerned clinically but are better seen on the screen during central venous pressure monitoring.

[**Fig. 206-1.** Normal jugular vein waves.]

The *a* waves are increased in pulmonary hypertension and tricuspid valve stenosis. Giant *a* waves (Cannon waves) are seen in atrioventricular dissociation when the atrium contracts while the tricuspid valve is closed. The *a* waves disappear in atrial fibrillation and are accentuated when RV compliance is poor (eg, in pulmonary hypertension or pulmonic stenosis). The *v* waves are very prominent in tricuspid regurgitation. The *x* descent is steep in cardiac tamponade. When RV compliance is poor, the *y* descent is very abrupt because the elevated column of venous blood rushes into the RV when the tricuspid valve opens, only to be stopped abruptly by the rigid RV wall (in restrictive myopathy) or the pericardium (in constrictive pericarditis).

Chest Inspection and Palpation

Chest contour and any visible cardiac impulses are inspected. The precordium is palpated for pulsations (determining apical impulse and thus cardiac situs) and thrills.

Inspection: Chest deformities, such as shield chest and pectus carinatum (a prominent birdlike sternum), may be associated with hereditary disorders involving congenital cardiac defects (eg, Turner's syndrome). Rarely, a localized upper chest bulge indicates aortic aneurysm due to syphilis. Pectus excavatum (depressed sternum) with a narrow anteroposterior chest diameter and an abnormally straight thoracic spine may suggest myxomatous degeneration of valves or chordae (particularly mitral) or Marfan syndrome.

Palpation: A central precordial heave is a palpable lifting sensation under the sternum and anterior chest wall to the left of the sternum; it suggests severe RV hypertrophy (RVH). Occasionally, in congenital

disorders that cause severe RVH, the precordium visibly bulges asymmetrically to the left of the sternum.

A sustained thrust at the apex (easily differentiated from the less focal, somewhat diffuse precordial heave of RVH) suggests LV hypertrophy (LVH). Abnormal focal systolic impulses in the precordium can sometimes be felt in patients with a dyskinetic ventricular aneurysm. An abnormal diffuse systolic impulse lifts the precordium in patients with severe mitral regurgitation. The lift occurs because the left atrium expands, causing anterior cardiac displacement. A diffuse and inferolaterally displaced apical impulse is found when the LV is dilated and hypertrophied (eg, in mitral regurgitation).

Location of thrills (palpable buzzing sensation present with particularly loud murmurs) suggests the cause (see
Table 206-2).

A sharp impulse at the 2nd intercostal space to the left of the sternum may result from exaggerated pulmonic valve closure in pulmonary hypertension. A similar early systolic impulse at the cardiac apex may represent closure of a stenotic mitral valve; opening of the stenotic valve sometimes can be felt at the beginning of diastole. These findings coincide with an augmented 1st heart sound and an opening snap of mitral stenosis, heard on auscultation.

Cardiac Auscultation

Auscultation of the heart requires excellent hearing and the ability to distinguish subtle

[**Table 206-2.** Location of Thrills and Associated Disorders]

differences in pitch and timing. Hearing-impaired health care practitioners can use amplified stethoscopes. High-pitched sounds are best heard with the diaphragm of the stethoscope. Low-pitched sounds are best heard with the bell. Very little pressure should be exerted when using the bell. Excessive pressure converts the underlying skin into a diaphragm and eliminates very low-pitched sounds.

The entire precordium is examined systematically, typically beginning over the apical impulse with the patient in the left lateral decubitus position. The patient rolls supine, and auscultation continues at the lower left sternal border, proceeds cephalad with auscultation of each interspace, then caudad from the right upper sternal border. The clinician also listens over the left axilla and above the clavicles. The patient sits upright for auscultation of the back, then leans forward to aid auscultation of aortic and pulmonic diastolic murmurs or pericardial friction rub.

Major auscultatory findings include

• Heart sounds

• Murmurs

• Rubs

Heart sounds are brief, transient sounds produced by valve opening and closure; they are divided into systolic and diastolic sounds.

Murmurs are produced by blood flow turbulence and are more prolonged than heart sounds; they may be systolic, diastolic, or continuous. They are graded by intensity (see
Table 206-3) and are described by their location and when they occur within the cardiac cycle.

Rubs are high-pitched, scratchy sounds often with 2 or 3 separate components; during tachycardia, the sound may be almost continuous.

The clinician focuses attention sequentially on each phase of the cardiac cycle, noting each heart sound and murmur. Intensity, pitch, duration, and timing of the sounds and the intervals between them are analyzed, often providing an accurate diagnosis. A diagram of the major auscultatory and palpatory

findings of the precordium should be routinely drawn in the patient's chart each time the patient's cardiovascular system is examined (see Fig. 206-2). With such diagrams, findings from each examination can be compared.

Systolic heart sounds: Systolic sounds include the following:

• 1st heart sound (S_1)

• Clicks

[**Table 206-3.** Heart Murmur Intensity]

S_1 and the 2nd heart sound (S_2, a diastolic heart sound) are normal components of the cardiac cycle, the familiar "lub-dub" sounds.

S_1 occurs just after the beginning of systole and is predominantly due to mitral closure but may also include tricuspid closure components. It is often split and has a high pitch. S_1 is loud in mitral stenosis. It may be soft or absent in mitral regurgitation due to valve leaflet sclerosis and rigidity but is often distinctly heard in mitral regurgitation due to myxomatous degeneration of the mitral apparatus or due to ventricular myocardial abnormality (eg, papillary muscle dysfunction, ventricular dilation).

Clicks occur only during systole; they are distinguished from S_1 and S_2 by their higher pitch and briefer duration. Some clicks occur at different times during systole as hemodynamics change. Clicks may be single or multiple.

Clicks in congenital aortic or pulmonic stenosis are thought to result from abnormal ventricular wall tension. These clicks occur early in systole (very near S_1) and are not affected by hemodynamic changes. Similar clicks occur in severe pulmonary hypertension. Clicks in mitral or tricuspid valve prolapse, typically occurring in mid to late systole, are thought to result from abnormal tension on redundant and elongated chordae tendineae or valve leaflets.

Clicks due to myxomatous degeneration of valves may occur any time during systole but move toward S_1 during maneuvers that transiently decrease ventricular filling volume (eg, standing, Valsalva maneuver). If ventricular filling volume is increased (eg, by lying supine), clicks move toward S_2, particularly in mitral valve prolapse. For unknown reasons, characteristics of the clicks may vary greatly between examinations, and clicks may come and go.

[**Fig. 206-2.** Diagram of physical findings in a patient with aortic stenosis and mitral regurgitation.]

Diastolic heart sounds: Diastolic sounds include the following:

• 2nd, 3rd, and 4th heart sounds (S_2, S_3, and S_4)

• Diastolic knocks

• Mitral valve sounds

Unlike systolic sounds, diastolic sounds are low-pitched; they are softer in intensity and longer in duration. Except for S_2, these sounds are always abnormal in adults.

S_2 occurs at the beginning of diastole, due to aortic and pulmonic valve closure. Aortic valve closure normally precedes pulmonic valve closure unless the former is late or the latter is early. Aortic valve closure is late in left bundle branch block or aortic stenosis; pulmonic valve closure is early in some forms of preexcitation phenomena. Delayed pulmonic valve closure may result from increased blood flow through the RV (eg, in atrial septal defect of the common secundum variety) or complete right bundle branch block. Increased RV flow in atrial septal defect also abolishes the normal respiratory variation in

aortic and pulmonic valve closure, producing a fixed split S_2. Left-to-right shunts with normal RV volume flow (eg, in membranous ventricular septal defects) do not cause fixed splitting. A single S_2 may occur when the aortic valve is regurgitant, severely stenotic, or atretic (in truncus arteriosus when there is a common valve).

S_3 occurs in early diastole, when the ventricle is dilated and noncompliant. It occurs during passive diastolic ventricular filling and indicates serious ventricular dysfunction in adults; in children, it can be normal. RV S_3 is heard best (sometimes only) during inspiration (because negative intrathoracic pressure augments RV filling volume) with the patient supine. LV S_3 is best heard during expiration (because the heart is nearer the chest wall) with the patient in the left lateral decubitus position.

S_4 is produced by augmented ventricular filling, caused by atrial contraction, near the end of diastole. It is similar to S_3 and heard best or only with the bell of the stethoscope. During inspiration, RV S_4 increases and LV S_4 decreases. S_4 is heard much more often than S_3 and indicates a lesser degree of ventricular dysfunction, usually diastolic. S_4 is absent in atrial fibrillation (because the atria do not contract) but is almost always present in active myocardial ischemia or soon after MI. S_3, with or without S_4, is usual in significant systolic LV dysfunction; S_4 without S_3 is usual in diastolic LV dysfunction.

A **summation gallop** occurs when S_3 and S_4 are present in a patient with tachycardia, which shortens diastole so that the 2 sounds merge. Loud S_3 and S_4 may be palpable at the apex when the patient is in the left lateral decubitus position.

A **diastolic knock** occurs at the same time as S_3, in early diastole. It is not accompanied by S_4 and is a louder, thudding sound, which indicates abrupt arrest of ventricular filling by a noncompliant, constricting pericardium.

An **opening snap** may occur in early diastole in mitral stenosis or, rarely, in tricuspid stenosis. Mitral opening snap is very high pitched, brief, and heard best with the diaphragm of the stethoscope. The more severe mitral stenosis is (ie, the higher the left atrial pressure), the closer the opening snap is to the pulmonic component of S_2. Intensity is related to the compliance of the valve leaflets: The snap sounds loud when leaflets remain elastic, but it gradually softens and ultimately disappears as sclerosis, fibrosis, and calcification of the valve develop. Mitral opening snap, although sometimes heard at the apex, is often heard best or only at the lower left sternal border.

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Table 206-4. Etiology of Murmurs by Timing]

Approach to murmurs: Timing of the murmur in the cardiac cycle correlates with the cause (see Table 206-4); auscultatory findings correlate with specific heart valve disorders. Various maneuvers (eg, inspiration, Valsalva, handgrip, squatting, amyl nitrate inhalation) can modify cardiac physiology slightly, making differentiation of causes of heart murmur possible (see Table 206-5).

All patients with heart murmurs are evaluated by chest x-ray and ECG. Most require echocardiography to confirm the diagnosis, determine severity, and track severity over time. Usually, a cardiac consultation is obtained if significant disease is suspected.

Systolic murmurs: Systolic murmurs may be normal or abnormal. They may be early, mid, or late systolic, or holosystolic (pansystolic). Systolic murmurs may be divided into ejection, regurgitant, and shunt murmurs.

Ejection murmurs are due to turbulent forward flow through narrowed or irregular valves or outflow tracts (eg, due to aortic or pulmonic stenosis). They are typically mid systolic and have a crescendo-diminuendo character that usually becomes louder and longer as flow becomes more obstructed. The greater the stenosis and turbulence, the longer the crescendo phase and the shorter the diminuendo

phase.

Systolic ejection murmurs may occur without hemodynamically significant outflow tract obstruction and thus do not necessarily indicate a disorder. In normal infants

[**Table 206-5.** Maneuvers that Aid in Diagnosis of Murmurs]

and children, flow is often mildly turbulent, producing soft ejection murmurs. The elderly often have ejection murmurs due to valve and vessel sclerosis.

During pregnancy, many women have soft ejection murmurs at the 2nd intercostal space to the left or right of the sternum. The murmurs occur because a physiologic increase in blood volume and cardiac output increases flow velocity through normal structures. The murmurs may be greatly exaggerated if severe anemia complicates the pregnancy.

Regurgitant murmurs represent retrograde or abnormal flow (eg, due to mitral regurgitation, tricuspid regurgitation, or ventricular septal defects) into chambers that are at lower resistance. They are typically holosystolic and tend to be louder with high-velocity, low-volume regurgitation or shunts and softer with high-volume regurgitation or shunts. Late systolic murmurs, which may or may not be preceded by a click, are typical of mitral valve prolapse or papillary muscle dysfunction. Various maneuvers are usually required for more accurate diagnosis of timing and type of murmur (see Table 206-5).

Shunt murmurs may originate at the site of the shunt (eg, patent ductus arteriosus, ventricular septal defects) or result from altered hemodynamics remote from the shunt (eg, pulmonic systolic flow murmur due to an atrial septal defect with left-to-right shunt).

Diastolic murmurs: Diastolic murmurs are always abnormal; most are early or mid diastolic, but they may be late diastolic (presystolic). Early diastolic murmurs are typically due to aortic or pulmonic regurgitation. Mid diastolic (or early to mid diastolic) murmurs are typically due to mitral or tricuspid stenosis. A late diastolic murmur may be due to rheumatic mitral stenosis in a patient in sinus rhythm.

A mitral or tricuspid murmur due to an atrial tumor or thrombus may be evanescent and may vary with position and from one examination to the next because the position of the intracardiac mass changes.

Continuous murmurs: Continuous murmurs occur throughout the cardiac cycle. They are always abnormal, indicating a constant shunt flow throughout systole and diastole. They may be due to various cardiac defects (see Table 206-4). Some defects produce a thrill; many are associated with signs of RVH and LVH. As pulmonary artery resistance increases in shunt lesions, the diastolic component gradually decreases. When pulmonary and systemic resistance equalize, the murmur may disappear.

Patent ductus arteriosus murmurs are loudest at the 2nd intercostal space just below the medial end of the left clavicle. Aorticopulmonary window murmurs are central and heard at the 3rd intercostal space level. Murmurs of systemic arteriovenous fistulas are best heard directly over the lesions; those of pulmonic arteriovenous fistulas and pulmonary artery branch stenosis are more diffuse and heard throughout the chest.

During pregnancy, a continuous venous hum from breast vessels (mammary souffle) may be mistaken for a continuous cardiac murmur.

Pericardial friction rub: A pericardial friction rub is caused by movement of inflammatory adhesions between visceral and parietal pericardial layers. It is a high-pitched or squeaking sound; it may be systolic, diastolic and systolic, or triphasic (when atrial contraction accentuates the diastolic component during late diastole). The rub sounds like pieces of leather squeaking as they are rubbed together. Rubs are best heard with the patient leaning forward or on hands and knees with breath held in expiration.

Extremity and Abdominal Examination

The extremities and abdomen are examined for signs of fluid overload, which may occur with heart failure

as well as noncardiac disorders (eg, renal, hepatic, lymphatic).

Extremities: In the extremities (primarily the legs), fluid overload is manifest as edema (see p. 2031), which is swelling of soft tissues due to increased interstitial fluid. Edema may be visible on inspection, but modest amounts of edema in very obese or muscular people may be difficult to recognize visually. Thus, extremities are palpated for presence and degree of pitting (visible and palpable depressions caused by pressure from the examiner's fingers, which displaces the interstitial fluid). The area of edema is examined for extent, symmetry (ie, comparing both extremities), warmth, erythema, and tenderness. With significant fluid overload, edema may also be present over the sacrum, genitals, or both.

Tenderness, erythema, or both, particularly when unilateral, suggests an inflammatory cause (eg, cellulitis or thrombophlebitis). Nonpitting edema is more suggestive of lymphatic or vascular obstruction than fluid overload.

Abdomen: In the abdomen, significant fluid overload manifests as ascites (see p. 206). Marked ascites causes visible abdominal distention, which is tense and nontender to palpation, with shifting dullness on abdominal percussion and a fluid wave. The liver may be distended and slightly tender, with a hepatojugular reflux (see p. 2019) present.

Chest Pain

Chest pain is a very common complaint. Many patients are well aware that it is a warning of potential life-threatening disorders and seek evaluation for minimal symptoms. Other patients, including many with serious disease, minimize or ignore its warnings. Pain perception (both character and severity) varies greatly between individuals as well as between men and women. However described, chest pain should never be dismissed without an explanation of its cause.

Pathophysiology

The heart, lungs, esophagus, and great vessels provide afferent visceral input through the same thoracic autonomic ganglia. A painful stimulus in these organs is typically perceived as originating in the chest, but because afferent nerve fibers overlap in the dorsal ganglia, thoracic pain may be felt (as referred pain) anywhere between the umbilicus and the ear, including the upper extremities.

Painful stimuli from thoracic organs can cause discomfort described as pressure, tearing, gas with the urge to eructate, indigestion, burning, aching, stabbing, and sometimes sharp needle-like pain. When the sensation is visceral in origin, many patients deny they are having pain and insist it is merely "discomfort."

Etiology

Many disorders cause chest pain or discomfort. These disorders may involve the cardiovascular, GI, pulmonary, neurologic, or musculoskeletal systems (see Table 206-6).

Some disorders are immediately life threatening:

- Acute coronary syndromes (acute MI/unstable angina)
- Thoracic aortic dissection
- Tension pneumothorax
- Esophageal rupture
- Pulmonary embolism (PE)

Other causes range from serious, potential threats to life to causes that are simply uncomfortable. Often, no cause can be confirmed even after full evaluation.

Overall, the most common causes are

• Chest wall disorders (ie, those involving muscle, rib, or cartilage)

• Pleural disorders

• GI disorders (eg, esophageal reflux or spasm, ulcer disease, cholelithiasis)

• Idiopathic

• Acute coronary syndromes

Evaluation

History: History of present illness should note the location, duration, character, and quality of the pain. The patient should be asked about any precipitating events (eg, straining or overuse of chest muscles), as well as any triggering and relieving factors. Specific factors to note include whether pain is present during exertion or at rest, presence of psychologic stress, whether pain occurs during respiration or coughing, difficulty swallowing, relationship to meals, and positions that relieve or exacerbate pain (eg, lying flat, leaning forward). Previous similar episodes and their circumstances should be noted with attention to the similarity or lack thereof. Important associated symptoms to seek include

[Table 206-6. Some Causes of Chest Pain]

dyspnea, palpitations, syncope, diaphoresis, nausea or vomiting, cough, fever, and chills.

Review of systems should seek symptoms of possible causes, including leg pain, swelling, or both (deep venous thrombosis [DVT] and therefore possible PE) and chronic weakness, malaise, and weight loss (cancer).

Past medical history should document known causes, particularly cardiovascular and GI disorders, and any cardiac investigations or procedures (eg, stress testing, catheterization). Risk factors for coronary artery disease (CAD—eg, hypertension, hyperlipidemia, diabetes, cerebrovascular disease, tobacco use) or PE (eg, lower extremity injury, recent surgery, immobilization, known cancer, pregnancy) should also be noted.

Drug history should note use of drugs that can trigger coronary artery spasm (eg, cocaine, triptans, phosphodiesterase inhibitors) or GI disease (particularly alcohol, NSAIDs).

Family history should note history of MI (particularly at an early age) and hyperlipidemia.

Physical examination: Vital signs and weight are measured, and body mass index (BMI) is calculated. Pulses are palpated in both arms and both legs, BP is measured in both arms, and pulsus paradoxus is measured.

General appearance is noted (eg, pallor, diaphoresis, cyanosis, anxiety).

Neck is inspected for venous distention and hepatojugular reflux, and the venous wave forms are noted. The neck is palpated for carotid pulses, lymphadenopathy, or thyroid abnormality. The carotid arteries are auscultated for bruit.

Lungs are percussed and auscultated for presence and symmetry of breath sounds, signs of congestion (dry or wet rales, rhonchi), consolidation (pectorilloquy), pleural friction rubs, and effusion (decreased breath sounds, dullness to percussion).

The cardiac examination notes the intensity and timing of the 1st heart sound (S_1) and 2nd heart sound (S_2), the respiratory movement of the pulmonic component of S_2, clicks and snap of the mitral apparatus,

pericardial friction rubs, murmurs, and gallops. When murmurs are detected, the timing, duration, pitch, shape, and intensity and the response to changes of position, handgrip, and the Valsalva maneuver should be noted. When gallops are detected, differentiation should be made between the 4th heart sound (S_4), which is often present with diastolic dysfunction or myocardial ischemia, and the 3rd heart sound (S_3), which is present with systolic dysfunction.

The chest is inspected for skin lesions of trauma or herpes zoster infection and palpated for crepitance (suggesting subcutaneous air) and tenderness. The abdomen is palpated for tenderness, organomegaly, and masses or tenderness, particularly in the epigastric and right upper quadrant regions.

The legs are examined for arterial pulses, adequacy of perfusion, edema, varicose veins, and signs of DVT (eg, swelling, erythema, and tenderness).

Red flags: Certain findings raise suspicion of a more serious etiology of chest pain:

• Abnormal vital signs (tachycardia, bradycardia, tachypnea, hypotension)

• Signs of hypoperfusion (eg, confusion, ashen color, diaphoresis)

• Shortness of breath

• Asymmetric breath sounds or pulses

• New heart murmurs

• Pulsus paradoxus > 10 mm Hg

Interpretation of findings: Symptoms and signs of thoracic disorders vary greatly, and those of serious and nonserious conditions often overlap. Although red flag findings indicate a high likelihood of serious disease, and many disorders have "classic" manifestations (see Table 206-6), many patients who have serious illness do not present with these classic symptoms and signs. For example, patients with myocardial ischemia may complain only of indigestion or have a very tender chest wall on palpation. A high index of suspicion is important when evaluating patients with chest pain. Nonetheless, some distinctions and generalizations are possible.

Duration of pain can provide clues to the severity of the disorder. Long-standing pain (ie, for weeks or months) is not a manifestation of a disorder that is immediately life threatening. Such pain is often musculoskeletal in origin, although GI origin or a cancer should be considered, particularly in patients who are elderly. Similarly, brief (< 5 sec), sharp, intermittent pains rarely result from serious disorders. Serious disorders typically manifest pain lasting minutes to hours, although episodes may be recurrent (eg, unstable angina may cause several bouts of pain over 1 or more days).

Patient age is helpful in evaluating chest pain. Chest pain in children and young adults (< 30 yr) is less likely to result from myocardial ischemia, although MI can occur in people in their 20s. Musculoskeletal and pulmonary disorders are more common causes in these age groups.

Exacerbation and relief of symptoms also are helpful in evaluating chest pain. Although angina can be felt anywhere between the ear and the umbilicus (and often not in the chest), it is typically consistently related to physical or emotional stress, ie, patients do not experience angina from climbing one flight of stairs one day and tolerate 3 flights the next day. Nocturnal angina is characteristic of heart failure or coronary artery spasm.

Pain from many disorders, both serious and minor, can be exacerbated by respiration, movement, or palpation of the chest. These findings are not specific for origin in the chest wall; about 15% of patients with acute MI have chest tenderness on palpation.

Nitroglycerin may relieve pain of both myocardial ischemia and noncardiac smooth muscle spasm (eg, esophageal or biliary disorders); its efficacy or lack thereof should not be used for diagnosis.

Associated findings may also suggest a cause. Fever is nonspecific but, if accompanied by cough, suggests a pulmonary cause. Patients with Raynaud's syndrome or migraine headaches sometimes have coronary spasm.

The presence or absence of risk factors for CAD (eg, hypertension, hypercholesterolemia, smoking, obesity, diabetes, positive family history) alters the probability of underlying CAD but does not help diagnose the cause of a given episode of acute chest pain. Patients with those factors may well have another cause of chest pain, and patients without them may have an acute coronary syndrome. However, known CAD in a patient with chest pain raises the likelihood of that diagnosis as the cause (particularly if the patient describes the symptoms as "like my angina" or "like my last heart attack").

Testing: For adults with acute chest pain, immediate life threats must be ruled out. Most patients should initially have pulse oximetry, ECG, and chest x-ray. If symptoms suggest an acute coronary syndrome or if no other cause is clear (particularly in at-risk patients), troponin and CK levels are measured. If a PE is considered possible, D-dimer testing is done. Expeditious evaluation is essential because if MI or other acute coronary syndrome is present, the patient should be sent immediately to the heart catheterization laboratory (when available); the therapeutic window for primary percutaneous coronary intervention is 90 min and that for thrombolysis is only slightly longer.

Some abnormal findings on these tests confirm a diagnosis (eg, acute MI, pneumothorax, pneumonia). Other abnormalities suggest a diagnosis or at least the need to pursue further investigation (eg, abnormal aortic contour suggests need for testing for thoracic aortic dissection). Thus, if these initial test results are normal, thoracic aortic dissection, tension pneumothorax, and esophageal rupture are highly unlikely. However, in acute coronary syndromes, ECG may not change for several hours or sometimes not at all, and in PE, oxygenation may be normal. Thus, other studies may need to be obtained based on findings from the history and physical examination (see Table 206-6).

Because a single normal set of cardiac markers does not rule out a cardiac cause, patients whose symptoms suggest an acute coronary syndrome should have serial measurement of cardiac markers (troponin and CK-MB fraction) and ECGs. Some clinicians follow these tests (acutely or within several days) with a stress ECG or a stress imaging test. Drug treatment is begun while awaiting results from the 2nd set of markers unless there is a clear contraindication. A diagnostic trial of sublingual nitroglycerin or an oral liquid antacid does not adequately differentiate myocardial ischemia from gastroesophageal reflux disease or gastritis. Either drug may relieve symptoms of either disorder. Troponin will be elevated in all acute coronary syndromes except new-onset angina and often in other disorders that damage the myocardium (eg, myocarditis, pericarditis, aortic dissection involving coronary artery flow, PE, heart failure, severe sepsis). CK may be elevated from damage to any muscle tissue, but CK-MB elevation is specific to damage to the myocardium. ST-segment abnormality on the ECG may be nonspecific or due to antecedent disorders, so comparison with previous ECGs is important.

The likelihood of PE is affected by a number of factors (see Table 194-2 on p. 1912), which can be used in an algorithm to derive an approach to testing.

In patients with chronic chest pain, immediate threats to life are unlikely. Most clinicians initially obtain a chest x-ray and do other tests based on symptoms and signs.

Treatment

Specific identified disorders are treated. If etiology is not clearly benign, patients are usually admitted to the hospital or an observation unit for cardiac monitoring and more extensive evaluation. Symptoms are treated with acetaminophen or opioids as needed (see p. 1623), pending a diagnosis. Pain relief following opioid treatment should not diminish the urgency of ruling out serious and life-threatening disease.

Geriatrics Essentials

The probability of serious and life-threatening disease increases with age. Many elderly patients recover more slowly than younger patients but survive for significant time if properly diagnosed and treated. Drug

doses are usually lower, and rapidity of dose escalation is slower. Chronic disorders (eg, decreased renal function) are often present and may complicate diagnosis and treatment.

Key Points

- Immediate life threats must be ruled out first.
- Some serious disorders, particularly coronary ischemia and PE, often do not have a classic presentation.
- Most patients should have pulse oximetry, ECG, cardiac markers, and chest x-ray.
- Evaluation must be prompt so that patients with ST-elevation MI can be in the heart catheterization laboratory (or have thrombolysis) within the 90-min standard.
- If PE is highly likely, antithrombin drugs should be given while the diagnosis is pursued; another embolus in a patient who is not receiving anticoagulants may be fatal.

Edema

Edema is swelling of soft tissues due to increased interstitial fluid. The fluid is predominantly water, but protein and cell-rich fluid can accumulate if there is infection or lymphatic obstruction.

Edema may be generalized or local (eg, limited to a single extremity or part of an extremity). It sometimes appears abruptly; patients complain that an extremity suddenly swells. More often, edema develops insidiously, beginning with weight gain, puffy eyes at awakening in the morning, and tight shoes at the end of the day. Slowly developing edema may become massive before patients seek medical care.

Edema itself causes few symptoms other than occasionally a feeling of tightness or fullness; other symptoms are usually related to the underlying disorder. Patients with edema due to heart failure (a common cause) often have dyspnea during exertion, orthopnea, and paroxysmal nocturnal dyspnea. Patients with edema due to deep venous thrombosis (DVT) often have pain.

Edema due to extracellular fluid volume expansion is often dependent. Thus, in ambulatory patients, edema is in the feet and lower legs; patients requiring bed rest develop edema in the buttocks, genitals, and posterior thighs. Women who lie on only one side may develop edema in the dependent breast. Lymphatic obstruction causes edema distal to the site of obstruction.

Pathophysiology

Edema results from increased movement of fluid from the intravascular to the interstitial space or decreased movement of water from the interstitium into the capillaries or lymphatic vessels. The mechanism involves one or more of the following:

- Increased capillary hydrostatic pressure
- Decreased plasma oncotic pressure
- Increased capillary permeability
- Obstruction of the lymphatic system

As fluid shifts into the interstitial space, intravascular volume is depleted. Intravascular volume depletion activates the renin-angiotensin-aldosterone-ADH system, resulting in renal Na retention. By increasing osmolality, renal Na retention triggers water retention by the kidneys and helps maintain plasma volume. Increased renal Na retention also may be a primary cause of fluid overload and hence edema. Excessive exogenous Na intake may also contribute.

Less often, edema results from decreased movement of fluid out of the interstitial space into the capillaries due to lack of adequate plasma oncotic pressure as in nephrotic syndrome, protein-losing enteropathy, or starvation.

Increased capillary permeability occurs in infections or as the result of toxin or inflammatory damage to the capillary walls.

The lymphatic system is responsible for removing protein and WBCs (along with some water) from the interstitium. Lymphatic obstruction allows these substances to accumulate in the interstitium.

Etiology

Generalized edema is most commonly caused by

• Heart failure

• Liver failure

• Kidney disorders (especially nephrotic syndrome)

Localized edema is most commonly caused by

• DVT or another venous obstruction (eg, by tumor)

• Infection

• Angioedema

• Lymphatic obstruction

Chronic venous insufficiency may involve one or both legs.

Common causes are listed by primary mechanism in Table 206-7.

Evaluation

History: History of present illness should include location and duration of edema and presence and degree of pain or discomfort.

[**Table 206-7.** Some Causes of Edema]

Female patients should be asked whether they are pregnant and whether edema seems related to menstrual periods. Having patients with chronic edema keep a log of weight gain or loss is valuable.

Review of systems should include symptoms of causative disorders, including dyspnea during exertion, orthopnea, and paroxysmal nocturnal dyspnea (heart failure); alcohol or hepatotoxin exposure, jaundice, and easy bruising (a liver disorder); malaise and anorexia (cancer or a liver or kidney disorder); and immobilization, extremity injury, or recent surgery (DVT).

Past medical history should include any disorders known to cause edema, including heart, liver, and kidney disorders and cancer (including any related surgery or radiation therapy). The history should also include predisposing conditions for these causes, including streptococcal infection, recent viral infection (eg, hepatitis), chronic alcohol abuse, and hypercoagulable disorders. Drug history should include specific questions about drugs known to cause edema (see Table 206-7). Patients are asked about the amount of Na used in cooking and at the table.

Physical examination: The area of edema is identified and examined for extent, warmth, erythema, and

tenderness; symmetry or lack of it is noted. Presence and degree of pitting (visible and palpable depressions caused by pressure from the examiner's fingers on the edematous area, which displaces the interstitial fluid) are noted.

In the general examination, the skin is inspected for jaundice, bruising, and spider angiomas (suggesting a liver disorder).

Lungs are examined for dullness to percussion, reduced or exaggerated breath sounds, crackles, rhonchi, and pleural friction rub.

The internal jugular vein height, waveform, and reflux are noted.

The heart is palpated for thrills, thrust, parasternal lift, and asynchronous abnormal systolic bulge. Auscultation for 3rd (S_3) or 4th (S_4) heart sounds, murmurs, and pericardial rub or knock is done; all suggest cardiac origin.

The abdomen is inspected, palpated, and percussed for ascites, hepatomegaly, and splenomegaly to check for a liver disorder or heart failure. The kidneys are palpated, and the bladder is percussed. An abnormal abdominal mass, if present, should be palpated.

Red flags: Certain findings raise suspicion of a more serious etiology of edema:

• Sudden onset

• Significant pain

• Shortness of breath

• History of a heart disorder or an abnormal cardiac examination

• Hemoptysis, dyspnea, or pleural friction rub

• Hepatomegaly, jaundice, ascites, splenomegaly, or hematemesis

• Unilateral leg swelling with tenderness

Interpretation of findings: Potential acute life threats, which typically manifest with sudden onset of focal edema, must be identified. Such a presentation suggests acute DVT, soft-tissue infection, or angioedema. Acute DVT may lead to pulmonary embolism (PE), which can be fatal. Soft-tissue infections range from minor to life threatening, depending on the infecting organism and the patient's health. Acute angioedema sometimes progresses to involve the airway, with serious consequences.

Dyspnea may occur with edema due to heart failure, DVT if PE has occurred, acute respiratory distress syndrome, or angioedema that involves the airways.

Generalized, slowly developing edema suggests a chronic heart, kidney, or liver disorder. Although these disorders can also be life threatening, complications tend to take much longer to develop.

These factors and other clinical features help suggest the cause (see Table 206-7).

Testing: For most patients with generalized edema, testing should include CBC, serum electrolytes, BUN, creatinine, liver function tests, serum protein, and urinalysis (particularly noting the presence of protein and microscopic hematuria). Other tests should be done based on the suspected cause (see Table 206-7)—eg, brain natriuretic peptide (BNP) for suspected heart failure or D-dimer for suspected PE.

Patients with isolated lower-extremity swelling should usually have venous obstruction excluded by ultrasonography.

Treatment

Specific causes are treated.

Patients with Na retention often benefit from restriction of dietary Na. Patients with heart failure should eliminate salt in cooking and at the table and avoid prepared foods with added salt. Patients with advanced cirrhosis or nephrotic syndrome often require more severe Na restriction (≤ 1 g/day). K salts are often substituted for Na salts to make Na restriction tolerable; however, care should be taken, especially in patients receiving K-sparing diuretics, ACE inhibitors, or angiotensin receptor blockers and in those with a kidney disorder because potentially fatal hyperkalemia can result.

People with conditions involving Na retention may also benefit from loop or thiazide diuretics. However, diuretics should not be prescribed only to improve the appearance caused by edema. When diuretics are used, K wasting can be dangerous in some patients; K-sparing diuretics (eg, amiloride, triamterene, spironolactone, eplerenone) inhibit Na reabsorption in the distal nephron and collecting duct. When used alone, they modestly increase Na excretion. Both triamterene and amiloride have been combined with a thiazide to prevent K wasting. An ACE inhibitor-thiazide combination also reduces K wasting.

Geriatrics Essentials

In the elderly, use of drugs that treat causes of edema requires special caution, such as the following:

- Starting doses low and evaluating patients thoroughly when the dose is changed
- Monitoring for orthostatic hypotension if diuretics, ACE inhibitors, angiotensin receptor blockers, or β-blockers are used
- Evaluating for bradycardia or heart block if digoxin, rate-limiting Ca channel blockers, or β-blockers are used
- Frequently testing for hypokalemia or hyperkalemia
- Not stopping Ca channel blockers because of pedal edema, which is benign

Logging daily weight helps in monitoring clinical improvement or deterioration immensely.

Key Points

- Edema may result from a generalized or local process.
- Main causes of generalized edema are chronic heart, liver, and kidney disorders.
- Sudden onset should trigger prompt evaluation.
- Edema may occur anywhere in the body, including the brain.
- Not all edema is harmful; consequences depend mainly on the cause.

Orthostatic Hypotension

Orthostatic (postural) hypotension is an excessive fall in BP when an upright position is assumed. The consensus definition is a drop of > 20 mm Hg systolic, 10 mm Hg diastolic, or both. Symptoms of faintness, light-headedness, dizziness, confusion, or blurred vision occur within seconds to a few minutes of standing and resolve rapidly on lying down. Some patients experience falls, syncope (see p. 2041), or even generalized seizures. Exercise or a heavy meal may exacerbate symptoms. Most other associated symptoms and signs relate to the cause. Orthostatic hypotension is a manifestation of abnormal BP regulation due to various conditions, not a specific disorder.

Postural orthostatic tachycardia syndrome (POTS): POTS (also called postural autonomic tachycardia or chronic or idiopathic orthostatic intolerance) is a syndrome of orthostatic intolerance in younger patients. Various symptoms (eg, fatigue, light-headedness, exercise intolerance, cognitive impairment) and tachycardia occur with standing; however, there is little or no fall in BP. The reason for symptoms is unclear.

Pathophysiology

Normally, the gravitational stress of suddenly standing causes blood (1/2 to 1 L) to pool in the capacitance veins of the legs and trunk. The subsequent transient decrease in venous return reduces cardiac output and thus BP. In response, baroreceptors in the aortic arch and carotid bodies activate autonomic reflexes to rapidly return BP to normal. The sympathetic system increases heart rate and contractility and increases vasomotor tone of the capacitance vessels. Simultaneous parasympathetic (vagal) inhibition also increases heart rate. In most people, changes in BP and heart rate with standing are minimal and transient, and symptoms do not occur.

With continued standing, activation of the renin-angiotensin-aldosterone system and ADH secretion cause Na and water retention and increase circulating blood volume.

Etiology

Homeostatic mechanisms may be inadequate to restore low BP if afferent, central, or efferent portions of the autonomic reflex arc are impaired by disorders or drugs, if myocardial contractility or vascular responsiveness is depressed, if hypovolemia is present, or if hormonal responses are faulty (see Table 206-8).

Causes differ depending on whether symptoms are acute or chronic.

The most common causes of acute orthostatic hypotension include

• Hypovolemia

• Drugs

• Prolonged bed rest

• Adrenal insufficiency

The most common causes of chronic orthostatic hypotension include

• Age-related changes in BP regulation

• Drugs

• Autonomic dysfunction

Postprandial orthostatic hypotension is also common. It may be caused by the insulin response to high-carbohydrate meals and blood pooling in the GI tract; this condition is worsened by alcohol intake.

Evaluation

Orthostatic hypotension is diagnosed when a marked fall in measured BP and symptoms suggesting hypotension are provoked by standing and relieved by lying down. A cause must be sought.

History: History of present illness should identify the duration and severity (eg, whether associated with syncope or falls) of symptoms. The patient is asked about known triggers (eg, drugs, bed rest, fluid loss) and the relationship of symptoms to meals.

Review of symptoms seeks symptoms of causative disorders, particularly symptoms of autonomic insufficiency such as visual impairment (due to mydriasis and loss of accommodation), incontinence or urinary retention, constipation, heat intolerance (due to impaired sweating), and erectile dysfunction. Other important symptoms include tremor, rigidity, and difficulty walking (Parkinson's disease, multiple system atrophy); weakness and fatigue (adrenal insufficiency, anemia); and black, tarry stool (GI hemorrhage). Other symptoms of neurologic and cardiovascular disorders and cancer are noted.

[**Table 206-8.** Causes of Orthostatic Hypotension]

Past medical history should identify known potential causes, including diabetes, Parkinson's disease, and cancer (ie, causing a paraneoplastic syndrome). The drug profile should be reviewed for offending prescription drugs (see Table 206-8) particularly antihypertensives and nitrates. A family history of orthostatic symptoms suggests possible familial dysautonomia.

Physical examination: BP and heart rate are measured after 5 min supine and at 1 and 3 min after standing; patients unable to stand may be assessed while sitting upright. Hypotension without a compensatory increase in heart rate (< 10 beats/min) suggests autonomic impairment. Marked increase (to > 100 beats/min or by > 30 beats/min) suggests hypovolemia or, if symptoms develop without hypotension, POTS.

The skin and mucosae are inspected for signs of dehydration and for pigment changes suggestive of Addison's disease (eg, hyperpigmented areas, vitiligo). A rectal examination is done to detect GI bleeding.

During the neurologic examination, GU and rectal reflexes are tested to evaluate autonomic function; assessment includes the cremasteric reflex (normally, stroking the thigh results in retraction of the testes), anal wink reflex (normally, stroking perianal skin results in contraction of the anal sphincter), and bulbocavernosus reflex (normally, squeezing the glans penis or clitoris results in contraction of the anal sphincter). Signs of peripheral neuropathy (eg, abnormalities of strength, sensation, and deep tendon reflexes) are assessed.

Red flags: Certain findings suggest a more serious etiology:

• Bloody or heme-positive stool

• Abnormal neurologic examination

Interpretation of findings: In patients with acute symptoms, the most common causes—drugs, bed rest, and volume depletion—are often apparent clinically.

In patients with chronic symptoms, an important goal is to detect any neurologic disorder causing autonomic dysfunction. Patients with movement abnormalities may have Parkinson's disease or multiple system atrophy. Patients with findings of peripheral neuropathy may have an apparent cause (eg, diabetes, alcoholism), but a paraneoplastic syndrome due to an occult cancer and amyloidosis must be considered. Patients who have only peripheral autonomic symptoms may have pure autonomic failure.

Testing: ECG and serum electrolytes and glucose are routinely checked. However, these and other tests are usually of little benefit unless suggested by specific symptoms.

Autonomic function can be evaluated with bedside cardiac monitoring. When the autonomic system is intact, heart rate increases in response to inspiration. The heart is monitored as the patient breathes slowly and deeply (about a 5-sec inspiration and a 7-sec expiration) for 1 min. The longest interbeat (R-R) interval during expiration is normally at least 1.15 times the minimum R-R interval during inspiration; a shorter interval suggests autonomic dysfunction. A similar variation in R-R interval should exist between rest and a 10- to 15-sec Valsalva maneuver. Patients with abnormal R-R intervals or with autonomic symptoms or signs require further evaluation for diabetes, Parkinson's disease, and possibly multiple system atrophy (see p. 1618) and pure autonomic failure (see p. 1619); the last may require plasma norepinephrine or ADH (vasopressin) measurements with the patient supine and upright.

The dose of a suspected drug may be reduced or the drug stopped to confirm the drug as the cause.

Tilt table testing (see p. 2065) may be done when autonomic dysfunction is suspected; it gives more consistent results than supine and upright BP assessment and eliminates augmentation of venous return by leg muscle contraction. The patient may remain upright for 30 to 45 min of BP assessment.

Treatment

Patients requiring prolonged bed rest should sit up each day and exercise in bed when possible. Patients should rise slowly from a recumbent or sitting position, consume adequate fluids, limit or avoid alcohol, and exercise regularly when feasible. Regular modest-intensity exercise promotes overall vascular tone and reduces venous pooling. Elderly patients should avoid prolonged standing. Sleeping with the head of the bed raised may relieve symptoms by promoting Na retention and reducing nocturnal diuresis.

Postprandial hypotension can often be prevented by reducing the size and carbohydrate content of meals, minimizing alcohol intake, and avoiding sudden standing after meals.

Waist-high fitted elastic hose may increase venous return, cardiac output, and BP after standing. In severe cases, inflatable aviator-type antigravity suits, although often poorly tolerated, may be needed to produce adequate leg and abdominal counterpressure.

Increasing Na intake may expand intravascular volume and lessen symptoms. In the absence of heart failure or hypertension, Na intake can be increased 5 to 10 g above the usual dietary level by liberally salting food or taking NaCl tablets. This approach risks heart failure, particularly in elderly patients and patients with impaired myocardial function; development of dependent edema without heart failure does not contraindicate continuing this approach.

Fludrocortisone, a mineralocorticoid, causes Na retention, which expands plasma volume, and often lessens symptoms but is effective only when Na intake is adequate. Dosage is 0.1 mg po at bedtime, increased weekly to 1 mg or until peripheral edema occurs. This drug may also improve the peripheral vasoconstrictor response to sympathetic stimulation. Supine hypertension, heart failure, and hypokalemia may occur; K supplements may be needed.

Midodrine, a peripheral α-agonist that is both an arterial and venous constrictor, is often effective. Dosage is 2.5 mg to 10 mg po tid. Adverse effects include paresthesias and itching (probably secondary to piloerection). This drug is not recommended for patients with coronary artery or peripheral arterial disease.

NSAIDs (eg, indomethacin 25 to 50 mg po tid) may inhibit prostaglandin-induced vasodilation, increasing peripheral vascular resistance. However, NSAIDs may cause GI symptoms and unwanted vasopressor reactions (reported with concurrent use of indomethacin and sympathomimetic drugs).

L-Dihydroxyphenylserine, a norepinephrine precursor, may be beneficial for autonomic dysfunction (reported in limited trials).

Propranolol or other β-blockers may enhance the beneficial effects of Na and mineralocorticoid therapy. β-Blockade with propranolol leads to unopposed α-adrenergic peripheral vascular vasoconstriction, preventing the vasodilation that occurs when some patients stand.

Geriatrics Essentials

Orthostatic hypotension occurs in about 20% of the elderly; it is more common among people with coexisting disorders, especially hypertension, and among residents of long-term care facilities. Many falls may result from unrecognized orthostatic hypotension.

The increased incidence in the elderly is due to decreased baroreceptor responsiveness plus decreased arterial compliance. Decreased baroreceptor responsiveness delays cardioacceleration and peripheral

vasoconstriction in response to standing. Paradoxically, hypertension may contribute to poor baroreceptor sensitivity, increasing vulnerability to orthostatic hypotension. The elderly also have decreased resting parasympathetic tone, so that cardioacceleration due to reflex vagal withdrawal is lessened.

Key Points

- Orthostatic hypotension typically involves volume depletion or autonomic dysfunction.
- Some degree of autonomic dysfunction is common in the elderly, but neurologic disorders must be ruled out.
- Bedside tests of autonomic function and often tilt table testing are done.
- Treatment involves physical measures to reduce venous pooling, increased Na intake, and sometimes fludrocortisone or midodrine.

Palpitations

Palpitations are the perception of cardiac activity. They are often described as a fluttering, racing, or skipping sensation. They are common; some patients find them unpleasant and alarming. Palpitations can occur in the absence of heart disease or can result from life-threatening heart disorders. The key to diagnosis and treatment is to "capture" the rhythm on ECG and make careful observations during the palpitations.

Pathophysiology

The mechanisms responsible for the sensation of palpitations are unknown. Ordinarily, sinus rhythm at a normal rate is not perceived, and palpitations thus usually reflect changes in cardiac rate, rhythm, or contractility. In all cases, it is the abnormal movement of the heart within the chest that is felt. In cases of isolated extrasystoles, the patient may actually perceive the augmented post-extrasystolic beat as the "skipped" beat rather than the premature beat itself, probably because the extrasystole blocks the next sinus beat and allows longer ventricular filling and thus a higher stroke volume.

The clinical perception of cardiac phenomena is highly variable. Some patients are aware of virtually every premature ventricular beat, but others are unaware of even complex atrial or ventricular tachyarrhythmias. Awareness is heightened in sedentary, anxious, or depressed patients and reduced in active, happy patients. In some cases, palpitations are perceived in the absence of any abnormal cardiac activity.

Etiology

Some patients simply have heightened awareness of normal cardiac activity, particularly when exercise, febrile illness, or anxiety increases heart rate. However, in most cases, palpitations result from arrhythmia. Arrhythmias range from benign to life threatening.

The **most common arrhythmias** include

- Premature atrial contractions (PACs)
- Premature ventricular contractions (PVCs)

Both of these arrhythmias usually are harmless.

Other common arrhythmias include

- Paroxysmal supraventricular tachycardia (PSVT)
- Atrioventricular nodal reentrant tachycardia

• Atrial fibrillation or flutter

• Ventricular tachycardia

• Bradyarrhythmias and heart block

Causes of arrhythmias: Some arrhythmias (eg, PACs, PVCs, PSVT) often occur spontaneously in patients without serious underlying disorders, but others are often caused by a serious cardiac disorder.

Serious cardiac causes include myocardial ischemia or other myocardial disorders, congenital heart disease, valvular heart disease, and conduction system disturbances (eg, disturbances that cause bradycardia or heart block). Patients with orthostatic hypotension commonly sense palpitations caused by sinus tachycardia on standing.

Noncardiac disorders that increase myocardial contractility (eg, thyrotoxicosis, pheochromocytoma, anxiety) may cause palpitations.

Some drugs, including digitalis, caffeine, alcohol, nicotine, and sympathomimetics (eg, albuterol, amphetamines, cocaine, dobutamine, epinephrine, ephedrine, isoproterenol, norepinephrine, and theophylline), frequently cause palpitations.

Metabolic disturbances, including anemia, hypoxia, hypovolemia, and electrolyte abnormalities (eg, diuretic-induced hypokalemia), can trigger or exacerbate palpitations.

Consequences: Many arrhythmias that cause palpitations have no adverse physiologic consequences of their own (ie, independent of the underlying disorder). However, bradyarrhythmias, tachyarrhythmias, and heart blocks can be unpredictable and may adversely affect cardiac output and cause hypotension or death. Ventricular tachycardia sometimes degenerates to ventricular fibrillation.

Evaluation

A complete history and physical examination are essential. Observations by other medical personnel or reliable observers should be sought.

History: History of present illness should cover the frequency and duration of palpitations and provoking or exacerbating factors (eg, emotional distress, activity, change in position, intake of caffeine or other drugs). Important associated symptoms include syncope, light-headedness, tunnel vision, dyspnea, and chest pain. Asking the patient to tap out the rate and cadence of palpitations is better than a verbal description and often allows a definitive diagnosis, as in the "missed beat" of atrial or ventricular extrasystoles or the rapid total irregularity of atrial fibrillation.

Review of systems should cover symptoms of causative disorders, including heat intolerance, weight loss, and tremor (hyperthyroidism); chest pain and dyspnea on exertion (cardiac ischemia); and fatigue, weakness, heavy vaginal bleeding, and dark tar-like stools (anemia).

Past medical history should identify known potential causes, including documented arrhythmias and heart or thyroid disorders. Family history should note occurrences of syncope or sudden death at an early age.

The drug profile should be reviewed for offending prescription drugs (eg, antiarrhythmics, digitalis, β-agonists, theophylline, and rate-limiting drugs); OTC drugs (eg, cold and sinus medications, dietary supplements containing stimulants), including alternative medicines; and illicit drugs (eg, cocaine, methamphetamines). Caffeine (eg, coffee, tea, numerous soft drinks and energy drinks), alcohol, and tobacco use should be determined.

Physical examination: The general examination should note whether an anxious demeanor or psychomotor agitation is present. Vital signs are reviewed for fever, hypertension, hypotension,

tachycardia, bradycardia, tachypnea, and low O_2 saturation. Orthostatic changes in BP and heart rate should be measured.

Examination of the head and neck should note any abnormality or dyssynchrony of the jugular pulse waves compared with the carotid pulse or auscultated heart rhythm and findings of hyperthyroidism, such as thyroid enlargement or tenderness and exophthalmos. The conjunctivae, palmar creases, and buccal mucosa should be inspected for pallor.

Cardiac auscultation should note the rate and regularity of the rhythm as well as any murmurs or extra heart sounds that might indicate underlying valvular or structural heart disease.

Neurologic examination should note whether resting tremors or brisk reflexes are present (suggesting excess sympathetic stimulation). An abnormal neurologic finding suggests that seizures rather than a cardiac disorder may be the cause if syncope is one of the symptoms.

Red flags: Certain findings suggest a more serious etiology:

• Light-headedness or syncope (particularly if injury occurs from syncope)

• Chest pain

• New onset of irregularly irregular heart rhythm

• Heart rate >120 beats/min or < 45 beats/min while at rest

• Significant underlying heart disease

• Family history of sudden death

Interpretation of findings: History (see Table 206-9) and, to a lesser extent, physical examination provide clues to the diagnosis.

Palpation of the arterial pulse and cardiac auscultation may reveal a rhythm disturbance. However, the examination is not always diagnostic of a specific rhythm, except when it identifies the unique irregular irregularity of some cases of rapid atrial fibrillation, the regular irregularity of coupled atrial or ventricular extrasystoles, the regular tachycardia at 150 beats/min of atrial flutter (in adults, this rate is rare with any other arrhythmia), and the regular bradycardia of < 35 beats/min of complete atrioventricular block. Careful examination of the jugular venous pulse waves simultaneously with cardiac auscultation and palpation of the carotid artery allows diagnosis of most arrhythmias if an ECG is not available, because the jugular waves will show the atrial rhythm while the auscultated sounds or the pulse in the carotids are the product of ventricular contraction.

[**Table 206-9.** Suggestive Historical Findings with Palpitations]

Thyroid enlargement or tenderness with exophthalmos suggests thyrotoxicosis. Marked hypertension and regular tachycardia suggest pheochromocytoma.

Testing: Testing typically is done.

• ECG, sometimes with ambulatory monitoring

• Laboratory testing

• Sometimes imaging studies, stress testing, or both

ECG is done, but unless the recording is done while symptoms are occurring, it may not provide a diagnosis. Many cardiac arrhythmias are intermittent and show no fixed ECG abnormalities; exceptions include

• Wolff-Parkinson-White syndrome

• Long QT syndrome

• Arrhythmogenic right ventricular dysplasia cardiomyopathy

• Brugada syndrome and its variants

If no diagnosis is apparent and symptoms are frequent, Holter monitoring for 24 to 48 h is useful; for intermittent symptoms, an event recorder worn for longer periods and activated by the patient when symptoms are felt is better. These tests are used mainly when a sustained arrhythmia is suspected, rather than when symptoms suggest only occasional skipped beats. Patients with very infrequent symptoms that clinicians suspect represent a serious arrhythmia may have a device implanted beneath the skin of the upper chest. This device continuously records the rhythm and can be interrogated by an external machine that allows the cardiac rhythm to be printed.

Laboratory testing is needed in all patients. All patients should have measurement of CBC, serum electrolytes including Mg and Ca, and C-reactive protein (indicating inflammation that may be affecting the heart or coronary arteries). Cardiac markers (eg, troponin and CK) should be measured in patients with ongoing arrhythmias, chest discomfort, or other symptoms suggesting active or recent coronary ischemia, myocarditis, or pericarditis.

Thyroid function tests are indicated when atrial fibrillation is newly diagnosed or there are symptoms of hyperthyroidism. Patients with paroxysms of high BP should be evaluated for pheochromocytoma.

Sometimes tilt-table testing is done in patients with postural syncope.

Imaging is often needed. Patients with findings suggesting cardiac dysfunction or structural heart disease require echocardiography and sometimes cardiac MRI. Patients with symptoms on exertion require stress testing sometimes with stress echocardiography, nuclear scanning, or PET.

Treatment

Precipitating drugs and substances are stopped. If dangerous or debilitating arrhythmias are caused by a necessary therapeutic drug, a different drug should be tried.

For isolated PACs and PVCs in patients without structural heart disease, simple reassurance is appropriate. For otherwise healthy patients in whom these phenomena are disabling, a β-blocker can be given provided efforts are made to avoid reinforcing the perception by anxious patients that they have a serious disorder.

Identified rhythm disturbances and underlying disorders are investigated and treated (see Table 206-10).

Geriatrics Essentials

Elderly patients are at particular risk of adverse effects of antiarrhythmics; reasons include lower GFR and concomitant use of other drugs. When drug treatment is needed, lower doses should be used to start. Subclinical conduction abnormalities may be present (recognized on ECG or other studies), which might worsen with use of antiarrhythmics; such patients may require a pacemaker to allow the use of antiarrhythmics.

Key Points

• Palpitations are a frequent but relatively nonspecific symptom.

• Palpitations are not a reliable indicator of a significant arrhythmia, but palpitations in a patient with

structural heart disease or an abnormal ECG may be a sign of a serious problem and warrant investigation.

- An ECG or other recording done during symptoms is essential; a normal ECG in a symptom-free interval does not rule out significant disease.

- Most antiarrhythmics themselves can cause arrhythmias.

- If in doubt about a rapid tachyarrhythmia in a patient in hemodynamic distress, use electrocardioversion first and ask questions later.

Syncope

Syncope is a sudden, brief loss of consciousness (LOC) with loss of postural tone followed by spontaneous revival. The patient

[Table 206-10. Some Treatments for Arrhythmias]

is motionless and limp and usually has cool extremities, a weak pulse, and shallow breathing.

Near syncope is light-headedness and a sense of an impending faint without LOC. It is usually classified and discussed with syncope because the causes are the same.

Seizures can cause sudden LOC but are not considered syncope. However, seizures must be considered in patients presenting for apparent syncope because history may be unclear or unavailable, and some seizures do not cause tonic-clonic convulsions. Furthermore, a brief (< 5 sec) seizure sometimes occurs with true syncope.

Diagnosis depends on a careful history, eyewitness accounts, or fortuitous examination during the event.

Pathophysiology

Most syncope results from insufficient cerebral blood flow. Some cases involve adequate flow but with insufficient cerebral substrate (O_2, glucose, or both).

Insufficient cerebral blood flow: Most deficiencies in cerebral blood flow result from decreased cardiac output (CO).

Decreased CO can be caused by

- Cardiac disorders that obstruct outflow

- Cardiac disorders of systolic dysfunction

- Cardiac disorders of diastolic dysfunction

- Arrhythmias (too fast or too slow)

- Conditions that decrease venous return

Outflow obstruction can be exacerbated by exercise, vasodilation, and hypovolemia (particularly in aortic stenosis and hypertrophic cardiomyopathy), which may precipitate syncope.

Arrhythmias cause syncope when the heart rate is too fast to allow adequate ventricular filling (eg, > 150 to 180 beats/min) or too slow to provide adequate output (eg, < 30 to 35 beats/min).

Venous return can be decreased by hemorrhage, increased intrathoracic pressure, increased vagal tone (which can also decrease heart rate), and loss of sympathetic tone (eg, from drugs, carotid sinus

pressure, autonomic dysfunction). Syncope involving these mechanisms (except for hemorrhage) is often termed **vasovagal** or neurocardiogenic and is common and benign.

Orthostatic hypotension, a common benign cause of syncope, results from failure of normal mechanisms (eg, sinus tachycardia, vasoconstriction, or both) to compensate for the temporary decrease in venous return that occurs with standing (see p. 2035).

Cerebrovascular disorders (eg, strokes, transient ischemic attacks) rarely cause syncope because most of them do not involve the centrencephalic structures that must be affected to produce LOC. However, basilar artery ischemia, due to transient ischemic attack or migraine, may cause syncope. Rarely, patients with severe cervical arthritis or spondylosis develop vertebrobasilar insufficiency with syncope when the head is moved in certain positions.

Insufficient cerebral substrate: The CNS requires O_2 and glucose to function. Even with normal cerebral blood flow, a significant deficit of either will cause LOC. In practice, hypoglycemia is the primary cause because hypoxia rarely develops in a manner causing abrupt LOC (other than in flying or diving incidents). LOC due to hypoglycemia is seldom as abrupt as in syncope or seizures because warning symptoms occur (except in patients taking β-blockers); however, the onset may be unclear to the examiner unless the event was witnessed.

Etiology

Causes are usually classified by the mechanism (see Table 206-11).

The **most common causes** are

• Vasovagal

• Idiopathic

Many cases never have a firm diagnosis but lead to no apparent harm. A smaller number of cases have a serious cause, usually cardiac.

Evaluation

Evaluation should be done as soon as possible after the event. The more remote the syncopal event, the more difficult the diagnosis. Information from witnesses is quite helpful and best obtained as soon as possible.

History: History of present illness should ascertain events leading up to the syncope, including the patient's activity (eg, exercising, arguing, in a potentially emotional situation), position (eg, lying or standing), and, if standing, for how long. Important associated symptoms immediately before or after the event include whether there was a sense of impending LOC, nausea, sweating, blurred or tunnel vision, tingling of lips or fingertips, chest pain, or palpitations. Witnesses, if any, should be sought and asked to describe events, particularly the presence and duration of any seizure activity.

Review of systems should ask about any areas of pain or injury, episodes of dizziness or near syncope on arising, and episodes of palpitations or chest pain with exertion. Patients should be asked about symptoms suggesting possible causes, including bloody or tarry stools, heavy menses (anemia); vomiting, diarrhea, or excess urination (dehydration or electrolyte abnormalities); and risk factors for pulmonary embolism (recent surgery or immobilization, known cancer, previous clots or hypercoagulable state).

Past medical history should ask about previous syncopal events, known cardiovascular disease, and known seizure disorders. Drugs used should be identified (particularly antihypertensives, diuretics, vasodilators, and antiarrhythmics—see Table 206-12). Family history should note presence at a young age of heart disease or sudden death in any family member.

Physical examination: Vital signs are essential. Heart rate and BP are measured with the patient supine and after 2 min of standing. Pulse is palpated for irregularity.

General examination notes patient's mental status, including any confusion or hesitancy suggesting a postictal state and any signs of injury (eg, bruising, swelling, tenderness, tongue bite).

The heart is auscultated for murmurs; if present, any change in the murmur with a Valsalva maneuver, standing, or squatting is noted.

Careful evaluation of the jugular venous waves (see Fig. 206-1) while palpating the carotid or auscultating the heart may allow diagnosis of an arrhythmia if an ECG is not available.

Some clinicians carefully apply unilateral carotid sinus pressure during ECG monitoring with the patient supine to detect bradycardia or heart block, suggesting carotid sinus hypersensitivity. Carotid sinus pressure should not be applied if a carotid bruit is present.

Abdomen is palpated for tenderness, and a rectal examination is done to check for gross or occult blood.

A full neurologic examination is done to identify any focal abnormalities, which suggest a CNS cause (eg, seizure disorder).

Red flags: Certain findings suggest a more serious etiology:

• Syncope during exertion

• Multiple recurrences within a short time

• Heart murmur or other findings suggesting structural heart disease (eg, chest pain)

[**Table 206-11.** Some Causes of Syncope]

• Older age

• Significant injury during syncope

• Family history of sudden unexpected death

Interpretation of findings: Although the cause is often benign, it is important to identify the occasional life-threatening cause (eg, tachyarrhythmia, heart block) because sudden death is a risk. Clinical findings (see Table 206-11) help suggest a cause in 40 to 50% of cases. A few generalizations are useful.

Benign causes often lead to syncope. Syncope precipitated by unpleasant physical or emotional stimuli (eg, pain, fright), usually occurring in the upright position and often preceded by vagally mediated warning symptoms (eg, nausea, weakness, yawning, apprehension, blurred vision, diaphoresis), suggests vasovagal syncope.

Syncope that occurs most often when assuming an upright position (particularly in elderly patients after prolonged bed rest or in patients taking drugs in certain classes) suggests orthostatic syncope. Syncope that occurs after standing for long periods without moving is usually due to venous pooling.

LOC that is abrupt in onset; is associated with muscular jerking or convulsions, incontinence, or tongue biting; and is followed by postictal confusion or somnolence suggests a seizure.

Red flag findings suggest a **dangerous cause**.

Syncope with exertion suggests cardiac outflow obstruction. Such patients sometimes also have chest pain, palpitations, or both. Cardiac findings may help identify a cause. A harsh, late-peaking, basal

murmur radiating to the carotid arteries suggests aortic stenosis; a systolic

[Table 206-12. Some Drug Causes of Syncope]

murmur that increases with the Valsalva maneuver and disappears with squatting suggests hypertrophic cardiomyopathy. A systolic click followed by a blowing systolic murmur that moves closer to the 1st heart sound on standing suggests mitral valve prolapse (suggesting the cause is an arrhythmia).

Syncope that begins and ends suddenly and spontaneously is typical of cardiac causes, most commonly an arrhythmia. Because vasovagal and orthostatic mechanisms do not cause syncope in the recumbent position, syncope while lying down also suggests an arrhythmia.

If the patient is injured during the episode of syncope, the likelihood of a cardiac cause or seizure is somewhat greater, and therefore the event is of greater concern. The warning signs and slower LOC that accompany benign vasovagal syncope somewhat reduce the likelihood of injury.

Testing: Testing typically is done.

• ECG

• Pulse oximetry

• Sometimes echocardiography

• Sometimes tilt table testing

• Blood tests only if clinically indicated

• CNS imaging rarely indicated

In general, if syncope results in an injury or is recurrent (particularly within a brief period), more intensive evaluation is warranted.

Patients with suspected arrhythmia, myocarditis, or ischemia should be evaluated as in-patients. Others may be evaluated as outpatients.

ECG is done for all patients. The ECG may reveal arrhythmia, a conduction abnormality, ventricular hypertrophy, pre-excitation, QT prolongation, pacemaker malfunction, myocardial ischemia, or MI. If there are no clinical clues, measuring cardiac markers and obtaining serial ECGs to rule out MI in older patients plus ECG monitoring for at least 24 h are prudent. Any detected arrhythmia must be associated with altered consciousness in order to be implicated as the cause, but most patients do not experience syncope during monitoring. On the other hand, the presence of symptoms in the absence of rhythm disturbance helps rule out a cardiac cause. An event recorder may be useful if warning symptoms precede syncope. A signal-averaged ECG may identify predisposition to ventricular arrhythmias in patients with ischemic heart disease or in post-MI patients.

Pulse oximetry should be done during or immediately after an episode to identify hypoxemia (which may indicate pulmonary embolism). If hypoxemia is present, a CT scan or lung scan is indicated to rule out pulmonary embolism.

Laboratory tests are done based on clinical suspicion; reflexively obtained laboratory panels are of little use. However, all females of childbearing age should have a pregnancy test. Hct is measured if anemia is suspected. Electrolytes are measured only if an abnormality is clinically suspected (eg, by symptoms or drug use). Cardiac markers (eg, serum troponin, CK-MB) are measured if acute MI is suspected.

Echocardiography is indicated for patients with exercise-induced syncope, cardiac murmurs, or suspected intracardiac tumors (eg, those with positional syncope).

Tilt table testing is done if history and physical examination indicate vasodepressor or other reflex-induced syncope. It is also used to evaluate exercise-induced syncope if echocardiography or exercise stress testing is negative.

Stress testing (exercise or pharmacologic) is done when intermittent myocardial ischemia is suspected. It is often done for patients with exercise-induced symptoms.

Invasive electrophysiologic testing is considered if noninvasive testing does not identify arrhythmia in patients with unexplained recurrent syncope; a negative response defines a low-risk subgroup with a high rate of remission of syncope. The use of electrophysiologic testing is controversial in other patients. Exercise testing is less valuable unless physical activity precipitated syncope.

EEG is warranted if a seizure disorder is suspected.

CT and **MRI** of the head and brain are indicated only if signs and symptoms suggest a focal CNS disorder.

Treatment

In witnessed syncope, pulses are checked immediately. If the patient is pulseless, CPR is begun and cardiac resuscitation is done. If pulses are present, severe bradycardia is treated with atropine or external transthoracic pacing. Isoproterenol can be used to maintain adequate heart rate while a temporary pacemaker is placed.

Tachyarrhythmias are treated (see also p. 2146); a direct-current synchronized shock is quicker and safer for unstable patients. Inadequate venous return is treated by keeping the patient supine, raising the legs, and giving IV normal saline. Tamponade is relieved by pericardiocentesis. Tension pneumothorax requires insertion of a pleural cannula and drainage. Anaphylaxis is treated with parenteral epinephrine.

Placing the patient in a horizontal position with legs elevated typically ends the syncopal episode if life-threatening disorders are ruled out. If the patient sits upright too rapidly, syncope may recur; propping the patient upright or transporting the patient in an upright position may prolong cerebral hypoperfusion and prevent recovery.

Specific treatment depends on the cause and its pathophysiology.

Geriatrics Essentials

The most common cause of syncope in the elderly is postural hypotension due to a combination of factors. Factors include rigid, noncompliant arteries, reduced skeletal muscle pumping of venous return due to physical inactivity, and degeneration of the sinoatrial node and conduction system due to progressive structural heart disease.

In the elderly, syncope often has more than one cause. For example, the combination of taking several heart and BP drugs and standing in a hot church during a long or emotional service may lead to syncope even though no single factor might cause syncope.

Key Points

- Syncope results from global CNS dysfunction, usually from insufficient cerebral blood flow.
- Most syncope results from benign causes.
- Some less common causes involve cardiac arrhythmia or outflow obstruction and are serious or potentially fatal.
- Vasovagal syncope usually has an apparent trigger, warning symptoms, and a few minutes of postrecovery symptoms.

- Syncope from cardiac arrhythmias typically occurs abruptly and with quick recovery.
- Seizures have a prolonged (eg, hours) recovery period.
- If a benign etiology is not clear, driving and use of machinery should be prohibited until the etiology is determined and treated—the next manifestation of an unrecognized cardiac cause may be fatal.

Chapter 207. Cardiovascular Tests and Procedures

Introduction

Many noninvasive and invasive tests can delineate cardiac structure and function (see Table 207-1). Also, treatments can be administered during certain invasive diagnostic tests (eg, percutaneous coronary intervention during cardiac catheterization, radiofrequency ablation during electrophysiologic testing).

Cardiac Catheterization

Cardiac catheterization is the passage of a catheter through peripheral arteries or veins into cardiac chambers and coronary arteries. Cardiac catheterization can be used to do various tests, including angiography, intravascular ultrasonography, measurement of cardiac output (CO), detection and quantification of shunts, endomyocardial biopsy, and measurements of myocardial metabolism. These tests define coronary artery anatomy, cardiac anatomy, and cardiac function to establish diagnoses and help select treatment. Cardiac catheterization is also the basis for several therapeutic interventions.

Procedure

Patients must be npo for 4 to 6 h before cardiac catheterization. Most patients do not require overnight hospitalization.

Left heart catheterization is most commonly used to assess coronary artery anatomy; it is also useful for assessing aortic BP and systemic vascular resistance, aortic and mitral valve function, and left ventricular (LV) pressure and function. The procedure is done by percutaneous femoral, radial, or brachial artery puncture, with a catheter passed into the coronary artery ostia or across the aortic valve into the LV. Catheterization of the left atrium (LA) and LV is occasionally done using transseptal perforation during right heart catheterization.

Right heart catheterization is most commonly used to assess right atrial (RA), right ventricular (RV), and pulmonary artery pressure and pulmonary artery occlusion pressure (PAOP—see Fig. 207-1 and p. 2245); PAOP approximates LA and LV end-diastolic pressure. In seriously ill patients, PAOP helps assess volume status and, with simultaneous measurements of CO, can help guide therapy. Right heart catheterization is also useful for assessing pulmonary vascular resistance, tricuspid

[**Table 207-1.** Tests for Assessing Cardiac Anatomy and Function]

or pulmonic valve function, and RV pressure; RV pressure may help in the diagnosis of cardiomyopathy, constrictive pericarditis, and cardiac tamponade when noninvasive testing is nondiagnostic. The procedure is done by femoral, subclavian, internal jugular, or antecubital vein puncture. A catheter is passed into the RA, through the tricuspid valve, into the RV, and across the pulmonary valve into the pulmonary artery (see p. 2244). Selective catheterization of the coronary sinus can also be done.

Specific Tests During Cardiac Catheterization

Angiography: Injection of radiopaque dye into coronary or pulmonary arteries, the aorta, and cardiac chambers is useful in certain circumstances. Digital subtraction angiography is used for nonmoving arteries and for chamber cineangiography.

Coronary angiography via left heart catheterization is used to evaluate coronary artery anatomy in various clinical situations, as in patients with suspected coronary atherosclerotic or congenital disease, valvular disorders before valvular replacement, or unexplained heart failure.

Pulmonary angiography via right heart catheterization is used to diagnose pulmonary embolism. Intraluminal filling defects or arterial cutoffs are diagnostic. Radiopaque dye is usually selectively injected into one or both pulmonary arteries and their segments. Computed tomographic pulmonary angiography

(CTPA) has largely replaced right heart catheterization for diagnosis of pulmonary embolism.

Aortic angiography via left heart catheterization is used to assess aortic regurgitation, coarctation, patent ductus arteriosus, and dissection.

Ventriculography is used to visualize ventricular wall motion and ventricular outflow tracts, including subvalvular, valvular, and supravalvular regions. After LV mass and volume are determined from single planar or biplanar ventricular angiograms, end-systolic and end-diastolic volumes and ejection fraction can be calculated.

Intravascular ultrasonography: Miniature ultrasound transducers on the end of coronary artery catheters can produce images of coronary vessel lumina and walls and delineate blood flow. This technique is being increasingly used at the same time as coronary angiography.

Tests for cardiac shunts: Measuring blood O_2 content at successive levels in the heart and great vessels can help determine the presence, direction, and volume of central shunts. The maximal normal difference in O_2 content is 0.5 mL/dL between the pulmonary artery and RV, 0.9 mL/dL between the RV and RA, and 1.9 mL/dL between the RA and superior vena cava. If the blood O_2 content in a chamber exceeds that of the more proximal chamber by more than these values, a left-to-right shunt at that level is probable. Right-to-left shunts are strongly suspected when LA, LV, or arterial O_2 saturation is low (≤ 92%) and does not improve when pure O_2 (fractional

[**Fig. 207-1.** Diagram of the cardiac cycle, showing pressure curves of the cardiac chambers, heart sounds, jugular pulse wave, and the ECG.]

inspirational O_2 = 1.0) is given. Left heart or arterial desaturation plus increased O_2 content in blood samples drawn beyond the shunt site on the right side of circulation suggests a bidirectional shunt.

Measurement of cardiac output and flow: CO is the volume of blood ejected by the heart per minute (normal at rest: 4 to 8 L/min). Techniques used to calculate CO include the Fick, indicator-dilution, and thermodilution techniques (see Table 207-2).

With the Fick technique, CO is proportional to O_2 consumption divided by arteriovenous O_2 difference.

Dilution techniques rely on the assumption that after an indicator is injected into the circulation, it appears and disappears proportionately to CO.

Usually, CO is expressed in relation to BSA as the cardiac index (CI) in L/min/m^2 (ie, CI = CO/BSA—see Table 207-3). BSA is calculated using DuBois' height (ht)-weight (wt) equation:

$$\text{BSA in } m^2 = (\text{wt in kg})^{0.425} \times (\text{ht in cm})^{0.725} \times 0.007184$$

Endomyocardial biopsy: This procedure helps assess transplant rejection and myocardial disorders due to infection or infiltrative diseases. The biopsy catheter (bioptome) can be passed into either ventricle, usually the right. Three to 5 samples of myocardial tissue are removed from the septal endocardium. The main complication, cardiac perforation, occurs in 0.3 to 0.5% of patients; it may cause hemopericardium leading to cardiac tamponade.

Coronary artery flow measurements: Coronary angiography shows the presence and degree of stenosis but not the functional significance of the lesion (ie, how much blood flows across the stenosis). Extremely thin guidewires are available with pressure sensors or Doppler flow sensors. Data from these sensors can be used to estimate blood flow, which is expressed as fractional flow reserve (FFR). FFR is the ratio of maximal flow through the stenotic area to normal maximal flow; an FFR of < 0.75 to 0.8 is considered abnormal. These flow estimates correlate well with the need for intervention and long-term outcome; lesions with good FFR do not seem to benefit from stenting. These flow measurements are

most useful with intermediate lesions (40 to 70% stenosis) and with multiple lesions (to identify those that are clinically most significant).

[**Table 207-2.** Cardiac Output Equations]

[**Table 207-3.** Normal Values for Cardiac Index and Related Measurements]

Contraindications

Relative contraindications to cardiac catheterization include

- Renal insufficiency
- Coagulopathy
- Fever
- Systemic infection
- Uncontrolled arrhythmia or hypertension
- Uncompensated heart failure
- Radiopaque dye allergies in patients who have not been appropriately premedicated (see p. 3404)

Complications

Injection of radiopaque dye produces a transient sense of warmth throughout the body in many patients. Tachycardia, a slight fall in systemic pressure, an increase in CO, nausea, vomiting, and coughing may occur. Serious complications (eg, cardiac arrest, anaphylactic reactions, shock, seizures, cyanosis, renal toxicity) are rare. Rarely, bradycardia occurs when a large amount of dye is injected; asking the patient to cough often restores normal rhythm. Patients with a high Hct are susceptible to thrombosis; the Hct should be < 65% before angiography is done. Allergic reactions may include urticaria and conjunctivitis, which usually respond to diphenhydramine 50 mg IV. Bronchospasm, laryngeal edema, and dyspnea are rare reactions; they are treated with salbutamol or epinephrine. Anaphylactic shock is treated with epinephrine and other supportive measures. If the catheter tip contacts the ventricular endocardium, ventricular arrhythmias commonly occur, but ventricular fibrillation is rare. If it occurs, direct current (DC) cardioversion is administered immediately (see p. 2260). Radiopaque dyes, all hypertonic, are excreted by the kidneys and may worsen renal insufficiency. For patients at risk, infusion of normal saline IV, and perhaps premedication with acetylcysteine, reduces this risk.

Mortality rate is 0.1 to 0.2%. MI (0.1%) and stroke (0.1%) may result in significant morbidity. Incidence of stroke is higher in patients > 80 yr. Dissection of a coronary artery can complicate angiography. Local vascular injury at the peripheral insertion site of catheterization can cause hemorrhage or formation of pseudoaneurysms or arteriovenous fistulas.

Coronary Artery Bypass Grafting

Coronary artery bypass grafting (CABG—see also p. 2098) involves bypassing native coronary arteries with high-grade stenosis or occlusion not amenable to angioplasty with stenting. Indications are changing as percutaneous interventions (see p. 2059) are being increasingly used.

Traditional CABG Procedure

The procedure involves thoracotomy via a midline (median) sternotomy. A heart-lung machine is used to establish cardiopulmonary bypass (CPB), allowing the heart to be stopped and emptied of blood to maximize operative exposure and facilitate vessel anastomosis; stopping the heart also markedly decreases myocardial O_2 demand. Before initiation of CPB, the patient is given a very high dose of

heparin to prevent clotting in the bypass circuit. Then the aorta is cross-clamped and the heart is stopped by injection of a cardioplegic solution (crystalloid or more commonly blood-based) that also contains substances that help myocardial cells tolerate ischemia and reperfusion. The cardioplegic solution and the heart are sometimes cooled slightly to enhance tolerance of ischemia; the patient's body is cooled via the CPB machine for similar reasons.

The left internal mammary artery is typically used as a pedicled graft to the left anterior descending coronary artery. Other grafts consist of segments of saphenous vein removed from the leg. Occasionally, the right internal mammary artery or radial artery from the non-dominant arm can be used.

On completion of the vascular anastomoses, the aorta is unclamped, allowing the coronary arteries to be perfused by oxygenated blood, which typically restores cardiac activity. Heparin anticoagulation is reversed by giving protamine. Despite cardioprotective measures, stopping the heart is not without consequences. During reperfusion, myocardial dysfunction is common and can lead to bradycardia, arrhythmias (eg, ventricular fibrillation), and low cardiac output; these events are treated by standard measures, such as pacing, defibrillation, and inotropic drugs.

Typically, hospital stays are 4 to 5 days unless prolonged by complications.

Complications: Complications and disadvantages of traditional CABG involve mainly

• Sternotomy

• CPB

Median sternotomy is surprisingly well tolerated; however, healing takes 4 to 6 wk. Also, wound infections occasionally cause mediastinitis or sternal osteomyelitis, which can be vexing to treat.

CPB causes several complications, including

• Bleeding

• Organ dysfunction

• Neuropsychiatric effects

• Stroke

Post-CPB bleeding is a common problem caused by various factors, including hemodilution, heparin use, platelet dysfunction due to exposure to the bypass pump, consumptive coagulopathy, and induced hypothermia. Also, the CPB machine evokes a systemic inflammatory response (probably due to exposure of blood components to the foreign material of the bypass circuit); this response can cause organ dysfunction in any system (eg, pulmonary, renal, brain, GI). Aortic cannulation, cross-clamping, and release can trigger release of emboli, causing stroke in about 1.5%; microemboli may contribute to post-CPB neuropsychiatric effects, which appear in about 5 to 10%.

Other common complications of CABG include focal and global myocardial ischemia and dysrhythmias. Perioperative MI occurs in about 1% of patients. Atrial fibrillation occurs in 15 to 40% of patients, typically 2 to 4 days after surgery. Nonsustained ventricular tachycardia may occur in up to 50% of patients.

Mortality depends mainly on patients' underlying health; operator and institutional experience (ie, number of annual procedures) also is important. In an experienced program, periprocedural mortality in otherwise healthy patients is typically < 1 to 3%.

Alternative CABG Procedures

Newer techniques seek to limit the complications of traditional CABG by

• Avoiding CPB (off-pump CABG)

• Avoiding median sternotomy (minimally invasive CABG)

• Both

CPB can be avoided in select patients by using new techniques that allow the surgeon to revascularize the beating heart. Various devices and methods stabilize a portion of the myocardium, holding the operative site relatively motionless. Off-pump procedures are more commonly done through small parasternal or intercostal incisions (minimally invasive CABG), sometimes with endoscopy or even robotic assistance, but they may be done through a traditional median sternotomy, which provides better operative exposure.

Allowing the heart to beat means that the myocardium requires more O_2 than when CPB is used. Thus, the heart is sensitive to the interruption of blood flow necessitated while the vascular anastomosis is done; this interruption can cause ischemia or infarction in the myocardium supplied by the affected vessel. Some surgeons place a temporary coronary artery shunt to provide distal perfusion.

The minimally invasive technique is somewhat more difficult to do and may not be suitable when multiple bypass grafts, particularly those involving vessels behind the heart, are required. Transfusion requirements, length of stay, and costs are typically less with off-pump CABG, but in some studies, the rate of the more serious complications of death, MI, and stroke are similar to that of CABG using CPB. Thus, the theoretic advantages of avoiding CPB do not seem to have been fully realized.

Minimally invasive CABG is usually done off-pump but may be done using CPB. In such cases, CPB is done endovascularly using special catheters inserted into the arterial and venous systems; the aorta is occluded by a balloon at the end of the aortic catheter rather than an external clamp. Although avoiding median sternotomy complications, this technique otherwise has similar rates of mortality and major perioperative complications as conventional techniques.

Echocardiography

Echocardiography uses ultrasound waves to produce an image of the heart and great vessels. It helps assess heart wall thickness (eg, in hypertrophy or atrophy) and motion and provides information about ischemia and infarction. It can be used to assess diastolic filling patterns of the left ventricle, which can help in the diagnosis of left ventricular hypertrophy, hypertrophic or restrictive cardiomyopathy, severe heart failure, constrictive pericarditis, and severe aortic regurgitation.

Techniques: There are 2 techniques for doing echocardiography:

• Transthoracic

• Transesophageal

In transthoracic echocardiography (TTE), the most common technique, a transducer is placed along the left or right sternal border, at the cardiac apex, at the suprasternal notch (to allow visualization of the aortic valve, left ventricular outflow tract, and descending aorta), or over the subxiphoid region. TTE provides 2- or 3-dimensional tomographic images of most major cardiac structures.

In transesophageal echocardiography (TEE), a transducer on the tip of an endoscope allows visualization of the heart via the esophagus. TEE is used to assess cardiac disorders when transthoracic study is technically difficult, as in obese patients and in patients with COPD. It reveals better detail of small abnormal structures (eg, endocarditic vegetations or patent foramen ovale) and posterior cardiac structures (eg, left atrium, left atrial appendage, interatrial septum) because they are closer to the esophagus than to the anterior chest wall. TEE can also produce images of the ascending aorta, which arises behind the 3rd costal cartilage; of structures < 3 mm (eg, thrombi, vegetations); and of prosthetic valves.

Methodology: Two-dimensional (cross-sectional) echocardiography is most commonly used; contrast and spectral Doppler echocardiography provide additional information.

Contrast echocardiography is 2-dimensional TTE done while agitated saline is rapidly injected into the cardiac circulation. Agitated saline develops microbubbles, which produce a cloud of echoes in the right cardiac chambers and which, if a septal defect is present, appear on the left side of the heart. Usually, the microbubbles do not traverse the pulmonary capillary bed; however, one agent, sonicated albumin microbubbles, can do so and can enter left heart structures after IV injection.

Spectral Doppler echocardiography can record velocity, direction, and type of blood flow. This technique is useful for detecting abnormal blood flow (eg, due to regurgitant lesions) or velocity (eg, due to stenotic lesions). Spectral Doppler echocardiography does not provide spatial information about the size or shape of the heart or its structures.

Color Doppler echocardiography combines 2-dimensional and spectral Doppler echocardiography to provide information about the size and shape of the heart and its structures as well as the velocity of and direction of blood flow around the valves and outflow tracts. Color is used to code blood flow information; by convention, red is toward and blue away from the transducer.

Tissue Doppler imaging uses Doppler techniques to measure the velocity of myocardial tissue contraction (rather than of blood flow). These data can be used to calculate myocardial strain (percentage change in length between contraction and relaxation) and myocardial strain rate (rate of change in length). Strain and strain rate measurements can help assess systolic and diastolic function and identify ischemia during stress testing.

Stress echocardiography: TTE is an alternative to radionuclide imaging to identify myocardial ischemia during and after exercise or pharmacologic stress. Stress echocardiography shows regional wall motion abnormalities that result from an imbalance in blood flow in epicardial coronary vessels during stress. Computer programs can provide side-by-side assessment of ventricular contraction during systole and diastole at rest and under stress. Exercise and pharmacologic protocols are the same as those used in radionuclide stress testing. Stress echocardiography and radionuclide stress testing detect ischemia equally well. The choice between tests is often based on availability, the provider's experience, and cost.

Electrocardiography

The standard ECG provides 12 different vector views of the heart's electrical activity as reflected by electrical potential differences between positive and negative electrodes placed on the limbs and chest wall. Six of these views are vertical (using frontal leads I, II, and III and limb leads aVR, aVL, and aVF), and 6 are horizontal (using precordial leads V_1, V_2, V_3, V_4, V_5, and V_6). The 12-lead ECG is crucial for establishing many cardiac diagnoses, especially arrhythmias and myocardial ischemia (see Table 207-4). It can also identify atrial enlargement, ventricular hypertrophy (see Table 207-5), and conditions that predispose to syncope or sudden death (eg, Wolff-Parkinson-White syndrome, long QT syndrome, Brugada syndrome).

Standard ECG Components

By convention, the ECG tracing is divided into the P wave, PR interval, QRS complex, QT interval, ST segment, T wave, and U wave (see Fig. 207-2).

P wave: The P wave represents atrial depolarization. It is upright in most leads except aVR. It may be biphasic in leads II and V_1; the initial component represents right atrial activity, and the 2nd component represents left atrial activity.

An increase in amplitude of either or both components occurs with atrial enlargement. Right atrial enlargement produces a P wave > 2 mm in leads II, III, and aVF (P pulmonale); left atrial enlargement produces a P wave that is broad and double-peaked in lead II (P mitrale). Normally, the P axis is between 0° and 75°.

PR interval: The PR interval is the time between onset of atrial depolarization and onset of ventricular depolarization. Normally, it is 0.10 to 0.20 sec; prolongation defines 1st-degree atrioventricular block.

QRS complex: The QRS complex represents ventricular depolarization. The Q wave is the initial downward deflection; normal Q waves last < 0.05 sec in all leads except V_{1-3}, in which any Q wave is considered abnormal, indicating past or current infarction. The R wave is the first upward deflection; criteria for normal height or size are not absolute, but taller R waves may be caused by ventricular hypertrophy. A 2nd upward deflection in a QRS complex is designated R´. The S wave is the 2nd downward deflection if there is a Q wave and the first downward deflection if not. The QRS complex may be R alone, QS (no R), QR (no S), RS (no Q), or RSR´, depending on the ECG lead, vector, and presence of heart disorders.

Normally, the QRS interval is 0.07 to 0.10 sec. An interval of 0.10 to 0.11 sec is considered incomplete bundle branch block or a nonspecific intraventricular conduction

[Table 207-4. Interpretation of Abnormal ECGs]

delay, depending on QRS morphology; ≥ 0.12 sec is considered complete bundle branch block or an intraventricular conduction delay. Normally, the QRS axis is 90° to -30°. An axis of -30° to -90° is considered left axis deviation and occurs in left anterior fascicular block (-60°) and inferior MI. An axis of 90° to 180° is considered right axis deviation; it occurs in any condition that increases pulmonary pressures and causes right ventricular hypertrophy (cor pulmonale, acute pulmonary embolism, pulmonary hypertension), and it sometimes occurs in right bundle branch block or left posterior fascicular block.

QT interval: The QT interval is the time between onset of ventricular depolarization and end of ventricular repolarization. The QT interval must be corrected for heart rate using the formula:

$$QTc = \frac{QT}{\sqrt{RR}}$$

where QT_C is the corrected QT interval; R-R interval is the time between 2 QRS complexes. All intervals are recorded in seconds. QT_C prolongation is strongly implicated in development

[Table 207-5. Criteria for ECG Diagnosis of Left Ventricular Hypertrophy]

of torsades de pointe ventricular tachycardia (see p. 2176). QT_C is often difficult to calculate because the end of the T wave is often unclear or followed by a U wave with which it merges.

ST segment: The ST segment represents completed ventricular myocardial depolarization. Normally, it is horizontal along the baseline of the PR (or TP) intervals or slightly off baseline.

ST segment elevation can be caused by

• Early repolarization

• Left ventricular hypertrophy

• Myocardial ischemia and infarction

• Left ventricular aneurysm

• Pericarditis

• Hyperkalemia

• Hypothermia

• Pulmonary embolism

ST segment depression can be caused by

• Hypokalemia

• Digoxin

• Subendocardial ischemia

• Reciprocal changes in acute MI

T wave: The T wave reflects ventricular repolarization. It usually takes the same direction as the QRS complex (concordance); opposite polarity (discordance) may indicate past or current infarction. The T wave is usually smooth and rounded but may be of low amplitude in hypokalemia and hypomagnesemia and may be tall and peaked in hyperkalemia, hypocalcemia, and left ventricular hypertrophy.

U wave: The U wave appears commonly in patients who have hypokalemia, hypomagnesemia, or ischemia. It is often present in healthy people.

Specialized ECG Tests

A standard 12-lead ECG represents only a single brief period of cardiac activity; enhanced techniques can provide additional information.

Additional precordial leads: Additional precordial leads are used to help diagnose right ventricular and posterior wall MI.

Right-sided leads are placed across the right side of the chest to mirror standard left-sided leads. They are labeled V_1R to V_6R; sometimes only V_4R is used, because it is the most sensitive for right ventricular MI.

Additional left-sided leads can be placed in the 5th intercostal space, with V_7 at the posterior axillary line, V_8 at the midscapular line, and V_9 at the left border of the spine. These leads are rarely used but may help diagnose a true posterior MI.

Esophageal lead: An esophageal lead is much closer to the atria than surface leads; it

[Fig. 207-2. ECG waves.]

is an option when the presence of P waves on a standard recording is uncertain and when detecting atrial electrical activity is important, as when atrial or ventricular origin of wide-complex tachycardia must be differentiated or when atrioventricular dissociation is suspected. An esophageal lead may also be used to monitor intraoperative myocardial ischemia or to detect atrial activity during cardioplegia. The lead is placed by having the patient swallow an electrode, which is then connected to a standard ECG machine, often in the lead II port.

Signal averaging: Signal-averaging of QRS waveforms creates a digital composite of several hundred cardiac cycles to detect high-frequency, low-amplitude potentials and microcurrents at the terminal part of the QRS complex. These findings represent areas of slow conduction through abnormal myocardium, indicating increased risk of reentrant ventricular tachycardia. Signal-averaged ECG is still largely a research technique but is occasionally used to assess risk of sudden cardiac death (eg, in post-MI patients without evidence of conduction delay, patients with myocardial ischemia and unexplained syncope, and those with nonischemic cardiomyopathy) and to assess efficacy of surgery to correct the arrhythmia. This technique may also be useful for assessing the proarrhythmic effects of antiarrhythmic

drugs and for detecting rejection of heart transplants. Signal averaging of P waves is being studied as a way to identify patients at risk of atrial fibrillation.

Continuous ST-segment monitoring: This type of monitoring is used for early detection of ischemia and serious arrhythmias. Monitoring can be automated (dedicated electronic monitoring units are available) or done clinically using serial ECGs. Applications include emergency department monitoring of patients with crescendo angina, evaluation after percutaneous intervention, intraoperative monitoring, and postoperative care.

QT dispersion: QT dispersion (the difference between the longest and shortest QT intervals on a 12-lead ECG) has been proposed as a measure of myocardial repolarization heterogeneity. Increased dispersion suggests electrically heterogeneous myocardium caused by ischemia or fibrosis, with increased risk of reentrant arrhythmias and sudden death. QT dispersion predicts mortality risk but is not widely measured because measurement error is common, values in patients with and without disease overlap substantially, there is no reference standard, and other validated risk predictors are available.

Heart rate variability: This measurement reflects the balance between sympathetic and parasympathetic (vagal) input to the heart. Decreased variability suggests decreased vagal input and increased sympathetic input, which predict increased risk of arrhythmias and mortality. The most common measure of variability is the mean of the standard deviations of all normal R-R intervals in a 24-h ECG recording. Heart rate variability is used primarily in research, but evidence suggests that it provides useful information about left ventricular dysfunction after MI, heart failure, and hypertrophic cardiomyopathy. Most Holter monitors have software that measures and analyzes heart rate variability.

Holter monitor: Holter monitoring is continuous monitoring and recording of the ECG, BP, or both for 24 or 48 h. It is useful for evaluating intermittent arrhythmias and, secondarily, for detecting hypertension. The Holter monitor is portable, enabling patients to participate in normal daily activities; it may also be used for sedentary hospitalized patients if automated monitoring is unavailable. Patients are asked to record symptoms and activities so that they may be correlated with events on the monitor. The Holter monitor does not automatically analyze the ECG data; a physician does so at a later date.

Event recorder: Event recorders are worn for up to 30 days and can detect infrequent rhythm disturbances that 24-h Holter monitoring may miss. The recorder does not operate continuously but is activated by the patient when symptoms occur. A memory loop enables information to be stored for seconds or minutes before and after activation. The patient can transmit ECG data by telephone to be read by a physician. If patients have serious events (eg, syncope) at intervals of > 30 days, an event recorder may be placed subcutaneously; it can be activated by a small magnet. Battery life for subcutaneous recorders is 14 mo.

Electrophysiologic Studies

In electrophysiologic studies, recording and stimulating electrodes are inserted via right- or left-sided cardiac catheterization into all 4 cardiac chambers. Atria are paced from the right or left atrium, ventricles are paced from the right ventricular apex or right ventricular outflow tract, and cardiac conduction is recorded. Programmed stimulation techniques may be used to trigger and terminate a reentrant arrhythmia.

Electrophysiologic studies are indicated primarily for evaluation and treatment of arrhythmias that are difficult to capture, serious, or sustained. These studies may be used to make a primary diagnosis, to evaluate the efficacy of antiarrhythmic drugs, or to map arrhythmia foci before radiofrequency catheter ablation (see p. 2161). Various mapping techniques are available.

Cardiac Imaging Tests

Standard imaging tests include echocardiography (see p. 2053), chest x-ray, CT, MRI, and various radionuclide techniques (see p. 2061). Standard CT and MRI have limited application because the heart constantly beats, but faster CT and MR techniques can provide useful cardiac images; sometimes patients are given a drug (eg, a β-blocker) to slow the heart rate during imaging. In addition, by

synchronizing image recording (or reconstruction) with the ECG (ECG gating), information from several cardiac cycles can be used to create single images of selected points in the cardiac cycle. CT gating that uses the ECG to trigger the x-ray beam at the desired portion of the cardiac cycle gives less x-ray exposure than gating that simply reconstructs information from only the desired portion of the cardiac cycle (gated reconstruction) and does not interrupt the x-ray beam.

Chest x-rays: Chest x-rays are often useful as a starting point in a cardiac diagnosis. Posteroanterior and lateral views provide a gross view of atrial and ventricular size and shape and pulmonary vasculature, but additional tests are almost always required for precise characterization of cardiac structure and function.

CT: Spiral (helical) CT may be used to evaluate pericarditis, congenital cardiac disorders (especially abnormal arteriovenous connections), disorders of the great vessels (eg, aortic aneurysm, aortic dissection), cardiac tumors, acute pulmonary embolism, chronic pulmonary thromboembolic disease, and arrhythmogenic right ventricular dysplasia. However, CT requires a radiopaque dye, which may limit its use in patients with renal impairment.

Electron beam CT, formerly called ultrafast CT or cine CT, unlike conventional CT, does not use a moving x-ray source and target. Instead, the direction of the x-ray beam is guided by a magnetic field and detected by an array of stationary detectors. Because mechanical motion is not required, images can be acquired in a fraction of a second (and targeted to a specific point in the cardiac cycle). Electron beam CT is used primarily to detect and quantify coronary artery calcification, an early sign of atherosclerosis. However, spatial resolution is poor and the equipment cannot be used for noncardiac disorders, so newer standard CT techniques are becoming preferred for cardiac use.

Multidetector CT (MDCT), with ≥ 64 detectors, has a very rapid scan time; some advanced machines may generate an image from a single heartbeat, although typical acquisition times are 30 sec. Dual-source CT uses 2 x-ray sources and 2 multidetector arrays on a single gantry, which cuts scan time in half. Both of these modalities appear able to identify coronary calcifications and flow-limiting (ie, > 50% stenosis) coronary artery obstruction. Typically, an IV contrast agent is used, although nonenhanced scans can detect coronary artery calcification.

MDCT is currently used mainly for patients with indeterminate stress imaging test results as a noninvasive alternative to coronary angiography. However, radiation dose is significant, about 15 mSv (vs 0.1 mSv for a chest x-ray and 7 mSv for coronary angiography). The presence of high-density calcified plaques creates imaging artifacts that interfere with interpretation.

MRI: Standard MRI is useful for evaluating areas around the heart, particularly the mediastinum and great vessels (eg, for studying aneurysms, dissections, and stenoses). With ECG-gated data acquisition, image resolution can approach that of CT or echocardiography, clearly delineating myocardial wall thickness and motion, chamber volumes, intraluminal masses or clot, and valve planes. Sequential MRI after injecting a paramagnetic contrast agent (gadolinium-diethylenetriamine pentaacetic acid [Gd-DTPA]) produces higher resolution of myocardial perfusion patterns than does radionuclide imaging. However, patients with impaired renal function can develop nephrogenic systemic fibrosis, a potentially life-threatening disorder, after use of gadolinium contrast. Using contrast, 3-dimensional information on infarct size and location can be obtained, and blood flow velocities in cardiac chambers can be measured. MRI can assess tissue viability by assessing the contractile response to inotropic stimulation with dobutamine or by using a contrast agent (eg, Gd-DTPA, which is excluded from cells with intact membranes).

Magnetic resonance angiography (MRA) is used to assess blood volumes of interest (eg, blood vessels in the chest or abdomen); all blood flow can be assessed simultaneously. MRA can be used to detect aneurysms, stenosis, or occlusions in the carotid, coronary, renal, or peripheral arteries. Use of this technique to detect deep venous thrombosis is being studied.

PET: PET can demonstrate myocardial perfusion and metabolism.

Perfusion agents include carbon-11 (^{11}C) CO_2, oxygen-15 (^{15}O) water, nitrogen-13 (^{13}N) ammonia, and

rubidium-82 (^{82}Rb). Only ^{82}Rb does not require an on-site cyclotron.

Metabolic agents include fluorine-18 (^{18}F)-labeled deoxyglucose (FDG) and ^{11}C acetate. FDG detects the enhancement of glucose metabolism under ischemic conditions, and can thus distinguish ischemic but still viable myocardium from scar tissue. Sensitivity is greater than with myocardial perfusion imaging, possibly making FDG imaging useful for selecting patients for revascularization and for avoiding such procedures when only scar tissue is present. This use may justify the greater expense of PET. Half-life of ^{18}F is long enough (110 min) that FDG can often be produced off-site. Techniques that enable FDG imaging to be used with conventional single-photon emission CT (SPECT) cameras may make this type of imaging widely available.

Uptake of ^{11}C acetate appears to reflect overall O_2 metabolism by myocytes. Uptake does not depend on such potentially variable factors as blood glucose levels, which can affect FDG distribution. ^{11}C acetate imaging may better predict postintervention recovery of myocardial function than FDG imaging. However, because of a 20-min half-life, ^{11}C must be produced by an on-site cyclotron.

Percutaneous Coronary Interventions

Percutaneous coronary interventions (PCI) include percutaneous transluminal coronary angioplasty (PTCA) with or without stenting. Primary indications are treatment of angina pectoris (stable or unstable), myocardial ischemia, and acute MI (particularly in patients with developing or established cardiogenic shock). Primary PTCA and stent placement within 90 min of onset of pain is the optimal treatment of transmural ST-segment-elevation MI. Elective PCI may be appropriate for post-MI patients who have recurrent or inducible angina before hospital discharge and for patients who have angina and remain symptomatic despite medical treatment. Percutaneous transluminal angioplasty (PTA) is used to treat peripheral arterial disease (see p. 2220).

Procedure: PTCA is done via percutaneous femoral, radial, or brachial artery puncture. A guiding catheter is inserted into a large peripheral artery and threaded to the appropriate coronary ostium. A balloon-tipped catheter, guided by fluoroscopy or intravascular ultrasonography, is aligned within the stenosis, then inflated to disrupt the atherosclerotic plaque and dilate the artery. Angiography is repeated after the procedure to document any changes. The procedure is commonly done in 2 or 3 vessels as needed.

Stents: Stents are most useful for

- Short lesions in large native coronary arteries not previously treated with PTCA
- Focal lesions in saphenous vein grafts
- Treatment of abrupt closure during PTCA

The role of stenting in acute MI, ostial or left main disease, chronic total occlusions, and bifurcation lesions is still evolving.

Types of stents: Bare metal stents (BMS) are made of nickel-titanium alloy. Drug eluting stents (DES) have drugs (eg, sirolimus, paclitaxel) bonded to the metal that limit neointimal proliferation to reduce the risk of restenosis. In intracoronary brachytherapy, the site of stenosis is exposed to radiation in the form of small pellets embedded in a nylon ribbon temporarily (eg, 30 min) placed in the coronary artery prior to stenting. This technique appears to decrease the risk of early restenosis, but it is unclear whether later stenosis is slightly increased; trials are ongoing. Radioactive stents have not proven effective at limiting restenosis.

Anticoagulation: Various anticoagulation regimens are used during and after angioplasty to reduce the incidence of thrombosis at the site of balloon dilation. Clopidogrel and glycoprotein IIb/IIIa inhibitors are the standard of care for patients with unstable non-ST-segment elevation MI. Clopidogrel (often in

combination with aspirin) is continued for 9 to 12 mo after PCI. Ca channel blockers and nitrates may also reduce risk of coronary spasm.

Contraindications

Absolute contraindications include

- Lack of cardiac surgical support
- Significant obstruction of the left main coronary artery without a nonobstructed bypass graft to the left anterior descending or left circumflex arteries

Relative contraindications include

- Coagulopathy
- Hypercoagulable states
- Diffusely diseased vessels without focal stenoses
- A single diseased vessel providing all perfusion to the myocardium
- Total occlusion of a coronary artery
- Stenosis < 50%

Complications

The main complications of balloon angioplasty and stenting are

- Thrombosis
- Restenosis

Thrombosis causes complete blockage and may occur at any time—acutely (immediately during or after the procedure), subacutely (within 30 days), or late (> 30 days). Stent thrombosis may be due to inadequate stent expansion or apposition at the time of the procedure, discontinuation of dual antiplatelet therapy (eg, from nonadherence, need for noncardiac surgery), or both.

Restenosis is typically due to collagen deposition and thus does not occur until several weeks after the procedure or later; it may cause partial or, less commonly, complete vessel blockage.

With balloon angioplasty, risk of acute thrombosis is about 5 to 10%, risk of subacute restenosis is about 5%, and the overall restenosis rate is about 30 to 45%. Use of stents has almost eliminated the need for emergency coronary artery bypass grafting following PCI. With stenting, the rate of acute and subacute thrombosis or restenosis is < 1%. With BMS, risk of late restenosis is decreased to 20 to 30%. Use of a DES lowers late restenosis risk to about 5 to 10%. However, using a DES increases risk of late stent thrombosis, about 0.6%/yr up to 3 yr.

Complications besides restenosis are similar to those of coronary angiography, although risk of death, MI, and stroke is greater. Of all angiographic procedures, PCI has the highest risk of contrast nephropathy; this risk can be reduced by preprocedural hydration and possibly by use of a nonionic contrast agent, acetylcysteine, or hemofiltration in patients with preexisting renal insufficiency. Stenting, in addition to the above, has complications of bleeding secondary to aggressive adjunctive anticoagulation, side branch occlusion, and stent embolism.

Radionuclide Imaging

Radionuclide imaging uses a special detector (gamma camera) to create an image following injection of radioactive material. This test is done to evaluate coronary artery disease (CAD), valvular or congenital cardiac disorders, cardiomyopathy, and other cardiac disorders. Radionuclide imaging exposes patients to less radiation than do comparable x-ray studies. However, because the radioactive material is retained in the patient briefly, sophisticated radiation alarms (eg, in airports) may be triggered by the patient for several days after such testing.

Single-photon emission computed tomography (SPECT): Planar techniques, which produce a 2-dimensional image, are rarely used; SPECT, which uses a rotating camera system and tomographic reconstruction to produce a 3-dimensional image, is more common in the US. With multihead SPECT systems, imaging can often be completed in ≤ 10 min. Visual comparison of stress and delayed images can be supplemented by quantitative displays. With SPECT, inferior and posterior abnormalities and small areas of infarction and the vessels responsible for infarction can be identified. The mass of infarcted and viable myocardium can be quantified, helping determine prognosis.

Myocardial Perfusion Imaging

In myocardial perfusion imaging, IV radionuclides are taken up by cardiac tissues in rough proportion to perfusion; thus, areas of decreased uptake represent areas of relative or absolute ischemia. For this reason, myocardial perfusion imaging is used with stress testing to evaluate patients with chest pain of uncertain origin, to determine the functional significance of coronary artery stenosis or collateral vessels seen on angiography, and to evaluate the success of reperfusion interventions (eg, coronary artery bypass grafting [CABG], percutaneous intervention, thrombolysis). After acute MI, myocardial perfusion imaging can help estimate prognosis because it can show extent of the perfusion abnormality due to acute MI, extent of scarring due to previous infarcts, and residual peri-infarct or other areas of reversible ischemia.

Radioactive thallium-201 (^{201}Tl), which acts as a K analog, was the original tracer used in stress testing. It is injected at peak stress and imaged with SPECT, followed 4 h later by injection of one half the original dose during rest and by repeat SPECT. The goal of this protocol is to evaluate reversible perfusion defects that may warrant intervention. After stress testing, the perfusion imbalance between normal coronary arteries and those distal to a stenosis appears as a relative decrease in ^{201}Tl uptake in the areas perfused by the stenosed arteries. Sensitivity of stress testing with ^{201}Tl for CAD is similar whether imaging is done after exercise or pharmacologic stress.

Because the imaging characteristics of ^{201}Tl are not ideal for the gamma camera, several technetium-99m (^{99m}Tc) myocardial perfusion markers have been developed: sestamibi (commonly used), tetrofosmin, and teboroxime (see Table 207-6). Protocols

[**Table 207-6.** Technetium-99M Myocardial Perfusion Markers]

include 2-day stress-rest, 1-day rest-stress, and 1-day stress-rest. Some protocols use dual isotopes (^{201}Tl and ^{99m}Tc), although this approach is expensive. With either of these markers, sensitivity is about 90%, and specificity is about 71%.

For 2-day protocols, imaging at rest may be omitted if the initial stress test shows no evidence of abnormal perfusion. When higher doses of ^{99m}Tc (> 30 mCi) are used, first-transit function studies (with ventriculography) may be used with perfusion imaging.

Other radionuclides include iodine-123 (^{123}I)-labeled fatty acids, which produces cold spots where myocardium is ischemic; gallium citrate-67 (^{67}Ga), which accumulates in sites of active inflammation (eg, in acute inflammatory cardiomyopathy); and ^{123}I metaiodobenzylguanidine, a neurotransmitter analog taken up and stored in neurons of the sympathetic nervous system and used in research to evaluate heart failure, diabetes, certain arrhythmias, and arrhythmogenic right ventricular dysplasia.

Attenuation of myocardial activity by overlying soft tissue may cause false-positive results. Attenuation by breast tissue in women is especially common. Attenuation by the diaphragm and abdominal contents may produce spurious inferior wall defects in both sexes but is more common among men. Attenuation is more likely with ^{99m}Tc than with ^{201}Tl.

Infarct Avid Imaging

Infarct avid imaging uses radiolabeled markers that accumulate in areas of damaged myocardium, such as ^{99m}Tc pyrophosphate and antimyosin (indium-111 [^{111}In]-labeled antibodies to cardiac myosin). Images usually become positive 12 to 24 h after acute MI and remain positive for about 1 wk; they may remain positive if myocardial necrosis continues post-MI or if aneurysms develop. This technique is rarely used now because other diagnostic tests for MI (eg, biomarkers) are more readily available and less expensive and because it provides no prognostic information other than infarct size.

Radionuclide Ventriculography

Radionuclide ventriculography is used to evaluate ventricular function. It is useful for measuring resting and exercise ejection fraction in CAD, valvular heart disease, and congenital heart disease. Some clinicians prefer it for serial assessment of ventricular function in patients taking cardiotoxic cancer chemotherapy (eg, anthracyclines). However, radionuclide ventriculography has been largely replaced by echocardiography, which is less expensive, does not require radiation exposure, and theoretically can measure ejection fractions as accurately.

^{99m}Tc-labeled RBCs are injected into the ventricles. Left ventricular (LV) and right ventricular (RV) function can be evaluated by first-transit studies (a type of beat-to-beat evaluation) or by gated (ECG-synchronized) blood pool imaging done over several minutes (multiple-gated acquisition [MUGA]). Either study can be done during rest or after exercise. First-transit studies are rapid and relatively easy, but MUGA provides better images and is more widely used.

In first-transit studies, 8 to 10 cardiac cycles are imaged as the marker mixes with blood and passes through the central circulation. First-transit studies are ideal for assessing RV function and intracardiac shunts.

In MUGA, imaging is synchronized with the R wave of the ECG. Multiple images are taken of short, sequential portions of each cardiac cycle for 5 to 10 min. Computer analysis generates an average blood pool configuration for each portion of the cardiac cycle and synthesizes the configurations into a continuous cinematic loop resembling a beating heart.

MUGA can quantitate numerous indexes of ventricular function, including regional wall motion, ejection fraction (EF); ratio of stroke volume to end-diastolic volume, ejection and filling rates, LV volume, and indexes of relative volume overload (eg, LV:RV stroke volume ratios). EF is used most commonly.

MUGA during rest has virtually no risk. It is used for serially evaluating RV and LV function in various disorders (eg, valvular heart disorders); for monitoring patients taking potentially cardiotoxic drugs (eg, doxorubicin); and for assessing the effects of angioplasty, CABG, thrombolysis, and other procedures in patients with CAD or MI. Arrhythmias are a relative contraindication because there may be few normal cardiac cycles.

LV: MUGA is useful for detecting LV aneurysms; sensitivity and specificity are > 90% for typical anterior or anteroapical true aneurysms. Conventional gated blood pool imaging shows inferoposterior LV aneurysms less well than it shows anterior and lateral aneurysms; additional views are required. Gated SPECT imaging takes longer (about 20 to 25 min with a multihead camera) than a single planar gated view (5 to 10 min) but shows all portions of the ventricles.

RV: MUGA is used to assess RV function in patients who have a lung disorder or an inferior LV infarct that may involve the RV. Normally, RVEF (40 to 55% with most techniques) is lower than LVEF. RVEF is

subnormal in many patients with pulmonary hypertension and in patients with RV infarction or cardiomyopathy affecting the RV. Idiopathic cardiomyopathy is usually characterized by biventricular dysfunction, unlike typical CAD, which usually causes more LV than RV dysfunction.

Valves: MUGA can be used with rest-stress protocols to assess valvular disorders that result in LV volume overload. In aortic regurgitation, a reduction in resting EF or no increase in EF with exercise is a sign of deteriorating cardiac function and may indicate a need for valvular repair. MUGA also can be used to calculate the regurgitant fraction in regurgitation of any valve. Normally, the stroke volume of the 2 ventricles is equal. However, in patients with left-sided valvular regurgitation, LV stroke volume exceeds that of the RV by an amount proportional to the regurgitant fraction. Thus, if the RV is normal, the regurgitant fraction of the LV can be calculated from the LV:RV stroke volume ratio.

Shunts: With MUGA and commercially available computer programs, size of a congenital shunt can be quantified by the stroke volume ratio or, during the first transit of the marker, by the ratio of abnormal early pulmonary recirculation of radioactivity to total pulmonary radioactivity.

Stress Testing

In stress testing, the heart is monitored by ECG and often imaging studies during an induced episode of increased cardiac demand so that ischemic areas potentially at risk of infarction can be identified. Heart rate is increased to 85% of age-predicted maximum (target heart rate) or until symptoms develop, whichever occurs first.

Stress testing is used for diagnosis of coronary artery disease (CAD) and for risk stratification and monitoring of patients with known CAD. In patients with CAD, a blood supply that is adequate at rest may be inadequate when cardiac demands are increased by exercise or other forms of stress. Stress testing is less invasive and less expensive than cardiac catheterization, and it detects pathophysiologic abnormalities of blood flow; however, it is less accurate for diagnosis in patients with a low pretest likelihood of CAD. It can define the functional significance of abnormalities in coronary artery anatomy identified with coronary angiography during catheterization. Because coronary artery plaques that are not significantly stenotic (ie, do not result in ischemia during stress testing) may nonetheless rupture and cause an acute coronary syndrome, a normal stress test result does not guarantee future freedom from MI.

Risks of stress testing include infarction and sudden death, which occur in about 1/5000 patients tested. Stress testing has several contraindications (see Table 207-7). Patients must be npo for 4 to 6 h before the test.

Stress Methodology

Cardiac demand can be increased by exercise or drugs.

[**Table 207-7.** Contraindications to Exercise Stress Testing]

Exercise stress testing: Exercise is preferred to drugs for increasing cardiac demand because it more closely replicates ischemia-inducing stressors. Usually, a patient walks on a conventional treadmill, following the Bruce protocol or a similar exercise schedule, until the target heart rate is reached or symptoms occur. The Bruce protocol increases treadmill speed and slope incrementally at roughly 3-min intervals.

Pharmacologic stress testing: Pharmacologic stress testing is usually used when patients cannot walk on a treadmill long enough to reach their target heart rate because of deconditioning, musculoskeletal disorders, obesity, peripheral arterial disease, or other disorders. Drugs used include IV dipyridamole, adenosine, and dobutamine.

Dipyridamole augments endogenous adenosine, causing coronary artery vasodilation. It increases myocardial blood flow in normal coronary arteries but not in arteries distal to a stenosis, creating a "steal" phenomenon from stenosed arteries and an imbalance in perfusion. Dipyridamole-induced ischemia or

other adverse effects (eg, nausea, vomiting, headache, bronchospasm) occur in about 10% of patients, but these effects can be reversed by IV aminophylline. Severe reactions occur in < 1% of patients. Contraindications include asthma, acute phase MI, unstable angina pectoris, critical aortic stenosis, and systemic hypotension (systolic BP < 90 mm Hg).

Adenosine has the same effect as dipyridamole but must be given in a continuous IV infusion because it is rapidly degraded in the plasma. Adverse effects include transient flushing and chest pain, which can be reversed by terminating the infusion.

Dobutamine is an inotrope, chronotrope, and vasodilator used mainly when dipyridamole and adenosine are contraindicated (eg, in patients with asthma or 2nd-degree atrioventricular block) and when echocardiography is used to image the heart. Dobutamine must be used with caution in patients who have severe hypertension or arrhythmia, left ventricular outflow tract obstruction, multiple previous MIs, or acute MI.

Xanthine compounds (eg, aminophylline, theophylline, caffeine) may produce a false-negative result during stress testing with dipyridamole, so such substances (including tea and coffee) should be avoided for 24 h before testing.

Diagnostic Methodology

Several imaging tests can detect ischemia after exercise or pharmacologic stress:

• ECG

• Radionuclide perfusion imaging

• Echocardiography

ECG is always used with stress testing to diagnose CAD and help determine prognosis. ECG is most useful in patients with intermediate likelihood of CAD based on age and sex and with a normal ECG at rest. Diagnosis involves assessment of ST-segment response (a measure of global subendocardial ischemia), BP response, and the patient's symptoms. Average sensitivity is 67%; average specificity is 72%. Sensitivity and specificity are lower in women partly because incidence of CAD is lower in young and middle-aged women. Prognosis worsens with depth of ST depression.

Radionuclide myocardial perfusion imaging (see p. 2061) is more sensitive (85 to 90%) and specific (70 to 80%) than ECG stress testing; combining findings from both tests increases sensitivity for CAD. Myocardial perfusion imaging is particularly useful for patients with baseline ECG abnormalities that may interfere with interpretation of ECG changes during a stress test (eg, patients with bundle branch block, those with fixed-rate pacemakers, those taking digitalis). It is also useful for groups with a high probability of false-positive results on exercise ECGs (eg, premenopausal women, patients with mitral valve prolapse). This imaging test can help determine the functional significance of coronary artery stenosis, identified by coronary angiography, when surgeons are choosing lesions to bypass or dilate via percutaneous transluminal coronary angioplasty.

Echocardiography is useful when information about more than just perfusion is needed; echocardiography detects wall motion abnormalities that are a sign of regional ischemia and, using Doppler techniques, helps evaluate valvular disorders that may contribute to or result from ischemia or valvular disorders unrelated to ischemia but which deserve concomitant evaluation (see p. 2053). The echocardiogram is typically obtained immediately before and after an exercise treadmill test or during dobutamine infusion. Echocardiography is relatively portable, does not use ionizing radiation, has a rapid acquisition time, and is inexpensive, but it is difficult to carry out in obese patients and in patients with COPD and lung hyperinflation. Done by experts, stress echocardiography has a predictive value similar to that of stress myocardial radionuclide perfusion testing.

Radionuclide ventriculography is occasionally used with exercise stress testing instead of echocardiography to assess exercise ejection fraction (EF), the best prognostic indicator in patients with

CAD. Normally, EF is ≥ 5 percentage points higher during exercise than at rest. Ventricular dysfunction (eg, due to valvular heart disorders, cardiomyopathy, or CAD) can decrease exercise EF below baseline or prevent it from increasing. In patients with CAD, the 8-yr survival rate is 80% with an exercise EF of 40 to 49%, 75% with an exercise EF of 30 to 39%, and 40% with an exercise EF of < 30%.

Tilt Table Testing

Tilt table testing is used to evaluate syncope in younger, apparently healthy patients and, when cardiac and other tests have not provided a diagnosis, in elderly patients. Tilt table testing produces maximal venous pooling, which can trigger vasovagal (neurocardiogenic) syncope and reproduce the symptoms and signs that accompany it (nausea, light-headedness, pallor, hypotension, bradycardia).

After an overnight fast, a patient is placed on a motorized table with a foot board at one end and is held in place by a single strap over the stomach; an IV line is inserted. After the patient remains supine for 15 min, the table is tilted nearly upright to 60 to 80° for 45 min. If vasovagal symptoms develop, vasovagal syncope is confirmed. If they do not occur, a drug (eg, isoproterenol) may be given to induce them. Sensitivity varies from 30 to 80% depending on the protocol used. The false-positive rate is 10 to 15%.

With vasovagal syncope, heart rate and BP usually decrease. Some patients have only a decrease in heart rate (cardioinhibitory); others have only a decrease in BP (vasodepressor). Other responses include a gradual decrease in systolic and diastolic BP with little change in heart rate (dysautonomic pattern), significant increase in heart rate (> 30 beats/min) with little change in BP (postural orthostatic tachycardia syndrome), and report of syncope with no hemodynamic changes (psychogenic syncope).

Relative contraindications include severe aortic or mitral stenosis, hypertrophic cardiomyopathy, and severe coronary artery disease (CAD). In particular, isoproterenol should not be used in patients with hypertrophic cardiomyopathy or severe CAD.

Chapter 208. Arterial Hypertension

Introduction

Hypertension is sustained elevation of resting systolic BP (≥ 140 mm Hg), diastolic BP (≥ 90 mm Hg), or both. Hypertension with no known cause (primary; formerly, essential hypertension) is most common. Hypertension with an identified cause (secondary hypertension) is usually due to a renal disorder. Usually, no symptoms develop unless hypertension is severe or long-standing. Diagnosis is by sphygmomanometry. Tests may be done to determine cause, assess damage, and identify other cardiovascular risk factors. Treatment involves lifestyle changes and drugs, including diuretics, β-blockers, ACE inhibitors, angiotensin II receptor blockers, and Ca channel blockers.

In the US, about 65 million people have hypertension. Only about 70% of these people are aware that they have hypertension, only 59% are being treated, and only 34% have adequately controlled BP. In adults, hypertension occurs more often in blacks (32%) than in whites (23%) or Mexican Americans (23%), and morbidity and mortality are greater in blacks.

BP increases with age. About two thirds of people > 65 have hypertension, and people with a normal BP at age 55 have a 90% lifetime risk of developing hypertension. Because hypertension becomes so common with age, the age-related increase in BP may seem innocuous, but higher BP increases morbidity and mortality risk. Hypertension may develop during pregnancy (see pp. 2645 and 2670).

Etiology

Hypertension may be primary (85 to 95% of cases) or secondary.

Primary hypertension: Hemodynamics and physiologic components (eg, plasma volume, activity of the renin-angiotensin system) vary, indicating that primary hypertension is unlikely to have a single cause. Even if one factor is initially responsible, multiple factors are probably involved in sustaining elevated BP (the mosaic theory). In afferent systemic arterioles, malfunction of ion pumps on sarcolemmal membranes of smooth muscle cells may lead to chronically increased vascular tone. Heredity is a predisposing factor, but the exact mechanism is unclear. Environmental factors (eg, dietary Na, obesity, stress) seem to affect only genetically susceptible people.

Secondary hypertension: Causes include renal parenchymal disease (eg, chronic glomerulonephritis or pyelonephritis, polycystic renal disease, connective tissue disorders, obstructive uropathy), renovascular disease (see p. 2077), pheochromocytoma, Cushing's syndrome, primary aldosteronism, congenital adrenal hyperplasia, hyperthyroidism, myxedema, and coarctation of the aorta. Excessive alcohol intake and use of oral contraceptives are common causes of curable hypertension. Use of sympathomimetics, NSAIDs, corticosteroids, cocaine, or licorice commonly contributes to hypertension.

Pathophysiology

Because BP equals cardiac output (CO) × total peripheral vascular resistance (TPR), pathogenic mechanisms must involve increased CO, increased TPR, or both.

In most patients, CO is normal or slightly increased, and TPR is increased. This pattern is typical of primary hypertension and hypertension due to pheochromocytoma, primary aldosteronism, renovascular disease, and renal parenchymal disease.

In other patients, CO is increased (possibly because of venoconstriction in large veins), and TPR is inappropriately normal for the level of CO. Later in the disorder, TPR increases and CO returns to normal, probably because of autoregulation. Some disorders that increase CO (thyrotoxicosis, arteriovenous fistula, aortic regurgitation), particularly when stroke volume is increased, cause isolated systolic hypertension. Some elderly patients have isolated systolic hypertension with normal or low CO, probably due to inelasticity of the aorta and its major branches. Patients with high, fixed diastolic pressures often have decreased CO.

Plasma volume tends to decrease as BP increases; rarely, plasma volume remains normal or increases. Plasma volume tends to be high in hypertension due to primary aldosteronism or renal parenchymal disease and may be quite low in hypertension due to pheochromocytoma. Renal blood flow gradually decreases as diastolic BP increases and arteriolar sclerosis begins. GFR remains normal until late in the disorder; as a result, the filtration fraction is increased. Coronary, cerebral, and muscle blood flow is maintained unless severe atherosclerosis coexists in these vascular beds.

Abnormal Na transport: In many cases of hypertension, Na transport across the cell wall is abnormal, because the Na-K pump (Na^+, K^+-ATPase) is defective or inhibited or because permeability to Na^+ is increased. The result is increased intracellular Na, which makes the cell more sensitive to sympathetic stimulation. Ca follows Na, so accumulation of intracellular Ca may be responsible for the increased sensitivity. Because Na^+, K^+-ATPase may pump norepinephrine back into sympathetic neurons (thus inactivating this neurotransmitter), inhibition of this mechanism could also enhance the effect of norepinephrine, increasing BP. Defects in Na transport may occur in normotensive children of hypertensive parents.

Sympathetic nervous system: Sympathetic stimulation increases BP, usually more in patients with prehypertension (systolic BP 120 to 139 mm Hg, diastolic BP 80 to 89 mm Hg) or hypertension (systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or both) than in normotensive patients. Whether this hyperresponsiveness resides in the sympathetic nervous system or in the myocardium and vascular smooth muscle is unknown. A high resting pulse rate, which may result from increased sympathetic nervous activity, is a well-known predictor of hypertension. In some hypertensive patients, circulating plasma catecholamine levels during rest are higher than normal.

Renin-angiotensin-aldosterone system: This system helps regulate blood volume and therefore BP. Renin, an enzyme formed in the juxtaglomerular apparatus, catalyzes conversion of angiotensinogen to angiotensin I. This inactive product is cleaved by ACE, mainly in the lungs but also in the kidneys and brain, to angiotensin II, a potent vasoconstrictor that also stimulates autonomic centers in the brain to increase sympathetic discharge and stimulates release of aldosterone and ADH. Aldosterone and ADH cause Na and water retention, elevating BP. Aldosterone also enhances K excretion; low plasma K (< 3.5 mEq/L) increases vasoconstriction through closure of K channels. Angiotensin III, present in the circulation, stimulates aldosterone release as actively as angiotensin II but has much less pressor activity. Because chymase enzymes also convert angiotensin I to angiotensin II, drugs that inhibit ACE do not fully suppress angiotensin II production.

Renin secretion is controlled by at least 4 mechanisms, which are not mutually exclusive: (1) A renal vascular receptor responds to changes in tension in the afferent arteriolar wall; (2) a macula densa receptor detects changes in the delivery rate or concentration of NaCl in the distal tubule; (3) circulating angiotensin has a negative feedback effect on renin secretion; and (4) via the renal nerve, the sympathetic nervous system stimulates renin secretion mediated by β-receptors.

Angiotensin is generally acknowledged to be responsible for renovascular hypertension, at least in the early phase, but the role of the renin-angiotensin-aldosterone system in primary hypertension is not established. However, in black and elderly patients with hypertension, renin levels tend to be low. The elderly also tend to have low angiotensin II levels.

Hypertension due to chronic renal parenchymal disease (renoprival hypertension) results from the combination of a renin-dependent mechanism and a volume-dependent mechanism. In most cases, increased renin activity is not evident in peripheral blood. Hypertension is typically moderate and sensitive to Na and water balance.

Vasodilator deficiency: Deficiency of a vasodilator (eg, bradykinin, nitric oxide) rather than excess of a vasoconstrictor (eg, angiotensin, norepinephrine) may cause hypertension. If the kidneys do not produce adequate amounts of vasodilators (because of renal parenchymal disease or bilateral nephrectomy), BP can increase. Vasodilators and vasoconstrictors (mainly endothelin) are also produced in endothelial cells. Therefore, endothelial dysfunction greatly affects BP.

Pathology and complications: No pathologic changes occur early in hypertension. Severe or prolonged hypertension damages target organs (primarily the cardiovascular system, brain, and kidneys), increasing risk of coronary artery disease (CAD), MI, stroke (particularly hemorrhagic), and renal failure. The mechanism involves development of generalized arteriolosclerosis and acceleration of atherogenesis (see p. 2081). Arteriolosclerosis is characterized by medial hypertrophy, hyperplasia, and hyalinization; it is particularly apparent in small arterioles, notably in the eyes and the kidneys. In the kidneys, the changes narrow the arteriolar lumen, increasing TPR; thus, hypertension leads to more hypertension. Furthermore, once arteries are narrowed, any slight additional shortening of already hypertrophied smooth muscle reduces the lumen to a greater extent than in normal-diameter arteries. These effects may explain why the longer hypertension has existed, the less likely specific treatment (eg, renovascular surgery) for secondary causes is to restore BP to normal.

Because of increased afterload, the left ventricle gradually hypertrophies, causing diastolic dysfunction. The ventricle eventually dilates, causing dilated cardiomyopathy and heart failure (HF) due to systolic dysfunction. Thoracic aortic dissection is typically a consequence of hypertension; almost all patients with abdominal aortic aneurysms have hypertension.

Symptoms and Signs

Hypertension is usually asymptomatic until complications develop in target organs. Dizziness, flushed facies, headache, fatigue, epistaxis, and nervousness are not caused by uncomplicated hypertension. Severe hypertension (hypertensive emergencies—see p. 2078) can cause severe cardiovascular, neurologic, renal, and retinal symptoms (eg, symptomatic coronary atherosclerosis, HF, hypertensive encephalopathy, renal failure).

A 4th heart sound is one of the earliest signs of hypertensive heart disease.

Retinal changes may include arteriolar narrowing, hemorrhages, exudates, and, in patients with encephalopathy, papilledema (see p. 616). Changes are classified (according to the Keith, Wagener, and Barker classification) into 4 groups with increasingly worse prognosis: constriction of arterioles only (grade 1), constriction and sclerosis of arterioles (grade 2), hemorrhages and exudates in addition to vascular changes (grade 3), and papilledema (grade 4).

Diagnosis

• Multiple measurements of BP to confirm

• Urinalysis and urinary albumin:creatinine ratio; if abnormal, consider renal ultrasonography

• Blood tests: Fasting lipids, creatinine, K

• Renal ultrasonography if creatinine increased

• Evaluate for aldosteronism if K decreased

• ECG: If left ventricular hypertrophy, consider echocardiography

• Sometimes thyroid-stimulating hormone measurement

• Evaluate for pheochromocytoma if BP elevation sudden and labile or severe

Hypertension is diagnosed and classified by sphygmomanometry. History, physical examination, and other tests help identify etiology and determine whether target organs are damaged.

BP must be measured twice—first with the patient supine or seated, then after the patient has been standing for ≥ 2 min—on 3 separate days. The average of these measurements is used for diagnosis. BP is classified as normal, prehypertension, or stage 1 (mild) or stage 2 hypertension (see

Table 208-1). Normal BP is much lower for infants and children.

Ideally, BP is measured after the patient rests > 5 min and at different times of day. A BP cuff is applied to the upper arm. An appropriately sized cuff covers two thirds of the biceps; the bladder is long enough to encircle > 80% of the arm, and bladder width equals at least 40% of the arm's circumference. Thus, obese patients require large cuffs. The health care practitioner inflates the cuff above the expected systolic pressure and gradually releases the air while listening over the brachial artery. The pressure at which the first heartbeat is heard as the pressure falls is systolic BP. Disappearance of the sound marks diastolic BP. The same principles are followed to measure BP in a forearm (radial artery) and thigh (popliteal artery). Sphygmomanometers that contain mercury are most accurate. Mechanical devices should be calibrated periodically; automated readers are often inaccurate.

BP is measured in both arms; if BP in one arm is much higher, the higher value is used. BP is also measured in a thigh (with a much larger cuff) to rule out coarctation of the aorta, particularly in patients with diminished or delayed femoral pulses; with coarctation, BP is significantly lower in the legs. If BP is in the low-hypertensive range or is markedly labile, more BP measurements are desirable. BP measurements may be sporadically high before hypertension becomes sustained; this phenomenon probably accounts for "white coat hypertension," in which BP is elevated when measured in the physician's office but normal when measured at home or by ambulatory BP monitoring. However, extreme BP elevation alternating with normal readings is unusual and possibly suggests pheochromocytoma or unacknowledged drug use.

[**Table 208-1.** JNC 7 Classification of Blood Pressure in Adults]

History: The history includes the known duration of hypertension and previously recorded levels; any history or symptoms of CAD, HF, or other relevant coexisting disorders (eg, stroke, renal dysfunction, peripheral arterial disease, dyslipidemia, diabetes, gout); and a family history of any of these disorders. Social history includes exercise levels and use of tobacco, alcohol, and stimulant drugs (prescribed and illicit). A dietary history focuses on intake of salt and stimulants (eg, tea, coffee, caffeine-containing sodas, energy drinks).

Physical examination: The physical examination includes measurement of height, weight, and waist circumference; funduscopic examination (see p. 616) for retinopathy; auscultation for bruits in the neck and abdomen; and a full cardiac, respiratory, and neurologic examination. The abdomen is palpated for kidney enlargement and abdominal masses. Peripheral arterial pulses are evaluated; diminished or delayed femoral pulses suggest aortic coarctation, particularly in patients < 30.

Testing: The more severe the hypertension and the younger the patient, the more extensive is the evaluation. Generally, when hypertension is newly diagnosed, routine testing to detect target-organ damage and cardiovascular risk factors is done. Tests include urinalysis, spot urine albumin:creatinine ratio, blood tests (creatinine, K, Na, fasting plasma glucose, lipid profile), and ECG. Thyroid-stimulating hormone is often measured. Ambulatory BP monitoring, renal radionuclide imaging, chest x-ray, screening tests for pheochromocytoma, and renin-Na profiling are not routinely necessary. Peripheral plasma renin activity is not helpful in diagnosis or drug selection.

Depending on results of initial tests and examination, other tests may be needed. If urinalysis detects albuminuria (proteinuria), cylindruria, or microhematuria or if serum creatinine is elevated (≥ 1.4 mg/dL in men; ≥ 1.2 mg/dL in women), renal ultrasonography to evaluate kidney size may provide useful information. Patients with hypokalemia unrelated to diuretic use are evaluated for primary aldosteronism (see p. 799) and high salt intake.

On ECG, a broad, notched P-wave indicates atrial hypertrophy and, although nonspecific, may be one of the earliest signs of hypertensive heart disease. Left ventricular hypertrophy, indicated by a sustained apical thrust and abnormal QRS voltage with or without evidence of ischemia, may occur later. If either of these findings is present, echocardiography is often done. In patients with an abnormal lipid profile or symptoms of CAD, tests for other cardiovascular risk factors (eg, C-reactive protein) may be useful.

If coarctation of the aorta is suspected, chest x-ray, echocardiography, CT, or MRI helps confirm the

diagnosis.

Patients with labile, significantly elevated BP and symptoms such as headache, palpitations, tachycardia, excessive perspiration, tremor, and pallor are screened for pheochromocytoma (eg, by measuring plasma free metanephrines—see p. 802).

Patients with symptoms suggesting Cushing's syndrome, a connective tissue disorder, eclampsia, acute porphyria, hyperthyroidism, myxedema, acromegaly, or CNS disorders are evaluated (see elsewhere in THE MANUAL).

Prognosis

The higher the BP and the more severe the retinal changes and other evidence of target-organ involvement, the worse is the prognosis. Systolic BP predicts fatal and nonfatal cardiovascular events better than diastolic BP. Without treatment, 1-yr survival is < 10% in patients with retinal sclerosis, cotton-wool exudates, arteriolar narrowing, and hemorrhage (grade 3 retinopathy), and < 5% in patients with the same changes plus papilledema (grade 4 retinopathy). CAD is the most common cause of death among treated hypertensive patients. Ischemic or hemorrhagic stroke is a common consequence of inadequately treated hypertension. However, effective control of hypertension prevents most complications and prolongs life.

General Treatment

• Weight loss and exercise

• Smoking cessation

• Diet: Increased fruits and vegetables, decreased salt, limited alcohol

• Drugs if BP is initially high (> 160/100 mm Hg) or unresponsive to lifestyle modifications

Primary hypertension has no cure, but some causes of secondary hypertension can be corrected. In all cases, control of BP can significantly limit adverse consequences. Despite the theoretical efficacy of treatment, BP is lowered to the desired level in only one third of hypertensive patients in the US.

For all patients, treatment aims to reduce BP to < 140/90 mm Hg; for those with a kidney disorder or diabetes, the goal is < 130/80 mm Hg or as near this level as tolerated. Even the elderly and frail elderly can tolerate a diastolic BP as low as 60 to 65 mm Hg well and without an increase in cardiovascular events. Ideally, patients or family members measure BP at home, provided they have been trained to do so, they are closely monitored, and the sphygmomanometer is regularly calibrated. Treatment of hypertension during pregnancy requires special considerations because some antihypertensive drugs can harm the fetus (see p. 2646).

Lifestyle modifications: Recommendations include regular aerobic physical activity at least 30 min/day most days of the week; weight loss to a body mass index of 18.5 to 24.9; smoking cessation; a diet rich in fruits, vegetables, and low-fat dairy products with reduced saturated and total fat content; dietary sodium [Na^+] of < 2.4 g/day (< 6 g NaCl); and alcohol consumption of ≤ 1 oz/day in men and ≤ 0.5 oz/day in women. In stage 1 (mild) hypertension with no signs of target-organ damage, lifestyle changes may make drugs unnecessary. Patients with uncomplicated hypertension do not need to restrict their activities as long as BP is controlled. Dietary modifications can also help control diabetes, obesity, and dyslipidemias. Patients with prehypertension are encouraged to follow these lifestyle recommendations.

Drugs: If systolic BP remains > 140 mm Hg or diastolic BP remains > 90 mm Hg after 6 mo of lifestyle modifications, antihypertensive drugs are required. Unless hypertension is severe, drugs are usually started at low doses. Drugs are initiated simultaneously with lifestyle changes for all patients with prehypertension or hypertension plus diabetes, a kidney disorder, target-organ damage, or cardiovascular risk factors and for those with an initial BP of > 160/100 mm Hg. Signs of hypertensive emergencies require immediate BP reduction with parenteral antihypertensives.

For most hypertensive patients, one drug, usually a thiazide-type diuretic, is given initially. Depending on the patient's characteristics and coexisting disorders, other drugs can be used initially or added to the thiazide. Low-dose aspirin (81 mg once/day) appears to reduce incidence of cardiac events in hypertensive patients and is recommended when tolerated and not contraindicated; some evidence suggests it is better to take the aspirin in the evening rather than in the morning—this timing appears to increase efficacy of antihypertensive drugs.

Some antihypertensives are contraindicated in certain disorders (eg, β-blockers in asthma) or are indicated particularly for certain disorders (eg, β-blockers or Ca channel blockers for angina pectoris, ACE inhibitors or angiotensin II receptor blockers for diabetes or proteinuria—see Tables 208-2 and 208-3). When a single drug is used, black men may respond best to a Ca channel blocker (eg, diltiazem). Thiazide-type diuretics appear to be particularly effective in people > 60 and in blacks.

If the initial drug is ineffective or has intolerable adverse effects, another drug can be substituted. If the initial drug is only partly effective but well tolerated, the dose can be increased or a second drug with a different mechanism added.

If initial systolic BP is > 160 mm Hg, 2 drugs are often used. Options include combining a diuretic with a β-blocker, an ACE inhibitor, or an angiotensin II receptor blocker and combining a Ca channel blocker with an ACE inhibitor or an angiotensin II receptor blocker. An appropriate combination and dose are determined; many are available as single tablets, which improve compliance (see Table 208-4). For severe or refractory hypertension, 3 or 4 drugs may be necessary.

Achieving adequate control often requires several evaluations and changes in drug therapy. Reluctance to titrate or add drugs until BP is at an acceptable level must be overcome. Lack of patient adherence, particularly because lifelong treatment is required, can interfere with adequate BP control. Education, with empathy and support, is essential for success.

Drugs for Hypertension

Diuretics: Main classes (see Table 208-5) are thiazide-type diuretics, loop diuretics, and K-sparing diuretics. Loop diuretics are used to treat hypertension only in patients who have lost > 50% of kidney function; these diuretics are given twice daily. Diuretics modestly reduce plasma volume and reduce vascular resistance, possibly via shifts in Na from intracellular to extracellular loci. These drugs are the least expensive initial therapy, and the dose needed is small, especially for the elderly (eg, for most people > 60 hydrochlorothiazide 12.5 mg is sufficient). Thiazide-type diuretics are most commonly used. In addition to other antihypertensive effects, they cause vasodilation as long as intravascular volume is normal. All thiazides are equally effective in equivalent doses.

All diuretics except the K-sparing distal tubular diuretics cause significant K loss, so serum K is measured every 1 mo until the

[**Table 208-2.** Choice of Antihypertensive Drug Class]

[**Table 208-3.** Antihypertensives for High-Risk Patients]

level stabilizes. Unless serum K is normalized, K channels in the arterial walls close and the resulting vasoconstriction makes achieving the BP goal difficult. Patients with K levels < 3.5 mEq/L are given K supplements. Supplements may be continued long-term at a lower dose, or a K-sparing diuretic (eg, daily spironolactone 25 to 100 mg, triamterene 50 to 150 mg, amiloride 5 to 10 mg) may be added. Supplements or addition of a K-sparing diuretic is also recommended for any patients who are also taking digitalis, have a known heart disorder, have an abnormal ECG, have ectopy or arrhythmias, or develop ectopy or arrhythmias while taking a diuretic. Although the K-sparing diuretics do not cause hypokalemia, hyperuricemia, or hyperglycemia, they are not as effective as thiazide-type diurectics in controlling hypertension and thus are not used for initial treatment. K-sparing diuretics or supplements are not

needed when an ACE inhibitor or angiotensin II receptor blocker is used because these drugs increase serum K.

In most patients with diabetes, thiazide-type diuretics do not affect control of diabetes. Uncommonly, diuretics precipitate or worsen type 2 diabetes in patients with metabolic syndrome.

Thiazide-type diuretics can increase serum cholesterol slightly (mostly low-density lipoprotein) and also increase triglyceride levels, although these effects may not persist > 1 yr. Furthermore, levels seem to increase in only a few patients. The increase is apparent within 4 wk of treatment and can be ameliorated by a low-fat diet. The possibility of a slight increase in lipid levels does not contraindicate diuretics in hyperlipidemic patients.

A hereditary predisposition probably explains the few cases of gout due to diuretic-induced hyperuricemia. Diuretic-induced hyperuricemia without gout does not require treatment or discontinuation of the diuretic.

β-Blockers: These drugs (see Table 208-6) slow heart rate and reduce myocardial contractility, thus reducing BP. All β-blockers are similar in antihypertensive efficacy. In patients with diabetes, chronic peripheral arterial disease, or COPD, a cardioselective β-blocker (acebutolol, atenolol, betaxolol, bisoprolol, metoprolol) may be preferable, although cardioselectivity is only relative and decreases as dose increases. Even cardioselective β-blockers are contraindicated in patients with asthma or in patients with COPD with a prominent bronchospastic component.

β-Blockers are particularly useful in patients who have angina, who have had an MI, or who have HF, although atenolol may worsen prognosis in patients with CAD. These drugs are no longer considered problematic for the elderly.

β-Blockers with intrinsic sympathomimetic activity (eg, acebutolol, carteolol, penbutolol, pindolol) do not adversely affect serum lipids; they are less likely to cause severe bradycardia.

β-Blockers have CNS adverse effects (sleep disturbances, fatigue, lethargy) and exacerbate depression. Nadolol affects the CNS the least and may be best when CNS effects must be avoided. β-Blockers are contraindicated in patients with 2nd- or 3rd-degree atrioventricular block, asthma, or sick sinus syndrome.

Ca channel blockers: Dihydropyridines (see Table 208-7) are potent peripheral vasodilators and reduce BP by decreasing TPR; they sometimes cause reflexive tachycardia. The nondihydropyridines verapamil and diltiazem slow the heart rate, decrease atrioventricular conduction, and decrease myocardial contractility. These drugs should not be prescribed for patients with 2nd- or

[**Table 208-4.** Combination Drugs Used for Hypertension]

3rd-degree atrioventricular block or with left ventricular failure.

Long-acting nifedipine, verapamil, or diltiazem is used to treat hypertension, but short-acting nifedipine and diltiazem are associated with a high rate of MI and are not recommended.

A Ca channel blocker is preferred to a β-blocker in patients with angina pectoris and a bronchospastic disorder, with coronary spasms, or with Raynaud's syndrome.

ACE inhibitors: These drugs (see Table 208-8) reduce BP by interfering with the conversion of angiotensin I to angiotensin II and by inhibiting the degradation of bradykinin, thereby decreasing peripheral vascular resistance without causing reflex tachycardia. These drugs reduce BP in many hypertensive patients, regardless of plasma renin activity. Because these drugs provide renal protection, they are the drugs of choice for patients with diabetes and may be preferred for blacks.

A dry, irritating cough is the most common adverse effect, but angioedema is the most serious and, if it affects the oropharynx, can be fatal. Angioedema is most common among blacks and smokers. ACE inhibitors may

[**Table 208-5.** Oral Diuretics for Hypertension]

[**Table 208-6.** Oral β-Blockers for Hypertension]

[**Table 208-7.** Oral Calcium Channel Blockers for Hypertension]

increase serum K and creatinine levels, especially in patients with chronic renal failure and those taking K-sparing diuretics, K supplements, or NSAIDs. ACE inhibitors are the least likely of the antihypertensives to cause erectile dysfunction. ACE inhibitors are contraindicated during pregnancy. In patients with a renal disorder, serum creatinine and K levels are monitored at least every 3 mo. Patients who have stage 3 nephropathy (estimated GFR of < 60 mL/min to > 30 mL/min) and are given ACE inhibitors can usually tolerate up to a 30 to 35% increase in serum creatinine above baseline. ACE inhibitors can cause acute renal failure in patients who are hypovolemic or who have severe HF, severe bilateral renal artery stenosis, or severe stenosis in the artery to a solitary kidney.

Thiazide-type diuretics enhance the antihypertensive activity of ACE inhibitors more than that of other classes of antihypertensives. Spironolactone and eplerenone also appear to enhance the effect of ACE inhibitors.

Angiotensin II receptor blockers: These drugs (see Table 208-8) block angiotensin II receptors and therefore interfere with the renin-angiotensin system. Angiotensin II receptor blockers and ACE inhibitors are equally effective as antihypertensives. Angiotensin II receptor blockers may provide added benefits via tissue ACE blockade. The 2 classes have the same beneficial effects in patients with left ventricular failure or with nephropathy due to type 1 diabetes. An angiotensin II receptor blocker used with an ACE inhibitor or a β-blocker reduces the hospitalization rate for patients with HF. Angiotensin II receptor blockers may be safely started in people < 60 with initial serum creatinine of ≤ 3 mg/dL.

Incidence of adverse events is low; angioedema occurs but much less frequently than with ACE inhibitors. Precautions for use of angiotensin II receptor blockers in patients with renovascular hypertension, hypovolemia, and severe HF are the same as those for ACE inhibitors. Angiotensin II receptor blockers are contraindicated during pregnancy.

Direct renin inhibitor: Aliskiren, a direct renin inhibitor, is used in the management of hypertension. Dosage is 150 to 300 mg po once/day, with a starting dose of 150 mg. Clinical trials are ongoing to assess its efficacy for slowing diabetic nephropathy and reducing mortality in HF.

[**Table 208-8.** Oral ACE Inhibitors and Angiotensin II Receptor Blockers for Hypertension]

Adrenergic modifiers: This class (see Table 208-9) includes central α_2-agonists, postsynaptic α_1-blockers, and peripheral-acting adrenergic blockers.

α_2-Agonists (eg, methyldopa, clonidine, guanabenz, guanfacine) stimulate α_2-adrenergic receptors in the brain stem and reduce sympathetic nervous activity, lowering BP. Because they have a central action, they are more likely than other antihypertensives to cause drowsiness, lethargy, and depression; they are no longer widely used. Clonidine can be applied transdermally once/wk as a patch; thus, it may be useful for nonadherent patients (eg, those with dementia).

Postsynaptic α_1-blockers (eg, prazosin, terazosin, doxazosin) are no longer used for primary treatment of hypertension because evidence suggests no reduction in mortality. Also, doxazosin used alone or with antihypertensives other than diuretics increases risk of HF.

Peripheral-acting adrenergic blockers (eg, reserpine, guanethidine, guanadrel) deplete tissue stores of

norepinephrine. Reserpine also depletes the brain of norepinephrine and serotonin. Guanethidine and guanadrel block sympathetic transmission at the neuroeffector junction. Guanethidine, in particular, is potent but difficult to titrate, so it is rarely used. Guanadrel is shorter acting and has fewer adverse effects. These 3 adrenergic blockers are not routinely recommended for initial therapy; they are used as 3rd or 4th drugs if required.

Direct vasodilators: These drugs (including minoxidil and hydralazine—see Table 208-10) work directly on vessels, independently of the autonomic nervous system. Minoxidil is more potent than hydralazine but has more adverse effects, including Na and water retention and hypertrichosis, which is poorly tolerated by women. Minoxidil should be reserved for severe, refractory hypertension. Hydralazine is used during pregnancy (eg, for preeclampsia) and as an adjunct antihypertensive. Long-term, high-dose (> 300 mg/day) hydralazine has been associated with a drug-induced lupus syndrome, which resolves when the drug is stopped.

[**Table 208-9.** Adrenergic Modifiers for Hypertension]

[**Table 208-10.** Direct Vasodilators for Hypertension]

Renovascular Hypertension

Renovascular hypertension is BP elevation due to partial or complete occlusion of one or more renal arteries or their branches. It is usually asymptomatic unless long-standing. A bruit can be heard over one or both renal arteries in < 50% of patients. Diagnosis is by physical examination and renal imaging with duplex ultrasonography, radionuclide imaging, or magnetic resonance angiography. Angiography is done before definitive treatment with surgery or angioplasty.

Renovascular disease is one of the most common causes of curable hypertension but accounts for < 2% of all cases of hypertension. Stenosis or occlusion of one or both main renal arteries, an accessory renal artery, or any of their branches can cause hypertension by stimulating release of renin from juxtaglomerular cells of the affected kidney. The area of the arterial lumen must be decreased by ≥ 70% before stenosis is likely to cause hypertension. For unknown reasons, renovascular hypertension is much less common among blacks than among whites.

Overall, about two thirds of cases are caused by atherosclerosis and one third by fibromuscular dysplasia. Atherosclerosis is more common among men > 50 and affects mainly the proximal one third of the renal artery. Fibromuscular dysplasia is more common among younger patients (usually women) and usually affects the distal two third of the main renal artery and the branches of the renal arteries. Rarer causes include emboli, trauma, inadvertent ligation during surgery, and extrinsic compression of the renal pedicle by tumors.

Renovascular hypertension is characterized by high cardiac output and high peripheral resistance.

Symptoms and Signs

Renovascular hypertension is usually asymptomatic. A systolic-diastolic bruit in the epigastrium, usually transmitted to one or both upper quadrants and sometimes to the back, is almost pathognomonic, but it is present in only about 50% of patients with fibromuscular dysplasia and is rare in patients with renal atherosclerosis.

Renovascular hypertension should be suspected if diastolic hypertension develops abruptly in a patient < 30 or > 50; if new or previously stable hypertension rapidly worsens within 6 mo; or if hypertension is initially very severe, associated with worsening renal function, or highly refractory to drug treatment. A history of trauma to the back or flank or acute pain in this region with or without hematuria suggests renovascular hypertension (possibly due to arterial injury), but these historical findings are rare. Asymmetric renal size (discovered incidentally during imaging tests) and recurrent episodes of unexplained acute pulmonary edema or heart failure also suggest it.

Diagnosis

• Initial identification with ultrasonography, magnetic resonance angiography, or radionuclide imaging

• Confirmation with renal angiography (also may be therapeutic)

If renovascular hypertension is suspected, ultrasonography, magnetic resonance angiography (MRA), or radionuclide imaging may be done to identify patients who should have renal angiography, the definitive test.

Duplex Doppler ultrasonography can assess renal blood flow and is a reliable noninvasive method for identifying significant stenosis (eg, > 60%) in the main renal arteries. Sensitivity and specificity approach 90% when experienced technicians do the test. It is less accurate in patients with branch stenosis.

MRA is a more accurate and specific noninvasive test to assess the renal arteries.

Radionuclide imaging is often done before and after an oral dose of captopril 50 mg. The ACE inhibitor causes the affected artery to narrow, decreasing perfusion on the scintiscan. Narrowing also causes an increase in serum renin, which is measured before and after captopril administration. This test may be less reliable in blacks and in patients with decreased renal function.

Renal angiography is done if MRA indicates a lesion amenable to angioplasty or stenting or if other screening tests are positive. Digital subtraction angiography with selective injection of the renal arteries can also confirm the diagnosis, but angioplasty or stent placement cannot be done in the same procedure.

Measurements of renal vein renin activity are sometimes misleading and, unless surgery is being considered, are not necessary. However, in unilateral disease, a renal vein renin activity ratio of > 1.5 (affected to unaffected side) usually predicts a good outcome with revascularization. The test is done when patients are depleted of Na, stimulating the release of renin.

Treatment

• Angioplasty sometimes with stent placement

• Rarely bypass graft

If the renal vein renin activity ratio is > 1.5:1, opening the obstructed renal artery using angioplasty with or without a stent usually relieves hypertension. Even when the ratio is lower, revascularization or removal of the affected kidney often cures hypertension.

Percutaneous transluminal angioplasty (PTA) is recommended for most patients, including younger patients with fibromuscular dysplasia of the renal artery. Placement of a stent reduces the risk of restenosis; antiplatelet drugs (aspirin, clopidogrel) are given afterward. Saphenous vein bypass grafting is recommended only when extensive disease in the renal artery branches makes PTA technically unfeasible. Sometimes complete surgical revascularization requires microvascular techniques that can only be done ex vivo with autotransplantation of the kidney. Cure rate is 90% in appropriately selected patients; surgical mortality rate is < 1%. Medical treatment is always preferable to nephrectomy in young patients whose kidneys cannot be revascularized for technical reasons.

Atherosclerotic lesions respond less well to surgery and angioplasty than do lesions due to fibromuscular dysplasia, presumably because patients are older and vascular disease is more extensive. Hypertension may persist, and surgical complications are more common. Surgical mortality rate is higher than that in young patients with fibromuscular dysplasia. Restenosis occurs within 2 yr after PTA in up to 50% of patients with renovascular atherosclerosis, especially when the lesion is located at the ostium of the renal artery, and, with stenting, in about 25%.

Without treatment, the prognosis is similar to that for patients with untreated primary hypertension. Medical treatment is inadequate without intervention to alleviate the stenosis, but aggressive medical

treatment in adherent patients usually ameliorates and sometimes controls hypertension.

Hypertensive Emergencies

A hypertensive emergency is severe hypertension with signs of damage to target organs (primarily the brain, cardiovascular system, and kidneys). Diagnosis is by BP measurement, ECG, urinalysis, and serum BUN and creatinine measurements. Treatment is immediate BP reduction with IV drugs (eg, nitroprusside, β-blockers, hydralazine).

Target-organ damage includes hypertensive encephalopathy, preeclampsia and eclampsia, acute left ventricular failure with pulmonary edema, myocardial ischemia, acute aortic dissection, and renal failure. Damage is rapidly progressive and often fatal.

Hypertensive encephalopathy may involve a failure of cerebral autoregulation of blood flow. Normally, as BP increases, cerebral vessels constrict to maintain constant cerebral perfusion. Above a mean arterial pressure (MAP) of about 160 mm Hg (lower for normotensive people whose BP suddenly increases), the cerebral vessels begin to dilate rather than remain constricted. As a result, the very high BP is transmitted directly to the capillary bed with transudation and exudation of plasma into the brain, causing cerebral edema, including papilledema. Pathophysiology of other target-organ manifestations is discussed elsewhere in THE MANUAL.

Although many patients with stroke and intracranial hemorrhage present with elevated BP, elevated BP is often a consequence rather than a cause of the condition. Whether rapidly lowering BP is beneficial in these conditions is unclear; it may even be harmful.

Hypertensive urgencies: Very high blood pressure (eg, diastolic pressure > 120 to 130 mm Hg) without target-organ damage (except perhaps grades 1 to 3 retinopathy—see p. 2067) may be considered a hypertensive urgency. BP at these levels often worries the physician; however, acute complications are unlikely, so immediate BP reduction is not required. However, patients should be started on a 2-drug oral combination (see p. 2070), and close evaluation (with evaluation of treatment efficacy) should be continued on an outpatient basis.

Symptoms and Signs

BP is elevated, often markedly (diastolic pressure > 120 mm Hg). CNS symptoms include rapidly changing neurologic abnormalities (eg, confusion, transient cortical blindness, hemiparesis, hemisensory defects, seizures). Cardiovascular symptoms include chest pain and dyspnea. Renal involvement may be asymptomatic, although severe azotemia due to advanced renal failure may cause lethargy or nausea.

Physical examination focuses on target organs, with neurologic examination, funduscopy, and cardiovascular examination. Global cerebral deficits (eg, confusion, obtundation, coma), with or without focal deficits, suggest encephalopathy; normal mental status with focal deficits suggests stroke. Severe retinopathy (sclerosis, cotton-wool spots, arteriolar narrowing, hemorrhage, papilledema) is usually present with hypertensive encephalopathy, and some degree of retinopathy is present in many other hypertensive emergencies. Jugular venous distention, basilar lung crackles, and a 3rd heart sound suggest pulmonary edema. Asymmetry of pulses between arms suggests aortic dissection.

Diagnosis

• Very high BP

• Identify target-organ involvement: ECG, urinalysis, BUN, creatinine; if neurologic findings, head CT

Testing typically includes ECG, urinalysis, and serum BUN and creatinine. Patients with neurologic findings require head CT to diagnose intracranial bleeding, edema, or infarction. Patients with chest pain or dyspnea require chest x-ray. ECG abnormalities suggesting target-organ damage include signs of left ventricular hypertrophy or acute ischemia. Urinalysis abnormalities typical of renal involvement include RBCs, RBC casts, and proteinuria.

Diagnosis is based on the presence of a very high BP and findings of target-organ involvement.

Treatment

• Admit to ICU

• Short-acting IV drug: nitrate, fenoldopam, nicardipine, or labetalol

• Goal: 20 to 25% reduction MAP in 1 to 2 h

Hypertensive emergencies are treated in an ICU; BP is progressively (although not abruptly) reduced using a short-acting, titratable IV drug. Choice of drug and speed and degree of reduction vary somewhat with the target organ involved, but generally a 20 to 25% reduction in MAP over an hour or so is appropriate, with further titration based on symptoms. Achieving "normal" BP urgently is not necessary. Typical first-line drugs include nitroprusside, fenoldopam, nicardipine, and labetalol (see Table 208-11). Nitroglycerin alone is less potent.

Oral drugs are not indicated because onset is variable and the drugs are difficult to titrate. Although short-acting oral nifedipine reduces BP rapidly, it may lead to acute cardiovascular and cerebrovascular events (sometimes fatal) and is therefore not recommended.

Nitroprusside is a venous and arterial dilator, reducing preload and afterload; thus, it is the most useful for hypertensive patients with heart failure. It is also used for hypertensive encephalopathy and, with β-blockers, for aortic dissection. Starting dose is 0.25 to 1.0 µg/kg/min titrated in increments of 0.5 µg/kg to a maximum of 8 to 10 µg/kg/min; maximum dose is given for ≤ 10 min to minimize risk of cyanide toxicity. The drug is rapidly broken down into cyanide and nitric oxide (the active moiety). Cyanide is detoxified to thiocyanate. However, administration of > 2 µg/kg/min can lead to cyanide accumulation with toxicity to the CNS and heart; manifestations include agitation, seizures, cardiac instability, and an anion gap metabolic acidosis. Prolonged administration (> 1 wk or, in patients with renal insufficiency, 3 to 6 days) leads to accumulation of thiocyanate, with lethargy, tremor, abdominal pain, and vomiting. Other adverse effects include transitory elevation of hair follicles (cutis anserina) if BP is reduced too rapidly. Thiocyanate levels should be monitored daily after 3 consecutive days of therapy, and the drug should be stopped if the serum thiocyanate level is > 12 mg/dL (> 2 mmol/L). Because the drug is broken down by ultraviolet light, the IV bag and tubing are wrapped in an opaque covering.

Fenoldopam is a peripheral dopamine-1 agonist that causes systemic and renal vasodilation and natriuresis. Onset is rapid and half-life is brief, making it an effective alternative to nitroprusside, with the added benefit that it does not cross the blood-brain barrier. Initial dosage is 0.1 µg/kg/min IV infusion, titrated upward by 0.1 µg/kg q 15 min to a maximum of 1.6 µg/kg/min.

Nitroglycerin is a vasodilator that affects veins more than arterioles. It can be used to manage hypertension during and after coronary artery bypass graft surgery, acute MI, unstable angina pectoris, and acute pulmonary edema. IV nitroglycerin is preferable to nitroprusside for patients with severe coronary artery disease because nitroglycerin increases coronary flow, whereas nitroprusside tends to decrease coronary flow to ischemic areas, possibly because of a "steal" mechanism. Starting dose is 10 to 20 µg/min titrated upward by 10 µg/min q 5 min to maximum antihypertensive effect. For long-term BP control, nitroglycerin must be used with other drugs. The most common adverse effect is headache (in about 2%); others include tachycardia, nausea, vomiting, apprehension, restlessness, muscular twitching, and palpitations.

Nicardipine, a dihydropyridine Ca channel blocker with less negative inotropic effects than nifedipine, acts primarily as a vasodilator. It is most often used for postoperative hypertension and during pregnancy. Dosage is 5 mg/h IV, increased q 15 min to a maximum of 15 mg/h. It may cause flushing, headache, and tachycardia; it can decrease GFR in patients with renal insufficiency.

[**Table 208-11.** Parenteral Drugs for Hypertensive Emergencies]

Labetalol is a β-blocker with some α_1-blocking effects, thus causing vasodilation without the typical accompanying reflex tachycardia. It can be given as a constant infusion or as frequent boluses; use of boluses has not been shown to cause significant hypotension. Labetalol is used during pregnancy, for intracranial disorders requiring BP control, and after MI. Infusion is 0.5 to 2 mg/min, titrated upward to a maximum of 4 to 5 mg/min. Boluses begin with 20 mg IV followed every 10 min by 40 mg, then 80 mg (up to 3 doses) to a maximum total of 300 mg. Adverse effects are minimal, but because of its β-blocking activity, labetalol should not be used for hypertensive emergencies in patients with asthma. Low doses may be used for left ventricular failure if nitroglycerin is given simultaneously.

Chapter 209. Arteriosclerosis

Introduction

Arteriosclerosis is a general term for several disorders that cause thickening and loss of elasticity in the arterial wall. Atherosclerosis, the most common form, is also the most serious because it causes coronary artery disease and cerebrovascular disease. Nonatheromatous forms of arteriosclerosis include arteriolosclerosis and Monckeberg's arteriosclerosis.

Atherosclerosis

Atherosclerosis is patchy intimal plaques (atheromas) in medium-sized and large arteries; the plaques contain lipids, inflammatory cells, smooth muscle cells, and connective tissue. Risk factors include dyslipidemia, diabetes, cigarette smoking, family history, sedentary lifestyle, obesity, and hypertension. Symptoms develop when growth or rupture of the plaque reduces or obstructs blood flow; symptoms vary by artery affected. Diagnosis is clinical and confirmed by angiography, ultrasonography, or other imaging tests. Treatment includes risk factor and dietary modification, physical activity, antiplatelet drugs, and antiatherogenic drugs.

Atherosclerosis can affect all large and medium-sized arteries, including the coronary, carotid, and cerebral arteries; the aorta; its branches; and major arteries of the extremities. It is the leading cause of morbidity and mortality in the US and in most developed countries. In recent years, age-related mortality attributable to atherosclerosis has been decreasing, but in 2005, cardiovascular disease, primarily coronary and cerebrovascular atherosclerosis still caused almost 870,000 deaths in the US (more than cancer and almost 9 times more than injuries). Atherosclerosis is rapidly increasing in prevalence in developing countries, and as people in developed countries live longer, incidence will increase. By 2020, atherosclerosis is expected to be the leading cause of death worldwide.

Pathophysiology

The hallmark of atherosclerosis is the atherosclerotic plaque, which contains lipids (intracellular and extracellular cholesterol and phospholipids), inflammatory cells (eg, macrophages, T cells), smooth muscle cells, connective tissue (eg, collagen, glycosaminoglycans, elastic fibers), thrombi, and Ca deposits. All stages of atherosclerosis—from initiation and growth to complication of the plaque—are considered an inflammatory response to injury. Endothelial injury is thought to have a primary role.

Atherosclerosis preferentially affects certain areas of the arterial tree. Nonlaminar or turbulent blood flow (eg, at branch points in the arterial tree) leads to endothelial dysfunction and inhibits endothelial production of nitric oxide, a potent vasodilator and anti-inflammatory molecule. Such blood flow also stimulates endothelial cells to produce adhesion molecules, which recruit and bind inflammatory cells. Risk factors for atherosclerosis (eg, dyslipidemia, diabetes, cigarette smoking, hypertension), oxidative stressors (eg, superoxide radicals), angiotensin II, and systemic infection and inflammation also inhibit nitric oxide production and stimulate production of adhesion molecules, proinflammatory cytokines, chemotactic proteins, and vasoconstrictors; exact mechanisms are unknown. The net effect is endothelial binding of monocytes and T cells, migration of these cells to the subendothelial space, and initiation and perpetuation of a local vascular inflammatory response. Monocytes in the subendothelium transform into macrophages. Lipids in the blood, particularly low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL), also bind to endothelial cells and are oxidized in the subendothelium. Uptake of oxidized lipids and macrophage transformation into lipid-laden foam cells result in the typical early atherosclerotic lesions called fatty streaks. Degraded erythrocyte membranes that result from rupture of vasa vasorum and intraplaque hemorrhage may be an important additional source of lipids within plaques.

Macrophages elaborate proinflammatory cytokines that recruit smooth muscle cell migration from the media and that further attract and stimulate growth of macrophages. Various factors promote smooth muscle cell replication and increase production of dense extracellular matrix. The result is a subendothelial fibrous plaque with a fibrous cap, made of intimal smooth muscle cells surrounded by connective tissue and intracellular and extracellular lipids. A process similar to bone formation causes

calcification within the plaque.

Atherosclerotic plaques may be stable or unstable. Stable plaques regress, remain static, or grow slowly over several decades until they may cause stenosis or occlusion. Unstable plaques are vulnerable to spontaneous erosion, fissure, or rupture, causing acute thrombosis, occlusion, and infarction long before they cause stenosis. Most clinical events result from unstable plaques, which do not appear severe on angiography; thus, plaque stabilization may be a way to reduce morbidity and mortality.

The strength of the fibrous cap and its resistance to rupture depend on the relative balance of collagen deposition and degradation. Plaque rupture involves secretion of metalloproteinases, cathepsins, and collagenases by activated macrophages in the plaque. These enzymes digest the fibrous cap, particularly at the edges, causing the cap to thin and ultimately rupture. T cells in the plaque contribute by secreting cytokines. Cytokines inhibit smooth muscle cells from synthesizing and depositing collagen, which normally reinforces the plaque.

Once the plaque ruptures, plaque contents are exposed to circulating blood, triggering thrombosis; macrophages also stimulate thrombosis because they contain tissue factor, which promotes thrombin generation in vivo. One of 5 outcomes may occur:

- The resultant thrombus may organize and be incorporated into the plaque, changing the plaque's shape and causing its rapid growth.

- The thrombus may rapidly occlude the vascular lumen and precipitate an acute ischemic event.

- The thrombus may embolize.

- The plaque may fill with blood, balloon out, and immediately occlude the artery.

- Plaque contents (rather than thrombus) may embolize, occluding vessels downstream.

Plaque stability depends on multiple factors, including plaque composition (relative proportion of lipids, inflammatory cells, smooth muscle cells, connective tissue, and thrombus), wall stress (cap fatigue), size and location of the core, and configuration of the plaque in relation to blood flow. By contributing to rapid growth and lipid deposition, intraplaque hemorrhage may play an important role in transforming stable into unstable plaques. In general, unstable coronary artery plaques have a high macrophage content, a thick lipid core, and a thin fibrous cap; they narrow the vessel lumen by < 50% and tend to rupture unpredictably. Unstable carotid artery plaques have the same composition but typically cause problems through severe stenosis and occlusion or deposition of platelet thrombi, which embolize rather than rupture. Low-risk plaques have a thicker cap and contain fewer lipids; they often narrow the vessel lumen by > 50% and may produce predictable exercise-induced stable angina.

Clinical consequences of plaque rupture in coronary arteries depend not only on plaque anatomy but also on relative balance of procoagulant and anticoagulant activity in the blood and on the vulnerability of the myocardium to arrhythmias.

A link between infection and atherosclerosis has been observed, specifically an association between serologic evidence of certain infections (eg, *Chlamydia pneumoniae*, cytomegalovirus) and coronary artery disease (CAD). Putative mechanisms include indirect effects of chronic inflammation in the bloodstream, cross-reactive antibodies, and inflammatory effects of infectious pathogens on the arterial wall.

Risk Factors

There are numerous risk factors (see Table 209-1). Certain factors tend to cluster as the metabolic syndrome, which is becoming increasingly prevalent. This syndrome includes abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, a prothrombotic state, and a proinflammatory state in sedentary patients (see p. 64). Insulin resistance is not synonymous with the metabolic syndrome but may be key in its etiology.

Dyslipidemia (high total, high LDL, or low high-density lipoprotein [HDL] cholesterol), hypertension, and diabetes promote atherosclerosis by amplifying or augmenting endothelial dysfunction and inflammatory pathways in vascular endothelium.

In dyslipidemia, subendothelial uptake and oxidation of LDL increases; oxidized lipids stimulate production of adhesion molecules and inflammatory cytokines and may be antigenic, inciting a T cell-mediated immune response and inflammation in the arterial

[**Table 209-1.** Risk Factors for Atherosclerosis]

wall. HDL protects against atherosclerosis via reverse cholesterol transport (see p. 889); it may also protect by transporting antioxidant enzymes, which can break down and neutralize oxidized lipids. The role of hypertriglyceridemia in atherogenesis is complex, although it may have a small independent effect.

Hypertension may lead to vascular inflammation via angiotensin II-mediated mechanisms. Angiotensin II stimulates endothelial cells, vascular smooth muscle cells, and macrophages to produce proatherogenic mediators, including proinflammatory cytokines, superoxide anions, prothrombotic factors, growth factors, and lectin-like oxidized LDL receptors.

Diabetes leads to the formation of advanced glycation end products, which increase the production of proinflammatory cytokines from endothelial cells. Oxidative stress and reactive O_2 radicals, generated in diabetes, directly injure the endothelium and promote atherogenesis.

Tobacco smoke contains nicotine and other chemicals that are toxic to vascular endothelium. Smoking, including passive smoking, increases platelet reactivity (possibly promoting platelet thrombosis) and plasma fibrinogen levels and Hct (increasing blood viscosity). Smoking increases LDL and decreases HDL; it also promotes vasoconstriction, which is particularly dangerous in arteries already narrowed by atherosclerosis. HDL increases by about 6 to 8 mg/dL (0.16 to 0.21 mmol/L) within 1 mo of smoking cessation.

Hyperhomocysteinemia increases risk of atherosclerosis, although not as much as the above risk factors. It may result from folate deficiency or a genetic metabolic defect. The pathophysiologic mechanism is unknown but may involve direct endothelial injury, stimulation of monocyte and T-cell recruitment, LDL uptake by macrophages, and smooth muscle cell proliferation.

Lipoprotein(a) is a modified form of LDL that has a cysteine-rich region homologous with the fibrin-binding domain of plasminogen. High levels of lipoprotein(a) may compete with fibrin to bind with plasminogen and thus interfere with thrombolysis, predisposing to atherothrombosis.

A high level of small, dense LDL, characteristic of diabetes, is highly atherogenic. Mechanisms may include increased susceptibility to oxidation and nonspecific endothelial binding (see p. 890).

A high C-reactive protein (CRP) level does not reliably predict extent of atherosclerosis but can predict increased likelihood of ischemic events. In the absence of other inflammatory disorders, it may indicate increased risk of atherosclerotic plaque rupture, ongoing ulceration or thrombosis, or increased activity of lymphocytes and macrophages. CRP may have a direct role in atherogenesis through multiple mechanisms, including downregulation of nitric oxide synthesis and upregulation of angiotensin type I receptors, chemoattractant proteins, and adhesion molecules.

C. pneumoniae infection or other infections (eg, viral, *Helicobacter pylori*) may cause endothelial dysfunction through direct infection, exposure to endotoxin, or stimulation of systemic or subendothelial inflammation.

Renal insufficiency promotes development of atherosclerosis via several pathways, including worsening hypertension and insulin resistance; decreased apolipoprotein A-I levels; and increased lipoprotein(a), homocysteine, fibrinogen, and CRP levels.

Prothrombotic states (see p. 973) increase likelihood of atherothrombosis.

5-Lipoxygenase polymorphisms (deletion or addition of alleles) may promote atherosclerosis by increasing leukotriene production within plaques, which causes vascular permeability and monocyte-macrophage migration, thus increasing subendothelial inflammation and dysfunction.

Documented vascular disease: The presence of atherosclerotic disease in one vascular territory increases the likelihood of disease in other vascular territories. Patients with non-coronary atherosclerotic vascular disease have cardiac event rates comparable to those of patients with known CAD, and they are now considered to have a CAD risk equivalent and should be treated as aggressively.

Symptoms and Signs

Atherosclerosis is initially asymptomatic, often for decades. Symptoms and signs develop when lesions impede blood flow. Transient ischemic symptoms (eg, stable exertional angina, transient ischemic attacks, intermittent claudication) may develop when stable plaques grow and reduce the arterial lumen by > 70%. Symptoms of unstable angina or infarction, ischemic stroke, or rest pain in the limbs may develop when unstable plaques rupture and acutely occlude a major artery, with superimposition of thrombosis or embolism. Atherosclerosis may also cause sudden death without preceding stable or unstable angina pectoris.

Atherosclerotic involvement of the arterial wall can lead to aneurysms and arterial dissection, which can manifest as pain, a pulsatile mass, absent pulses, or sudden death.

Diagnosis

Approach depends on the presence or absence of symptoms.

Symptomatic patients: Patients with symptoms and signs of ischemia are evaluated for the amount and location of vascular occlusion by various invasive and noninvasive tests, depending on the organ involved (see elsewhere in THE MANUAL). Such patients also should be evaluated for atherosclerosis risk factors by using

- History and physical examination
- Fasting lipid profile
- Plasma glucose and glycosylated hemoglobin (HbA_{1c}) levels

Patients with documented disease at one site (eg, peripheral arteries) should be evaluated for disease at other sites (eg, coronary and carotid arteries).

Because not all atherosclerotic plaques have similar risk, various imaging technologies are being studied as a way to identify plaques especially vulnerable to rupture. Most technologies are catheter-based; they include intravascular ultrasonography (which uses an ultrasound transducer on the tip of a catheter to produce images of the arterial lumen and wall), angioscopy, plaque thermography (to detect the increased temperature in plaques with active inflammation), optical coherence tomography (which uses infrared laser light for imaging), and elastography (to identify soft, lipid-rich plaques). Immunoscintigraphy is a noninvasive alternative using radioactive tracers that localize in vulnerable plaque.

Some clinicians measure serum markers of inflammation. CRP levels > 3 mg/dL (> 3000 µg/L) are highly predictive of cardiovascular events. High levels of lipoprotein-associated phospholipase A2 appear to predict cardiovascular events in patients with a normal or low LDL level.

Asymptomatic patients (screening): In patients with risk factors for atherosclerosis but no symptoms or signs of ischemia, the role of additional testing beyond the fasting lipid profile is unclear. Although imaging studies such as electron beam or multidetector row CT, MRI, and ultrasonography (see p. 3402) can detect atherosclerotic plaque, they probably do not improve prediction of ischemic events over

assessment of risk factors or established prediction tools (eg, Framingham risk index—see Table 100-6 on p. 899; see Table 100-7 on p. 900) and are not routinely recommended.

Urinary microalbuminuria (> 30 mg albumin/24 h) is a marker for renal disorders and their progression, as well as a strong predictor of cardiovascular and noncardiovascular morbidity and mortality; however, the direct relationship between microalbuminuria and atherosclerosis has not been established.

Treatment

• Lifestyle changes (diet, smoking, physical activity)

• Drug treatment of diagnosed risk factors

• Antiplatelet drugs

• Possibly statins, ACE inhibitors, β-blockers

Treatment involves aggressive modification of risk factors to slow progression and induce regression of existing plaques. Recent evidence suggests that LDL should be < 70 mg/dL (< 1.81 mmol/L) in patients with disease or at high risk of cardiovascular events. Lifestyle changes include diet modification, smoking cessation, and regular participation in physical activity. Drugs to treat dyslipidemia, hypertension, and diabetes are often required. These lifestyle changes and drugs directly or indirectly improve endothelial function, reduce inflammation, and improve clinical outcome. The statins can decrease atherosclerosis-related morbidity and mortality even when serum cholesterol is normal or slightly high. Antiplatelet drugs help all atherosclerotic patients. Patients with CAD may benefit additionally from ACE inhibitors and β-blockers.

Diet: Several changes are beneficial:

• Less saturated fat

• No trans fats

• More fruits and vegetables

• More fiber

• Moderate (if any) alcohol

Substantial decreases in saturated fat and simple carbohydrate intake and increases in fruit, vegetable, and fiber intake are recommended. These dietary changes are a prerequisite for lipid control and weight reduction and are essential for all patients. Calorie intake should be limited to keep weight within the normal range.

Small decreases in fat intake do not appear to lessen or stabilize atherosclerosis. Effective change requires limiting fat intake to 20 g/day, consisting of 6 to 10 g of polyunsaturated fat with ω-6 (linoleic acid) and ω-3 (eicosapentaenoic acid, docosahexaenoic acid) fatty acids in equal proportion, ≤ 2 g of saturated fat, and the rest as monounsaturated fat. Trans fats, which are highly atherogenic, should be avoided.

Increasing carbohydrates to compensate for decreasing saturated fats in the diet increases plasma triglyceride levels and reduces HDL levels. Thus, any caloric deficiency should be made up with proteins and unsaturated fats rather than simple carbohydrates. Excessive sugar intake should be avoided, although sugar intake has not been directly related to cardiovascular risk. Instead, consumption of complex carbohydrates (eg, vegetables, whole grains) is encouraged.

Fruits and vegetables (5 daily servings) seem to decrease risk of coronary atherosclerosis, but whether

this effect is due to phytochemicals or to a proportional decrease in saturated fat intake and increase in fiber and vitamin intake is unclear. Phytochemicals called flavonoids (in red and purple grapes, red wine, black teas, and dark beers) appear especially protective; high concentrations in red wine may help explain why incidence of coronary atherosclerosis in the French is relatively low, even though they use more tobacco and consume more fat than Americans do. But no clinical data indicate that eating flavonoid-rich foods or using supplements instead of foods prevents atherosclerosis.

Increased fiber intake decreases total cholesterol and may have a beneficial effect on glucose and insulin levels. Daily intake of at least 5 to 10 g of soluble fiber (eg, oat bran, beans, soy products, psyllium) is recommended; this amount decreases LDL by about 5%. Insoluble fiber (eg, cellulose, lignin) does not appear to affect cholesterol but may confer additional health benefits (eg, reduced risk of colon cancer, possibly by stimulating bowel movement or reducing contact time with dietary carcinogens). However, excessive fiber interferes with the absorption of certain minerals and vitamins. In general, foods rich in phytochemicals and vitamins are also rich in fiber.

Alcohol increases HDL and has poorly defined antithrombotic, antioxidant, and anti-inflammatory properties. These effects appear to be the same for wine, beer, and hard liquor, and occur at moderate levels of consumption; about 30 mL (1 oz) 5 to 6 times/wk protects against coronary atherosclerosis. However, at higher doses, alcohol can cause significant health problems. Thus, the relationship between alcohol and total mortality rate is J-shaped; mortality rate is lowest for men who consume < 14 drinks/wk and women who consume < 9 drinks/wk.

There is little evidence that dietary supplementation with vitamins, phytochemicals, and trace minerals reduces risk of atherosclerosis. The one exception is fish oil supplements (see p. 903). Although alternative medicines and health foods are becoming more popular, and some may have minor effects on blood pressure or cholesterol, these treatments are not always proven safe or effective and may have negative interactions with proven drugs. Levels of coenzyme Q10, which is necessary for the basic functioning of cells, tend to decrease with age and may be low in patients with certain heart and other chronic diseases; thus, coenzyme Q10 supplementation has been used or recommended, but its therapeutic benefit remains controversial.

Physical activity: Regular physical activity (eg, 30 to 45 min of walking, running, swimming, or cycling 3 to 5 times/wk) reduces incidence of some risk factors (hypertension, dyslipidemia, diabetes), CAD (eg, MI), and death attributable to atherosclerosis in patients with and without previous ischemic events. Whether the association is causal or merely indicates that healthier people are more likely to exercise regularly is unclear. Optimal intensity, duration, frequency, and type of exercise have not been established, but most evidence suggests an inverse linear relationship between aerobic physical activity and risk. Walking regularly increases the distance patients with peripheral vascular disease can walk without pain.

An exercise program that involves aerobic exercise has a clear role in preventing atherosclerosis and promoting weight loss (see p. 3292). Before starting a new exercise program, the elderly and people who have risk factors for atherosclerosis or who have had recent ischemic events should probably be evaluated by a physician. Evaluation includes history, physical examination, and assessment of risk factor control.

Antiplatelet drugs: Oral antiplatelet drugs are essential because most complications result from plaque fissure or rupture with platelet activation and thrombosis. The following are used:

• Aspirin

• Sometimes clopidogrel

Aspirin is most widely used but, despite its proven benefits, remains underused. It is indicated for secondary prevention and recommended for primary prevention of coronary atherosclerosis in patients at high risk (eg, patients with diabetes with or without atherosclerosis, patients with ≥ 20% risk of cardiac events within 10 yr). Optimal dose and duration are unknown, but 75 to 325 mg po once/day indefinitely is commonly used for primary and secondary prevention because it is effective while minimizing risk of

bleeding. In about 10 to 20% of patients taking aspirin for secondary prevention, ischemic events recur. The reason may be aspirin resistance; assays to detect lack of thromboxane suppression (indicated by elevated urinary 11-dehydro thromboxane B_2) are being studied for clinical use. Some evidence suggests that ibuprofen can interfere with aspirin's antithrombotic effect, so other NSAIDs are recommended for patients taking aspirin for prevention. However, all NSAIDs, some more than others, including COX-2 selective inhibitors (eg, rofecoxib), appear to increase cardiovascular risks.

Clopidogrel (usually 75 mg/day) is substituted for aspirin when ischemic events recur in patients taking aspirin and in patients intolerant of aspirin. Clopidogrel in combination with aspirin is effective in treating acute ST-segment and non-ST-segment elevation MI (see p. 2101); the combination is also given for 9 to 12 mo after percutaneous intervention (PCI) to reduce risk of recurrent ischemic events.

Ticlopidine is no longer widely used because it causes severe neutropenia in 1% of users and has severe GI adverse effects.

Other drugs: ACE inhibitors, angiotensin II receptor blockers, statins, and thiazolidinediones (eg, rosiglitazone, pioglitazone) have anti-inflammatory properties that reduce risk of atherosclerosis independent of their effects on BP, lipids, and glucose. ACE inhibitors inhibit the contributions of angiotensin to endothelial dysfunction and inflammation. Statins enhance endothelial nitric oxide production, stabilize atherosclerotic plaques, reduce lipid accumulation in the arterial wall, and induce regression of plaques. Thiazolidinediones may control expression of proinflammatory genes, although recent studies suggest that they may increase the risk of coronary events. Routine use of statins for primary prevention of ischemic events is controversial. However, several well-controlled studies support their use in high-risk patients (eg, diabetics with normal BP and lipid levels and patients with multiple risk factors, including hyperlipidemia and/or hypertension). Statins are sometimes recommended for patients with normal LDL and high CRP; few data now support this practice, but it is under study.

Folate (folic acid) 0.8 mg po bid has been previously used to treat hyperhomocysteinemia but does not appear to reduce the risk of acute coronary events. Vitamins B_6 and B_{12} also lower homocysteine levels, but current data do not justify their use alone or in combination with folate. Macrolide and other antibiotics are being studied to determine whether treating chronic occult *C. pneumoniae* infections can suppress inflammation and alter the course and manifestations of atherosclerosis.

Nonatheromatous Arteriosclerosis

Nonatheromatous arteriosclerosis is age-related fibrosis in the aorta and its major branches.

Nonatheromatous arteriosclerosis causes intimal thickening and weakens and disrupts the elastic lamellae. The smooth muscle (media) layer atrophies, and the lumen of the affected artery widens (becomes ectatic), predisposing to aneurysm or dissection. Hypertension is a major factor in development of aortic arteriosclerosis and aneurysm. Intimal injury, ectasia, and ulceration may lead to thrombosis, embolism, or complete arterial occlusion.

Arteriolosclerosis affects distal arteries in patients with diabetes or hypertension. Hyaline arteriolosclerosis affects small arteries and arterioles in patients with diabetes; typically, hyaline thickening occurs, the arteriolar wall degenerates, and the lumen narrows, causing diffuse ischemia, especially in the kidneys. Hyperplastic arteriolosclerosis occurs more often in patients with hypertension; typically, laminated, concentric thickening and luminal narrowing occur, sometimes with fibrinoid deposits and vessel wall necrosis (necrotizing arteriolitis). Hypertension promotes these changes, and arteriolosclerosis, by increasing arteriolar rigidity and increasing peripheral resistance, may help sustain the hypertension.

Monckeberg's arteriosclerosis (medial calcific sclerosis) affects patients > 50; age-related medial degeneration occurs with focal calcification and even bone formation within the arterial wall. Segments of the artery may become a rigid calcified tube without luminal narrowing. The diagnosis is usually obvious by plain x-ray. This disorder is clinically important only because it can greatly reduce arterial compressibility, causing extremely but falsely elevated BP readings.

Chapter 210. Coronary Artery Disease

Introduction

Coronary artery disease (CAD) involves impairment of blood flow through the coronary arteries, most commonly by atheromas. Clinical presentations include silent ischemia, angina pectoris, acute coronary syndromes (unstable angina, MI), and sudden cardiac death. Diagnosis is by symptoms, ECG, stress testing, and sometimes coronary angiography. Prevention consists of modifying reversible risk factors (eg, hypercholesterolemia, hypertension, physical inactivity, obesity, and smoking). Treatment includes drugs and procedures to reduce ischemia and restore or improve coronary blood flow.

In developed countries, CAD is the leading cause of death in both sexes, accounting for about one third of all deaths. Mortality rate among white men is about 1/10,000 at ages 25 to 34 and nearly 1/100 at ages 55 to 64. Mortality rate among white men aged 35 to 44 is 6.1 times that among age-matched white women. For unknown reasons, the sex difference is less marked in nonwhites. Mortality rate among women increases after menopause and, by age 75, equals or even exceeds that of men.

Etiology

Usually, CAD is due to subintimal deposition of atheromas in large and medium-sized coronary arteries (atherosclerosis—see p. 2081). Less often, CAD is due to coronary spasm. Rare causes include coronary artery embolism, dissection, aneurysm (eg, in Kawasaki disease), and vasculitis (eg, in SLE, syphilis).

Pathophysiology

Coronary atherosclerosis is often irregularly distributed in different vessels but typically occurs at points of turbulence (eg, vessel bifurcations). As the atheromatous plaque grows, the arterial lumen progressively narrows, resulting in ischemia (often causing angina pectoris). The degree of stenosis required to produce ischemia varies with O_2 demand.

Occasionally, an atheromatous plaque ruptures or splits. Reasons are unclear but probably relate to plaque morphology, plaque Ca content, and plaque softening due to an inflammatory process. Rupture exposes collagen and other thrombogenic material, which activates platelets and the coagulation cascade, resulting in an acute thrombus, which interrupts coronary blood flow and causes some degree of myocardial ischemia. The consequences of acute ischemia, collectively referred to as acute coronary syndromes (ACS), depend on the location and degree of obstruction and range from unstable angina to transmural infarction.

Coronary artery spasm is a transient, focal increase in vascular tone, markedly narrowing the lumen and reducing blood flow; symptomatic ischemia (variant angina—see p. 2098) may result. Marked narrowing can trigger thrombus formation, causing infarction or life-threatening arrhythmia. Spasm can occur in arteries with or without atheroma. In arteries without atheroma, basal coronary artery tone is probably increased, and response to vasoconstricting stimuli is probably exaggerated. The exact mechanism is unclear but may involve abnormalities of nitric oxide production or an imbalance between endothelium-derived contracting and relaxing factors. In arteries with atheroma, the atheroma may cause local hypercontractility; proposed mechanisms include loss of sensitivity to intrinsic vasodilators (eg, acetylcholine) and increased production of vasoconstrictors (eg, angiotensin II, endothelin, leukotrienes, serotonin, thromboxane) in the area of the atheroma. Recurrent spasm may damage the intima, leading to atheroma formation. Use of vasoconstricting drugs (eg, cocaine, nicotine) and emotional stress also can trigger coronary spasm.

Risk Factors

Risk factors for CAD are the same as those for atherosclerosis: high blood levels of low-density lipoprotein (LDL) cholesterol and lipoprotein a, low blood levels of high-density lipoprotein (HDL) cholesterol, diabetes mellitus (particularly type 2), smoking, obesity, and physical inactivity. Smoking may

be a stronger predictor of MI in women (especially those < 45). Genetic factors play a role, and several systemic disorders (eg, hypertension, hypothyroidism) and metabolic disorders (eg, hyperhomocysteinemia) contribute to risk. A high level of apoprotein B (apo B) is an important risk factor; it may identify increased risk when total cholesterol or LDL level is normal.

High blood levels of C-reactive protein indicate plaque instability and inflammation and may be a stronger predictor of risk of ischemic events than high levels of LDL. High blood levels of triglycerides and insulin (reflecting insulin resistance) may be risk factors, but data are less clear. CAD risk is increased by smoking; a diet high in fat and calories and low in phytochemicals (found in fruits and vegetables), fiber, and vitamins C and E; a diet relatively low in ω-3 (n-3) polyunsaturated fatty acids (PUFAs), at least in some people; and poor stress management.

Anatomy

The right and left coronary arteries arise from the right and left coronary sinuses in the root of the aorta just above the aortic valve orifice. The coronary arteries divide into large and medium-sized arteries that run along the heart's surface (epicardial coronary arteries) and subsequently send smaller arterioles into the myocardium. The left coronary artery begins as the left main artery and quickly divides into the left anterior descending (LAD) and circumflex arteries. The LAD artery usually follows the anterior interventricular groove and, in some people, continues over the apex. This artery supplies the anterior septum (including the proximal conduction system) and the anterior free wall of the left ventricle (LV). The circumflex artery, which is usually smaller than the LAD artery, supplies the lateral LV free wall. Most people have right dominance: The right coronary artery passes along the atrioventricular (AV) groove over the right side of the heart; it supplies the sinus node (in 55%), right ventricle, and usually the AV node and inferior myocardial wall. About 10 to 15% of people have left dominance: The circumflex artery is larger and continues along the posterior AV groove to supply the posterior wall and AV node.

Treatment

• Percutaneous coronary intervention

• For acute thrombosis, sometimes fibrinolytic drugs

• Coronary artery bypass grafting

Treatment generally aims to reduce cardiac workload, improve coronary artery blood flow, and, over the long term, halt and reverse the atherosclerotic process. Coronary blood flow can be improved by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). An acute coronary thrombosis may sometimes be dissolved by fibrinolytic drugs (see p. 2110).

PCI: At first, PCI was done with balloon angioplasty alone. However, roughly 50% of patients developed restenosis within 6 mo, and 1 in 3 ultimately required repeat angioplasty or CABG. Insertion of a bare-metal stent following angioplasty reduced the rate of restenosis, but many patients still required repeat treatment. Drug-eluting stents, which secrete an antiproliferative drug (eg, sirolimus, paclitaxel) over a period of several weeks, have reduced the rate of restenosis to about 10%. Now, most PCI is done with stents, and about three fourths of all stents used in the US are drug-eluting stents. With the recent controversy over drug-eluting stents and abrupt restenosis, use of the new drug-eluting stents appears to be decreasing in most centers. Patients with acute stenoses (ie, with unstable angina or acute MI) seem to do better with bare-metal stents. Patients without significant infarct or complications may quickly return to work and usual activities, but strenuous activities should be avoided for 6 wk.

In-stent thrombosis occurs because of the inherent thrombogenicity of metallic stents. Most cases occur within the first 24 to 48 h. However, late stent thrombosis, occurring after 30 days and as late as ≥ 1 yr, can occur with both bare-metal and drug-eluting stents, especially after cessation of antiplatelet therapy. Progressive endothelialization of the bare-metal stent occurs within the first few months and reduces the risk of thrombosis. However, the antiproliferative drugs secreted by drug-eluting stents inhibit this process and prolong the risk of thrombosis. Thus, patients who undergo stent placement are treated with various antiplatelet drugs and anticoagulants (see p. 2109). The current standard regimen for patients with a

bare-metal or drug-eluting stent consists of aspirin given indefinitely, either clopidogrel or prasugrel for at least 12 mo, and intraprocedural anticoagulation with heparin or a similar agent (eg, bivalirudin, particularly those at high risk of bleeding). Glycoprotein IIb/IIIa inhibitors are no longer routinely used in stable patients (ie, no comorbidities, no acute coronary syndrome) having elective stent placement. Although controversial, they may be beneficial in some patients with an acute coronary syndrome but should not be considered routine. It is unclear whether it is beneficial to give glycoprotein IIb/IIIa inhibitors before arrival in the cardiac catheterization laboratory. After stent insertion, a HMG-CoA reductase inhibitor (statin) is added if one is not already being used.

Overall risk of PCI is comparable with that for CABG. Mortality rate is 1 to 3%; MI rate is 3 to 5%. In < 3%, intimal dissection causes obstruction requiring emergency CABG.

CABG: CABG uses sections of autologous veins (eg, saphenous) or, preferably, arteries (eg, internal mammary, radial) to bypass diseased segments. At 1 yr, about 85% of venous bypass grafts are patent, but after 10 yr, as many as 97% of internal mammary artery grafts are patent. Arteries also hypertrophy to accommodate increased flow.

CABG is typically done during cardiopulmonary bypass with the heart stopped; a bypass machine pumps and oxygenates blood. Risks of the procedure include stroke and MI. For patients with a normal-sized heart, no history of MI, good ventricular function, and no additional risk factors, risk is < 5% for perioperative MI, 2 to 3% for stroke, and ≤ 1% for mortality; risk increases with age and presence of underlying disease. Operative mortality rate is 3 to 5 times higher for a second bypass than for the first; thus, timing of the first bypass should be optimal.

After cardiopulmonary bypass, about 25 to 30% of patients develop cognitive dysfunction, possibly caused by microemboli originating in the bypass machine. Dysfunction ranges from mild to severe and may persist for weeks to years. To minimize this risk, some centers use a beating heart technique (ie, no cardiopulmonary bypass), in which a device mechanically stabilizes the part of the heart upon which the surgeon is working.

CAD may progress despite bypass surgery. Postoperatively, the rate of proximal obstruction of bypassed vessels increases. Vein grafts become obstructed early if thrombi form and later (several years) if atherosclerosis causes slow degeneration of the intima and media. Aspirin prolongs vein graft patency. Continued smoking has a profound adverse effect on patency.

Prevention

Prevention of CAD involves modifying atherosclerosis risk factors (see p. 2084): smoking cessation, weight loss, a healthful diet, regular exercise, modification of serum lipid levels, and control of hypertension and diabetes. Antihypertensives should be used to achieve a goal blood pressure of < 130/80 mm Hg. Modification of serum lipid levels (particularly with statins) may slow or even partially reverse the progression of CAD. LDL targets are < 100 mg/dL (< 2.59 mmol/L) for patients with known CAD or 70 to 80 mg/dL (1.81 to 2.07 mmol/L) for those with a history of an ischemic event. Nicotinic acid or a fibrate should be added for patients with an HDL < 40 mg/dL (< 1.03 mmol/L).

Angina Pectoris

Angina pectoris is a clinical syndrome of precordial discomfort or pressure due to transient myocardial ischemia without infarction. It is typically precipitated by exertion or psychologic stress and relieved by rest or sublingual nitroglycerin. Diagnosis is by symptoms, ECG, and myocardial imaging. Treatment may include nitrates, β-blockers, Ca channel blockers, and coronary angioplasty or coronary artery bypass graft surgery.

Etiology

Angina pectoris occurs when cardiac workload and resultant myocardial O_2 demand exceed the ability of coronary arteries to supply an adequate amount of oxygenated blood, as can occur when the arteries are narrowed. Narrowing usually results from atherosclerosis but may result from coronary artery spasm or,

rarely, coronary artery embolism. Acute coronary thrombosis can cause angina if obstruction is partial or transient, but it usually causes MI.

Because myocardial O_2 demand is determined mainly by heart rate, systolic wall tension, and contractility, narrowing of a coronary artery typically results in angina that occurs during exertion and is relieved by rest.

In addition to exertion, cardiac workload can be increased by disorders such as hypertension, aortic stenosis, aortic regurgitation, or hypertrophic cardiomyopathy. In such cases, angina can result whether atherosclerosis is present or not. These disorders can also decrease relative myocardial perfusion because myocardial mass is increased (causing decreased diastolic flow).

A decreased O_2 supply, as in severe anemia or hypoxia, can precipitate or aggravate angina.

Pathophysiology

In stable angina, the relationship between workload or demand and ischemia is usually relatively predictable. However, atherosclerotic arterial narrowing is not entirely fixed; it varies with the normal fluctuations in arterial tone that occur in all people. Thus, more people have angina in the morning, when arterial tone is relatively high. Also, abnormal endothelial function may contribute to variations in arterial tone; eg, in endothelium damaged by atheromas, stress of a catecholamine surge causes vasoconstriction rather than dilation (normal response).

As the myocardium becomes ischemic, coronary sinus blood pH falls, cellular K is lost, lactate accumulates, ECG abnormalities appear, and ventricular function deteriorates. Left ventricular (LV) diastolic pressure usually increases during angina, sometimes inducing pulmonary congestion and dyspnea. The exact mechanism by which ischemia causes discomfort is unclear but may involve nerve stimulation by hypoxic metabolites.

Symptoms and Signs

Angina may be a vague, barely troublesome ache or may rapidly become a severe, intense precordial crushing sensation. It is rarely described as pain. Discomfort is most commonly felt beneath the sternum, although location varies. Discomfort may radiate to the left shoulder and down the inside of the left arm, even to the fingers; straight through to the back; into the throat, jaws, and teeth; and, occasionally, down the inside of the right arm. It may also be felt in the upper abdomen. The discomfort of angina is never above the ears or below the umbilicus.

Some patients have atypical angina (eg, bloating, gas, abdominal distress), often ascribing symptoms to indigestion; belching may even seem to relieve the symptoms. Others have dyspnea due to the sharp, reversible increase in LV filling pressure that often accompanies ischemia. Frequently, the patient's description is imprecise, and whether the problem is angina, dyspnea, or both may be difficult to determine. Because ischemic symptoms require a minute or more to resolve, brief, fleeting sensations rarely represent angina.

Between and even during attacks of angina, physical findings may be normal. However, during the attack, heart rate may increase modestly, BP is often elevated, heart sounds become more distant, and the apical impulse is more diffuse. The 2nd heart sound may become paradoxical because LV ejection is more prolonged during an ischemic attack. A 4th heart sound is common, and a 3rd heart sound may develop. A mid or late systolic apical murmur shrill—or blowing but not especially loud—may occur if ischemia causes localized papillary muscle dysfunction, causing mitral regurgitation.

Angina pectoris is typically triggered by exertion or strong emotion, usually persists no more than a few minutes, and subsides with rest. Response to exertion is usually predictable, but in some patients, exercise that is tolerated one day may precipitate angina the next because of variations in arterial tone. Symptoms are exaggerated when exertion follows a meal or occurs in cold weather; walking into the wind or first contact with cold air after leaving a warm room may precipitate an attack. Symptom severity is often classified by the degree of exertion resulting in angina (see

Table 210-1).

[**Table 210-1.** Canadian Cardiovascular Classification System of Angina Pectoris]

Attacks may vary from several a day to symptom-free intervals of weeks, months, or years. They may increase in frequency (called crescendo angina) to a fatal outcome or gradually decrease or disappear if adequate collateral coronary circulation develops, if the ischemic area infarcts, or if heart failure or intermittent claudication supervenes and limits activity.

Nocturnal angina may occur if a dream causes striking changes in respiration, pulse rate, and BP. Nocturnal angina may also be a sign of recurrent LV failure, an equivalent of nocturnal dyspnea. The recumbent position increases venous return, stretching the myocardium and increasing wall stress, which increases O_2 demand.

Angina may occur spontaneously during rest (called angina decubitus). It is usually accompanied by a modestly increased heart rate and a sometimes markedly higher BP, which increase O_2 demand. These increases may be the cause of rest angina or the result of ischemia induced by plaque rupture and thrombus formation. If angina is not relieved, unmet myocardial O_2 demand increases further, making MI more likely.

Unstable angina: Because angina characteristics are usually predictable for a given patient, any changes (ie, rest angina, new-onset angina, increasing angina) should be considered serious. Such changes are termed unstable angina and require prompt evaluation and treatment.

Unstable angina is classified based on severity and clinical situation (see Table 210-2). Also considered are whether unstable angina occurs during treatment for chronic stable angina and whether transient changes in ST-T waves occur during angina. If angina has occurred within 48 h and no contributory extracardiac condition is present, troponin levels may be measured to help estimate prognosis; troponin-negative indicates a better prognosis than troponin-positive.

Diagnosis

• Typical symptoms

• ECG

• Stress testing with ECG or imaging (echocardiographic or nuclear)

• Coronary angiography for significant symptoms or positive stress test

Diagnosis is suspected if chest discomfort is typical and is precipitated by exertion and relieved by rest. Patients whose chest discomfort lasts > 20 min or occurs during rest or who have syncope or heart failure are evaluated for an acute coronary syndrome (see p. 2099). Chest discomfort may also be caused by GI disorders (eg, reflux, esophageal spasm, indigestion, cholelithiasis), costochondritis, anxiety, panic attacks, hyperventilation, and other cardiac disorders (eg, pericarditis, mitral valve prolapse, supraventricular tachycardia, atrial fibrillation), even when coronary blood flow is not compromised (see p. 2025).

ECG: If typical exertional symptoms are present, ECG is indicated. Because angina resolves quickly with rest, ECG rarely can be done during an attack except during stress testing. If done during an attack, ECG is likely to show reversible ischemic changes: T wave discordant to the QRS vector, ST-segment depression (typically), ST-segment elevation, decreased R-wave height, intraventricular or bundle branch conduction disturbances, and arrhythmia (usually ventricular extrasystoles). Between attacks, the ECG (and usually LV function) at rest is normal

[**Table 210-2.** Braunwald Classification of Unstable Angina*]

in about 30% of patients with a typical history of angina pectoris, even those with extensive 3-vessel disease. In the remaining 70%, the ECG shows evidence of previous infarction, hypertrophy, or nonspecific ST-segment and T-wave (ST-T) abnormalities. An abnormal resting ECG alone does not establish or refute the diagnosis.

Stress testing: More specific tests include stress testing with ECG or with myocardial imaging (eg, echocardiography, radionuclide imaging) and coronary angiography. Further testing is needed to confirm the diagnosis, evaluate disease severity, determine appropriate exercise levels for the patient, and help predict prognosis.

Noninvasive tests are considered first. For coronary artery disease (CAD), the most accurate are stress echocardiography and myocardial perfusion imaging with single-photon emission CT (SPECT) or PET. However, these tests are more expensive than simple stress testing with ECG.

If a patient has a normal resting ECG and can exercise, exercise stress testing with ECG is done. In men with chest discomfort suggesting angina, stress ECG testing has a specificity of 70%; sensitivity is 90%. Sensitivity is similar in women, but specificity is lower, particularly in women < 55 (< 70%). However, women are more likely than men to have an abnormal resting ECG when CAD is present (32% vs 23%). Although sensitivity is reasonably high, exercise ECG can miss severe CAD (even left main or 3-vessel disease). In patients with atypical symptoms, a negative stress ECG usually rules out angina pectoris and CAD; a positive result may or may not represent coronary ischemia and indicates need for further testing.

When the resting ECG is abnormal, false-positive ST-segment shifts are common on the stress ECG, so patients should have stress testing with myocardial imaging. Exercise or pharmacologic stress (eg, with dobutamine or dipyridamole infusion) may be used. The choice of imaging technique depends on institutional availability and expertise. Imaging tests can help assess LV function and response to stress; identify areas of ischemia, infarction, and viable tissue; and determine the site and extent of myocardium at risk. Stress echocardiography can also detect ischemia-induced mitral regurgitation.

Angiography: Coronary angiography (see also p. 2049) is the standard for diagnosing CAD but is not always necessary to confirm the diagnosis. It is indicated primarily to locate and assess severity of coronary artery lesions when revascularization (percutaneous intervention [PCI] or coronary artery bypass grafting [CABG]) is being considered. Angiography may also be indicated when knowledge of coronary anatomy is necessary to advise about work or lifestyle needs (eg, discontinuing job or sports activities). Obstruction is assumed to be physiologically significant when the luminal diameter is reduced > 70%. This reduction correlates well with the presence of angina pectoris unless spasm or thrombosis is superimposed.

Intravascular ultrasonography provides images of coronary artery structure. An ultrasound probe on the tip of a catheter is inserted in the coronary arteries during angiography. This test can provide more information about coronary anatomy than other tests; it is indicated when the nature of lesions is unclear or when apparent disease severity does not match symptom severity. Used with angioplasty, it can help ensure optimal placement of stents.

Imaging: Electron beam CT can detect the amount of Ca present in coronary artery plaque. The Ca score (from 1 to 100) is roughly proportional to the risk of subsequent coronary events. However, because Ca may be present in the absence of significant stenosis, the score does not correlate well with the need for angioplasty or CABG. Thus, the American Heart Association recommends that screening with electron beam CT should be done only for select groups of patients and is most valuable when combined with historical and clinical data to estimate risk of death or nonfatal MI. These groups may include asymptomatic patients with an intermediate Framingham 10-yr risk estimate of 10 to 20% and symptomatic patients with equivocal stress test results.

Multidetector row CT (MDRCT) coronary angiography can accurately identify coronary stenosis and has a number of advantages. The test is noninvasive, can exclude coronary stenosis with high accuracy, can establish stent or bypass graft patency, can visualize cardiac and coronary venous anatomy, and can assess calcified and noncalcified plaque burden. However, radiation exposure is significant, and the test is not suitable for patients with a heart rate of > 65 beats/min, those with irregular heart beats, and

pregnant women. Patients must also be able to hold their breath for 15 to 20 sec, 3 to 4 times during the study.

Evolving indications for MDRCT coronary angiography include

- Asymptomatic high-risk patients or patients with atypical or typical angina who have inconclusive exercise stress test results, cannot undergo exercise stress testing, or need to undergo major noncardiac surgery

- Patients in whom invasive coronary angiography was unable to locate a major coronary artery or graft

Cardiac MRI has become invaluable in evaluating many cardiac and great vessel abnormalities. It may be used to evaluate CAD by several techniques, which enable direct visualization of coronary stenosis, assessment of flow in the coronary arteries, evaluation of myocardial perfusion and metabolism, evaluation of wall motion abnormalities during stress, and assessment of infracted myocardium vs viable myocardium.

Current indications for cardiac MRI include evaluation of cardiac structure and function, assessment of myocardial viability, and possibly diagnosis and risk assessment of patients with either known or suspected CAD.

Prognosis

The main adverse outcomes are unstable angina, MI, and sudden death due to arrhythmias. Annual mortality rate is about 1.4% in patients with angina, no history of MI, a normal resting ECG, and normal BP. However, women with CAD tend to have a worse prognosis. Mortality rate is about 7.5% when systolic hypertension is present, 8.4% when the ECG is abnormal, and 12% when both are present. Type 2 diabetes about doubles the mortality rate for each scenario.

Prognosis worsens with increasing age, increasingly severe anginal symptoms, presence of anatomic lesions, and poor ventricular function. Lesions in the left main coronary artery or proximal left anterior descending artery indicate particularly high risk. Although prognosis correlates with number and severity of coronary arteries affected, prognosis is surprisingly good for patients with stable angina, even those with 3-vessel disease, if ventricular function is normal.

Treatment

- Modification of risk factors (smoking, BP, lipids)

- Antiplatelet drugs (aspirin plus clopidogrel)

- β-Blockers

- Nitroglycerin and Ca channel blockers for symptom control

- Revascularization if symptoms persist despite medical therapy

- ACE inhibitors and statins

Reversible risk factors are modified as much as possible (see also p. 2084). Smokers should stop smoking; ≥ 2 yr after stopping smoking, risk of MI is reduced to that of people who never smoked. Hypertension is treated diligently because even mild hypertension increases cardiac workload. Weight loss alone often reduces the severity of angina. Sometimes treatment of mild LV failure markedly lessens angina. Paradoxically, digitalis occasionally intensifies angina, presumably because increased myocardial contractility increases O_2 demand, arterial tone is increased, or both. Aggressive reduction of total and LDL cholesterol (via diet plus drugs as necessary) slows the progression of CAD, may cause some lesions to regress (see p. 896), and improves endothelial function and thus arterial response to stress. An exercise program emphasizing walking often improves the sense of well-being, reduces CAD risk, and

improves exercise tolerance.

Drugs: The main goals are to relieve acute symptoms, prevent or reduce ischemia (see Table 210-3), and prevent future ischemic events. For an acute attack, sublingual nitroglycerin is the most effective drug.

To prevent ischemia, all patients diagnosed with CAD or at high risk of developing CAD should take an antiplatelet drug daily. β-Blockers, unless contraindicated or not tolerated, are given to most patients. For some patients, prevention of symptoms requires Ca channel blockers or long-acting nitrates.

Antiplatelet drugs inhibit platelet aggregation. Aspirin binds irreversibly to platelets and inhibits cyclooxygenase and platelet aggregation. Clopidogrel blocks adenosine diphosphate-induced platelet aggregation. Either drug can reduce risk of ischemic events (MI, sudden death), but the drugs are most effective when given together. Patients unable to tolerate one should receive the other drug alone.

β-Blockers limit symptoms and prevent infarction and sudden death better than other drugs. β-Blockers block sympathetic stimulation of the heart and reduce systolic BP, heart rate, contractility, and cardiac output, thus decreasing myocardial O_2 demand and increasing exercise tolerance. They also increase the threshold for ventricular fibrillation. Most patients tolerate these drugs well. Many β-blockers are available and effective. Dose is titrated upward as needed until limited by bradycardia or adverse effects. Patients who cannot tolerate β-blockers are given a Ca channel blocker with negative chronotropic effects (eg, diltiazem, verapamil). Those at risk of β-blocker intolerance (eg, those with asthma) may be tried on a cardioselective β-blocker (eg, carvedilol), perhaps with pulmonary function testing before and after drug administration to detect drug-induced bronchospasm.

Nitroglycerin is a potent smooth-muscle relaxant and vasodilator. Its main sites of action are in the peripheral vascular tree, especially in the venous or capacitance system, and in coronary blood vessels. Even severely atherosclerotic vessels may dilate in areas without atheroma. Nitroglycerin lowers systolic BP and dilates systemic veins, thus reducing myocardial wall tension, a major determinant of myocardial O_2 need. Sublingual nitroglycerin is given for an acute attack or for prevention before exertion. Dramatic relief usually occurs within 1.5 to 3 min, is complete by about 5 min, and lasts up to 30 min. The dose may be repeated every 4 to 5 min up to 3 times if relief is incomplete. Patients should always carry nitroglycerin tablets or aerosol spray to use promptly at the onset of an angina attack. Patients should store tablets in a tightly sealed, light-resistant glass container, so that potency is not lost. Because the drug deteriorates quickly, small amounts should be obtained frequently.

Long-acting nitrates (oral or transdermal) are used if symptoms persist after the β-blocker dose is maximized. If angina occurs at predictable times, a nitrate is given to cover those times. Oral nitrates include isosorbide dinitrate and mononitrate (the active metabolite of the dinitrate). They are effective within 1 to 2 h; their effect lasts 4 to 6 h. Sustained-release formulations of isosorbide mononitrate appear to be effective throughout the day. For transdermal use, cutaneous nitroglycerin patches have largely replaced nitroglycerin ointments primarily because ointments are inconvenient and messy. Patches slowly release the drug for a prolonged effect; exercise capacity improves 4 h after patch application and wanes in 18 to 24 h. Nitrate tolerance may occur, especially when plasma concentrations are kept constant. Because MI risk is highest in early morning, an afternoon or early evening respite period from nitrates is reasonable unless a patient commonly has angina at that time. For nitroglycerin, an 8- to 10-h respite period seems sufficient. Isosorbide may require a 12-h respite period. If given once/day, sustained-release isosorbide mononitrate does not appear to elicit tolerance.

Ca channel blockers may be used if symptoms persist despite use of nitrates or if nitrates are not tolerated. Ca channel blockers are particularly useful if hypertension or coronary spasm is also present. Different types of Ca channel blockers have different effects. Dihydropyridines (eg, nifedipine, amlodipine, felodipine) have no chronotropic effects and vary substantially in their negative inotropic effects. Shorter-acting dihydropyridines may cause reflex tachycardia and are associated with increased mortality in CAD patients; they should not be used to treat stable angina.

[**Table 210-3.** Drugs for Coronary Artery Disease]

Longer-acting formulations of dihydropyridines have fewer tachycardic effects; they are most commonly used with a β-blocker. In this group, amlodipine has the weakest negative inotropic effects; it may be used in patients with LV systolic dysfunction. Diltiazem and verapamil, other types of Ca channel blockers, have negative chronotropic and inotropic effects. They can be used alone in patients with β-blocker intolerance or asthma and normal LV systolic function but may increase cardiovascular mortality in patients with LV systolic dysfunction.

Revascularization: Revascularization, either with PCI (eg, angioplasty, stenting) or CABG should be considered if angina persists despite drug therapy and worsens quality of life or if anatomic lesions (noted during angiography) put a patient at high risk of mortality. The choice between PCI and CABG depends on extent and location of anatomic lesions, the experience of the surgeon and medical center, and, to some extent, patient preference.

PCI is usually preferred for 1- or 2-vessel disease with suitable anatomic lesions. Lesions that are long or near bifurcation points are often not amenable to PCI. However, as stent technology improves, PCI is being used for more complicated cases.

CABG is very effective in selected patients with angina. The ideal candidate has severe angina pectoris and localized disease, or diabetes mellitus. About 85% of patients have complete or dramatic symptom relief. Exercise stress testing shows positive correlation between graft patency and improved exercise tolerance, but exercise tolerance sometimes remains improved despite graft closure.

CABG improves survival for patients with left main disease, those with 3-vessel disease and poor LV function, and some patients with 2-vessel disease. However, for patients with mild or moderate angina (class I or II) or 3-vessel disease and good ventricular function, CABG appears to only marginally improve survival. For patients with 1-vessel disease, outcomes with drug therapy, PCI, and CABG are similar; exceptions are left main disease and proximal left anterior descending disease, for which revascularization appears advantageous.

Variant Angina

Variant angina is angina pectoris secondary to epicardial coronary artery spasm (Prinzmetal's angina).

Most patients with variant angina have significant fixed proximal obstruction of at least one major coronary artery. Spasm usually occurs within 1 cm of the obstruction (often accompanied by ventricular arrhythmia).

Symptoms are anginal discomfort occurring mainly during rest, often at night, and only rarely and inconsistently during exertion (unless significant coronary artery obstruction is also present). Attacks tend to occur regularly at certain times of day.

Diagnosis is suspected if ST-segment elevation occurs during the attack. Between anginal attacks, the ECG may be normal or show a stable abnormal pattern. Confirmation is by provocative testing with ergonovine or acetylcholine, which may precipitate coronary artery spasm, identified by significant ST-segment elevation or by observation of a reversible spasm during cardiac catheterization. Testing is done most commonly in a cardiac catheterization laboratory and occasionally in a coronary care unit.

Average survival at 5 yr is 89 to 97%, but mortality risk is greater for patients with both variant angina and atherosclerotic coronary artery obstruction. Usually, sublingual nitroglycerin promptly relieves variant angina. Ca channel blockers may effectively prevent symptoms. Theoretically, β-blockers may exacerbate spasm by allowing unopposed α-adrenergic vasoconstriction, but this effect has not been proved clinically. Oral drugs most commonly used are sustained-release diltiazem 120 to 540 mg once/day, sustained-release verapamil 120 to 480 mg once/day (dose must be reduced in patients with renal or hepatic dysfunction), or amlodipine 15 to 20 mg once/day (dose must be reduced in elderly patients and patients with hepatic dysfunction). In refractory cases, amiodarone may be useful. Although these drugs relieve symptoms, they do not appear to alter prognosis.

Syndrome X

Syndrome X is cardiac microvascular dysfunction or constriction causing angina (microvascular angina).

Some patients with typical angina that is relieved by rest or nitroglycerin have normal coronary arteriograms (eg, no atherosclerosis, embolism, or inducible arterial spasm). Some of these patients have ischemia detected during stress testing; others do not. In some patients, the cause of ischemia seems to be reflex intramyocardial coronary constriction and reduced coronary flow reserve. Other patients have microvascular dysfunction within the myocardium: The abnormal vessels do not dilate in response to exercise or other cardiovascular stressors; sensitivity to cardiac pain may also be increased. Prognosis is good, although symptoms of ischemia may recur for years. In many patients, β-blockers relieve symptoms. This disorder should not be confused with variant angina due to epicardial coronary spasm or with another disorder called syndrome X, which refers to the metabolic syndrome (see p. 64).

Silent Ischemia

Patients with CAD (particularly diabetics) may have ischemia without symptoms. Ischemia is evidenced by transient asymptomatic ST-T abnormalities seen during 24-h Holter monitoring. Radionuclide studies can sometimes document asymptomatic myocardial ischemia during physical or mental stress (eg, mental arithmetic). Silent ischemia and angina pectoris may coexist, occurring at different times. Prognosis depends on severity of CAD.

Acute Coronary Syndromes

(Unstable Angina; Acute MI)

Acute coronary syndromes (ACS) result from acute obstruction of a coronary artery. Consequences depend on degree and location of obstruction and range from unstable angina to non-ST-segment elevation MI (NSTEMI), ST-segment elevation MI (STEMI), and sudden cardiac death. Symptoms are similar in each of these syndromes (except sudden death) and include chest discomfort with or without dyspnea, nausea, and diaphoresis. Diagnosis is by ECG and the presence or absence of serologic markers. Treatment is antiplatelet drugs, anticoagulants, nitrates, β-blockers, and, for STEMI, emergency reperfusion via fibrinolytic drugs, percutaneous intervention, or, occasionally, coronary artery bypass graft surgery.

In the US, about 1.5 million MIs occur annually. MI results in death for 400,000 to 500,000 people, with about half dying before they reach the hospital (see Cardiac Arrest on p. 2255).

Etiology

These syndromes usually occur when an acute thrombus forms in an atherosclerotic coronary artery. Atheromatous plaque sometimes becomes unstable or inflamed, causing it to rupture or split, exposing thrombogenic material, which activates platelets and the coagulation cascade and produces an acute thrombus. Platelet activation involves a conformational change in membrane glycoprotein (GP) IIb/IIIa receptors, allowing cross-linking (and thus aggregation) of platelets. Even atheromas causing minimal obstruction can rupture and result in thrombosis; in > 50% of cases, stenosis is < 40%. The resultant thrombus abruptly interferes with blood flow to parts of the myocardium. Spontaneous thrombolysis occurs in about two thirds of patients; 24 h later, thrombotic obstruction is found in only about 30%. However, in virtually all cases, obstruction lasts long enough to cause tissue necrosis.

Rarely, these syndromes are caused by arterial embolism (eg, in mitral or aortic stenosis, infective endocarditis, or marantic endocarditis). Cocaine use and other causes of coronary spasm can sometimes result in MI. Spasm-induced MI may occur in normal or atherosclerotic coronary arteries.

Pathophysiology

Initial consequences vary with size, location, and duration of obstruction and range from transient

ischemia to infarction. Measurement of newer, more sensitive markers indicates that some cell necrosis probably occurs even in mild forms; thus, ischemic events occur on a continuum, and classification into subgroups, although useful, is somewhat arbitrary. Sequelae of the acute event depend primarily on the mass and type of cardiac tissue infarcted.

Myocardial dysfunction: Ischemic (but not infarcted) tissue has impaired contractility, resulting in hypokinetic or akinetic segments; these segments may expand or bulge during systole (called paradoxical motion). The size of the affected area determines effects, which range from minimal to mild heart failure to cardiogenic shock. Some degree of heart failure occurs in about two thirds of hospitalized patients with acute MI. It is termed ischemic cardiomyopathy if low cardiac output and heart failure persist. Ischemia involving the papillary muscle may lead to mitral valve regurgitation.

MI: MI is myocardial necrosis resulting from abrupt reduction in coronary blood flow to part of the myocardium. Infarcted tissue is permanently dysfunctional; however, there is a zone of potentially reversible ischemia adjacent to infarcted tissue.

MI affects predominantly the left ventricle (LV), but damage may extend into the right ventricle (RV) or the atria. RV infarction usually results from obstruction of the right coronary or a dominant left circumflex artery; it is characterized by high RV filling pressure, often with severe tricuspid regurgitation and reduced cardiac output. An inferoposterior infarction causes some degree of RV dysfunction in about half of patients and causes hemodynamic abnormality in 10 to 15%. RV dysfunction should be considered in any patient who has inferoposterior infarction and elevated jugular venous pressure with hypotension or shock. RV infarction complicating LV infarction may significantly increase mortality risk.

Anterior infarcts tend to be larger and result in a worse prognosis than inferoposterior infarcts. They are usually due to left coronary artery obstruction, especially in the anterior descending artery; inferoposterior infarcts reflect right coronary or dominant left circumflex artery obstruction.

Transmural infarcts involve the whole thickness of myocardium from epicardium to endocardium and are usually characterized by abnormal Q waves on ECG. Nontransmural or subendocardial infarcts do not extend through the ventricular wall and cause only ST-segment and T-wave (ST-T) abnormalities. Subendocardial infarcts usually involve the inner one third of myocardium, where wall tension is highest and myocardial blood flow is most vulnerable to circulatory changes. These infarcts may follow prolonged hypotension. Because the transmural depth of necrosis cannot be precisely determined clinically, infarcts are usually classified by the presence or absence of ST-segment elevation or Q waves on the ECG. Volume of myocardium destroyed can be roughly estimated by the extent and duration of CK elevation.

Electrical dysfunction: Ischemic and necrotic cells are incapable of normal electrical activity, resulting in various ECG changes (predominantly ST-T abnormalities), arrhythmias, and conduction disturbances. ST-T abnormalities of ischemia include ST-segment depression (often downsloping from the J point), T-wave inversion, ST-segment elevation (often referred to as injury current), and peaked T waves in the hyperacute phase of infarction. Conduction disturbances can reflect damage to the sinus node, the atrioventricular (AV) node, or specialized conduction tissues. Most changes are transient; some are permanent.

Classification

Classification is based on ECG changes and presence or absence of cardiac markers in blood. Distinguishing NSTEMI and STEMI is useful because prognosis and treatment are different.

Unstable angina (acute coronary insufficiency, preinfarction angina, intermediate syndrome) is defined as:

- Rest angina that is prolonged (usually > 20 min)
- New-onset angina of at least class III severity in the Canadian Cardiovascular Society (CCS) classification (see Table 210-1)

- Increasing angina, ie, previously diagnosed angina that has become distinctly more frequent, more severe, longer in duration, or lower in threshold (eg, increased by ≥ 1 CCS class or to at least CCS class III)

Also, ECG changes such as ST-segment depression, ST-segment elevation, or T-wave inversion may occur during unstable angina but are transient. Of cardiac markers, CK is not elevated but troponin I or T may be slightly increased. Unstable angina is clinically unstable and often a prelude to MI or arrhythmias or, less commonly, to sudden death.

Non-ST-segment elevation MI (NSTEMI, subendocardial MI) is myocardial necrosis (evidenced by cardiac markers in blood; troponin I or T and CK will be elevated) without acute ST-segment elevation or Q waves. ECG changes such as ST-segment depression, T-wave inversion, or both may be present.

ST-segment elevation MI (STEMI, transmural MI) is myocardial necrosis with ECG changes showing ST-segment elevation that is not quickly reversed by nitroglycerin or showing new left bundle branch block. Q waves may be present. Both troponin and CK are elevated.

Symptoms and Signs

Symptoms of ACS depend somewhat on the extent and location of obstruction and are quite variable. Except when infarction is massive, recognizing the amount of ischemia by symptoms alone is difficult.

After the acute event, many complications can occur. They usually involve electrical dysfunction (eg, conduction defects, arrhythmias), myocardial dysfunction (eg, heart failure, interventricular septum or free wall rupture, ventricular aneurysm, pseudoaneurysm, mural thrombus formation, cardiogenic shock), or valvular dysfunction (typically mitral regurgitation). Electrical dysfunction can be significant in any form of ACS, but usually, large parts of myocardium must be ischemic to cause significant myocardial dysfunction. Other complications of ACS include recurrent ischemia and pericarditis. Pericarditis that occurs 2 to 10 wk after an MI is known as post-MI syndrome or Dressler's syndrome.

Unstable angina: Symptoms are those of angina pectoris (see p. 2090), except that the pain or discomfort of unstable angina usually is more intense, lasts longer, is precipitated by less exertion, occurs spontaneously at rest (as angina decubitus), is progressive (crescendo) in nature, or involves any combination of these features.

NSTEMI and STEMI: Symptoms of NSTEMI and STEMI are the same. Days to weeks before the event, about two thirds of patients experience prodromal symptoms, including unstable or crescendo angina, shortness of breath, and fatigue. Usually, the first symptom of infarction is deep, substernal, visceral pain described as aching or pressure, often radiating to the back, jaw, left arm, right arm, shoulders, or all of these areas. The pain is similar to angina pectoris but is usually more severe and long-lasting; more often accompanied by dyspnea, diaphoresis, nausea, and vomiting; and relieved little or only temporarily by rest or nitroglycerin. However, discomfort may be mild; about 20% of acute MIs are silent (ie, asymptomatic or causing vague symptoms not recognized as illness by the patient), more commonly in diabetics. Some patients present with syncope. Patients often interpret their discomfort as indigestion, particularly because spontaneous relief may be falsely attributed to belching or antacid consumption. Women are more likely to present with atypical chest discomfort. Elderly patients may report dyspnea more than ischemic-type chest pain. In severe ischemic episodes, the patient often has significant pain and feels restless and apprehensive. Nausea and vomiting may occur, especially with inferior MI. Dyspnea and weakness due to LV failure, pulmonary edema, shock, or significant arrhythmia may dominate.

Skin may be pale, cool, and diaphoretic. Peripheral or central cyanosis may be present. Pulse may be thready, and BP is variable, although many patients initially have some degree of hypertension during pain.

Heart sounds are usually somewhat distant; a 4th heart sound is almost universally present. A soft systolic blowing apical murmur (reflecting papillary muscle dysfunction) may occur. During initial examination, a friction rub or more striking murmurs suggest a preexisting heart disorder or another

diagnosis. Detection of a friction rub within a few hours after onset of MI symptoms suggests acute pericarditis rather than MI. However, friction rubs, usually evanescent, are common on days 2 and 3 post-STEMI. The chest wall is tender when palpated in about 15% of patients.

In RV infarction, signs include elevated RV filling pressure, distended jugular veins (often with Kussmaul's sign—see p. 2019), clear lung fields, and hypotension.

Diagnosis

• Serial ECGs

• Serial cardiac markers

• Immediate coronary angiography for patients with STEMI or complications (eg, persistent chest pain, markedly elevated cardiac markers, unstable arrhythmias)

• Delayed angiography (24 to 48 h) for patients with NSTEMI or unstable angina

[Fig. 210-1. Acute anterior left ventricular infarction (tracing obtained within a few hours of onset of illness).]

[Fig. 210-2. Acute anterior left ventricular infarction (after the first 24 h).]

[Fig. 210-3. Acute anterior left ventricular infarction (several days later).]

[Fig. 210-4. Acute inferior (diaphragmatic) left ventricular infarction (tracing obtained within a few hours of onset of illness).]

[Fig. 210-5. Acute inferior (diaphragmatic) left ventricular infarction (after the first 24 h).]

[Fig. 210-6. Acute inferior (diaphragmatic) left ventricular infarction (several days later).]

ACS should be considered in men > 30 yr and women > 40 yr (younger in patients with diabetes) whose main symptom is chest pain or discomfort. Pain must be differentiated from the pain of pneumonia, pulmonary embolism, pericarditis, rib fracture, costochondral separation, esophageal spasm, acute aortic dissection, renal calculus, splenic infarction, or various abdominal disorders. In patients with previously diagnosed hiatus hernia, peptic ulcer, or a gallbladder disorder, the clinician must be wary of attributing new symptoms to these disorders.

The approach is the same when any ACS is suspected: initial and serial ECG and serial cardiac marker measurements, which distinguish among unstable angina, NSTEMI, and STEMI. Every emergency department should have a triage system to immediately identify patients with chest pain for rapid assessment and ECG. Pulse oximetry and chest x-ray (particularly to look for mediastinal widening, which suggests aortic dissection) is also done.

ECG: ECG is the most important test and should be done within 10 min of presentation. It is the center of the decision pathway because fibrinolytics benefit patients with STEMI but may increase risk for those with NSTEMI. Also, urgent cardiac catheterization is indicated for patients with acute STEMI but not for those with NSTEMI.

For STEMI, initial ECG is usually diagnostic, showing ST-segment elevation ≥ 1 mm in 2 or more

contiguous leads sub-tending the damaged area (see Figs. 210-1, 210-2, 210-3, 210-4, 210-5, and 210-6).

Pathologic Q waves are not necessary for the diagnosis. The ECG must be read carefully because ST-segment elevation may be subtle, particularly in the inferior leads (II, III, aVF); sometimes the reader's attention is mistakenly focused on leads with ST-segment depression. If symptoms are characteristic, ST-segment elevation on ECG has a specificity of 90% and a sensitivity of 45% for diagnosing MI. Serial tracings (obtained every 8 h for 1 day, then daily) showing a gradual evolution toward a stable, more normal pattern or development of abnormal Q waves over a few days tends to confirm the diagnosis.

Because nontransmural (non-Q-wave) infarcts are usually in the subendocardial or midmyocardial layers, they do not produce diagnostic Q waves or distinct ST-segment elevation on the ECG. Instead, they commonly produce only varying degrees of ST-T abnormalities that are less striking, variable, or nonspecific and sometimes difficult to interpret (NSTEMI). If such abnormalities resolve (or worsen) on repeat ECGs, ischemia is very likely. However, when repeat ECGs are unchanged, acute MI is unlikely and, if still suspected clinically, requires other evidence to make the diagnosis. A normal ECG taken when a patient is pain free does not rule out unstable angina; a normal ECG taken during pain, although it does not rule out angina, suggests that the pain is not ischemic.

If RV infarction is suspected, a 15-lead ECG is usually recorded; additional leads are placed at V_4R, and, to detect posterior infarction, V_8 and V_9.

ECG diagnosis of MI is more difficult when a left bundle branch block configuration is present because it resembles STEMI changes. ST-segment elevation concordant with the QRS complex strongly suggests MI as does > 5-mm ST-segment elevation in at least 2 precordial leads. But generally, any patient with suggestive symptoms and new-onset (or not known to be old) left bundle branch block is treated as for STEMI.

Cardiac markers: Cardiac markers are cardiac enzymes (eg, CK-MB) and cell contents (eg, troponin I, troponin T, myoglobin) that are released into the bloodstream after myocardial cell necrosis. The markers appear at different times after injury and decrease at different rates (see Fig. 210-7).

Usually, several different markers are measured at regular intervals, typically every 6 to 8 h for 1 day. Newer bedside tests, which are more convenient, can be just as sensitive when done at shorter intervals (eg, time 0, 1, 3, and 6 h after presentation).

Troponins are most specific for MI but can also be elevated by ischemia without infarction; elevated levels (actual number varies with assay used) are considered diagnostic. Borderline elevated troponin levels in patients with unstable angina indicate increased risk of adverse events and thus the need for further evaluation and treatment. False-positives sometimes occur in heart failure and renal failure. CK-MB is slightly less specific. False-positives occur in renal failure, hypothyroidism, and skeletal muscle injury. Myoglobin is not specific for MI but, because it increases earlier than other markers, may be an early warning sign to assist in triage of patients with nondiagnostic ECGs.

Coronary angiography: Coronary angiography most often combines diagnosis with percutaneous coronary intervention (PCI, ie, angioplasty, stenting). Angiography is obtained urgently for patients with STEMI, patients with persistent chest pain despite maximal medical therapy, and patients with complications (eg, markedly elevated cardiac markers, presence of cardiogenic shock, acute mitral regurgitation, ventricular septal

[**Fig. 210-7.** Relative timing and levels of cardiac markers in blood after acute MI.]

defect, unstable arrhythmias). Patients with uncomplicated NSTEMI or unstable angina whose symptoms have resolved typically undergo angiography within the first 24 to 48 h of hospitalization to detect lesions that may require treatment.

After initial evaluation and therapy, coronary angiography may be used in patients with evidence of

ongoing ischemia (ECG findings or symptoms), hemodynamic instability, recurrent ventricular tachyarrhythmias, and other abnormalities that suggest recurrence of ischemic events. Some experts also recommend that angiography be done before hospital discharge in STEMI patients with inducible ischemia on stress imaging or an ejection fraction < 40%.

Other tests: Routine laboratory tests are nondiagnostic but, if obtained, show non-specific abnormalities compatible with tissue necrosis (eg, increased ESR, moderately elevated WBC count with a shift to the left). A fasting lipid profile should be obtained within the first 24 h for all patients hospitalized with ACS.

Myocardial imaging (see also p. 2058) is not needed to make the diagnosis if cardiac markers or ECG is positive. However, in patients with MI, bedside echocardiography is invaluable for detecting mechanical complications. Before or shortly after discharge, patients with symptoms suggesting an ACS but nondiagnostic ECGs and normal cardiac markers should have a stress imaging test (radionuclide or echocardiographic imaging with pharmacologic or exercise stress). Imaging abnormalities in such patients indicate increased risk of complications in the next 3 to 6 mo.

Right heart catheterization using a balloon-tipped pulmonary artery catheter (see p. 2244) can be used to measure right heart, pulmonary artery, and pulmonary artery occlusion pressures and cardiac output. This test is usually done only if patients have significant complications (eg, severe heart failure, hypoxia, hypotension).

Prognosis

Unstable angina: About 30% of patients with unstable angina have an MI within 3 mo of onset; sudden death is less common. Marked ECG changes with chest pain indicate higher risk of subsequent MI or death.

NSTEMI and STEMI: Overall mortality rate is about 30%, with 50 to 60% of these patients dying before reaching the hospital (typically due to ventricular fibrillation). Inhospital mortality rate is about 10% (typically due to cardiogenic shock) but varies significantly with severity of LV failure (see Table 210-4).

Most patients who die of cardiogenic shock have an infarct or a combination of scar and new infarct affecting ≥ 50% of LV mass. Five clinical characteristics predict 90% of the mortality in patients who present with STEMI (see Table 210-5): older age (31% of

[**Table 210-4.** Killip Classification and Mortality Rate of Acute MI*]

total mortality), lower systolic BP (24%), Killip class > 1 (15%), faster heart rate (12%), and anterior location (6%). Mortality rate of diabetics and women tends to be higher.

Mortality rate of patients who survive initial hospitalization is 8 to 10% in the year after acute MI. Most fatalities occur in the first 3 to 4 mo. Persistent ventricular arrhythmia, heart failure, poor ventricular function, and recurrent ischemia indicate high risk. Many authorities recommend stress ECG before hospital discharge or within 6 wk. Good exercise performance without ECG abnormalities is associated with a favorable prognosis; further evaluation is usually not required. Poor exercise performance is associated with a poor prognosis.

Cardiac performance after recovery depends largely on how much functioning myocardium survives the acute attack. Scars from previous infarcts add to the acute damage. When > 50% of LV mass is damaged, prolonged survival is unusual.

General Treatment

• Monitoring and O_2

• Bed rest initially, with early ambulation

• Low-salt, low-fat diet

• Stool softeners and anxiolytics as needed

Treatment is designed to relieve distress, interrupt thrombosis, reverse ischemia, limit infarct size, reduce cardiac workload, and prevent and treat complications. An ACS is a medical emergency; outcome is greatly influenced by rapid diagnosis and treatment.

Treatment occurs simultaneously with diagnosis. A reliable IV route must be established, O_2 given (typically 2 L by nasal cannula), and continuous single-lead ECG monitoring started. Prehospital interventions by ambulance personnel (including ECG, chewed aspirin (325 mg), early thrombolysis when indicated and possible, and triage to the appropriate hospital) can reduce risk of mortality and complications. Early diagnostic data and response to treatment can help determine the need for and timing of revascularization (see p. 2111).

Bedside cardiac marker tests can help identify low-risk patients with a suspected ACS (eg, those with initially negative cardiac markers and nondiagnostic ECGs), who can be managed in 24-h observation units or chest pain centers. Higher-risk patients should be admitted to a monitored inpatient unit or coronary care unit (CCU). Several validated tools can help stratify risk. Thrombolysis in MI (TIMI) risk scores may be the most widely used (see Tables 210-5 and 210-6).

Patients with suspected NSTEMI and intermediate or high risk should be admitted to an inpatient care unit. Those with STEMI should be admitted to a CCU.

Only heart rate and rhythm recorded by single-lead ECG are consistently useful for routine, continuous monitoring. However, some clinicians recommend routine multilead monitoring with continuous ST-segment recording to identify transient, recurrent ST-segment elevations or depressions. Such findings, even in patients without symptoms, suggest ischemia and identify higher-risk patients who may require more aggressive evaluation and treatment.

Qualified nurses can interpret the ECG for arrhythmia and initiate protocols for its treatment. All staff members should know how to do CPR.

[**Table 210-5.** Mortality Risk at 30 Days in Stemi]

Contributing disorders (eg, anemia, heart failure) are aggressively treated.

The care unit should be a quiet, calm, restful area. Single rooms are preferred; privacy consistent with monitoring should be ensured. Usually, visitors and telephone calls are restricted to family members during the first few days. A wall clock, a calendar, and an outside window help orient the patient and prevent a sense of isolation, as can access to a radio, television, and newspaper.

Bed rest is mandatory for the first 24 h. On day 1, patients without complications (eg, hemodynamic instability, ongoing ischemia), including those in whom reperfusion with fibrinolytics or PCI is successful, can sit in a chair, begin passive exercises, and use a

[**Table 210-6.** Risk of Adverse Events* at 14 Days in Nstemi]

commode. Walking to the bathroom and doing nonstressful paperwork is allowed shortly thereafter. Recent studies have shown that patients with successful, uncomplicated primary PCI for acute MI may be ambulated quickly and be safely discharged in 3 to 4 days. If reperfusion is not successful or complications are present, patients require longer bed rest, but they (particularly elderly patients) are mobilized as soon as possible. Prolonged bed rest results in rapid physical deconditioning, with development of orthostatic hypotension, decreased work capacity, increased heart rate during exertion, and increased risk of deep venous thrombosis. Prolonged bed rest also intensifies feelings of depression

and helplessness.

Anxiety, mood changes, and denial are common. A mild tranquilizer (usually a benzodiazepine) is often given, but many experts believe such drugs are rarely needed.

Reactive depression is common by the 3rd day of illness and is almost universal at some time during recovery. After the acute phase of illness, the most important tasks are often management of depression, rehabilitation, and institution of long-term preventive programs. Overemphasis on bed rest, inactivity, and the seriousness of the disorder reinforces anxiety and depressive tendencies, so patients are encouraged to sit up, get out of bed, and engage in appropriate activities as soon as possible. The effects of the disorder, prognosis, and individualized rehabilitation program should be explained to the patient.

Maintaining normal bowel function with stool softeners (eg, docusate) to prevent straining is important. Urinary retention is common among elderly patients, especially after several days of bed rest or if atropine was given. A catheter may be required but can usually be removed when the patient can stand or sit to void.

Because smoking is prohibited, a hospital stay should be used to encourage smoking cessation. All caregivers should devote considerable effort to making smoking cessation permanent.

Although acutely ill patients have little appetite, tasty food in modest amounts is good for morale. Patients are usually offered a soft diet of 1500 to 1800 kcal/day with Na reduction to 2 to 3 g. Na reduction is not required after the first 2 or 3 days if there is no evidence of heart failure. Patients are given a diet low in cholesterol and saturated fats, which is used to teach healthy eating.

For diabetic patients with STEMI, intensive glucose control is no longer recommended; guidelines call for an insulin-based regimen to achieve and maintain glucose levels < 180 mg/dL while avoiding hypoglycemia.

Because the chest pain of MI usually subsides within 12 to 24 h, any chest pain that remains or recurs later is investigated. It may indicate such complications as recurrent ischemia, pericarditis, pulmonary embolism, pneumonia, gastritis, or ulcer.

Drugs

- Aspirin, clopidogrel, or both (prasugrel is an alternative to clopidogrel if fibrinolytic therapy has not been given)
- β-Blocker
- GP IIb/IIIa inhibitor considered for certain patients undergoing PCI and for some others at high risk (eg, with markedly elevated cardiac markers, TIMI risk score ≥ 4, persistent symptoms)
- A heparin (unfractionated or low molecular weight heparin) or bivalirudin (particularly in STEMI patients at high risk of bleeding)
- IV nitroglycerin (unless low-risk, uncomplicated MI)
- Fibrinolytics for select patients with STEMI when timely PCI unavailable
- ACE inhibitor (as early as possible) and a statin

Antiplatelet and antithrombotic drugs, which stop clots from forming, are used routinely. Anti-ischemic drugs (eg, β-blockers, IV nitroglycerin) are frequently added, particularly when chest pain or hypertension is present (see Table 210-3). Fibrinolytics *should be used if not contraindicated* for STEMI if primary PCI is not immediately available but worsen outcome for unstable angina and NSTEMI.

Chest pain can be treated with morphine or nitroglycerin. Morphine 2 to 4 mg IV, repeated q 15 min as

needed, is highly effective but can depress respiration, can reduce myocardial contractility, and is a potent venous vasodilator. Hypotension and bradycardia secondary to morphine can usually be overcome by prompt elevation of the lower extremities. Nitroglycerin is initially given sublingually, followed by continuous IV drip if needed.

BP is normal or slightly elevated in most patients on arrival at the emergency department; BP gradually falls over the next several hours. Continued hypertension requires treatment with antihypertensives, preferably IV nitroglycerin, to lower BP and reduce cardiac workload. Severe hypotension or other signs of shock are ominous and must be treated aggressively with IV fluids and sometimes vasopressors (see p. 2296).

Antiplatelet drugs: Aspirin, clopidogrel, ticlopidine, and GP IIb/IIIa inhibitors are examples. All patients are given aspirin 160 to 325 mg (not enteric-coated), if not contraindicated, at presentation and 81 mg once/day indefinitely thereafter. Chewing the first dose before swallowing quickens absorption. Aspirin reduces short- and long-term mortality risk. If aspirin cannot be taken, clopidogrel 75 mg once/day or ticlopidine 250 mg bid may be used. Clopidogrel has largely replaced ticlopidine for routine use because neutropenia is a risk with ticlopidine and the WBC count must be monitored regularly. Patients with unstable angina or NSTEMI in whom intervention is not possible or recommended are given both aspirin and clopidogrel for at least 1 mo. The optimal duration of double antiplatelet therapy for these patients is the subject of ongoing investigation.

In patients undergoing PCI, a clopidogrel loading dose (300 to 600 mg po once) improves outcomes, particularly when administered 24 h in advance. However, delaying PCI for 24 h is not appropriate for many patients. Further, such a loading dose increases risk of perioperative bleeding in patients who require coronary artery bypass grafting (CABG) because their coronary anatomy proves unfavorable for PCI. Thus, many clinicians administer a clopidogrel loading dose only in the catheterization laboratory once coronary anatomy and lesions have been proven to be amenable to PCI.

For patients receiving a stent for revascularization, aspirin is continued indefinitely, and clopidogrel should be used for at least 1 mo in patients with a bare-metal stent. Patients with a drug-eluting stent have a prolonged risk of thrombosis and may benefit from 12 mo of clopidogrel treatment, although the recommended duration is still unclear.

GP IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide) are potent antiplatelet drugs that must be given IV. Although there is some controversy, evidence indicates that patients with ACS undergoing PCI may benefit from a GP IIb/IIIa inhibitor; results appear to be better if the drug is initiated at least 6 h before PCI and continued for 18 to 24 h thereafter. If PCI is not being done, some clinicians give a GP IIb/IIIa inhibitor to all high-risk patients (eg, those with markedly elevated cardiac markers, a TIMI risk score ≥ 4, or persistent symptoms despite adequate drug therapy). The GP IIb/IIIa inhibitor is continued for 24 to 36 h, and angiography is done before the infusion period is over. GP IIb/IIIa inhibitors are not recommended for patients receiving fibrinolytics. Abciximab, tirofiban, and eptifibatide appear to have equivalent efficacy, and the choice of drug should depend on other factors (eg, cost, availability, familiarity).

Anticoagulant drugs: Either a low molecular weight heparin (LMWH), unfractionated heparin, or bivalirudin is given routinely to patients with ACS unless contraindicated (eg, by active bleeding or planned use of streptokinase or anistreplase). Choice of agent is somewhat involved.

Unfractionated heparin is more complicated to use because it requires frequent (q 6 h) dosing adjustments to achieve an activated PTT (aPTT) 1.5 to 2 times the control value. In patients undergoing angiography, further dosing adjustment is done to achieve an activated clotting time (ACT) of 200 to 250 sec if the patient is treated with a GP IIb/IIIa inhibitor and 250 to 300 sec if a GP IIb/IIIa inhibitor is not being given. However, the effects of unfractionated heparin are shorter and can be reversed (with prompt discontinuation of heparin infusion and with administration of protamine sulfate) if bleeding develops following catheterization.

The LMWHs have better bioavailability, are given by simple weight-based dose without monitoring aPTT and dose titration, and have lower risk of heparin-induced thrombocytopenia. They also may produce an incremental benefit in outcomes relative to unfractionated heparin in patients with ACS. Of the LMWHs,

enoxaparin appears to be superior to dalteparin or nadroparin. However, enoxaparin may pose a higher bleeding risk in patients with STEMI who are > 75, and its effects are not completely reversible with protamine.

Thus, taking all into account, many published guidelines recommend LMWH (eg, enoxaparin) over unfractionated heparin in patients with unstable angina or NSTEMI and in patients < 75 with STEMI who are not undergoing PCI. By contrast, unfractionated heparin is recommended when emergency PCI is done (eg, patients with acute STEMI who proceed to the catheterization laboratory), when CABG is indicated within the next 24 h, and when patients are at high risk of bleeding complications (eg, history of GI bleeding within the last 6 mo) or have creatinine clearance < 30 mL/min. Ongoing studies should help clarify the choice between LMWH and unfractionated heparin.

Bivalirudin is an acceptable anticoagulant for patients undergoing primary PCI who are at high risk of bleeding and is recommended for those with a known or suspected history of heparin-induced thrombocytopenia. For patients with unstable angina or NSTEMI, dose is an initial bolus of 0.1 mg/kg IV followed by a drip of 0.25 mg/kg/h. For patients with STEMI, initial dose is 0.75 mg/kg IV followed by 1.75 mg/kg/h.

For patients undergoing PCI, postprocedure heparin is no longer recommended unless patients are at high risk of thromboembolic events (eg, those with large anterior MI, known LV thrombus, atrial fibrillation), because postprocedure ischemic events have decreased with the use of stents and antiplatelet drugs. For patients not undergoing PCI, heparin is continued for 48 h (or longer if symptoms persist).

The difficulties with the heparins (including bleeding complications, the possibility of heparin-induced thrombocytopenia, and, with unfractionated heparin, the need for dosing adjustments) have led to the search for better anticoagulants. The direct thrombin inhibitors, bivalirudin and argatroban, may have a lower incidence of serious bleeding and improved outcomes, particularly in patients with renal insufficiency (hirudin, another direct thrombin inhibitor, appears to cause more bleeding than the other drugs). The factor Xa inhibitor, fondaparinux, reduces mortality and reinfarction in patients with NSTEMI who undergo PCI without increasing bleeding but may result in worse outcomes than unfractionated heparin in patients with STEMI. Although routine use of these alternative anticoagulants is thus not currently recommended, they should be used in place of unfractionated heparin or LMWH in patients with a known or suspected history of heparin-induced thrombocytopenia.

Patients at high risk of systemic emboli also require long-term therapy with oral warfarin. Conversion to warfarin should begin 48 h after symptom resolution or PCI.

β-Blockers: These drugs are recommended unless contraindicated (eg, by bradycardia, heart block, hypotension, or asthma), especially for high-risk patients. β-Blockers reduce heart rate, arterial pressure, and contractility, thereby reducing cardiac workload and O_2 demand. IV β-blockers given within the first few hours improve prognosis by reducing infarct size, recurrence rate, incidence of ventricular fibrillation, and mortality risk. Infarct size largely determines cardiac performance after recovery.

Heart rate and BP must be carefully monitored during treatment with β-blockers. Dosage is reduced if bradycardia or hypotension develops. Excessive adverse effects may be reversed by infusion of the β-adrenergic agonist isoproterenol 1 to 5 µg/min.

Nitrates: A short-acting nitrate, nitroglycerin, is used to reduce cardiac workload in selected patients. Nitroglycerin dilates veins, arteries, and arterioles, reducing LV preload and afterload. As a result, myocardial O_2 demand is reduced, lessening ischemia. IV nitroglycerin is recommended during the first 24 to 48 h for patients with heart failure, large anterior MI, persistent chest discomfort, or hypertension. BP can be reduced by 10 to 20 mm Hg but not to < 80 to 90 mm Hg systolic. Longer use may benefit patients with recurrent chest pain or persistent pulmonary congestion. In high-risk patients, nitroglycerin given in the first few hours reduces infarct size and short-term and possibly long-term mortality risk. Nitroglycerin is not routinely given to low-risk patients with uncomplicated MI.

Fibrinolytics: Tenecteplase (TNK), alteplase (rTPA), reteplase (rPA), streptokinase, and anistreplase

(anisoylated plasminogen activator complex—APSAC), all given IV, are plasminogen activators. They convert single chain plasminogen to double-chain plasminogen, which has fibrinolytic activity. They have different characteristics and dosing regimens (see Table 210-7) and are appropriate only for selected patients with STEMI (see p. 2113).

Tenecteplase and reteplase are recommended most often because of their simplicity of administration; tenecteplase is given as a single bolus over 5 sec and reteplase as a double bolus 30 min apart. Administration time and drug errors are reduced compared with other fibrinolytics. Tenecteplase, like alteplase, has an intermediate risk of intracranial hemorrhage, has a higher rate of recanalization than other fibrinolytics, and is expensive. Reteplase has the highest risk of intracranial hemorrhage and a recanalization rate similar to that of tenecteplase, and it is expensive.

Streptokinase may induce allergic reactions, especially if it has been used previously, and must be given by infusion over 30 to 60 min; however, it has a low incidence of intracerebral hemorrhage and is relatively inexpensive. Anistreplase, related to streptokinase, is similarly allergenic and slightly more expensive but can be given as a single bolus. Neither drug requires concomitant heparin use. For both, recanalization rate is lower than that with other plasminogen activators. Because of the possibility of allergic reactions, patients who previously received streptokinase or anistreplase are not given that drug.

[**Table 210-7.** IV Fibrinolytic Drugs Available in the US]

Alteplase is given in an accelerated or front-loaded dosage over 90 min. Alteplase with concomitant IV heparin improves patency, is nonallergenic, has a higher recanalization rate than other fibrinolytics, and is expensive.

Other drugs: ACE inhibitors appear to reduce mortality risk in MI patients, especially in those with anterior infarction, heart failure, or tachycardia. The greatest benefit occurs in the highest-risk patients early during convalescence. ACE inhibitors are given > 24 h after thrombolysis stabilization and, because of continued beneficial effect, may be prescribed long-term.

Angiotensin II receptor blockers may be an effective alternative for patients who cannot tolerate ACE inhibitors (eg, because of cough). Currently, they are not first-line treatment after MI. Contraindications include hypotension, renal failure, bilateral renal artery stenosis, and known allergy.

HMG-CoA reductase inhibitors (statins) have long been used for prevention of coronary artery disease and ACS, but there is now increasing evidence that they also have short-term benefits, such as stabilizing plaque, reversing endothelial dysfunction, decreasing thrombogenicity, and reducing inflammation. Thus, all patients without contraindications to therapy should receive a statin as early as possible following ACS. LDL levels of 70 to 80 mg/dL (1.81 to 2.07 mmol/L) are the recommended ultimate target.

Revascularization Modalities and Indications

Revascularization is the restoration of blood supply to ischemic myocardium in an effort to limit ongoing damage, reduce ventricular irritability, and improve short-term and long-term outcomes. Modes of revascularization include thrombolysis with fibrinolytic drugs, PCI with or without stent placement, and CABG.

The use, timing, and modality of revascularization depend on which ACS is present, timing of presentation, extent and location of anatomic lesions, and availability of personnel and facilities (see Fig. 210-8).

Unstable angina and NSTEMI: Immediate reperfusion is not as urgent in patients with uncomplicated NSTEMI (in whom a completely occluded infarct-related artery at presentation is uncommon) or in those with unstable angina who respond to medical therapy. Such

[**Fig. 210-8.** Approach to acute coronary syndromes.]

patients typically undergo angiography within the first 24 to 48 h of hospitalization to identify coronary lesions requiring PCI or CABG. A noninterventional approach and a trial of medical management are used for those in whom angiography demonstrates only a small area of myocardium at risk, lesion morphology not amenable to PCI, anatomically insignificant disease (< 50% coronary stenosis), or significant left main disease in patients who are candidates for CABG. Further, angiography or PCI should be deferred in favor of medical management for patients with a high risk of procedure-related morbidity or mortality.

By contrast, patients with persistent chest pain despite maximal medical therapy or complications (eg, markedly elevated cardiac markers, presence of cardiogenic shock, acute mitral regurgitation, ventricular septal defect, unstable arrhythmias) should proceed directly to the cardiac catheterization laboratory to identify coronary lesions requiring PCI or CABG.

As in patients with stable angina, CABG is generally preferred over PCI for patients with left main or left main equivalent disease, for those with 3- or 2-vessel disease involving the left anterior descending artery, and for those with left ventricular dysfunction or diabetes. CABG must also be considered when PCI is unsuccessful, cannot be used (eg, in lesions that are long or near bifurcation points), or causes acute coronary artery dissection.

Fibrinolytics are not indicated for unstable angina or NSTEMI. Risk outweighs potential benefit.

STEMI: Emergency PCI is the preferred treatment of STEMI when available in a timely fashion (door to balloon-inflation time < 90 min) by an experienced operator. Indications for urgent PCI later in the course of STEMI include hemodynamic instability, malignant arrhythmias requiring transvenous pacing or repeated cardioversion, and age > 75. If the lesions necessitate CABG, there is about 4 to 12% mortality and a 20 to 43% morbidity rate.

If there is likely to be a significant delay in availability of PCI, thrombolysis should be done for STEMI patients meeting criteria (see Table 210-8). Reperfusion using fibrinolytics is most effective if given in the first few minutes to hours after onset of MI. The earlier a fibrinolytic is begun, the better. The goal is a door-to-needle time of 30 to 60 min. Greatest benefit occurs within 3 h, but the drugs may be effective up to 12 h. Used with aspirin, fibrinolytics reduce hospital mortality rate by 30 to 50% and improve ventricular function. Although controversial, prehospital use of fibrinolytics by trained paramedics can significantly reduce time to treatment and should be considered in situations in which PCI within 90 min is not possible, particularly in patients presenting within 3 h of symptom onset.

[**Table 210-8.** Fibrinolytic Therapy for Stemi]

Regardless, most patients who undergo thrombolysis will ultimately require transfer to a PCI-capable facility for elective angiography and PCI as necessary prior to discharge. PCI should be considered after fibrinolytics if chest pain or ST-segment elevation persists ≥ 60 min after initiation of fibrinolytics or if pain and ST-segment elevation recur, but only if PCI can be initiated < 90 min after onset of recurrence. If PCI is unavailable, fibrinolytics can be repeated.

Characteristics and selection of fibrinolytic drugs are discussed on p. 2110.

Complications

Electrical dysfunction occurs in > 90% of MI patients (see also p. 2142). Electrical dysfunction that commonly causes mortality in the first 72 h includes tachycardia (from any focus) rapid enough to reduce cardiac output and lower BP, Mobitz type II block (2nd degree) or complete (3rd degree) AV block, ventricular tachycardia (VT), and ventricular fibrillation (VF). Asystole is uncommon, except as a terminal manifestation of progressive LV failure and shock. Patients with disturbances of cardiac rhythm are checked for hypoxia and electrolyte abnormalities, which can be causative or contributory.

Sinus node disturbances: If the artery supplying the sinus node is affected, sinus node disturbances can occur; they are more likely if there is a preexisting sinus node disorder (common among the elderly). Sinus bradycardia, the most common sinus node disturbance, is usually not treated unless there is hypotension or the heart rate is < 50 beats/min. A lower heart rate, if not extreme, means reduced cardiac

workload and possibly reduced infarct size. For bradycardia with hypotension (which may reduce myocardial perfusion), atropine sulfate 0.5 to 1 mg IV is used; it can be repeated after several minutes if response is inadequate. Several small doses are best because high doses may induce tachycardia. Occasionally, a temporary transvenous pacemaker must be inserted.

Persistent sinus tachycardia is usually ominous, often reflecting LV failure and low cardiac output. Without heart failure or another evident cause, this arrhythmia may respond to a β-blocker, given po or IV depending on degree of urgency.

Atrial arrhythmias: Atrial arrhythmias (atrial ectopic beats, atrial fibrillation [AF], and, less commonly, atrial flutter) occur in about 10% of MI patients and may reflect LV failure or right atrial infarction. Paroxysmal atrial tachycardia is uncommon and usually occurs in patients who have had previous episodes of it. Atrial ectopy is usually benign but if frequency increases, causes, particularly heart failure, are sought. Frequent atrial ectopic beats may respond to a β-blocker.

AF is usually transient if it occurs within the first 24 h. Risk factors include age > 70, heart failure, previous history of MI, large anterior infarction, atrial infarction, pericarditis, hypokalemia, hypomagnesemia, a chronic lung disorder, and hypoxia. Fibrinolytics reduce incidence. Recurrent paroxysmal AF is a poor prognostic sign and increases risk of systemic emboli.

For AF, heparin is usually used because systemic emboli are a risk (see p. 2165). IV β-blockers (eg, atenolol 2.5 to 5.0 mg over 2 min to total dose of 10 mg in 10 to 15 min, metoprolol 2 to 5 mg q 2 to 5 min to a total dose of 15 mg in 10 to 15 min) slow the ventricular rate. Heart rate and BP are closely monitored. Treatment is withheld when ventricular rate decreases satisfactorily or systolic BP is < 100 mm Hg. IV digoxin, which is not as effective as β-blockers, is used cautiously and only in patients with AF and LV systolic dysfunction. Usually, digoxin takes at least 2 h to effectively slow heart rate and may rarely aggravate ischemia in patients with recent ACS. For patients without evident LV systolic dysfunction or conduction delay manifested by a wide QRS complex, IV verapamil or IV diltiazem may be considered. Diltiazem may be given as an IV infusion to control heart rate for long periods.

If AF compromises circulatory status (eg, causing LV failure, hypotension, or chest pain), urgent electrical cardioversion is done. If AF returns after cardioversion, IV amiodarone should be considered.

For atrial flutter, rate is controlled as for AF, but heparin is not required. Low-energy direct current (DC) cardioversion will terminate atrial flutter.

Conduction defects: Mobitz type I block (Wenckebach block, progressive prolongation of PR interval) is relatively common with an inferior-diaphragmatic infarction; it is usually self-limited and rarely progresses to higher grade block. Mobitz type II block (dropped beats) usually indicates massive anterior MI, as does complete heart block with wide QRS complexes (atrial impulses do not reach the ventricle); both are uncommon. Frequency of complete (3rd degree) AV block depends on site of infarction. Complete AV block occurs in 5 to 10% of patients with inferior infarction and is usually transient. It occurs in < 5% with uncomplicated anterior infarction but in up to 26% of those with right bundle branch block and left posterior hemiblock.

Mobitz type I block usually does not warrant treatment. For true Mobitz type II block with dropped beats or for AV block with slow, wide QRS complexes, temporary transvenous pacing is the treatment of choice. External pacing can be used until a temporary transvenous pacemaker can be placed. Although isoproterenol infusion may restore rhythm and rate temporarily, it is not used because it increases O_2 demand and risk of rhythm abnormalities. Atropine 0.5 mg IV q 3 to 5 min to a total dose of 2.5 mg may be useful for narrow-complex AV block with a slow ventricular rate but is not recommended for new wide-complex AV block.

Ventricular arrhythmias: These arrhythmias are common and may result from hypoxia, electrolyte imbalance (hypokalemia, possibly hypomagnesemia), or sympathetic overactivity in ischemic cells adjacent to infarcted tissue (which is not electrically active). Treatable causes of ventricular arrhythmias are sought and corrected. Serum K should be kept above 4.0 mEq/L. IV KCl is recommended; usually, 10 mEq/h can be infused, but for severe hypokalemia (K < 2.5 mEq/L), 20 to 40 mEq/h can be infused

through a central venous line.

Ventricular ectopic beats, which are common after MI, do not warrant specific treatment.

Nonsustained VT (ie, < 30 sec) and even sustained slow VT (accelerated idioventricular rhythm) without hemodynamic instability do not usually require treatment in the first 24 to 48 h. Polymorphic VT, sustained (≥ 30 sec) monomorphic VT, or any VT with symptoms of instability (eg, heart failure, hypotension, chest pain) is treated with synchronized cardioversion. VT without hemodynamic instability may be treated with IV lidocaine, procainamide, or amiodarone. Some clinicians also treat complex ventricular arrhythmias with Mg sulfate 2 g IV over 5 min whether or not serum Mg is low. VT may occur months after MI. Late VT is more likely to occur in patients with transmural infarction and to be sustained.

VF occurs in 5 to 12% of patients during the first 24 h after MI, usually within 6 h. Late VF usually indicates continued or recurrent myocardial ischemia and, when accompanied by hemodynamic deterioration, is a poor prognostic sign. VF is treated with immediate unsynchronized cardioversion (see p. 2262).

An IV β-blocker early in MI followed by continued oral β-blockers reduces the incidence of ventricular arrhythmias (including VF) and mortality in patients who do not have heart failure or hypotension. Prophylaxis with other drugs (eg, lidocaine) increases mortality risk and is not recommended.

After the acute phase, the presence of complex ventricular arrhythmias or nonsustained VT, especially with significant LV systolic dysfunction, increases mortality risk. An implantable cardioverter-defibrillator (ICD) should be considered. Programmed endocardial stimulation can help select the most effective antiarrhythmics or determine the need for an ICD. Before treatment with an antiarrhythmic or ICD, coronary angiography and other tests are done to look for recurrent myocardial ischemia, which may require PCI or CABG.

Heart failure: Patients with large infarctions (determined by ECG or serum markers) and those with mechanical complications, hypertension, or diastolic dysfunction are more likely to develop heart failure. Clinical findings depend on infarct size, elevation of LV filling pressure, and degree of reduction in cardiac output. Dyspnea, inspiratory rales at the lung bases, and hypoxemia are common.

Treatment depends on severity. For mild cases, a loop diuretic (eg, furosemide 20 to 40 mg IV once/day or bid) to reduce ventricular filling pressure is often sufficient. For severe cases, vasodilators (eg, IV nitroglycerin) are often used to reduce preload and afterload; during treatment, pulmonary artery occlusion pressure is often measured via right heart (Swan-Ganz) catheterization. ACE inhibitors are used as long as systolic BP remains > 100 mm Hg. A short-acting ACE inhibitor given in low doses (eg, captopril 3.125 to 6.25 mg po q 4 to 6 h, increasing doses as tolerated) is best for initial treatment. Once the maximum dose is reached (maximum for captopril, 50 mg tid), a longer-acting ACE inhibitor (eg, fosinopril, lisinopril, ramipril) is substituted for the long-term. If heart failure remains in New York Heart Association class II or worse (see Table 211-2 on p. 2124), an aldosterone inhibitor (eg, eplerenone, spironolactone) should be added. For severe heart failure, an intraarterial counterpulsation balloon pump may provide temporary hemodynamic support. When revascularization or surgical repair is not feasible, heart transplantation is considered. Long-term LV or biventricular implantable assist devices may be used as a bridge to transplantation; if transplantation is impossible, the LV assist device is occasionally used as permanent treatment. Occasionally, use of such a device results in recovery and can be removed in 3 to 6 mo.

If heart failure causes hypoxemia, O_2 is given by nasal prongs (to maintain PaO_2 at about 100 mg Hg). It may help oxygenate myocardium and limit the ischemic zone.

Papillary muscle disorders: Functional papillary muscle insufficiency occurs in about 35% of patients during the first few hours of infarction. Papillary muscle ischemia causes incomplete coaptation of the mitral valve leaflets, which is transient in most patients. But in some patients, papillary muscle or free wall scarring causes permanent mitral regurgitation. Functional papillary muscle insufficiency is characterized by an apical late systolic murmur and typically resolves without treatment.

Papillary muscle rupture occurs most often after an inferoposterior infarct due to right coronary artery occlusion. It produces acute, severe mitral regurgitation. Papillary muscle rupture is characterized by the sudden appearance of a loud apical holosystolic murmur and thrill, usually with pulmonary edema. Occasionally, when severe regurgitation is silent but suspected clinically, echocardiography is done. Mitral valve repair or replacement is effective.

Myocardial rupture: Interventricular septum or free wall rupture occurs in 1% of patients with acute MI. It causes 15% of hospital mortality.

Interventricular septum rupture, although rare, is 8 to 10 times more common than papillary muscle rupture. Intraventricular septum rupture is characterized by the sudden appearance of a loud systolic murmur and thrill medial to the apex along the left sternal border in the 3rd or 4th intercostal space, accompanied by hypotension with or without signs of LV failure. Diagnosis may be confirmed using a balloon-tipped catheter and comparing blood O_2 saturation or PO_2 of right atrial, RV, and pulmonary artery samples. A significant increase in RV PO_2 is diagnostic, as is Doppler echocardiography, which may demonstrate the actual shunt of blood across the ventricular septum. Treatment is surgery, which should be delayed for up to 6 wk after MI so that infarcted myocardium can heal maximally; if hemodynamic instability persists, earlier surgery is indicated despite a high mortality risk.

Free wall rupture increases in incidence with age and is more common among women. It is characterized by sudden loss of arterial pressure with momentary persistence of sinus rhythm and often by signs of cardiac tamponade. Surgery is rarely successful. Rupture of a free wall is almost always fatal.

Ventricular aneurysm: A localized bulge in the ventricular wall, usually the LV wall, can occur at the site of a large infarction. Ventricular aneurysms are common, especially with a large transmural infarct (usually anterior). Aneurysms may develop in a few days, weeks, or months. They are unlikely to rupture but may lead to recurrent ventricular arrhythmias, low cardiac output, and mural thrombosis with systemic embolism. A ventricular aneurysm may be suspected when paradoxical precordial movements are seen or felt. ECG shows persistent ST-segment elevation, and chest x-ray shows a characteristic bulge of the cardiac shadow. Echocardiography is done to confirm the diagnosis and determine whether a thrombus is present. Surgical excision may be indicated when LV failure or arrhythmia persists. Use of ACE inhibitors during acute MI modifies LV remodeling and may reduce the incidence of aneurysm.

Pseudoaneurysm is incomplete rupture of the free LV wall; it is limited by the pericardium. Pseudoaneurysms almost always contain a thrombus and often rupture completely. They are repaired surgically.

Hypotension and cardiogenic shock: Hypotension may be due to decreased ventricular filling or loss of contractile force secondary to massive MI. Marked hypotension (eg, systolic BP < 90 mm Hg) with tachycardia and symptoms of end-organ hypoperfusion (reduced urine output, mental confusion, diaphoresis, cold extremities) is termed cardiogenic shock (see also p. 2294). Pulmonary congestion develops rapidly in cardiogenic shock.

Decreased LV filling is most often caused by reduced venous return secondary to hypovolemia, especially in patients receiving intensive loop diuretic therapy, but it may reflect RV infarction. Marked pulmonary congestion suggests loss of LV contractile force (LV failure) as the cause. Treatment depends on the cause. In some patients, determining the cause requires use of a pulmonary artery catheter to measure intracardiac pressures. If pulmonary artery occlusion pressure is < 18 mm Hg, decreased filling, usually due to hypovolemia, is likely; if pressure is > 18 mm Hg, LV failure is likely. For hypotension due to hypovolemia, cautious fluid replacement with 0.9% saline is usually possible without left heart overload (excessive rise in left atrial pressure). However, sometimes LV function is so compromised that adequate fluid replacement sharply increases pulmonary artery occlusion pressure to levels associated with pulmonary edema (> 25 mm Hg). If left atrial pressure is high, hypotension is probably due to LV failure, and if diuretics are ineffective, inotropic therapy or circulatory support may be required.

In cardiogenic shock, an α- or β-agonist may be temporarily effective. Dopamine, a catecholamine with α and β1 effects, is given at 0.5 to 1 μg/kg/min, increased until response is satisfactory or dose is about 10 μg/kg/min. Higher doses induce vasoconstriction and atrial and ventricular arrhythmias. Dobutamine, a β-

agonist, may be given IV at 2.5 to 10 µg/kg/min or in higher doses. It often causes or exacerbates hypotension; it is most effective when hypotension is secondary to low cardiac output with increased peripheral vascular resistance. Dopamine may be more effective than dobutamine when a vasopressor effect is also required. In refractory cases, dobutamine and dopamine may be combined. An intraaortic counterpulsation balloon pump can often temporarily support the patient. Definitive treatment for postinfarction cardiogenic shock is revascularization by thrombolysis of the clot, angioplasty, or emergency CABG. Revascularization usually greatly improves ventricular function. PCI or CABG may be considered for persistent ischemia, refractory ventricular arrhythmia, hemodynamic instability, or shock if coronary anatomy is suitable.

RV ischemia or infarction: RV infarction rarely occurs in isolation; it usually accompanies inferior LV infarction, and the first sign may be hypotension developing in a previously stable patient. Right-sided ECG leads may show ST-segment changes. Volume loading with 1 to 2 L of 0.9% saline is often effective. Dobutamine may help. Nitrates and diuretics are not used; they reduce preload (and hence cardiac output), causing severe hypotension. Increased right-sided filling pressure should be maintained by IV fluid infusion.

Recurrent ischemia: Any chest pain that remains or recurs 12 to 24 h post-MI may represent recurrent ischemia. Post-MI ischemic pain indicates that more myocardium is at risk of infarction. Usually, recurrent ischemia can be identified by reversible ST-T changes on the ECG; BP may be elevated. However, because recurrent ischemia may be silent (ECG changes without pain) in up to one third of patients, serial ECGs are routinely obtained every 8 h for 1 day and then daily. Recurrent ischemia is treated similarly to unstable angina. Sublingual or IV nitroglycerin is usually effective. Coronary angiography and PCI or CABG should be considered to salvage ischemic myocardium.

Mural thrombosis: Mural thrombosis occurs in about 20% of patients with acute MI. Systemic embolism occurs in about 10% of patients with LV thrombosis; risk is highest in the first 10 days but persists at least 3 mo. Risk is highest (about 60%) for patients with large anterior infarctions (especially involving the distal septum and apex), a dilated and diffusely hypokinetic LV, or chronic AF. Anticoagulants are given to reduce risk of emboli. If not contraindicated, full-dose IV heparin followed by warfarin for 3 to 6 mo is given to maintain INR between 2 and 3. Anticoagulants are continued indefinitely when a dilated diffusely hypokinetic LV, LV aneurysm, or chronic AF is present. Aspirin may also be given indefinitely.

Pericarditis: Pericarditis (see p. 2201) results from extension of myocardial necrosis through the wall to the epicardium; it develops in about one third of patients with acute transmural MI. A friction rub usually begins 24 to 96 h after MI onset. Earlier onset of the friction rub is unusual, although hemorrhagic pericarditis occasionally complicates the early phase of MI. Acute tamponade is rare. Pericarditis is diagnosed by ECG, which shows diffuse ST-segment elevation and sometimes PR-interval depression. Echocardiography is frequently done, but results are usually normal. Occasionally, small pericardial effusions and even unsuspected tamponade are detected. Aspirin or another NSAID usually relieves symptoms. High doses or prolonged use of NSAIDs or corticosteroids may impair infarct healing and should be avoided. Anticoagulation is not contraindicated in early peri-infarction pericarditis but is contraindicated in later post-MI (Dressler's) syndrome.

Post-MI syndrome (Dressler's syndrome): Post-MI syndrome develops in a few patients several days to weeks or even months after acute MI; incidence appears to have decreased in recent years. It is characterized by fever, pericarditis with a friction rub, pericardial effusion, pleurisy, pleural effusions, pulmonary infiltrates, and joint pain. This syndrome is caused by an autoimmune reaction to material from necrotic myocytes. It may recur. Differentiating post-MI syndrome from extension or recurrence of infarction may be difficult. However, in post-MI syndrome, cardiac markers do not increase significantly, and ECG changes are nonspecific. NSAIDs are usually effective, but the syndrome can recur several times. In severe cases, a short, intensive course of another NSAID or a corticosteroid may be necessary. High doses of an NSAID or a corticosteroid are not used for more than a few days because they may interfere with early ventricular healing after an acute MI.

Rehabilitation and Postdischarge Treatment

• Functional evaluation

• Changes in lifestyle: Regular exercise, diet modification, weight loss, smoking cessation

• Drugs: Continuation of aspirin, β-blockers, ACE inhibitors, and statins

Functional evaluation: Patients who did not have coronary angiography during admission, have no high-risk features (eg, heart failure, recurrent angina, VT or VF after 24 h,

[
Table 210-9. Functional Evaluation After MI]

mechanical complications such as new murmurs, shock), and have an ejection fraction > 40% whether or not they received fibrinolytics usually should have stress testing of some sort before or shortly after discharge (see Table 210-9).

Activity: Physical activity is gradually increased during the first 3 to 6 wk after discharge. Resumption of sexual activity, often of great concern to the patient, and other moderate physical activities may be encouraged. If good cardiac function is maintained 6 wk after acute MI, most patients can return to all their normal activities. A regular exercise program consistent with lifestyle, age, and cardiac status reduces risk of ischemic events and enhances general well-being.

Risk factors: The acute illness and treatment of ACS should be used to strongly motivate the patient to modify risk factors. Evaluating the patient's physical and emotional status and discussing them with the patient, advising about lifestyle (eg, smoking, diet, work and play habits, exercise), and aggressively managing risk factors may improve prognosis.

Drugs: Several drugs clearly reduce mortality risk post-MI and are used unless contraindicated or not tolerated.

Aspirin reduces mortality and reinfarction rates in post-MI patients by 15 to 30%. Enteric-coated aspirin 81 mg once/day is recommended long-term. Data suggest that warfarin with or without aspirin reduces mortality and reinfarction rates.

β-Blockers are considered standard therapy. Most available β-blockers (eg, acebutolol, atenolol, metoprolol, propranolol, timolol) reduce post-MI mortality rate by about 25% for at least 7 yr.

ACE inhibitors are given to all post-MI patients. These drugs may provide long-term cardioprotection by improving endothelial function. If an ACE inhibitor is not tolerated because of cough or rash (but not angioedema or renal dysfunction), an angiotensin II receptor blocker may be substituted.

Statins are prescribed. Reducing cholesterol levels after MI reduces rates of recurrent ischemic events and mortality in patients with elevated or normal cholesterol levels. Statins appear to benefit post-MI patients regardless of their initial cholesterol level. Post-MI patients whose primary problem is a low HDL level or an elevated triglyceride level may benefit from a fibrate, but evidence of benefit is less clear. A lipid-lowering drug should be continued indefinitely, unless significant adverse effects occur, and dose should be increased to achieve an LDL level of 70 to 80 mg/dL (1.81 to 2.07 mmol/L).

Chapter 211. Heart Failure

Introduction

(Congestive Heart Failure) (For heart failure in children, see p. 2947.)

Heart failure (HF) is a syndrome of ventricular dysfunction. Left ventricular failure causes shortness of breath and fatigue, and right ventricular failure causes peripheral and abdominal fluid accumulation; the ventricles can be involved together or separately. Diagnosis is initially clinical, supported by chest x-ray, echocardiography, and levels of plasma natriuretic peptides. Treatment includes diuretics, ACE inhibitors, angiotensin II receptor blockers, β-blockers, aldosterone antagonists, digitalis, specialized implantable pacemakers, and correction of the underlying disorder.

HF affects about 5 million people in the US; > 500,000 new cases occur each year.

Physiology

Cardiac contractility (force and velocity of contraction), ventricular performance, and myocardial O_2 requirements are determined by preload, afterload, substrate availability (eg, O_2, fatty acids, glucose), heart rate and rhythm, and amount of viable myocardium. Cardiac output (CO) is the product of stroke volume and heart rate; it is also affected by venous return, peripheral vascular tone, and neurohumoral factors.

Preload is the loading condition of the heart at the end of its relaxation phase (diastole) just before contraction (systole). Preload represents the degree of end-diastolic fiber stretch and end-diastolic volume, which is influenced by ventricular diastolic pressure and the composition of the myocardial wall. Typically, left ventricular (LV) end-diastolic pressure, especially if higher than normal, is a reasonable measure of preload. LV dilation, hypertrophy, and changes in myocardial distensibility (compliance) modify preload.

Afterload is the force resisting myocardial fiber contraction at the start of systole; it is determined by chamber pressure, volume, and wall thickness at the time the aortic valve opens. Clinically, systemic systolic BP at or shortly after the aortic valve opens represents peak systolic wall stress and approximates afterload.

The Frank-Starling principle describes the relationship between preload and cardiac performance. It states that, normally, systolic contractile performance (represented by stroke volume or CO) is proportional to preload within the normal physiologic range (see Fig. 211-1). Contractility is difficult to measure without cardiac catheterization but is reasonably reflected by the ejection fraction (EF), which is the percentage of end-diastolic volume ejected with each contraction (LV stroke volume/end-diastolic volume); contractility can generally be adequately assessed noninvasively with echocardiography.

Cardiac reserve is the ability of the heart to increase its performance above resting levels in response to emotional or physical stress; body O_2 consumption may increase from 250 to ≥ 1500 mL/min during maximal exertion. Mechanisms include increasing heart rate, systolic and diastolic volume, stroke volume, and tissue extraction of O_2 (the difference between O_2 content in arterial blood and mixed venous or pulmonary artery blood). In well-trained young adults during maximal exercise, heart rate may increase from 55 to 70 beats/min at rest to 180 beats/min, and CO may increase from 6 to ≥ 25 L/min. At rest, arterial blood contains about 18 mL O_2/dL of blood, and mixed venous or pulmonary artery blood contains about 14 mL/dL. O_2 extraction is thus about 4 mL/dL, but when demand is increased, it may increase to 12 to 14 mL/dL. This mechanism also helps compensate for reduced tissue blood flow in HF.

[**Fig. 211-1.** Frank-Starling principle.]

Pathophysiology

In HF, the heart may not provide tissues with adequate blood for metabolic needs, and cardiac-related elevation of pulmonary or systemic venous pressures may result in organ congestion. This condition can result from abnormalities of systolic or diastolic function or, commonly, both. Although a primary abnormality may be a change in myocyte function, there are also changes in collagen turnover of the extracellular matrix. Cardiac structural defects (eg, congenital defects, valvular disorders), rhythm abnormalities (including persistently high heart rate), and high metabolic demands (eg, from thyrotoxicosis) also can cause HF.

Systolic dysfunction: In systolic dysfunction, the ventricle contracts poorly and empties inadequately, leading initially to increased diastolic volume and pressure and decreased EF. Many defects in energy utilization, energy supply, electrophysiologic functions, and contractile element interaction occur, with abnormalities in intracellular Ca modulation and cAMP production.

Predominant systolic dysfunction is common in HF due to MI, myocarditis, and dilated cardiomyopathy. Systolic dysfunction may affect primarily the LV or the right ventricle (RV); LV failure often leads to RV failure.

Diastolic dysfunction: In diastolic dysfunction (also called HF with preserved systolic function or HF with preserved/normal EF), ventricular filling is impaired, resulting in reduced ventricular end-diastolic volume, increased end-diastolic pressure, or both. Contractility and hence EF remain normal; EF may even increase as the poorly filled LV empties more completely to maintain CO. Markedly reduced LV filling can cause low CO and systemic symptoms. Elevated left atrial pressures can cause pulmonary hypertension and pulmonary congestion.

Diastolic dysfunction usually results from impaired ventricular relaxation (an active process), increased ventricular stiffness, valvular disease, or constrictive pericarditis. Acute myocardial ischemia is also a cause of diastolic dysfunction. Resistance to filling increases with age, probably reflecting myocyte loss and increased interstitial collagen deposition; thus, diastolic dysfunction is particularly common among the elderly. Diastolic dysfunction predominates in hypertrophic cardiomyopathy, disorders with ventricular hypertrophy (eg, hypertension, significant aortic stenosis), and amyloid infiltration of the myocardium. LV filling and function may also be impaired if marked increases in RV pressure shift the interventricular septum to the left.

Diastolic dysfunction is increasingly being recognized as a cause of HF. Estimates vary, but about 50% of patients with HF have diastolic dysfunction and a normal EF; the prevalence increases with age.

LV failure: In failure due to LV dysfunction, CO decreases and pulmonary venous pressure increases. When pulmonary capillary pressure exceeds the oncotic pressure of plasma proteins (about 24 mm Hg), fluid extravasates from the capillaries into the interstitial space and alveoli, reducing pulmonary compliance and increasing the work of breathing. Lymphatic drainage increases but cannot compensate for the increase in pulmonary fluid. Marked fluid accumulation in alveoli (pulmonary edema) significantly alters ventilation-perfusion (V/Q) relationships: Deoxygenated pulmonary arterial blood passes through poorly ventilated alveoli, decreasing systemic arterial oxygenation (PaO_2) and causing dyspnea. However, dyspnea may occur before V/Q abnormalities, probably because of elevated pulmonary venous pressure and increased work of breathing; the precise mechanism is unclear. In severe or chronic LV failure, pleural effusions characteristically develop in the right hemithorax and later bilaterally, further aggravating dyspnea. Minute ventilation increases; thus, $PaCO_2$ decreases and blood pH increases (respiratory alkalosis). Marked interstitial edema of the small airways may interfere with ventilation, elevating $PaCO_2$—a sign of impending respiratory failure.

RV failure: In failure due to RV dysfunction, systemic venous pressure increases, causing fluid extravasation and consequent edema, primarily in dependent tissues (feet and ankles of ambulatory patients) and abdominal viscera. The liver is affected most, but the stomach and intestine also become congested; fluid accumulation in the peritoneal cavity (ascites) can occur. RV failure commonly causes moderate hepatic dysfunction, with usually modest increases in conjugated and unconjugated bilirubin,

PT, and hepatic enzymes (eg, alkaline phosphatase, AST, ALT). The impaired liver breaks down less aldosterone, further contributing to fluid accumulation. Chronic venous congestion in the viscera can cause anorexia, malabsorption of nutrients and drugs, protein-losing enteropathy (characterized by diarrhea and marked hypoalbuminemia), chronic GI blood loss, and rarely ischemic bowel infarction.

Cardiac response: If ventricular function is impaired, a higher preload is required to maintain CO. As a result, the ventricles are remodeled over time: The LV becomes less ovoid and more spherical, dilates, and hypertrophies; the RV dilates and may hypertrophy. Initially compensatory, these changes eventually increase diastolic stiffness and wall tension (ie, diastolic dysfunction develops), compromising cardiac performance, especially during physical stress. Increased wall stress raises O_2 demand and accelerates apoptosis (programmed cell death) of myocardial cells. Dilation of the ventricles can also cause mitral or tricuspid valve regurgitation with further increases in end-diastolic volumes.

Hemodynamic responses: With reduced CO, tissue O_2 delivery is maintained by increasing O_2 extraction and sometimes shifting the oxyhemoglobin dissociation curve (see Fig. 189-4 on p. 1857) to the right to favor O_2 release.

Reduced CO with lower systemic BP activates arterial baroreflexes, increasing sympathetic tone and decreasing parasympathetic tone. As a result, heart rate and myocardial contractility increase, arterioles in selected vascular beds constrict, venoconstriction occurs, and Na and water are retained. These changes compensate for reduced ventricular performance and help maintain hemodynamic homeostasis in the early stages of HF. However, these compensatory changes increase cardiac work, preload, and afterload; reduce coronary and renal perfusion; cause fluid accumulation resulting in congestion; increase K excretion; and may cause myocyte necrosis and arrhythmias.

Renal responses: As cardiac function deteriorates, renal blood flow and GFR decrease, and blood flow within the kidneys is redistributed. The filtration fraction and filtered Na decrease, but tubular resorption increases, leading to Na and water retention. Blood flow is further redistributed away from the kidneys during exercise, but renal blood flow improves during rest, possibly contributing to nocturia.

Decreased perfusion of the kidneys (and possibly decreased arterial systolic stretch secondary to declining ventricular function) activates the renin-angiotensin-aldosterone system (see also p. 2066), increasing Na and water retention and renal and peripheral vascular tone. These effects are amplified by the intense sympathetic activation accompanying HF.

The renin-angiotensin-aldosterone-vasopressin (antidiuretic hormone [ADH]) system causes a cascade of potentially deleterious long-term effects. Angiotensin II worsens HF by causing vasoconstriction, including efferent renal vasoconstriction, and by increasing aldosterone production, which not only enhances Na reabsorption in the distal nephron but also causes myocardial and vascular collagen deposition and fibrosis. Angiotensin II increases norepinephrine release, stimulates release of ADH, and triggers apoptosis. Angiotensin II may be involved in vascular and myocardial hypertrophy, thus contributing to the remodeling of the heart and peripheral vasculature, potentially worsening HF. Aldosterone can be synthesized in the heart and vasculature independently of angiotensin II (perhaps mediated by corticotropin, nitric oxide, free radicals, and other stimuli) and may have deleterious effects in these organs.

HF that causes progressive renal dysfunction (including that renal dysfunction caused by drugs used to treat HF) contributes to worsening HF and has been termed the cardiorenal syndrome.

Neurohumoral responses: In conditions of stress, neurohumoral responses help increase heart function and maintain BP and organ perfusion, but chronic activation of these responses is detrimental to the normal balance between myocardial-stimulating and vasoconstricting hormones and between myocardial-relaxing and vasodilating hormones.

The heart contains many neurohumoral receptors (α_1, β_1, β_2, β_3, angiotensin II type 1 [AT_1] and type 2 [AT_2], muscarinic, endothelin, serotonin, adenosine, cytokine); the role of these receptors is not yet fully defined. In patients with HF, β_1 receptors (which constitute 70% of cardiac β receptors) are down-

regulated, probably in response to intense sympathetic activation. The result of down-regulation is impaired myocyte contractility and increased heart rate.

Plasma norepinephrine levels are increased, largely reflecting sympathetic nerve stimulation because plasma epinephrine levels are not increased. Detrimental effects include vasoconstriction with increased preload and afterload, direct myocardial damage including apoptosis, reduced renal blood flow, and activation of other neurohumoral systems, including the renin-angiotensin-aldosterone-ADH system.

ADH is released in response to a fall in BP via various neurohormonal stimuli. Increased ADH decreases renal excretion of free water, possibly contributing to hyponatremia in HF. ADH levels in HF with normal BP vary.

Atrial natriuretic peptide is released in response to increased atrial volume and pressure; brain (B-type) natriuretic peptide (BNP) is released from the ventricle in response to ventricular stretching. These peptides enhance renal excretion of Na, but in patients with HF, the effect is blunted by decreased renal perfusion pressure, receptor downregulation, and perhaps enhanced enzymatic degradation.

Because endothelial dysfunction occurs in HF, fewer endogenous vasodilators (eg, nitric oxide, prostaglandins) are produced, and more endogenous vasoconstrictors (eg, endothelin) are produced, thus increasing afterload.

The failing heart and other organs produce tumor necrosis factor (TNF)-α. This cytokine increases catabolism and is possibly responsible for cardiac cachexia (loss of lean tissue ≥ 10%), which may accompany severely symptomatic HF, and for other detrimental changes. The failing heart also undergoes metabolic changes with increased free fatty acid utilization and decreased glucose utilization; these changes may become therapeutic targets.

Changes with aging: Age-related changes in the heart and cardiovascular system lower the threshold for expression of HF. Interstitial collagen within the myocardium increases, the myocardium stiffens, and myocardial relaxation is prolonged. These changes lead to a significant reduction in diastolic LV function, even in healthy elderly people. Modest decline in systolic function also occurs with aging. An age-related decrease in myocardial and vascular responsiveness to β-adrenergic stimulation further impairs the ability of the cardiovascular system to respond to increased work demands.

As a result of these changes, peak exercise capacity decreases significantly (about 8%/decade after age 30), and CO at peak exercise decreases more modestly. This decline can be slowed by regular physical exercise. Thus, elderly patients are more prone than are younger ones to develop HF symptoms in response to the stress of systemic disorders or relatively modest cardiovascular insults. Stressors include infections (particularly pneumonia), hyperthyroidism, anemia, hypertension, myocardial ischemia, hypoxia, hyperthermia, renal failure, perioperative IV fluid loads, nonadherence to drug regimens or to low-salt diets, and use of certain drugs (including NSAIDs, β-blockers, and certain Ca channel blockers).

Etiology

Both cardiac and systemic factors can impair cardiac performance and cause or aggravate HF (see Table 211-1).

Classification

The traditional distinction of left and right ventricular failure is somewhat misleading because the heart is an integrated pump, and changes in one chamber ultimately affect the whole heart. However, these terms indicate the major site of pathology leading to HF and can be useful for initial evaluation and treatment. Other common descriptive terms include acute or chronic; congestive; high output or low output; systolic or diastolic; dilated or nondilated; and ischemic, hypertensive, or idiopathic dilated cardiomyopathy.

LV failure characteristically develops in ischemic heart disease, hypertension, mitral or aortic valvular regurgitation, aortic stenosis, most forms of cardiomyopathy, and congenital heart disorders (eg, ventricular septal defect or patent ductus arteriosus with large shunts).

RV failure is most commonly caused by previous LV failure (which increases pulmonary venous pressure and leads to pulmonary arterial hypertension, thus overloading the RV) or by a severe lung disorder (when it is called cor pulmonale—see p. 2132). Other causes are multiple pulmonary emboli, RV infarction, primary pulmonary hypertension, tricuspid regurgitation or stenosis, mitral

[**Table 211-1.** Causes of Heart Failure]

stenosis, pulmonary artery or valve stenosis, pulmonary venous occlusive disease, or congenital disorders such as Ebstein's anomaly or Eisenmenger's syndrome. Some conditions mimic RV failure, except cardiac function may be normal; they include volume overload and increased systemic venous pressure in polycythemia or overtransfusion, acute renal failure with retention of Na and water, obstruction of either vena cava, and hypoproteinemia from any cause resulting in low plasma oncotic pressure and peripheral edema.

Biventricular failure results from disorders that affect the whole myocardium (eg, viral myocarditis, amyloidosis, Chagas' disease) or long-standing LV failure causing RV failure.

High-output HF results from a persistently high CO, which may eventually result in an inability of a normal heart to maintain adequate output. Conditions that may increase CO include severe anemia, beriberi, thyrotoxicosis, advanced Paget's disease, arteriovenous fistula, and persistent tachycardia. CO is high in various forms of cirrhosis, but much of the observed fluid retention is due to hepatic mechanisms.

Cardiomyopathy is a general term reflecting disease of the myocardium. Most commonly, the term refers to a primary disorder of the ventricular myocardium that is not caused by congenital anatomic defects; valvular, systemic, or pulmonary vascular disorders; isolated pericardial, nodal, or conduction system disorders; or epicardial coronary artery disease (CAD). The term is sometimes used to reflect etiology (eg, ischemic vs hypertensive cardiomyopathy). Cardiomyopathy does not always lead to symptomatic HF. It is often idiopathic and is classified as dilated congestive, hypertrophic, infiltrative-restrictive, or apical-ballooning cardiomyopathy.

Symptoms and Signs

Manifestations differ depending on the extent to which the LV and RV are initially affected. Clinical severity varies significantly and is usually classified according to the New York Heart Association system (see Table 211-2); the examples of ordinary activity may be modified for elderly, debilitated patients. Severe LV failure may cause pulmonary edema (see p. 2131) or cardiogenic shock (see p. 2294).

History: In LV failure, the most common symptoms are dyspnea, reflecting pulmonary congestion, and fatigue, reflecting low CO. Dyspnea usually occurs during exertion and is relieved by rest. As HF worsens, dyspnea can occur during rest and at night, sometimes causing nocturnal cough. Dyspnea occurring immediately or soon after lying flat and relieved promptly by sitting up (orthopnea) is common as HF advances. In paroxysmal nocturnal dyspnea (PND), dyspnea awakens patients several hours after they lie down and is relieved only after they sit up for 15 to 20 min. In severe HF, periodic cycling of breathing (Cheyne-Stokes respiration—see p. 1827)—a brief period of increased breathing [hyperpnea] followed by a brief period of no breathing [apnea]—can occur during the day or night); the sudden hyperpneic phase may awaken the patient from sleep. This breathing differs from PND in that the hyperpneic phase is short, lasting only a few seconds and resolving in < 1 min. PND is associated with pulmonary congestion, and Cheyne-Stokes respiration with low CO. Sleep-related breathing disorders, such as sleep apnea (see p. 1903), are common in HF and may aggravate HF. Severely reduced cerebral blood flow and hypoxemia can cause chronic irritability and impair mental performance.

In RV failure, the most common symptoms are ankle swelling and fatigue. Sometimes patients feel a sensation of fullness in the abdomen or neck. Hepatic congestion can cause right upper quadrant abdominal discomfort, and stomach and intestinal congestion can cause anorexia and abdominal bloating.

Less specific HF symptoms include cool peripheries, postural light-headedness, nocturia, and decreased daytime micturition. Skeletal muscle wasting can occur in severe biventricular failure and may reflect some disuse but also increased catabolism associated with increased cytokine production. Significant weight loss (cardiac cachexia) is an ominous sign associated with high mortality.

In the elderly, presenting complaints may be atypical, such as confusion, delirium, falls, sudden functional decline, nocturnal urinary incontinence, or sleep disturbance. Coexisting cognitive impairment and depression may also influence assessment and therapeutic interventions and may be worsened by the HF.

Examination: General examination may detect signs of systemic disorders that cause or aggravate HF (eg, anemia, hyperthyroidism, alcoholism, hemochromatosis).

In LV failure, tachycardia and tachypnea may occur. Patients with severe LV failure may appear visibly dyspneic or cyanotic, hypotensive, and confused or agitated because of hypoxia and poor cerebral perfusion. Some of these less specific symptoms (eg, confusion) are more common in the elderly.

Central cyanosis (affecting all of the body, including warm areas such as the tongue and mucous membranes) reflects severe hypoxemia.

[**Table 211-2.** New York Heart Association (Nyha) Classification of Heart Failure]

Peripheral cyanosis of the lips, fingers, and toes reflects low blood flow with increased O_2 extraction. If vigorous massage improves nail bed color, cyanosis may be peripheral; increasing local blood flow does not improve color if cyanosis is central.

Cardiac findings in LV systolic dysfunction include a diffuse, sustained, and laterally displaced apical impulse; audible and occasionally palpable 3rd (S_3) and 4th (S_4) heart sounds, and an accentuated pulmonic component (P_2) of the 2nd heart sound (S_2). A pansystolic murmur of mitral regurgitation at the apex may occur. Pulmonary findings include inspiratory basilar crackles that do not clear with coughing and, if pleural effusion is present, dullness to percussion and diminished breath sounds at lung bases.

Signs of RV failure include nontender peripheral pitting edema (digital pressure leaves visible and palpable imprints, sometimes quite deep) in the feet and ankles; an enlarged and sometimes pulsatile liver palpable below the right costal margin; abdominal swelling and ascites; and visible elevation of the jugular venous pressure, sometimes with large *a* or *v* waves that are visible even when the patient is seated or standing (see
Fig. 206-1 on p. 2020). In severe cases, peripheral edema can extend to the thighs or even the sacrum, scrotum, lower abdominal wall, and occasionally even higher. Severe edema in multiple areas is termed anasarca. Edema may be asymmetric if patients lie predominantly on one side.

With hepatic congestion, the liver may be palpably enlarged or tender, and hepatojugular or abdominal-jugular reflux may be detected (see p.
2019). Precordial palpation may detect the left parasternal lift of RV enlargement, and auscultation may detect the murmur of tricuspid regurgitation or the RV S_3 along the left sternal border; both findings are augmented upon inspiration.

Diagnosis

• Sometimes only clinical evaluation

• Chest x-ray

• Echocardiography

• Sometimes BNP or N-terminal-proBNP (NT-proBNP) levels

• ECG and other tests for etiology as needed

Clinical findings (eg, exertional dyspnea or fatigue, orthopnea, edema, tachycardia, pulmonary crackles, S_3, jugular venous distention) suggest HF but are not apparent early. Similar symptoms may result from COPD or recurrent pneumonia or may be erroneously attributed to obesity or old age. Suspicion for HF should be high in patients with a history of MI, hypertension, or valvular disorders or murmurs and should be moderate in any elderly or diabetic patient.

Chest x-ray, ECG, and an objective test of cardiac function, typically echocardiography, should be done. Blood tests, except for BNP levels, are not used for diagnosis but are useful for identifying cause and systemic effects.

Chest x-ray: Chest x-ray findings suggesting HF include an enlarged cardiac silhouette, pleural effusion, fluid in the major fissure, and horizontal lines in the periphery of lower posterior lung fields (Kerley B lines). These findings reflect chronic elevation of left atrial pressure and chronic thickening of the intralobular septa due to edema. Upper lobe pulmonary venous congestion and interstitial or alveolar edema may also be present. Careful examination of the cardiac silhouette on a lateral projection can identify specific ventricular and atrial chamber enlargement. The x-ray may also suggest alternative diagnoses (eg, COPD, pneumonia, interstitial pulmonary fibrosis, lung cancer).

ECG: ECG findings are not diagnostic, but an abnormal ECG, especially showing previous MI, LV hypertrophy, left bundle branch block, or tachyarrhythmia (eg, rapid atrial fibrillation), increases suspicion for HF and may help identify the cause. An entirely normal ECG is uncommon in chronic HF.

Imaging: Echocardiography can help evaluate chamber dimensions, valve function, EF, wall motion abnormalities, LV hypertrophy, and pericardial effusion. Intracardiac thrombi, tumors, and calcifications within the heart valves, mitral annulus, and aortic wall abnormalities can be detected. Localized or segmental wall motion abnormalities strongly suggest underlying CAD but can also be present with patchy myocarditis. Doppler or color Doppler echocardiography accurately detects valvular disorders and shunts. Doppler studies of mitral and pulmonary venous inflow often help identify and quantify LV diastolic dysfunction; tissue Doppler imaging is more accurate. Measuring LVEF can distinguish between predominant diastolic dysfunction (EF > 0.50) and systolic dysfunction (EF < 0.40). It is important to re-emphasize that HF can occur with a normal LVEF. Three-dimensional echocardiography may become important but currently is available only in specialized centers.

Radionuclide imaging also can help assess systolic and diastolic function, previous MI, and inducible ischemia or myocardial hibernation. Cardiac MRI provides accurate images of cardiac structures and is becoming more widely available. In many centers, multimode imaging (eg, stress MIBI [thallium and sestamibi stress tests] plus CT angiography) is becoming common, although there is growing concern about the radiation dose with CT angiography.

Blood tests: Serum BNP levels are high in HF; this finding may help when clinical findings are unclear or other diagnoses (eg, COPD) need to be excluded. It may be particularly useful for patients with a history of both pulmonary and cardiac disorders. NT-proBNP, an inactive moiety created when proBNP is cleaved, can be used similarly.

Recommended blood tests include CBC, creatinine, BUN, electrolytes (including Mg and Ca), glucose, albumin, and liver function tests. Thyroid function tests are recommended for patients with atrial fibrillation and for selected, especially elderly, patients.

Other tests: Coronary angiography is indicated when CAD is suspected or the etiology of HF is uncertain. Cardiac catheterization with intracardiac pressure measurements may be helpful in the diagnosis of restrictive cardiomyopathies and constrictive pericarditis.

Endocardial biopsy is sometimes done when an infiltrative cardiomyopathy is strongly suspected but cannot be confirmed with noninvasive imaging (eg, cardiac MRI).

Prognosis

Generally, patients with HF have a poor prognosis unless the cause is correctable. Mortality rate at 1 yr from first hospitalization for HF is about 30%. In chronic HF, mortality depends on severity of symptoms and ventricular dysfunction and can range from 10 to 40%/yr. Specific factors that suggest a poor prognosis include hypotension, low EF, presence of CAD, troponin release, elevation of BUN, reduced GFR, hyponatremia, and poor functional capacity (eg, as tested by a 6-min walk test).

HF usually involves gradual deterioration, interrupted by bouts of severe decompensation, and ultimately death, although the time course is being lengthened with modern therapies. However, death can also be sudden and unexpected, without prior worsening of symptoms.

End-of-life care: All patients and family members should be taught about disease progression. For some patients, improving quality of life is as important as increasing quantity of life. Thus, it is important to determine patients' wishes about resuscitation (eg, endotracheal intubation, CPR) if their condition deteriorates, especially when HF is already severe. All patients should be reassured that symptoms will be relieved, and they should be encouraged to seek medical attention early if their symptoms change significantly. Involvement of pharmacists, nurses, social workers, and clergy, who may be part of an interdisciplinary team or disease management program already in place, is particularly important in end-of-life care.

Treatment

• Diet and lifestyle changes

• Treatment of cause

• Drugs (numerous classes)

• Sometimes device therapy (eg, implantable cardioverter-defibrillator, biventricular pacing)

• Multidisciplinary care

Immediate inpatient treatment is required for patients with acute or worsening HF due to certain disorders (eg, acute MI, atrial fibrillation with a very rapid ventricular rate, severe hypertension, acute valvular regurgitation), as well as for patients with pulmonary edema (see p. 2131), severe symptoms, new-onset HF, or HF unresponsive to outpatient treatment. Patients with mild exacerbations of previously diagnosed HF can be treated at home.

The primary goal is to diagnose and to correct or treat the disorder that led to HF.

Short-term goals include relieving symptoms; improving hemodynamics; avoiding hypokalemia, renal dysfunction, and symptomatic hypotension; and correcting neurohumoral activation.

Long-term goals include correcting hypertension, preventing MI and atherosclerosis, improving cardiac function, reducing hospitalizations, and improving survival and quality of life. Treatment involves dietary and lifestyle changes, drugs (see p. 2128), devices, and sometimes percutaneous coronary interventions or surgery.

Treatment is tailored to the patient, considering causes, symptoms, and response to drugs, including adverse effects. Treatment of systolic and diastolic dysfunction has become more similar, although there are more evidence-based therapies for systolic HF.

General management: General measures, especially patient and caregiver education and diet and lifestyle modifications, are important for all HF patients.

• Education

• Na restriction

• Appropriate weight and fitness levels

• Correction of underlying conditions

Patient and caregiver education are critical to long-term success. The patient and family should be involved in treatment choices. They should be taught the importance of drug adherence, warning signs of decompensation, and how to link cause with effect (eg, increased salt in the diet with weight gain or symptoms).

Many centers (eg, specialized outpatient clinics) have integrated health care practitioners from different disciplines (eg, HF nurses, pharmacists, social workers, rehabilitation specialists) into multidisciplinary teams or outpatient HF management programs. These approaches can improve outcomes and reduce hospitalizations and are most effective in the sickest patients.

Dietary Na restriction helps limit fluid retention. All patients should eliminate salt in cooking and at the table and avoid salted foods; the most severely ill should limit Na to < 2 g/day by consuming only low-Na foods. Monitoring daily morning weight helps detect Na and water accumulation early. If weight increases > 2 kg over a few days, patients may be able to adjust their diuretic dose themselves, but if weight gain continues or symptoms occur, patients should seek medical attention. Intensive case management, particularly by monitoring drug adherence and frequency of unscheduled visits to the physician or emergency department and hospitalizations, can identify when intervention is needed. Specialized HF nurses are valuable in education, follow-up, and dosage adjustment according to predefined protocols.

Patients with atherosclerosis or diabetes should strictly follow a diet appropriate for their disorder. Obesity may cause and always aggravates the symptoms of HF; patients should attain a body mass index (BMI) of 21 to 25.

Regular light activity (eg, walking), tailored to symptoms, is generally encouraged. Activity prevents skeletal muscle deconditioning, which worsens functional status; whether this measure improves survival is under study. Rest is appropriate during acute exacerbations. The role of formal exercise rehabilitation programs is being studied; initial results appear favorable.

If hypertension, severe anemia, hemochromatosis, uncontrolled diabetes, thyrotoxicosis, beriberi, alcoholism, Chagas' disease, or toxoplasmosis is successfully treated, patients may dramatically improve. Significant myocardial ischemia should be treated aggressively; treatment may include revascularization by percutaneous coronary intervention (see p. 2059) or bypass surgery (see p. 2052). Management of extensive ventricular infiltration (eg, in amyloidosis) remains unsatisfactory.

Arrhythmias (see also p. 2142): It is important to identify and treat the cause of an arrhythmia.

• Electrolytes are normalized.

• Atrial and ventricular rate are controlled.

• Sometimes antiarrhythmic drugs are given.

Sinus tachycardia, a common compensatory change in HF, usually subsides when HF treatment is effective. If it does not, associated causes (eg, hyperthyroidism, pulmonary emboli, fever, anemia) should be sought. If it persists despite correction of causes, a β-blocker, given in gradually increasing doses, should be considered.

Atrial fibrillation with an uncontrolled ventricular rate must be treated; the target resting ventricular rate is typically < 80 beats/min. β-Blockers are the treatment of choice, although rate-limiting Ca channel blockers may be used cautiously if systolic function is preserved. Adding digoxin or low-dose amiodarone may help some patients. Routine conversion to and maintenance of sinus rhythm has not been shown to be superior to rate control alone in a recent large clinical trial. If rapid atrial fibrillation does not respond to

drugs, permanent pacemaker insertion with complete or partial ablation of the atrioventricular node may be considered in selected patients.

Isolated ventricular premature beats, which are common in HF, do not require specific treatment. However, optimization of HF treatments and correction of electrolyte abnormalities (especially K and Mg) reduce the risk of ventricular arrhythmias. Sustained ventricular tachycardia that persists despite correction of cause (eg, low K or Mg, ischemia) and optimal medical treatment of HF may require an antiarrhythmic drug. Amiodarone and β-blockers are the drugs of choice because other antiarrhythmics have adverse proarrhythmic effects when LV systolic dysfunction is present. Because amiodarone increases digoxin levels, the digoxin dose should be decreased by half. Because long-term use of amiodarone can cause adverse effects, a low-dose (200 to 300 mg po once/day) is used when possible; blood tests for liver function and thyroid-stimulating hormone are done every 6 mo, and if chest x-ray is abnormal or dyspnea worsens significantly, chest x-ray and pulmonary function tests are done yearly to check for pulmonary fibrosis. For sustained ventricular arrhythmias, amiodarone may be required; to reduce risk of sudden death, a loading dose of 400 to 800 mg po bid is given for 1 to 3 wk until rhythm control is adequate, then dose is decreased over 1 mo to a maintenance dose of 400 mg po once/day.

Device therapy: Use of an implantable cardioverter-defibrillator (ICD) or biventricular pacing is appropriate for some patients.

An ICD is recommended for patients with an otherwise good life expectancy if they have symptomatic sustained ventricular tachycardia (especially if it causes syncope), ventricular fibrillation, or an LVEF persistently < 0.30 while receiving good medical therapy.

Biventricular pacing (cardiac resynchronization therapy [CRT]) may relieve symptoms and reduce HF hospitalizations for patients who have HF, LVEF < 0.35, and a widened QRS complex (> 0.12 sec). Better ways of detecting ventricular dyssynchrony may help identify patients most likely to respond to CRT. CRT devices are effective but expensive, and patients must be appropriately selected.

Ultrafiltration (venovenous filtration) can be useful in selected hospitalized patients with severe volume overload if they have not responded well to diuretic therapy and have rising serum creatinine (cardiorenal syndrome). Long-term benefits are still unclear.

An intra-aortic counterpulsation balloon pump is helpful in selected patients who have a good chance of recovery (eg, acute HF following MI). LV assist devices are implantable pumps that augment LV output. They were initially used only as a short-term intervention to maintain patients with severe HF awaiting transplant but are sometimes now used for extended periods (1 to 2 yr) in patients who are not transplant candidates. However, although survival can be prolonged, few patients are able to recover sufficiently to tolerate device removal.

Surgery: Surgery may be appropriate when certain underlying disorders are present. Usually, surgery in HF patients should be done in a specialized center. Surgical closure of congenital or acquired intracardiac shunts can be curative. Coronary artery bypass grafting to reduce ischemia may help some patients with ischemic cardiomyopathy and is currently being studied in a large clinical trial of HF patients with ischemic systolic dysfunction. If HF is primarily due to a valvular disorder, valve repair or replacement is considered (see Ch. 214). Patients with primary mitral regurgitation are more likely to benefit than patients with mitral regurgitation secondary to LV dilation, in whom myocardial function is likely to continue to be poor postoperatively. Surgery is preferably done before myocardial dilation and damage become irreversible.

Heart transplantation (see p. 1131) is the treatment of choice for patients < 60 who have severe, refractory HF and no other life-threatening conditions and who are highly adherent to management recommendations. Some older patients with otherwise excellent health may be considered. Survival is 82% at 1 yr and 75% at 3 yr; however, mortality rate while waiting for a donor is 12 to 15%. Human organ donation remains low. LV assist devices can be a bridge to transplantation or recovery in carefully selected patients.

Experimental therapies: Artificial hearts are not yet a viable alternative. Stem cell transplantation is in

early-stage trials. Surgical options studied include implantation of restraining devices to reduce progressive dilation and a modified aneurysmectomy called surgical ventricular restoration, but neither showed clinical benefit.

Dynamic cardiomyoplasty, endocardial laser therapy, and excision of segments of dilated myocardium are no longer recommended.

Persistent HF: After treatment, symptoms often persist. Reasons include persistence of the underlying disorder (eg, hypertension, ischemia, valvular regurgitation) despite treatment; suboptimal treatment of HF; drug nonadherence; excess intake of dietary Na or alcohol; and presence of an undiagnosed thyroid disorder, anemia, or supervening arrhythmia (eg, atrial fibrillation with rapid ventricular response, intermittent ventricular tachycardia). Also, drugs used to treat other disorders may interfere with HF treatment. NSAIDs, thiazolidinediones (eg, pioglitazone) for diabetes, and short-acting dihydropyridine or nondihydropyridine Ca channel blockers can worsen HF and should be avoided unless no alternative exists; patients who must take such drugs should be followed closely.

Drugs

• Symptom relief: Diuretics, nitrates, or digoxin

• Long-term management and improved survival: ACE inhibitors, β-blockers, aldosterone receptor blockers, or angiotensin II receptor blockers (ARBs)

All these drug classes have been studied in systolic dysfunction, but fewer have been adequately studied in diastolic dysfunction. However, ACE inhibitors, ARBs, and β-blockers are generally used to treat diastolic HF. In patients with severe diastolic dysfunction, diuretics and nitrates should be used in lower doses because these patients do not tolerate reduced BP or plasma volume well. In patients with hypertrophic cardiomyopathy (see p. 2138), digoxin is not effective and may be harmful. All patients should be given clear and explicit information about their drugs, including the importance of timely prescription renewal and adherence to therapy, how to recognize adverse effects, and when to contact their physician. Research is seeking plasma biomarkers that may predict which patients might respond best to which drug or drug combination.

Diuretics: Diuretics (see Table 208-5 on p. 2073) are given to all patients with symptomatic systolic dysfunction and current or previous volume overload; dose is adjusted to the lowest dose that stabilizes weight and relieves symptoms. Loop diuretics are preferred. Furosemide is used most often, starting at 20 to 40 mg po once/day, increased to 120 mg once/day (or 60 mg bid) if needed based on response and renal function. Bumetanide is an alternative. In refractory cases, furosemide 40 to 160 mg IV, ethacrynic acid 50 to 100 mg IV, bumetanide 0.5 to 2 mg po or 0.5 to 1.0 mg IV, or metolazone 2.5 to 10 mg po may have an additive effect. IV infusion of furosemide (5 to 10 mg/h) may be helpful in selected patients with severe edema. Loop diuretics (particularly when used with metolazone) may cause hypovolemia with hypotension, hyponatremia, hypomagnesemia, and severe hypokalemia. The dose of diuretic required acutely can usually be gradually reduced when HF improves, and the diuretic may be stopped if other drugs improve heart function and clear HF symptoms. Using larger than required doses of diuretics lowers CO, impairs renal function, causes hypokalemia, and increases mortality. Serum electrolytes are monitored, initially daily (when diuretics are given IV) and subsequently as needed, particularly after a dose increase.

A K-sparing diuretic, either spironolactone or eplerenone (which are aldosterone receptor blockers), can be added to offset the K-losing effects of higher-dose loop diuretics. Hyperkalemia may result, especially when ACE inhibitors or ARBs are also taken, so electrolytes must still be monitored, especially during a dehydrating illness that could cause renal dysfunction. These drugs may have particular benefit in chronic RV failure, in which hepatic congestion results in elevated aldosterone levels as its metabolism is reduced.

Thiazide diuretics are not normally used as a single agent unless hypertension is present but may be added to furosemide for added diuresis.

Reliable patients are taught to take additional diuretic doses as needed when weight or peripheral edema increases. They should seek medical attention promptly if weight gain persists.

Experimental ADH blockers increase water excretion and serum Na levels and may cause less hypokalemia and renal dysfunction. Their clinical role remains to be defined.

ACE inhibitors: All patients with systolic dysfunction are given oral ACE inhibitors unless contraindicated (eg, by plasma creatinine > 2.8 mg/dL [> 250 µmol/L], bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, or previous angioedema due to ACE inhibitors).

ACE inhibitors reduce production of angiotensin II and breakdown of bradykinin, mediators that affect the sympathetic nervous system, endothelial function, vascular tone, and myocardial performance. Hemodynamic effects include arterial and venous vasodilation, sustained decreases in LV filling pressure during rest and exercise, decreased systemic vascular resistance, and favorable effects on ventricular remodeling. ACE inhibitors prolong survival and reduce HF hospitalizations. For patients with atherosclerosis and a vascular disorder, these drugs reduce MI and stroke risk. For patients with diabetes, they delay onset of nephropathy. Thus, ACE inhibitors may be used in patients with diastolic dysfunction and any of these disorders.

The starting dose typically should be low (usually one fourth to one half of the target dose depending on BP and renal function); the dose is gradually adjusted upward over 8 wk as tolerated, then continued indefinitely. Usual target doses of representative drugs include enalapril 10 to 20 mg bid, lisinopril 20 to 30 mg once/day, ramipril 5 mg bid, and captopril 50 mg tid.

If the hypotensive effect (more marked in patients with hyponatremia or volume depletion) is troublesome, it can often be minimized by separating administration of other BP-lowering drugs or reducing the dose of concomitant diuretics. ACE inhibitors often cause mild to moderate reversible serum creatinine elevation due to vasodilation of the efferent glomerular arteriole. An initial 20 to 30% increase in creatinine is no reason to stop the drug but does require slower increases in dose, reduction in diuretic dose, or avoidance of NSAIDs. Because aldosterone's effect is reduced, K retention may result, especially in patients receiving K supplements. Cough occurs in 5 to 15% of patients, probably because bradykinin accumulates, but other causes of cough should also be considered. Occasionally, rash or dysgeusia occurs. Angioedema is rare but can be life threatening and is a contraindication to this class of drugs. Alternatively, ARBs can be used, although rarely cross-reactivity is reported. Both are contraindicated in pregnancy.

Serum electrolytes and renal function should be measured before an ACE inhibitor is started, at 1 mo, and after each significant increase in dose or change in clinical condition. If dehydration or poor renal function due to acute illness develops, the ACE inhibitor dose may need to be reduced or the drug may be temporarily withheld.

ARBs: These drugs are not demonstrably superior to ACE inhibitors but are less likely to cause cough and angioedema; they may be used when these adverse effects prohibit ACE inhibitor use. ACE inhibitors and ARBs are equally effective post MI; however, their equivalence is less clear in chronic HF, and the best dose is still under study. Usual oral target doses are valsartan 160 mg bid, candesartan 32 mg once/day, and losartan 50 to 100 mg once/day. Introduction, upward titration, and monitoring of ARBs and ACE inhibitors are similar. Like ACE inhibitors, ARBs can cause reversible renal dysfunction, and the dose may need to be reduced or withheld temporarily during an acute dehydrating illness.

Adding an ARB to a regimen of an ACE inhibitor, β-blocker, and diuretic should be considered for HF patients with persistent symptoms and repeated hospitalizations. Such combination therapy requires increased monitoring of BP, serum electrolytes, and renal function.

Aldosterone receptor blockers: Because aldosterone can be produced independently of the renin-angiotensin system, its adverse effects are not inhibited completely even by maximal use of ACE inhibitors and ARBs. Thus, the aldosterone receptor blockers spironolactone, 25 to 50 mg po once/day, and eplerenone, 10 mg po once/day (does not cause gynecomastia in males), can reduce mortality, including from sudden death, in patients with LVEF < 30% and severe chronic HF or acute HF

complicating acute MI. K supplements should be stopped. Serum K and creatinine should be checked every 1 to 2 wk for the first 4 to 6 wk and after dose changes; dose is lowered if K is between 5.5 and 6.0 mEq/L and stopped if K is > 6.0 mEq/L, if creatinine increases above 2.5 mg/dL (220 µmol/L), or if ECG changes of hyperkalemia are present. These drugs are usually not used in patients receiving both an ACE inhibitor and an ARB because of the high risk of hyperkalemia and renal dysfunction.

β-Blockers: β-Blockers, unless otherwise contraindicated (by asthma, 2nd- or 3rd-degree atrioventricular block, or previous intolerance), are an important addition to ACE inhibitors for chronic systolic dysfunction in most patients, including the elderly, and for diastolic dysfunction in hypertension and hypertrophic cardiomyopathy. They are best started when the patient has no evidence of pulmonary congestion. Some of these drugs improve LVEF, survival, and other major cardiovascular outcomes in patients with chronic systolic dysfunction, including those with severe symptoms. β-Blockers are particularly useful for diastolic dysfunction because they reduce heart rate, prolonging diastolic filling time, and possibly improve ventricular relaxation.

The starting dose should be low (one fourth of the target daily dose), then dose is gradually increased over 8 wk as tolerated. The acute negative inotropic effects of β-blockade may cause cardiac depression and fluid retention. In such cases, a temporary increase in diuretic dose and slower upward titration of the β-blocker dose is warranted. Tolerance may improve over time, and efforts should be made to reach target doses. Usual oral target doses are carvedilol 25 mg bid (50 mg bid for patients ≥ 85 kg), bisoprolol 10 mg once/day, and metoprolol 50 to 75 mg bid (tartrate) or 200 mg once/day (succinate extended-release). Carvedilol, a 3rd-generation nonselective β-blocker, is also a vasodilator with α-blocking and antioxidant effects; it is the preferred and most widely studied β-blocker but is more expensive in many countries. Some β-blockers (eg, bucindolol, xamoterol) do not appear beneficial and may be harmful.

During a severe, acute decompensation, β-blockers should not be started until patients are stabilized and have little evidence of fluid retention. For patients already taking a β-blocker, the dose may be temporarily reduced or, in severe decompensation, temporarily withheld but restarted and titrated again when patients are stable. For milder decompensations, the β-blocker dose should be continued with a temporary increase in diuretic dose.

After initial treatment, heart rate and myocardial O_2 consumption decrease, and stroke volume and filling pressure are unchanged. With the slower heart rate, diastolic function improves. Ventricular filling returns to a more normal pattern (increasing in early diastole), which appears less restrictive. Improved myocardial function is measurable in some patients after 6 to 12 mo but may take longer; EF and CO increase, and LV filling pressure decreases. Exercise capacity improves.

Vasodilators: Hydralazine plus isosorbide dinitrate may help patients truly intolerant of ACE inhibitors or ARBs (usually because of significant renal dysfunction), although long-term benefit of this combination is limited. In African-American patients, this combination may also provide some additional benefits when added to standard therapy. As vasodilators, these drugs improve hemodynamics, reduce valvular regurgitation, and increase exercise capacity without causing significant renal impairment. Hydralazine is started at 25 mg po qid and increased every 3 to 5 days to a target total dose of 300 mg/day, although many patients cannot tolerate > 200 mg/day because of hypotension. Isosorbide dinitrate is started at 20 mg po tid (with a 12-h nitrate-free interval) and increased to a target of 40 to 50 mg tid. Whether lower doses (frequently used in clinical practice) provide long-term benefit is unknown. In general, vasodilators have been replaced by ACE inhibitors, which are easier to use, are usually better tolerated, and have greater proven benefit.

Nitrates alone can relieve HF symptoms; patients can be taught to use sublingual nitroglycerin spray as needed for acute dyspnea and a transdermal patch for nocturnal dyspnea. Nitrates are safe, effective, and well tolerated and are particularly helpful in patients with HF and angina. Adverse effects include hypotension and headache.

Other vasodilators such as Ca channel blockers are not used to treat systolic dysfunction. Short-acting dihydropyridines (eg, nifedipine) and nondihydropyridines (eg, diltiazem, verapamil) may be deleterious. However, amlodipine and felodipine are well tolerated and may be useful for patients with HF and associated angina or hypertension. Both drugs may cause peripheral edema; rarely, amlodipine causes

pulmonary edema. Felodipine should not be taken with grapefruit juice, which significantly increases plasma levels and adverse effects by inhibiting cytochrome P-450 metabolism. In patients with diastolic dysfunction, Ca channel blockers may be used as needed to treat hypertension or ischemia or to control ventricular rate in atrial fibrillation. Verapamil may be used in hypertrophic cardiomyopathy.

Digitalis preparations: These drugs inhibit the Na-K pump (Na^+, K^+-ATPase). As a result, they cause weak positive inotropism, reduce sympathetic activity, block the atrioventricular node (slowing the ventricular rate in atrial fibrillation or prolonging the PR interval in sinus rhythm), reduce vasoconstriction, and improve renal blood flow. Digoxin is the most commonly prescribed digitalis preparation. It is excreted by the kidneys; elimination half-life is 36 to 40 h in patients with normal renal function.

Digoxin has no proven survival benefit but, when used with diuretics and an ACE inhibitor, may help control symptoms and reduce the likelihood of hospitalization. Digoxin is most effective in patients with large LV end-diastolic volumes and an S_3. Acute withdrawal of digoxin may increase the hospitalization rate and worsen symptoms. In patients with normal renal function, digoxin, 0.125 to 0.375 mg po once/day depending on age, sex, and body size, achieves full digitalization in about 1 wk (5 half-lives). More rapid digitalization can be achieved with digoxin 0.5 mg IV over 15 min followed by 0.25 mg IV at 8 and 16 h or with 0.5 mg po followed by 0.25 mg po at 8, 16, and 24 h. Prescription patterns vary widely by physician and by country, but in general, doses are lower than those used in the past, and a trough (8- to 12-h post-dose) digoxin level of 1 ng/mL is acceptable.

Toxicity is a concern, especially in patients with renal dysfunction and perhaps in women. These patients may need a lower oral dose, as may elderly patients, patients with a low lean body mass, and patients also taking amiodarone; patients > 80 kg may need a higher dose. Digoxin (and all digitalis glycosides) has a narrow therapeutic window. The most important toxic effects are life-threatening arrhythmias (eg, ventricular fibrillation, ventricular tachycardia, complete atrioventricular block). Bidirectional ventricular tachycardia, nonparoxysmal junctional tachycardia in the presence of atrial fibrillation, and hyperkalemia are serious signs of digitalis toxicity. Nausea, vomiting, anorexia, diarrhea, confusion, amblyopia, and, rarely, xerophthalmia may occur. If hypokalemia or hypomagnesemia (often due to diuretic use) is present, lower doses and serum levels can still cause toxicity. Electrolyte levels should be monitored in patients taking diuretics and digoxin, so that abnormalities can be prevented if possible; K-sparing diuretics may be helpful.

When digitalis toxicity occurs, the drug should be stopped; electrolyte abnormalities should be corrected (IV if abnormalities are severe and toxicity is acute). Patients with severe toxicity are admitted to a monitored unit, and digoxin immune Fab (ovine antidigoxin antibody fragments) is given if arrhythmias are present or if significant overingestion is accompanied by a serum K of > 5 mEq/L. This drug is also useful for glycoside toxicity due to plant ingestion. Dose is based on the steady-state serum digoxin level or total amount ingested. Ventricular arrhythmias are treated with lidocaine or phenytoin. Atrioventricular block with a slow ventricular rate may require a temporary transvenous pacemaker. Isoproterenol is contraindicated because it increases risk of ventricular arrhythmia.

Other drugs: Various positive inotropic drugs have been evaluated in HF but, except for digoxin, they increase mortality risk. Regular outpatient IV infusions of inotropes (eg, dobutamine) increase mortality and are not recommended. Drugs under study include Ca sensitizers (eg, levosimendan), cytokine blockers, endothelin blockers, matrix metalloproteinase (MMP) inhibitors, and immune modulators.

Pulmonary Edema

Pulmonary edema is acute, severe left ventricular failure with pulmonary venous hypertension and alveolar flooding. Findings are severe dyspnea, diaphoresis, wheezing, and sometimes blood-tinged frothy sputum. Diagnosis is clinical and by chest x-ray. Treatment is with O_2, IV nitrates, diuretics, and sometimes morphine and short-term IV positive inotropes, endotracheal intubation, and mechanical ventilation.

If left ventricular (LV) filling pressure increases suddenly, plasma fluid moves rapidly from pulmonary capillaries into interstitial spaces and alveoli, causing pulmonary edema. Although precipitating causes

vary by age and country, about one half of cases result from acute coronary ischemia; some from decompensation of significant underlying heart failure (HF), including diastolic dysfunction HF due to hypertension; and the rest from arrhythmia, an acute valvular disorder, or acute volume overload often due to IV fluids. Drug or dietary nonadherence is often involved.

Symptoms and Signs

Patients present with extreme dyspnea, restlessness, and anxiety with a sense of suffocation. Cough producing blood-tinged sputum, pallor, cyanosis, and marked diaphoresis are common; some patients froth at the mouth. Frank hemoptysis is uncommon. The pulse is rapid and low volume, and BP is variable. Marked hypertension indicates significant cardiac reserve; hypotension with systolic BP < 100 mg Hg is ominous. Inspiratory fine crackles are widely dispersed anteriorly and posteriorly over both lung fields. Marked wheezing (cardiac asthma) may occur. Noisy respiratory efforts often make cardiac auscultation difficult; a summation gallop—merger of 3rd (S_3) and 4th (S_4) heart sounds—may be present. Signs of right ventricular (RV) failure (eg, neck vein distention, peripheral edema) may be present.

Diagnosis

• Clinical evaluation showing severe dyspnea and pulmonary crackles

• Chest x-ray

• Sometimes serum brain natriuretic peptide (BNP) or N-terminal-pro BNP (NT-pro-BNP)

• ECG, cardiac markers, and other tests for etiology as needed

A COPD exacerbation can mimic pulmonary edema due to LV failure or even that due to biventricular failure if cor pulmonale (see below) is present. Pulmonary edema may be the presenting symptom in patients without a history of cardiac disorders, but COPD patients with such severe symptoms usually have a history of COPD, although they may be too dyspneic to relate it.

A chest x-ray, done immediately, is usually diagnostic, showing marked interstitial edema. Bedside measurement of serum BNP levels (elevated in pulmonary edema; normal in COPD exacerbation) is helpful if the diagnosis is in doubt. ECG, pulse oximetry, and blood tests (cardiac markers, electrolytes, BUN, creatinine, and, for severely ill patients, ABGs) are done. An echocardiogram may be helpful to determine the cause of the pulmonary edema (eg, MI, valvular dysfunction, hypertensive heart disease, dilated cardiomyopathy) and may influence the choice of therapies. Hypoxemia can be severe. CO_2 retention is a late, ominous sign of secondary hypoventilation.

Treatment

• O_2

• Furosemide

• Nitrates

• IV morphine

• Ventilatory assistance as needed

• Treatment of cause

Initial treatment includes 100% O_2 by nonrebreather mask; upright position; furosemide 0.5 to 1.0 mg/kg IV; nitroglycerin 0.4 mg sublingually q 5 min, followed by an IV drip at 10 to 20 µg/min, titrated upward at 10 µg/min q 5 min as needed to a maximum 300 µg/min if systolic BP is > 100 mm Hg; and morphine 1 to

5 mg IV once or twice. If hypoxia is significant, noninvasive ventilatory assistance with bilevel positive airway pressure (BiPAP) is helpful, but if CO_2 retention is present or the patient is obtunded, tracheal intubation and assisted ventilation are required.

Specific additional treatment depends on etiology:

- For acute MI or another acute coronary syndrome, thrombolysis or direct percutaneous coronary angioplasty with or without a stent
- For severe hypertension, an IV vasodilator
- For supraventricular or ventricular tachycardia, direct-current cardioversion
- For rapid atrial fibrillation, to slow the ventricular rate, an IV β-blocker, IV digoxin, or cautious use of an IV Ca channel blocker (cardioversion is preferred)

Other treatments, such as IV BNP (nesiritide) and new inotropic drugs (levosimendan), remain under study to elucidate safety profiles and efficacy. Because fluid status before onset of pulmonary edema is usually normal in patients with acute MI, diuretics are less useful than in patients with chronic HF and may precipitate hypotension. If systolic BP falls < 100 mm Hg or shock develops, IV dobutamine and an intra-aortic balloon pump (counterpulsation) may be required (see p. 2297).

Once patients are stabilized, long-term HF treatment is as described on p. 2126.

Cor Pulmonale

Cor pulmonale is right ventricular enlargement secondary to a lung disorder that causes pulmonary artery hypertension. Right ventricular failure follows. Findings include peripheral edema, neck vein distention, hepatomegaly, and a parasternal lift. Diagnosis is clinical and by echocardiography. Treatment is directed at the cause.

Cor pulmonale results from a disorder of the lung or its vasculature; it does not refer to right ventricular (RV) enlargement secondary to left ventricular (LV) failure, a congenital heart disorder (eg, ventricular septal defect), or an acquired valvular disorder. Cor pulmonale is usually chronic but may be acute and reversible. Primary pulmonary hypertension (ie, not caused by a pulmonary or cardiac disorder) is discussed elsewhere (see p. 2065).

Pathophysiology

Lung disorders cause pulmonary hypertension by several mechanisms:

- Loss of capillary beds (eg, due to bullous changes in COPD or thrombosis in pulmonary embolism)
- Vasoconstriction caused by hypoxia, hypercapnia, or both
- Increased alveolar pressure (eg, in COPD, during mechanical ventilation)
- Medial hypertrophy in arterioles (often a response to pulmonary hypertension due to other mechanisms)

Pulmonary hypertension increases afterload on the RV, resulting in a cascade of events that is similar to what occurs in LV failure, including elevated end-diastolic and central venous pressure and ventricular hypertrophy and dilation. Demands on the RV may be intensified by increased blood viscosity due to hypoxia-induced polycythemia. Rarely, RV failure affects the LV if a dysfunctional septum bulges into the LV, interfering with filling and thus causing diastolic dysfunction.

Etiology

Acute cor pulmonale has few causes. Chronic cor pulmonale is usually caused by COPD, but there are

several less common causes (see Table 211-3). In patients with COPD, an acute exacerbation or pulmonary infection may trigger RV overload. In chronic cor pulmonale, risk of venous thromboembolism is increased.

Symptoms and Signs

Initially, cor pulmonale is asymptomatic, although patients usually have significant symptoms due to the underlying lung disorder (eg, dyspnea, exertional fatigue). Later, as RV pressures increase, physical signs commonly include a left parasternal systolic lift, a loud pulmonic component of the 2nd heart sound (S_2), and murmurs of functional tricuspid and pulmonic insufficiency. Later, an RV gallop rhythm (3rd [S_3] and 4th [S_4] heart sounds) augmented during inspiration, distended jugular veins (with a dominant *a* wave unless tricuspid regurgitation is present), hepatomegaly, and lower-extremity edema may occur.

[**Table 211-3.** Causes of Cor Pulmonale]

Diagnosis

• Clinical suspicion

• Echocardiography

Cor pulmonale should be suspected in all patients with one of its causes. Chest x-rays show RV and proximal pulmonary artery enlargement with distal arterial attenuation. ECG evidence of RV hypertrophy (eg, right axis deviation, QR wave in lead V_1, and dominant R wave in leads V_1 to V_3) correlates well with degree of pulmonary hypertension. However, because pulmonary hyperinflation and bullae in COPD cause realignment of the heart, physical examination, x-rays, and ECG may be relatively insensitive. Echocardiography or radionuclide imaging is done to evaluate LV and RV function; echocardiography can assess RV systolic pressure but is often technically limited by the lung disorder. Right heart catheterization may be required for confirmation.

Treatment

• Treatment of cause

Treatment is difficult; it focuses on the cause (see elsewhere in THE MANUAL), particularly alleviation or moderation of hypoxia. Early identification and treatment are important before structural changes become irreversible.

If peripheral edema is present, diuretics may seem appropriate, but they are helpful only if LV failure and pulmonary fluid overload are also present; they may be harmful because small decreases in preload often worsen cor pulmonale. Pulmonary vasodilators (eg, hydralazine, Ca channel blockers, nitrous oxide, prostacyclin, phosphodiesterase inhibitors), although beneficial in primary pulmonary hypertension, are not effective. Bosentan, an endothelin receptor blocker, also may benefit patients with primary pulmonary hypertension, but its use is not well studied in cor pulmonale. Digoxin is effective only if patients have concomitant LV dysfunction; caution is required because patients with COPD are sensitive to digoxin's effects. Phlebotomy during hypoxic cor pulmonale has been suggested, but the benefits of decreasing blood viscosity are not likely to offset the harm of reducing O_2-carrying capacity unless significant polycythemia is present. For patients with chronic cor pulmonale, long-term anticoagulants reduce risk of venous thromboembolism.

Chapter 212. Cardiomyopathies

Introduction

A cardiomyopathy is a primary disorder of the heart muscle. It is distinct from structural cardiac disorders such as coronary artery disease, valvular disorders, and congenital heart disorders. Cardiomyopathies are divided into 3 main types: dilated, hypertrophic, and restrictive (see Fig. 212-1) based on the pathologic features. The term ischemic cardiomyopathy refers to the dilated, poorly contracting myocardium that sometimes occurs in patients with severe coronary artery disease (with or without areas of infarction). Although it does not describe a primary myocardial disorder, the term remains in common use.

Manifestations of cardiomyopathies are usually those of heart failure and vary depending on whether there is systolic dysfunction, diastolic dysfunction, or both (see p. 2119). Some cardiomyopathies may also cause chest pain, syncope, or sudden death.

Evaluation typically includes ECG and echocardiography and sometimes MRI. Some patients require endomyocardial biopsy (transvenous right ventricular or retrograde left ventricular). Other tests are done as needed to determine the cause. Treatment depends on the specific type and cause of cardiomyopathy (see Table 212-1).

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is myocardial dysfunction causing heart failure in which ventricular dilation and systolic dysfunction predominate. Symptoms include dyspnea, fatigue, and peripheral edema. Diagnosis is clinical and by chest x-ray and echocardiography. Treatment is directed at the cause; if progressive and severe, heart transplantation may be needed.

Pathophysiology

In some patients, DCM is believed to start with acute myocarditis (probably viral in most cases), followed by a variable latent phase, a phase with diffuse necrosis of myocardial myocytes (due to an autoimmune reaction to virus-altered myocytes), and chronic fibrosis. Regardless of the cause, the myocardium dilates, thins, and hypertrophies in compensation (see Fig. 212-1), often leading to functional mitral or tricuspid regurgitation and atrial dilation.

The disorder affects both ventricles in most patients, only the left ventricle (LV) in a few (unless with an ischemic etiology), and only the right ventricle (RV) rarely.

Mural thrombi frequently form once chamber dilation is significant, especially during the acute myocarditis phase. Cardiac arrhythmias often complicate the acute myocarditis and late chronic dilated phases as may atrioventricular (AV) block. Atrial fibrillation commonly occurs as the left atrium dilates.

Etiology

DCM has many known and probably many unidentified causes (see Table 212-2). The most common cause in temperate zones is diffuse coronary artery disease (CAD) with diffuse ischemic myopathy. More than 20 viruses can cause DCM; in temperate zones, coxsackievirus B is most common. In Central and South America, Chagas' disease due to *Trypanosoma cruzi* is the most common infectious cause. DCM is becoming increasingly common among patients with HIV infection. Other causes include toxoplasmosis, thyrotoxicosis, and beriberi. Many toxic substances, particularly alcohol, various organic solvents, and certain chemotherapeutic drugs (eg, doxorubicin, trastuzumab), damage the heart.

Stress and other hyperadrenergic states can trigger acute DCM that is typically reversible (as is that caused by prolonged episodes of tachycardia). An example is acute apical ballooning cardiomyopathy (takotsubo cardiomyopathy); in this disorder, only the apex of the LV is affected, causing regional wall

dysfunction and sometimes focal dilation (ballooning).

Genetic factors play a role in 20 to 35% of cases; several genes and loci have been implicated.

Symptoms and Signs

Onset is usually gradual except in acute myocarditis, acute apical ballooning cardiomyopathy, and tachyarrhythmia-induced myopathy. Symptoms depend on which ventricle is affected. LV dysfunction causes exertional dyspnea and fatigue due to elevated LV diastolic pressure and low cardiac output. RV failure causes peripheral edema and neck vein distention. Infrequently the RV is predominantly affected in younger patients, and atrial arrhythmias and sudden death due to malignant ventricular tachyarrhythmias are typical. About 25% of all patients with DCM have atypical chest pain.

[**Fig. 212-1.** Forms of cardiomyopathy.]

[**Table 212-1.** Diagnosis and Treatment of Cardiomyopathies]

Diagnosis

• Chest x-ray

• ECG

• Echocardiography

• Testing for cause as indicated

Diagnosis is by history, physical examination, and exclusion of other common causes of ventricular failure (eg, systemic hypertension, primary valvular disorders, MI—see Table 212-1). Thus, chest x-ray, ECG, and echocardiography are required. If acute symptoms or chest pain is present, serum cardiac markers are measured; although typically indicative of coronary ischemia, troponin levels can be elevated in heart failure, especially if renal function is decreased. Specific causes suspected clinically are diagnosed (see elsewhere in THE MANUAL). If no specific cause is clinically apparent, serum ferritin and iron-binding capacity and thyroid-stimulating hormone levels are measured and serologic tests for *Toxoplasma*, *T. cruzi*,

[**Table 212-2.** Causes of Dilated Cardiomyopathy]

coxsackievirus, and echovirus may be done in appropriate cases.

Chest x-ray shows cardiomegaly, usually of all chambers. Pleural effusion, particularly on the right, often accompanies increased pulmonary venous pressure and interstitial edema.

The **ECG** may show sinus tachycardia and nonspecific ST-segment depression with low voltage or inverted T waves. Sometimes pathologic Q waves are present in the precordial leads, simulating previous MI. Left bundle branch block is common.

Echocardiography shows dilated, hypokinetic cardiac chambers and rules out primary valvular disorders. Segmental wall motion abnormalities, typical of MI, can also occur in DCM because the process may be patchy. Echocardiography may also show a mural thrombus. MRI is not routinely done but may be useful when detailed imaging of myocardial structure or function is needed. In cardiomyopathy, MRI may show abnormal myocardial tissue texture.

Coronary angiography is required when the diagnosis is in doubt after noninvasive tests, particularly for patients with chest pain or several cardiovascular risk factors or for elderly patients, who are more likely to have CAD. However, nonobstructive coronary artery lesions detected by angiography may not be the cause of DCM. Either ventricle can be biopsied during catheterization, but biopsy is not usually done because the yield can be low, the disease process can be patchy, and results may not change treatment.

Prognosis

Prognosis generally is poor, although prognosis has improved with current management regimens (eg, use of β-blockers): About 20% die in the first year and then about 10%/yr thereafter; about 40 to 50% of deaths are sudden, due to a malignant arrhythmia or an embolic event. Prognosis is better if compensatory hypertrophy preserves ventricular wall thickness and is worse if ventricular walls thin markedly and the ventricle dilates.

Treatment

• Cause (if any) treated

• Measures for heart failure

• Anticoagulants in some patients

• Possibly implantable cardioverter-defibrillator, biventricular pacing, or transplantation

Treatable primary causes (eg, toxoplasmosis, hemochromatosis, thyrotoxicosis, beriberi) are corrected. Otherwise, treatment is the same as for heart failure (see p. 2126): ACE inhibitors, β-blockers, aldosterone receptor blockers, angiotensin II receptor blockers, diuretics, digoxin, and nitrates. Corticosteroids, azathioprine, and equine antithymocyte globulin are no longer used; although they may shorten the acute phase of certain inflammatory myocarditic myopathies (eg, acute postviral or sarcoid myocarditis), they do not improve long-term outcome. Antivirals are not helpful.

Because mural thrombi may form, prophylactic oral anticoagulants (see p. 2228) are often given to help prevent systemic or pulmonary emboli, and a large randomized trial is underway to test whether this approach is effective. Patients with a previous cerebrovascular embolism, those with acute severe myocarditis, and some with severe LV dilation should receive anticoagulants.

Aggressive treatment of heart failure reduces risk of arrhythmia, but significant cardiac arrhythmias may be treated with antiarrhythmic drugs. Permanent pacemakers may be required if AV block occurs during the chronic dilated phase. However, AV block during acute myocarditis often resolves, so permanent pacemakers are usually not needed. If patients have a widened QRS interval with a low LV ejection fraction and severe symptoms despite optimized medical treatment, biventricular pacing should be considered. An implantable cardioverterdefibrillator may be used to prevent sudden arrhythmia-induced death.

Because prognosis may be poor, patients with DCM may become candidates for heart transplantation. Selection criteria include absence of associated systemic disorders and psychologic disorders and high, irreversible pulmonary vascular resistance; because donor hearts are scarce, younger patients (usually < 60) are given higher priority.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a congenital or acquired disorder characterized by marked ventricular hypertrophy with diastolic dysfunction but without increased afterload (eg, from valvular aortic stenosis, coarctation of the aorta, systemic hypertension). Symptoms include dyspnea, chest pain, syncope, and sudden death. A systolic murmur, increased by Valsalva maneuver, is typically present in the hypertrophic obstructive type. Diagnosis is by echocardiography. Treatment is with β-blockers, verapamil, disopyramide, and sometimes chemical reduction or surgical removal of outflow tract obstruction.

HCM is a common cause of sudden death in young athletes (see p. 2236). It may cause unexplained syncope and may not be diagnosed before autopsy.

Etiology

Most cases of HCM are inherited. At least 50 different mutations that are inherited in an autosomally dominant pattern have been identified; spontaneous mutations are common. Perhaps 1 in 500 people is affected; phenotypic expression varies markedly.

Pathophysiology

The myocardium is abnormal with cellular and myofibrillar disarray, although this finding is not specific for HCM. In the most common form, the upper interventricular septum below the aortic valve is markedly hypertrophied and thickened, with little or no hypertrophy of the left ventricular (LV) posterior wall; this pattern is called asymmetric septal hypertrophy. During systole, the septum thickens, and sometimes the anterior leaflet of the mitral valve, already abnormally oriented because of the abnormally shaped ventricle, is sucked toward the septum by a Venturi effect of high velocity blood flow, further obstructing the outflow tract and decreasing cardiac output. The resulting disorder may be termed hypertrophic obstructive cardiomyopathy. Less commonly, midventricular hypertrophy leads to an intracavitary gradient at the papillary muscle level. In both forms, the distal LV may ultimately thin and dilate. Apical hypertrophy can also occur but does not obstruct outflow, although it may obliterate the apical portion of the LV during systole. Sometimes the hypertrophy is diffuse and symmetrical.

Contractility is grossly normal, resulting in a normal ejection fraction (EF). Later, EF is elevated because the ventricle has a small volume and empties nearly completely to maintain cardiac output.

Hypertrophy results in a stiff, noncompliant chamber (usually the LV) that resists diastolic filling, elevating end-diastolic pressure and thus increasing pulmonary venous pressure. As resistance to filling increases, cardiac output decreases, an effect worsened by any outflow tract gradient present. Because tachycardia allows less time for filling, symptoms tend to appear mainly during exercise or tachyarrhythmias.

Coronary blood flow may be impaired, causing angina pectoris, syncope, or arrhythmias in the absence of epicardial coronary artery disease (CAD). Flow may be impaired because capillary density relative to myocyte size is inadequate (capillary/myocyte imbalance) or lumen diameter of intramyocardial coronary arteries is narrowed by intimal and medial hyperplasia and hypertrophy. Also, exercise lowers peripheral vascular resistance and aortic root diastolic pressure, thus reducing coronary perfusion pressure.

In some cases, myocytes gradually die, probably because capillary/myocyte imbalance causes chronic diffuse ischemia. As myocytes die, they are replaced by diffuse fibrosis. Then, the hypertrophied ventricle with diastolic dysfunction gradually dilates and systolic dysfunction also develops.

Infective endocarditis can complicate HCM because of the mitral valve abnormality and because of rapid blood flow through the outflow tract during early systole. Atrioventricular block is sometimes a late complication.

Symptoms and Signs

Typically, symptoms appear between ages 20 and 40 and are exertional. They include dyspnea, chest pain (usually resembling typical angina—see p. 2090), palpitations, and syncope. Because systolic function is preserved, fatigability is seldom reported.

Syncope usually occurs without warning during exertion either because outflow obstruction worsens with the increased contractility or because of nonsustained ventricular or atrial arrhythmia. *Syncope is a marker of increased risk of sudden death,* which is thought to result from ventricular tachycardia or fibrillation.

BP and heart rate are usually normal, and signs of increased venous pressure are rare. When the outflow tract is obstructed, the carotid pulse has a brisk upstroke, bifid peak, and rapid downstroke. The apex beat may have a sustained thrust due to LV hypertrophy. A 4th heart sound (S_4) is often present and is associated with a forceful atrial contraction against a poorly compliant LV in late diastole.

Septal hypertrophy produces a systolic ejection-type murmur that does not radiate to the neck and may

be heard at the left sternal edge in the 3rd or 4th intercostal space. A mitral regurgitation murmur due to distortion of the mitral apparatus may be heard at the apex. When the right ventricular outflow tract is narrowed, a systolic ejection murmur is sometimes heard in the 2nd interspace at the left sternal border. The LV outflow ejection murmur of HCM can be increased by a Valsalva maneuver (which reduces venous return and LV diastolic volume), by measures to lower aortic pressure (eg, nitroglycerin), or by a postextrasystolic contraction (which increases the outflow tract pressure gradient). Handgrip increases aortic pressure, thereby reducing the murmur's intensity.

Diagnosis

• Clinical suspicion (syncope and murmur)

• Echocardiography

Diagnosis is suspected based on a typical murmur and symptoms. Unexplained syncope in young athletes should always raise suspicion. HCM must be distinguished from aortic stenosis and CAD, which cause similar symptoms. ECG and 2-dimensional echocardiography (the best noninvasive confirmatory test) are done. Chest x-ray is often taken but is usually normal because the ventricles are not dilated (although the left atrium may be enlarged). Patients with syncope or sustained arrhythmias should be evaluated as inpatients. Exercise testing and 24-h ambulatory monitoring may be helpful for patients considered at high risk, although identifying such patients is difficult.

The ECG usually shows voltage criteria for LV hypertrophy (eg, S wave in lead V_1 plus R wave in lead V_5 or V_6 > 35 mm). Very deep septal Q waves in leads I, aVL, V_5, and V_6 are often present with asymmetric septal hypertrophy; HCM sometimes produces a QRS complex in V_1 and V_2, simulating previous septal infarction. T waves are usually abnormal; the most common finding is deep symmetric T-wave inversion in leads I, aVL, V_5, and V_6. ST-segment depression in the same leads is common (particularly in the apical obliterative form). The P wave is often broad and notched in leads II, III, and aVF, with a biphasic P wave in leads V_1 and V_2, indicating left atrial hypertrophy. Incidence of preexcitation phenomenon of the Wolff-Parkinson-White syndrome type, which may cause palpitations, is increased. Bundle branch block is common.

Two-dimensional Doppler echocardiography can differentiate the forms of cardiomyopathy (see Fig. 212-1) and quantify the degree of outflow tract obstruction, including pressure gradient and area of the stenotic segment. These measurements are particularly useful for monitoring the effect of medical or surgical treatment. Midsystolic closure of the aortic valve sometimes occurs when outflow tract obstruction is severe.

Cardiac catheterization is usually done only when invasive therapy is considered. Usually, no significant stenoses are present in the coronary arteries, but elderly patients may have coexisting CAD.

Prognosis

Overall, annual mortality is 1 to 3% for adults but is higher for children. Mortality rate is inversely proportional to the age at which symptoms appear and is highest in patients who have frequent nonsustained ventricular tachycardia or syncope or have been resuscitated after sudden cardiac arrest. Prognosis is worse for young patients with a family history of sudden death and for patients > 45 yr with angina or exertional dyspnea. Death is usually sudden, and sudden death is the most common sequelae; chronic heart failure occurs less often. Genetic counseling is appropriate for patients with asymmetric septal hypertrophy, which appears to accelerate during puberty.

Treatment

• β-Blockers

• Rate-limiting and negative inotropic Ca channel blockers

• Avoidance of nitrates, diuretics, and ACE inhibitors

• Possibly implantable cardioverter-defibrillator and sometimes surgery or ablative procedures

Treatment is directed primarily at abnormal diastolic compliance. β-Blockers and rate-limiting Ca channel blockers with a lower arterial dilation capacity (usually verapamil), alone or combined, are the mainstays. By decreasing myocardial contractility, these drugs dilate the heart. By slowing the heart rate, they prolong the diastolic filling period. Both effects decrease outflow obstruction, thus improving ventricular diastolic function. In severe cases, disopyramide may be added for its negative inotropic effect.

Drugs that reduce preload (eg, nitrates, diuretics, ACE inhibitors, angiotensin II receptor blockers) decrease chamber size and worsen symptoms and signs. Vasodilators increase the outflow tract gradient and cause a reflex tachycardia that further worsens ventricular diastolic function. Inotropic drugs (eg, digitalis glycosides, catecholamines) worsen outflow tract obstruction, do not relieve the high end-diastolic pressure, and may induce arrhythmias.

If syncope or sudden cardiac arrest has occurred or if ventricular arrhythmia is confirmed by ECG or 24-h ambulatory monitoring, an implantable cardioverter-defibrillator or antiarrhythmics should be considered. Competitive sports should be avoided because many sudden deaths occur during increased exertion.

Treatment of the dilated congestive phase of HCM is the same as that of dilated cardiomyopathy with predominant systolic dysfunction.

If septal hypertrophy and outflow tract obstruction cause significant symptoms despite medical therapy, surgery is needed. Catheter alcohol ablation is variably effective but is becoming more widely used; surgical septal myotomy or myomectomy reduces symptoms more reliably but does not prolong life.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is characterized by noncompliant ventricular walls that resist diastolic filling; one or both ventricles, most commonly the left, may be affected. Symptoms include fatigue and exertional dyspnea. Diagnosis is by echocardiography and cardiac catheterization. Treatment is often unsatisfactory and is best directed at the cause. Surgery is sometimes useful.

RCM is the least prevalent form of cardiomyopathy. It is classified as

• Nonobliterative (myocardial infiltration by an abnormal substance)

• Obliterative (fibrosis of the endocardium and subendocardium)

Either type may be diffuse or nondiffuse (when the disorder affects only one ventricle or part of one ventricle unevenly).

Etiology

The cause is usually unknown; identified causes are listed in Table 212-3. Some disorders that cause RCM also affect other tissues (eg, amyloidosis, hemochromatosis). Some myocardial infiltrative disorders also affect other cardiac tissue. Rarely, amyloidosis affects coronary arteries. Sarcoidosis and Fabry's disease may also affect nodal conduction tissue. Loffler's syndrome (a subcategory of hypereosinophilic syndrome with primary cardiac involvement), which occurs in the tropics, begins as an acute arteritis with eosinophilia, followed by thrombus formation on the endocardium, chordae, and atrioventricular (AV) valves, progressing to fibrosis. Endocardial fibroelastosis, which occurs in temperate zones, affects only the left ventricle.

Pathophysiology

Endocardial thickening or myocardial infiltration (sometimes with death of myocytes, papillary muscle

infiltration, compensatory myocardial hypertrophy, and fibrosis) may occur in one, typically the left, or both ventricles. As a result, the mitral or tricuspid valves may malfunction, leading to regurgitation. Functional AV valve regurgitation may result from myocardial infiltration or endocardial thickening. If nodal and conduction tissues are affected, the sinoatrial node malfunctions, sometimes causing various grades of AV block.

[**Table 212-3.** Causes of Restrictive Cardiomyopathy]

The main hemodynamic consequence is diastolic dysfunction (see p. 2120) with a rigid, noncompliant ventricle, impaired diastolic filling, and high filling pressure, leading to pulmonary venous hypertension. Systolic function may deteriorate if compensatory hypertrophy of infiltrated or fibrosed ventricles is inadequate. Mural thrombi can form, resulting in systemic emboli.

Symptoms and Signs

Symptoms are exertional dyspnea, orthopnea, and, when the right ventricle is affected, peripheral edema. Fatigue results from a fixed cardiac output due to resistance to ventricular filling. Atrial and ventricular arrhythmias and AV block are common; angina and syncope are uncommon. Symptoms and signs closely mimic those of constrictive pericarditis (see p. 2203).

Physical examination detects a quiet precordium, a low-volume and rapid carotid pulse, pulmonary crackles, and pronounced neck vein distention with a rapid *y* descent (see Fig. 206-1 on p. 2020). A 4th heart sound (S_4) is almost always present; a 3rd heart sound (S_3) may occur and must be differentiated from the precordial knock of constrictive pericarditis. In some cases, a murmur of functional mitral or tricuspid regurgitation results because myocardial or endocardial infiltration or fibrosis changes chordae or ventricular geometry. Pulsus paradoxus does not occur.

Diagnosis

• Echocardiography

• Testing for cause

ECG, chest x-ray, and echocardiography are required. The ECG is usually nonspecifically abnormal, showing ST-segment and T-wave abnormalities and sometimes low voltage. Pathologic Q waves, not due to previous MI, sometimes occur. Left ventricular hypertrophy due to compensatory myocardial hypertrophy sometimes occurs. On chest x-ray, the heart size is often normal or small but can be enlarged in late-stage amyloidosis or hemochromatosis.

Echocardiography shows normal systolic function. Common findings include dilated atria and myocardial hypertrophy. RCM due to amyloidosis has an unusually bright echo pattern from the myocardium. Echocardiography helps differentiate constrictive pericarditis with its thickened pericardium, but paradoxical septal motion can occur in either disorder. If the diagnosis is still in doubt, CT may be more sensitive in showing whether the pericardium is normal, and MRI can show abnormal myocardial texture in disorders with myocardial infiltration (eg, by amyloid or iron).

Cardiac catheterization and myocardial biopsy are not often necessary. If done, catheterization detects high atrial pressure in RCM, with a prominent *y* descent and an early diastolic dip followed by a high diastolic plateau in the ventricular pressure curve. In contrast to constrictive pericarditis findings, diastolic pressure is usually a few mm Hg higher in the left ventricle than in the right. Angiography detects normal-sized ventricular cavities with normal or decreased systolic shortening. AV valve regurgitation may be present. Biopsy can detect endocardial fibrosis and thickening, myocardial infiltration by iron or amyloid, and chronic myocardial fibrosis. Coronary angiography is normal, except when amyloidosis affects epicardial coronary arteries. Occasionally, cardiac catheterization is not diagnostic, and rarely, thoracotomy is required to explore the pericardium.

Tests for the most common causes of RCM (eg, rectal biopsy for amyloidosis, iron tests or liver biopsy for

hemochromatosis) should be done.

Prognosis

Prognosis is poor (see Table 212-1) because the diagnosis is often made at a late stage. No treatment is available for most patients; symptomatic, supportive care can be provided.

Treatment

• Cause treated

• Diuretics considered

Diuretics may be used for patients with edema or pulmonary vascular congestion but must be given cautiously because they can lower preload; the noncompliant ventricles depend on preload to maintain cardiac output. Digitalis does little to alter hemodynamic abnormalities and may cause serious arrhythmias in cardiomyopathy due to amyloidosis, in which extreme digitalis sensitivity is common. If heart rate is elevated, β-blockers or rate-limiting Ca channel blockers may be used cautiously in low doses. Afterload reducers (eg, nitrates) may cause profound hypotension and usually are not useful.

If the diagnosis is made at an early stage, specific treatment of hemochromatosis, sarcoidosis, and Loffler's syndrome may help.

Transplantation is not recommended because the disorder may recur in the transplanted heart.

Chapter 213. Arrhythmias and Conduction Disorders

Introduction

The normal heart beats in a regular, coordinated way because electrical impulses generated and spread by myocytes with unique electrical properties trigger a sequence of organized myocardial contractions. Arrhythmias and conduction disorders are caused by abnormalities in the generation or conduction of these electrical impulses or both.

Any heart disorder, including congenital abnormalities of structure (eg, accessory atrioventricular connection) or function (eg, hereditary ion channelopathies), can disturb rhythm. Systemic factors that can cause or contribute to a rhythm disturbance include electrolyte abnormalities (particularly low K or Mg), hypoxia, hormonal imbalances (eg, hypothyroidism, hyperthyroidism), and drugs and toxins (eg, alcohol, caffeine).

Anatomy

At the junction of the superior vena cava and high lateral right atrium is a cluster of cells that generates the initial electrical impulse of each normal heart beat, called the sinoatrial (SA) or sinus node. Electrical discharge of these pacemaker cells stimulates adjacent cells, leading to stimulation of successive regions of the heart in an orderly sequence. Impulses are transmitted through the atria to the atrioventricular (AV) node via preferentially conducting internodal tracts and unspecialized atrial myocytes. The AV node is located on the right side of the interatrial septum. It has a slow conduction velocity and thus delays impulse transmission. AV nodal transmission time is heart-rate-dependent and is modulated by autonomic tone and circulating catecholamines to maximize cardiac output at any given atrial rate.

The atria are electrically insulated from the ventricles by the annulus fibrosus except in the anteroseptal region. There, the bundle of His, the continuation of the AV node, enters the top of the interventricular septum, where it bifurcates into the left and right bundle branches, which terminate in Purkinje fibers. The right bundle branch conducts impulses to the anterior and apical endocardial regions of the right ventricle. The left bundle branch fans out over the left side of the interventricular septum. Its anterior portion (left anterior hemifascicle) and its posterior portion (left posterior hemifascicle) stimulate the left side of the interventricular septum, which is the first part of the ventricles to be electrically activated. Thus, the interventricular septum depolarizes left to right, followed by near-simultaneous activation of both ventricles from the endocardial surface through the ventricular walls to the epicardial surface.

Physiology

An understanding of normal cardiac physiology is essential before rhythm disturbances can be understood.

Electrophysiology: The passage of ions across the myocyte cell membrane is regulated through specific ion channels that cause cyclical depolarization and repolarization of the cell, called an action potential. The action potential of a working myocyte begins when the cell is depolarized from its diastolic -90 mV transmembrane potential to a potential of about -50 mV. At this threshold potential, voltage-dependent fast Na channels open, causing rapid depolarization mediated by Na influx down its steep concentration gradient. The fast Na channel is rapidly inactivated and Na influx stops, but other time- and voltage-dependent ion channels open, allowing Ca to enter through slow Ca channels (a depolarizing event) and K to leave through K channels (a repolarizing event). At first, these 2 processes are balanced, maintaining a positive transmembrane potential and prolonging the plateau phase of the action potential. During this phase, Ca entering the cell is responsible for electromechanical coupling and myocyte contraction. Eventually, Ca influx ceases, and K efflux increases, causing rapid repolarization of the cell back to the -90 mV resting transmembrane potential. While depolarized, the cell is resistant (refractory) to a subsequent depolarizing event. Initially, a subsequent depolarization is not possible (absolute refractory period), and after partial but incomplete repolarization, a subsequent depolarization is possible but occurs slowly (relative refractory period).

There are 2 general types of cardiac tissue:

• Fast-channel tissues

• Slow-channel tissues

Fast-channel tissues (working atrial and ventricular myocytes, His-Purkinje system) have a high density of fast Na channels and action potentials characterized by little or no spontaneous diastolic depolarization (and thus very slow rates of pacemaker activity), very rapid initial depolarization rates (and thus rapid conduction velocity), and loss of refractoriness coincident with repolarization (and thus short refractory periods and the ability to conduct repetitive impulses at high frequencies).

Slow-channel tissues (SA and AV nodes) have a low density of fast Na channels and action potentials characterized by more rapid spontaneous diastolic depolarization (and thus more rapid rates of pacemaker activity), slow initial depolarization rates (and thus slow conduction velocity), and loss of refractoriness that is delayed after repolarization (and thus long refractory periods and the inability to conduct repetitive impulses at high frequencies).

Normally, the SA node has the most rapid rate of spontaneous diastolic depolarization, so its cells produce spontaneous action potentials at a higher frequency than other tissues. Thus, the SA node is the dominant automatic tissue (pacemaker) in a normal heart. If the SA node does not produce impulses, tissue with the next highest automaticity rate, typically the AV node, functions as the pacemaker. Sympathetic stimulation increases the discharge frequency of pacemaker tissue, and parasympathetic stimulation decreases it.

Normal rhythm: The resting sinus heart rate in adults is usually 60 to 100 beats/min. Slower rates (sinus bradycardia) occur in young people, particularly athletes (see p. 2238), and during sleep. Faster rates (sinus tachycardia) occur with exercise, illness, or emotion through sympathetic neural and circulating catecholamine drive. Normally, a marked diurnal variation in heart rate occurs, with lowest rates just before early morning awakening. A slight increase in rate during inspiration with a decrease in rate during expiration (respiratory sinus arrhythmia) is also normal; it is mediated by oscillations in vagal tone and is particularly common among healthy young people. The oscillations lessen but do not entirely disappear with age. Absolute regularity of the sinus rhythm rate is pathologic and occurs in patients with autonomic denervation (eg, in advanced diabetes) or with severe heart failure.

Most cardiac electrical activity is represented on the ECG (see Fig. 207-1 on p. 2050), although SA node, AV node, and His-Purkinje depolarization does not involve enough tissue to be detected. The P wave represents atrial depolarization. The QRS complex represents ventricular depolarization, and the T wave represents ventricular repolarization.

The PR interval (from the beginning of the P wave to the beginning of the QRS complex) is the time from the beginning of atrial activation to the beginning of ventricular activation. Much of this interval reflects slowing of impulse transmission in the AV node. The R-R interval (time between 2 QRS complexes) represents the ventricular rate. The QT interval (from the beginning of the QRS complex to the end of the T wave) represents the duration of ventricular depolarization. Normal values for the QT interval are slightly longer in women; they are also longer with a slower heart rate. The QT interval is corrected (QTc) for influence of heart rate. The most common formula (all intervals in sec) is:

$$QTc = \frac{QT}{\sqrt{RR}}$$

Pathophysiology

Rhythm disturbances result from abnormalities of impulse formation, impulse conduction, or both. Bradyarrhythmias result from decreased intrinsic pacemaker function or blocks in conduction, principally within the AV node or the His-Purkinje system. Most tachyarrhythmias are caused by reentry; some result from enhanced normal automaticity or from abnormal mechanisms of automaticity.

Reentry is the circular propagation of an impulse around 2 interconnected pathways with different

conduction characteristics and refractory periods (see Fig. 213-1).

Under certain conditions, typically precipitated by a premature beat, reentry can produce continuous circulation of an activation wavefront, causing a tachyarrhythmia (see Fig. 213-2). Normally, reentry is prevented by tissue refractoriness following stimulation. However, 3 conditions favor reentry: shortening of tissue refractoriness (eg, by sympathetic stimulation), lengthening of the conduction pathway (eg, by hypertrophy or abnormal conduction pathways), and slowing of impulse conduction (eg, by ischemia).

Symptoms and Signs

Arrhythmia and conduction disturbances may be asymptomatic or cause palpitations (sensation of skipped beats or rapid or forceful beats—see p. 2038), symptoms of hemo-dynamic compromise (eg, dyspnea, chest discomfort, presyncope, syncope), or cardiac arrest. Occasionally, polyuria results from release of atrial natriuretic peptide during prolonged supraventricular tachycardias (SVTs).

Palpation of pulse and cardiac auscultation can determine ventricular rate and its regularity or irregularity. Examination of the jugular venous pulse waves may help in the diagnosis of AV blocks and atrial tachyarrhythmias. For example, in complete AV block, the atria intermittently contract when the AV valves are closed, producing large *a* (cannon) waves in the jugular venous pulse (see p. 2020). Other physical findings of arrhythmias are few.

Diagnosis

• ECG

History and physical examination may detect an arrhythmia and suggest possible causes, but diagnosis requires a 12-lead ECG or, less reliably, a rhythm strip, preferably obtained during symptoms to establish the relationship between symptoms and rhythm.

The ECG is approached systematically; calipers measure intervals and identify subtle irregularities. The key diagnostic features are rate of atrial activation, rate and regularity of ventricular activation, and the relationship between the two. Irregular activation signals are classified as regularly irregular or irregularly irregular (no detectible pattern). Regular irregularity is intermittent irregularity in an otherwise regular rhythm (eg, premature beats) or a predictable pattern of irregularity (eg, recurrent relationships between groups of beats).

A narrow QRS complex (< 0.12 sec) indicates a supraventricular origin (above the His

[**Fig. 213-1.** Mechanism of typical reentry.]

bundle bifurcation). A wide QRS complex (≥ 0.12 sec) indicates a ventricular origin (below the His bundle bifurcation) or a supraventricular rhythm conducted with an intraventricular conduction defect or with ventricular preexcitation in the Wolff-Parkinson-White syndrome.

Bradyarrhythmias: ECG diagnosis of bradyarrhythmias depends on the presence or absence of P waves, morphology of the P waves, and the relationship between P waves and QRS complexes.

A bradyarrhythmia with no relationship between P waves and QRS complexes indicates AV dissociation; the escape rhythm can be junctional (narrow QRS complex) or ventricular (wide QRS complex).

A regular QRS rhythm with a 1:1 relationship between P waves and QRS complexes indicates absence of AV block. P waves preceding QRS complexes indicate sinus bradycardia (if P waves are normal) or sinus arrest with an escape atrial bradycardia (if P waves are abnormal). P waves after QRS complexes indicate sinus arrest with a junctional or ventricular escape rhythm and retrograde atrial activation. A ventricular escape rhythm results in a wide QRS complex; a junctional escape

[**Fig. 213-2.** Initiation of an atrioventricular nodal reentry tachycardia.]

rhythm usually has a narrow QRS (or a wide QRS with bundle branch block or preexcitation).

When the QRS rhythm is irregular, P waves usually outnumber QRS complexes; some P waves produce QRS complexes, but some do not (indicating 2nd-degree AV block—see p. 2163). An irregular QRS rhythm with a 1:1 relationship between P waves and the following QRS complexes usually indicates sinus arrhythmia with gradual acceleration and deceleration of the sinus rate (if P waves are normal).

Pauses in an otherwise regular QRS rhythm may be caused by blocked P waves (an abnormal P wave can usually be discerned just after the preceding T wave or distorting the morphology of the preceding T wave), sinus arrest, or sinus exit block (see p. 2161), as well as by 2nd-degree AV block.

Tachyarrhythmias: Tachyarrhythmias may be divided into 4 groups, defined by being visibly regular vs irregular and by having a narrow vs wide QRS complex.

Irregular, narrow QRS complex tachyarrhythmias include atrial fibrillation (AF), atrial flutter or true atrial tachycardia with variable AV conduction, and multifocal atrial tachycardia. Differentiation is based on atrial ECG signals, which are best seen in the longer pauses between QRS complexes. Atrial ECG signals that are continuous, irregular in timing and morphology, and very rapid (> 300/min) without discrete P waves indicate AF. Discrete P waves that vary from beat to beat with at least 3 different morphologies suggest multifocal atrial tachycardia. Regular, discrete, uniform atrial signals without intervening isoelectric periods suggest atrial flutter.

Irregular, wide QRS complex tachyarrhythmias include the above 4 atrial tachyarrhythmias, conducted with either bundle branch block or ventricular preexcitation, and polymorphic ventricular tachycardia (VT). Differentiation is based on atrial ECG signals and the presence in polymorphic VT of a very rapid rate (> 250/min).

Regular, narrow QRS complex tachyarrhythmias include sinus tachycardia, atrial flutter or true atrial tachycardia with a consistent AV conduction ratio, and paroxysmal SVTs (AV nodal reentrant SVT, orthodromic reciprocating AV tachycardia in the presence of an accessory AV connection, and SA nodal reentrant SVT). Vagal maneuvers or pharmacologic AV nodal blockade can help distinguish among these tachycardias. With these maneuvers, sinus tachycardia is not terminated, but it slows or AV block develops, disclosing normal P waves. Similarly, atrial flutter and true atrial tachycardia are usually not terminated, but AV block discloses flutter waves or abnormal P waves. The most common forms of paroxysmal SVT (AV nodal reentry and orthodromic reciprocating tachycardia) must terminate if AV block occurs.

Regular, wide QRS complex tachyarrhythmias include those listed for a regular, narrow QRS complex tachyarrhythmia, each with bundle branch block or ventricular pre-excitation, and monomorphic VT. Vagal maneuvers can help distinguish among them. ECG criteria to distinguish between VT and SVT with an intraventricular conduction defect have been proposed (see Table 213-1). When in doubt, the rhythm is assumed to be VT because some drugs for SVTs can worsen the clinical state if the rhythm is VT; however, the reverse is not true.

Treatment

• Treatment of cause

• Sometimes antiarrhythmic drugs, implantable cardioverter-defibrillators, and pacemakers

The need for treatment varies; it is guided by symptoms and risks of the arrhythmia. Asymptomatic arrhythmias without serious risks do not require treatment even if they

[**Table 213-1.** Modified Brugada Criteria for Ventricular Tachycardia]

worsen. Symptomatic arrhythmias may require treatment to improve quality of life. Potentially life-

threatening arrhythmias require treatment.

Treatment is directed at causes. If necessary, direct antiarrhythmic therapy, including anti-arrhythmic drugs, cardioversion-defibrillation, pacemakers, or a combination, is used. Patients with arrhythmias that have caused or are likely to cause symptoms of hemodynamic compromise may have to be restricted from driving until response to treatment has been assessed.

Drugs for Arrhythmias

Most antiarrhythmic drugs are grouped into 4 main classes (Vaughan Williams classification) based on their dominant cellular electrophysiologic effect (see Table 213-2). Digoxin and adenosine are not included in the Vaughan Williams classification. Digoxin shortens atrial and ventricular refractory periods and is vagotonic, thereby prolonging AV nodal conduction and AV nodal refractory periods. Adenosine slows or blocks AV nodal conduction and can terminate tachyarrhythmias that rely upon AV nodal conduction for their perpetuation.

Class I: Na channel blockers (membrane-stabilizing drugs) block fast Na channels, slowing conduction in fast-channel tissues (working atrial and ventricular myocytes, His-Purkinje system). In the ECG, this effect may be reflected as widening of the P wave, widening of the QRS complex, prolongation of the PR interval, or a combination.

Class I drugs are subdivided based on the kinetics of the Na channel effects. Class Ib drugs have fast kinetics, class Ic drugs have slow kinetics, and class Ia drugs have intermediate kinetics. The kinetics of Na channel blockade determine the heart rates at which their electrophysiologic effects become manifest. Because class Ib drugs have fast kinetics, they express their electrophysiologic effects only at fast heart rates. Thus, an ECG obtained during normal rhythm at normal rates usually shows no evidence of fast-channel tissue conduction slowing. Class Ib drugs are not very potent antiarrhythmics and have minimal effects on atrial tissue. Because class Ic drugs have slow kinetics, they express their electrophysiologic effects at all heart rates. Thus, an ECG obtained during normal rhythm at normal heart rates usually shows fast-channel tissue conduction slowing. Class Ic drugs are more potent antiarrhythmics. Because class Ia drugs have intermediate kinetics, their fast-channel tissue conduction slowing effects may or may not be evident on an ECG obtained during normal rhythm at normal rates. Class Ia drugs also block repolarizing K channels, prolonging the refractory periods of fast-channel tissues. On the ECG, this effect is reflected as QT-interval prolongation even at normal rates. Class Ib drugs and class Ic drugs do not block K channels directly.

The primary indications are SVTs for class Ia and Ic drugs and VTs for all class I drugs. The most worrisome adverse effect is proarrhythmia, a drug-related arrhythmia worse than the arrhythmia being treated. Class Ia drugs may cause torsades de pointes VT; class Ia and class Ic drugs may organize and slow atrial tachyarrhythmias enough to permit 1:1 AV conduction with marked acceleration of the ventricular response rate. All class I drugs may worsen VTs. They also tend to depress ventricular contractility. Because these adverse effects are more likely to occur in patients with a structural heart disorder, class I drugs are not generally recommended for such patients. Thus, these drugs are usually used only in patients who do not have a structural heart disorder or in patients who have a structural heart disorder but who have no other therapeutic alternatives.

Class II: Class II drugs are β-blockers, which affect predominantly slow-channel tissues (SA and AV nodes), where they decrease rate of automaticity, slow conduction velocity, and prolong refractoriness. Thus, heart rate is slowed, the PR interval is lengthened, and the AV node transmits rapid atrial depolarizations at a lower frequency. Class II drugs are used primarily to treat SVTs, including sinus tachycardia, AV nodal reentry, AF, and atrial flutter. These drugs are also used to treat VTs to raise the threshold for ventricular fibrillation (VF) and reduce the ventricular proarrhythmic effects of β-adrenoceptor stimulation. β-Blockers are generally well tolerated; adverse effects include lassitude, sleep disturbance, and GI upset. These drugs are contraindicated in patients with asthma.

Class III: Class III drugs are primarily K channel blockers, which prolong action potential duration and refractoriness in slow-and fast-channel tissues. Thus, the capacity of all cardiac tissues to transmit impulses at high frequencies is reduced, but conduction velocity is not significantly affected. Because the

action potential is prolonged, rate of automaticity is reduced. The predominant effect on the ECG is QT-interval prolongation. These drugs are used to treat SVTs and VTs. Class III drugs have a risk of ventricular

[**Table 213-2.** Antiarrhythmic Drugs (Vaughan Williams Classification)]

proarrhythmia, particularly torsades de pointes VT.

Class IV: Class IV drugs are the nondihydropyridine Ca channel blockers, which depress Ca-dependent action potentials in slow channel tissues and thus decrease the rate of automaticity, slow conduction velocity, and prolong refractoriness. Heart rate is slowed, the PR interval is lengthened, and the AV node transmits rapid atrial depolarizations at a lower frequency. These drugs are used primarily to treat SVTs.

Devices and Procedures

Direct-current (DC) cardioversiondefibrillation: A transthoracic DC shock of sufficient magnitude depolarizes the entire myocardium, rendering the entire heart momentarily refractory to repeat depolarization. Thereafter, the most rapid intrinsic pacemaker, usually the SA node, reassumes control of heart rhythm. Thus, DC cardioversion-defibrillation very effectively terminates tachyarrhythmias that result from reentry. However, it is less effective for terminating tachyarrhythmias that result from automaticity because the return rhythm is likely to be the automatic tachyarrhythmia. For tachyarrhythmias other than VF, the DC shock must be synchronized to the QRS complex (called DC cardioversion) because a shock that falls during the vulnerable period (near the peak of the T wave) can induce VF. In VF, synchronization of a shock to the QRS complex is neither necessary nor possible. A DC shock applied without synchronization to a QRS complex is DC defibrillation.

When DC cardioversion is elective, patients should fast for 6 to 8 h to avoid the possibility of aspiration. Because the procedure is frightening and painful, brief general anesthesia or IV analgesia and sedation (eg, fentanyl 1 µg/kg, then midazolam 1 to 2 mg q 2 min to a maximum of 5 mg) is necessary. Equipment and personnel to maintain the airways must be present.

The electrodes (pads or paddles) used for cardioversion may be placed anteroposteriorly (along the left sternal border over the 3rd and 4th intercostal spaces and in the left infrascapular region) or anterolaterally (between the clavicle and the 2nd intercostal space along the right sternal border and over the 5th and 6th intercostal spaces at the apex of the heart). After synchronization to the QRS complex is confirmed on the monitor, a shock is given. The most appropriate energy level varies with the tachyarrhythmia being treated. Cardioversion efficacy increases with use of biphasic shocks, in which the current polarity is reversed part way through the shock waveform. Complications are usually minor and include atrial and ventricular premature beats and muscle soreness. Less commonly, but more likely if patients have marginal left ventricular function or multiple shocks are used, cardioversion precipitates myocyte damage and electromechanical dissociation.

DC cardioversion-defibrillation can also be applied directly to the heart during a thoracotomy or through use of an intracardiac electrode catheter; then, much lower energy levels are required.

Pacemakers: Pacemakers sense electrical events and respond when necessary by delivering electrical stimuli to the heart. Permanent pacemaker leads are placed via thoracotomy or transvenously, but some temporary emergency pacemaker leads can be placed on the chest wall.

Indications are numerous (see Table 213-3) but generally involve symptomatic bradycardia or high-grade AV block. Some tachyarrhythmias may be terminated by over-drive pacing with a brief period of pacing at a faster rate; the pacemaker is then slowed to the desired rate. Nevertheless, ventricular tachyarrhythmias are better treated with devices that can cardiovert and defibrillate as well as pace (implantable cardioverter defibrillators).

Types of pacemakers are designated by 3 to 5 letters (see Table 213-4), representing which cardiac chambers are paced, which chambers are sensed, how the

pacemaker responds to a sensed event (inhibits or triggers pacing), whether it can increase heart rate during exercise (rate-modulating), and whether pacing is multisite (in both atria, both ventricles, or more than one pacing lead in a single chamber). For example, a VVIR pacemaker paces (V) and senses (V) events in the ventricle, inhibits pacing in response to sensed event (I), and can increase its rate during exercise (R).

VVI and DDD pacemakers are the devices most commonly used. They offer equivalent survival benefits. Compared with VVI pacemakers, physiologic pacemakers (AAI, DDD, VDD) appear to reduce risk of AF and heart failure and slightly improve quality of life.

Advances in pacemaker design include lower-energy circuitry, new battery designs, and corticosteroid-eluting leads (which reduce pacing threshold), all of which increase pacemaker longevity. Mode switching refers to an automatic change in the mode of pacing in response to sensed events (eg, from DDDR to VVIR during AF).

Pacemakers may malfunction by oversensing or undersensing events, failing to pace or

[Table 213-3. Indications for Permanent Pacemakers]

[Table 213-4. Pacemaker Codes]

capture, or pacing at an abnormal rate. Tachycardias are an especially common complication. Rate-modulating pacemakers may increase stimuli in response to vibration, muscle activity, or voltage induced by magnetic fields during MRI. In pacemaker-mediated tachycardia, a normally functioning dual-chamber pacemaker senses a ventricular premature or paced beat transmitted to the atrium through the AV node or a retrograde-conducting accessory pathway, which triggers ventricular stimulation in a rapid, repeating cycle.

Additional complications associated with normally functioning devices include crosstalk inhibition, in which sensing of the atrial pacing impulse by the ventricular channel of a dual-chamber pacemaker leads to inhibition of ventricular pacing, and pacemaker syndrome, in which AV asynchrony induced by ventricular pacing causes fluctuating, vague cerebral (eg, light-headedness), cervical (eg, neck pulsations), or respiratory (eg, dyspnea) symptoms. Pacemaker syndrome is managed by restoring AV synchrony by atrial pacing (AAI), single-lead atrial sensing ventricular pacing (VDD), or dual-chamber pacing (DDD), most commonly the latter.

Environmental interference comes from electromagnetic sources such as surgical electrocautery and MRI, although MRI may be safe when the pacemaker generator and leads are not inside the magnet. Cellular telephones and electronic security devices are a potential source of interference; telephones should not be placed close to the device but are not a problem when used normally for talking. Walking through metal detectors does not cause pacemaker malfunction as long as patients do not linger.

Complications during implantation are uncommon but may include myocardial perforation, bleeding, and pneumothorax. Postoperative complications include infection, lead migration, and impulse generator migration.

Implantable cardioverter-defibrillators (ICDs): ICDs cardiovert or defibrillate the heart in response to VT or VF. Contemporary tiered-therapy ICDs also provide antibradycardia pacing and antitachycardia pacing (to terminate responsive atrial or ventricular tachycardias) and store intracardiac electrograms. ICDs are implanted subcutaneously or subpectorally, with electrodes inserted transvenously into the right ventricle and sometimes also the right atrium. A biventricular ICD has a left ventricular epicardial lead placed.

ICDs are the preferred treatment for patients who have had an episode of VF or hemodynamically significant VT not due to reversible or transient conditions (eg, electrolyte disturbance, antiarrhythmic drug proarrhythmia, acute MI). ICDs may also be indicated for patients with VT or VF inducible during an electrophysiologic study and for patients with idiopathic or ischemic cardiomyopathy, a left ventricular ejection fraction of < 35%, and a high risk of VT or VF. Other indications are less clear (see

Table 213-5).

Because ICDs treat rather than prevent VT or VF, patients prone to these arrhythmias may require an ICD and antiarrhythmic drugs to reduce the number of episodes and need for uncomfortable shocks; this approach also prolongs the life of the ICD.

Impulse generators for ICDs typically last about 5 yr. ICDs may malfunction by delivering inappropriate pacing or shocks in response to sinus rhythm or SVTs or by not delivering appropriate pacing or shocks when needed. Causes include lead or impulse generator migration, undersensing and an

[**Table 213-5.** Indications for Implantable Cardioverter-Defibrillators in Ventricular Tachycardia and Ventricular Fibrillation]

increase in pacing threshold due to epicardial fibrosis at the site of prior shocks, and battery depletion.

In patients who report that the ICD has discharged but that no associated symptoms of syncope, dyspnea, chest pain or persistent palpitations occurred, follow up with the electro-physiologist within the week is appropriate. The ICD can then be electronically interrogated to determine the reason for discharge. If such associated symptoms were present, or the patient received multiple shocks, emergency department referral is indicated to look for a treatable cause (eg, coronary ischemia, electrolyte abnormality) or device malfunction.

Radiofrequency (RF) ablation: If a tachyarrhythmia depends on a specific pathway or ectopic site of automaticity, the site can be ablated by low-voltage, high-frequency (300 to 750 MHz) electrical energy, applied through an electrode catheter. This energy heats and necroses an area < 1 cm in diameter and up to 1 cm deep. Before energy can be applied, the target site or sites must be mapped during an electrophysiologic study (see p. 2058).

Success rate is > 90% for reentrant tachycardias (via the AV node or an accessory pathway), focal atrial tachycardia and flutter, and focal idiopathic VTs (right ventricular outflow tract, left septal, or bundle branch reentrant VT). Because AF often originates or is maintained by an arrhythmogenic site in the pulmonary veins, this site can be ablated directly or, more commonly, electrically isolated by ablations at the pulmonary vein-left atrial junction or in the left atrium. Alternatively, in patients with refractory AF and rapid ventricular rates, the AV node may be ablated after permanent pacemaker implantation. RF ablation is sometimes successful in patients with VT refractory to drugs and with ischemic heart disease.

RF ablation is safe; mortality is < 1/2000. Complications include valvular damage, pulmonary vein stenosis or occlusion (if used to treat atrial fibrillation), stroke or other embolism, cardiac perforation, tamponade (1%), and unintended AV node ablation.

Surgery: Surgery to remove a focus of a tachyarrhythmia is becoming less necessary as the less invasive RF ablation techniques evolve. But it is still indicated when an arrhythmia is refractory to RF ablation or when another indication requires a cardiac surgical procedure, most commonly when patients with AF require valve replacement or repair or when patients with VT require revascularization or resection of a left ventricular aneurysm.

Sinus Node Dysfunction

(Sick Sinus Syndrome)

Sinus node dysfunction refers to a number of conditions causing physiologically inappropriate atrial rates. Symptoms may be minimal or include weakness, palpitations, and syncope. Diagnosis is by ECG. Symptomatic patients require a pacemaker.

Sinus node dysfunction includes inappropriate sinus bradycardia, alternating bradycardia and atrial tachyarrhythmias (bradycardiatachycardia syndrome), sinus pause or arrest, and sinoatrial (SA) exit block. Sinus node dysfunction affects mainly the elderly, especially those with another cardiac disorder or diabetes.

Sinus pause is temporary cessation of sinus node activity, seen on ECG as disappearance of P waves for seconds to minutes. The pause usually triggers escape activity in lower pacemakers (eg, atrial or junctional), preserving heart rate and function, but long pauses cause dizziness and syncope.

In SA exit block, the SA node depolarizes, but conduction of impulses to atrial tissue is impaired. In 1st-degree SA block, the SA node impulse is merely slowed, and ECG is normal. In type I 2nd-degree SA (SA Wenckebach) block, impulse conduction slows before blocking, seen on the ECG as a P-P interval that decreases progressively until the P wave drops altogether, creating a pause and the appearance of grouped beats; the duration of the pause is less than 2 P-P cycles. In type II 2nd-degree SA block, conduction of impulses is blocked without slowing beforehand, producing a pause that is a multiple (usually twice) of the P-P interval and the appearance of grouped beats. In 3rd-degree SA block, conduction is blocked; P waves are absent, giving the appearance of sinus arrest.

The most common cause of sinus node dysfunction is idiopathic SA node fibrosis, which may be accompanied by degeneration of lower elements of the conducting system. Other causes include drugs, excessive vagal tone, and many ischemic, inflammatory, and infiltrative disorders.

Symptoms and Signs

Many patients are asymptomatic, but depending on the heart rate, all the symptoms of bradycardias and tachycardias can occur (see p. 2144).

Diagnosis

A slow, irregular pulse suggests the diagnosis, which is confirmed by ECG, rhythm strip, or continuous 24-h ECG recording. Some patients present with atrial fibrillation (AF), and the underlying sinus node dysfunction manifests only after conversion to sinus rhythm.

Prognosis

Prognosis is mixed; without treatment, mortality is about 2%/yr, primarily resulting from an underlying structural heart disorder. Each year, about 5% of patients develop AF with its risks of heart failure and stroke.

Treatment

• Pacemaker

Treatment is pacemaker implantation. Risk of AF is greatly reduced when a physiologic (atrial or atrial and ventricular) pacemaker rather than a ventricular pacemaker is used. Newer dual chamber pacemakers that minimize ventricular pacing may further reduce risk of AF. Antiarrhythmic drugs may prevent paroxysmal tachyarrhythmias after pacemaker insertion. Theophylline and hydralazine are options to increase heart rate in healthy, younger patients who have bradycardia without syncope.

Ectopic Supraventricular Rhythms

Various rhythms result from supraventricular foci (usually in the atria); many are asymptomatic and require no treatment.

Atrial premature beats: Atrial premature beats (APBs), or premature atrial contractions (PACs), are common episodic impulses. They may occur in normal hearts with or without precipitating factors (eg, coffee, tea, alcohol, pseudoephedrine) or may be a sign of a cardiopulmonary disorder. They are common in patients with COPD. They occasionally cause palpitations. Diagnosis is by ECG (see Fig. 213-3).

APBs may be normally, aberrantly, or not conducted and are usually followed by a non-compensatory pause. Aberrantly conducted APBs (usually with right bundle branch block morphology) must be

distinguished from premature beats of ventricular origin.

Atrial escape beats are ectopic atrial beats that emerge after long sinus pauses or sinus arrest. They may be single or multiple; escape beats from a single focus may produce a continuous rhythm (called ectopic atrial rhythm). Heart rate is typically slower, P wave morphology is typically different, and PR interval is slightly shorter than in sinus rhythm.

Wandering atrial pacemaker: Wandering atrial pacemaker (multifocal atrial rhythm) is an irregularly irregular rhythm caused by the random discharge of multiple ectopic atrial foci. By definition, heart rate is ≤ 100 beats/min. This arrhythmia most typically occurs in patients who have a pulmonary disorder and are hypoxic, acidotic, theophylline-intoxicated, or a combination. On ECG, P-wave morphology differs from beat to beat, and there are ≥ 3 distinct P-wave morphologies. The presence of P waves distinguishes wandering atrial pacemaker from atrial fibrillation.

Multifocal atrial tachycardia: Multifocal atrial tachycardia (chaotic atrial tachycardia) is an irregularly irregular rhythm caused by the random discharge of multiple ectopic atrial foci. By definition, heart rate is > 100 beats/min. Except for the rate, features are the same as those of wandering atrial pacemaker. Symptoms, when they occur, are those of rapid tachycardia. Treatment is directed at the underlying pulmonary disorder.

Atrial tachycardia: Atrial tachycardia is a regular rhythm caused by the consistent, rapid atrial activation from a single atrial focus. Heart rate is usually 150 to 200 beats/min; however, with a very rapid atrial rate, nodal dysfunction, or digitalis toxicity, atrioventricular (AV) block may be present, and ventricular rate may be slower. Mechanisms include enhanced atrial automaticity and intra-atrial reentry. Atrial tachycardia is the least common form (5%) of supraventricular tachycardia and

[**Fig. 213-3.** Atrial premature beat (APB).]

[
Fig. 213-4. True atrial tachycardia.]

usually occurs in patients with a structural heart disorder. Other causes include atrial irritation (eg, pericarditis), drugs (eg, digoxin), alcohol, and toxic gas inhalation. Symptoms are those of other tachycardias. Diagnosis is by ECG; P waves, which differ in morphology from normal sinus P waves, precede QRS complexes but may be hidden within the preceding T wave (see Fig. 213-4).

Vagal maneuvers may be used to slow the heart rate, allowing visualization of P waves when they are hidden, but these maneuvers do not usually terminate the arrhythmia (demonstrating that the AV node is not an obligate part of the arrhythmia circuit). Treatment involves managing causes and slowing ventricular response rate using a β-blocker or Ca channel blocker. An episode may be terminated by direct-current cardioversion. Pharmacologic approaches to termination and prevention of atrial tachycardia include antiarrhythmic drugs in class Ia, Ic, or III. If these noninvasive measures are ineffective, alternatives include overdrive pacing and radiofrequency ablation.

Nonparoxysmal junctional tachycardia: Nonparoxysmal junctional tachycardia is caused by abnormal automaticity in the AV node or adjacent tissue, which typically follows open heart surgery, acute inferior MI, myocarditis, or digitalis toxicity. Heart rate is 60 to 120 beats/min; thus, symptoms are usually absent. ECG shows regular, normal-appearing QRS complexes without identifiable P waves or with retrograde P waves (inverted in the inferior leads) that occur shortly before (< 0.1 sec) or after the QRS complex. The rhythm is distinguished from paroxysmal supraventricular tachycardia by the lower heart rate and gradual onset and offset. Treatment is directed at causes.

Atrioventricular Block

Atrioventricular (AV) block is partial or complete interruption of impulse transmission from the atria to the ventricles. The most common cause is idiopathic fibrosis and sclerosis of the conduction system. Diagnosis is by ECG; symptoms and treatment depend on degree of block, but treatment, when necessary, usually involves pacing.

AV block is caused by idiopathic fibrosis and sclerosis of the conduction system in about 50% of patients and by ischemic heart disease in 40%; the rest are due to drugs (eg, β-blockers, Ca channel blockers, digoxin, amiodarone); increased vagal tone; valvulopathy; or congenital heart, genetic, or other disorders.

First-degree AV block: All normal P waves are followed by QRS complexes, but the PR interval is longer than normal (> 0.20 sec—see Fig. 213-5).

First-degree AV block may be physiologic in younger patients with high vagal tone and in well-trained athletes. First-degree AV block is rarely symptomatic and no treatment is required, but further investigation may be indicated when it accompanies another heart disorder or appears to be caused by drugs.

Second-degree AV block: Some normal P waves are followed by QRS complexes, but some are not. Three types exist:

In Mobitz type I 2nd-degree AV block, the PR interval progressively lengthens with each beat until the atrial impulse is not conducted and the QRS complex is dropped (Wenckebach phenomenon); AV nodal conduction resumes with the next beat, and the sequence is repeated (see Fig. 213-6).

Mobitz type I 2nd-degree AV block may be physiologic in younger and more athletic

[**Fig. 213-5.** Atrioventricular block.]

[**Fig. 213-6.** Mobitz type I 2nd-degree atrioventricular block.]

[
Fig. 213-7. Mobitz type II 2nd-degree atrioventricular block.]

patients. The block occurs at the AV node in about 75% of patients with a narrow QRS complex and at infranodal sites (His bundle, bundle branches, or fascicles) in the rest. If the block becomes complete, a reliable junctional escape rhythm typically develops. Treatment is therefore unnecessary unless the block causes symptomatic bradycardia and transient or reversible causes have been excluded. Treatment is pacemaker insertion, which may also benefit asymptomatic patients with Mobitz type I 2nd-degree AV block at infranodal sites detected by electrophysiologic studies done for other reasons.

In Mobitz type II 2nd-degree AV block, the PR interval remains constant. Beats are intermittently nonconducted and QRS complexes dropped, usually in a repeating cycle of every 3rd (3:1 block) or 4th (4:1 block) P wave (see Fig. 213-7).

Mobitz type II 2nd-degree AV block is always pathologic; the block occurs at the His bundle in 20% of patients and in the bundle branches in the rest. Patients may be asymptomatic or experience light-headedness, presyncope, and syncope, depending on the ratio of conducted to blocked beats. Patients are at risk of developing symptomatic high-grade or complete AV block, in which the escape rhythm is likely to be ventricular and thus too slow and unreliable to maintain systemic perfusion; therefore, a pacemaker is indicated.

In high-grade 2nd-degree AV block, every 2nd (or more) P wave is blocked (see Fig. 213-8).

The distinction between Mobitz type I and Mobitz type II block is difficult to make because

[**Fig. 213-8.** Second-degree atrioventricular block (high grade).]

[
Fig. 213-9. Third-degree atrioventricular block.]

2 P waves are never conducted in a row. Risk of complete AV block is difficult to predict, and a pacemaker is indicated.

Patients with any form of 2nd-degree AV block and a structural heart disorder should be considered candidates for permanent pacing unless there is a transient or reversible cause.

Third-degree AV block: Heart block is complete (see Fig. 213-9).

There is no electrical communication between the atria and ventricles and no relationship between P waves and QRS complexes (AV dissociation). Cardiac function is maintained by an escape junctional or ventricular pacemaker. Escape rhythms originating above the bifurcation of the His bundle produce narrow QRS complexes, relatively rapid (> 40 beats/min) and reliable heart rates, and mild symptoms (eg, fatigue, postural light-headedness, effort intolerance). Escape rhythms originating below the bifurcation produce wider QRS complexes, slower and unreliable heart rates, and more severe symptoms (eg, presyncope, syncope, heart failure). Signs include those of AV dissociation, such as cannon *a* waves, BP fluctuations, and changes in loudness of the 1st heart sound (S_1). Risk of asystole-related syncope and sudden death is greater if low escape rhythms are present.

Most patients require a pacemaker (see Table 213-4). If the block is caused by anti-arrhythmic drugs, stopping the drug may be effective, although temporary pacing may be needed. A block caused by acute inferior MI usually reflects AV nodal dysfunction and may respond to atropine or resolve spontaneously over several days. A block caused by anterior MI usually reflects extensive myocardial necrosis involving the His-Purkinje system and requires immediate transvenous pacemaker insertion with interim external pacing as necessary. Spontaneous resolution may occur but warrants evaluation of AV nodal and infranodal conduction (eg, electrophysiologic study, exercise testing, 24-h ECG).

Most patients with congenital 3rd-degree AV block have a junctional escape rhythm that maintains a reasonable rate, but they require a permanent pacemaker before they reach middle age. Less commonly, patients with congenital AV block have a slow escape rhythm and require a permanent pacemaker at a young age, perhaps even during infancy.

Atrial Fibrillation

Atrial fibrillation (AF) is a rapid, irregularly irregular atrial rhythm. Symptoms include palpitations and sometimes weakness, dyspnea, and presyncope. Atrial thrombi often form, causing a significant risk of embolic stroke. Diagnosis is by ECG. Treatment involves rate control with drugs, prevention of thromboembolism with anticoagulation, and sometimes conversion to sinus rhythm by drugs or cardioversion.

AF has been attributed to multiple wave-lets with chaotic reentry within the atria. However, in many cases, firing of an ectopic focus within venous structures adjacent to the atria (usually the pulmonary veins) is responsible for initiation and perhaps maintenance of AF. In AF, the atria do not contract, and the atrioventricular (AV) conduction system is bombarded with many electrical stimuli, causing inconsistent impulse transmission and an irregularly irregular ventricular rate, which is usually in the tachycardia rate range.

AF is one of the most common arrhythmias, affecting about 2.3 million adults in the US. Men and whites are more likely to have AF than women and blacks. Prevalence increases with age; almost 10% of people > 80 yr are affected. It tends to occur in patients with a heart disorder, sometimes precipitating heart failure because cardiac output decreases. The absent atrial contractions predispose to thrombus formation; annual risk of cerebrovascular embolic events is about 7%. Risk of stroke is higher in patients with a rheumatic valvular disorder, hyperthyroidism, hypertension, diabetes, left ventricular systolic dysfunction, or previous thromboembolic events. Systemic emboli can also cause malfunction or necrosis of other organs (eg, heart, kidneys, GI tract, eyes) or a limb.

Etiology

The most common causes are hypertension, ischemic or nonischemic cardiomyopathy, mitral or tricuspid

valvular disorders, hyperthyroidism, and binge alcohol drinking (holiday heart). Less common causes include pulmonary embolism, atrial septal and other congenital heart defects, COPD, myocarditis, and pericarditis. AF without an identifiable cause in patients < 60 yr is called lone AF.

Classification

Acute AF is new-onset AF lasting < 48 h.

Paroxysmal AF is recurrent AF that typically lasts < 48 h and that converts spontaneously to normal sinus rhythm.

Persistent AF lasts > 1 wk and requires treatment to convert to normal sinus rhythm.

Permanent AF cannot be converted to sinus rhythm. The longer AF is present, the less likely is spontaneous conversion and the more difficult is cardioversion because of atrial remodeling (rapid atrial rate-induced changes in atrial electrophysiology that are dominated by a decrease in atrial refractoriness and may also include increase in spatial dispersion of atrial refractoriness slowed atrial conduction velocity, or both).

Symptoms and Signs

AF is often asymptomatic, but many patients have palpitations, vague chest discomfort, or symptoms of heart failure (eg, weakness, light-headedness, dyspnea), particularly when the ventricular rate is very rapid (often 140 to 160 beats/min). Patients may also present with symptoms and signs of acute stroke or of other organ damage due to systemic emboli.

The pulse is irregularly irregular with loss of *a* waves in the jugular venous pulse. A pulse deficit (the apical ventricular rate is faster than the rate palpated at the wrist) may be present because left ventricular stroke volume is not always sufficient to produce a peripheral pressure wave at fast ventricular rates.

Diagnosis

• ECG

• Echocardiography

• Thyroid function tests

Diagnosis is by ECG. Findings include absence of P waves, f (fibrillatory) waves between QRS complexes (irregular in timing, irregular in morphology; baseline undulations at rates > 300/min not always apparent in all leads), and irregularly irregular R-R intervals (see Fig. 213-10).

Other irregular rhythms may resemble AF on ECG but can be distinguished by the presence of discrete P or flutter waves, which can sometimes be made more visible with vagal maneuvers. Muscle tremor or electrical interference may resemble f waves, but the underlying rhythm is regular. AF may also cause a phenomenon that mimics ventricular extrasystoles or ventricular tachycardia (Ashman phenomenon). This phenomenon typically occurs when a short R-R interval follows a long R-R interval; the longer interval lengthens the refractory period of the infra-Hisian conduction system, and subsequent QRS complexes are conducted aberrantly, typically with right bundle branch morphology.

Echocardiography and thyroid function tests are important in the initial evaluation. Echocardiography is done to assess structural heart defects (eg, left atrial enlargement, left ventricular wall motion abnormalities suggesting past or present ischemia, valvular disorders, cardiomyopathy) and to identify additional risk factors for stroke (eg, atrial blood stasis or thrombus, complex aortic plaque). Atrial thrombi are more likely in the atrial appendages, where they are best detected by transesophageal rather than transthoracic echocardiography.

Treatment

• Rate control with drugs or AV node radio-frequency ablation

• Sometimes rhythm control with cardioversion, drugs, or AF substrate ablation

• Prevention of thromboembolism

If a significant underlying disorder is suspected, patients with new-onset AF may benefit from hospitalization, but those with recurrent episodes do not require hospitalization unless

[**Fig. 213-10.** Atrial fibrillation.]

other symptoms suggest the need for it. Once causes have been managed, treatment of AF focuses on ventricular rate control, rhythm control, and prevention of thromboembolism.

Ventricular rate control: Patients with AF of any duration require rate control (typically to < 80 beats/min at rest) to control symptoms and prevent tachycardia-induced cardiomyopathy.

For acute paroxysms of rapid rate (eg, 140 to 160 beats/min), IV AV node blockers are used (for doses, see Table 213-2). CAUTION*: AV node blockers should not be used in patients with Wolff-Parkinson-White syndrome when an accessory AV pathway is involved (indicated by wide QRS duration); these drugs increase frequency of conduction via the bypass tract, possibly causing ventricular fibrillation.* β-Blockers (eg, metoprolol, esmolol) are preferred if excess catecholamines are suspected (eg, in thyroid disorders, exercise-triggered cases). Nondihydropyridine Ca channel blockers (eg, verapamil, diltiazem) are also effective. Digoxin is the least effective but may be preferred if heart failure is present. These drugs may be used orally for long-term rate control. When β-blockers, nondihydropyridine Ca channel blockers, and digoxin—separately or in combination—are ineffective, amiodarone may be required.

Rhythm control: In patients with heart failure or other hemodynamic compromise directly attributable to new-onset AF, restoration of normal sinus rhythm is indicated to improve cardiac output. In other cases, conversion of AF to normal sinus rhythm is optimal, but the antiarrhythmic drugs that are capable of doing so (class Ia, Ic, III) have a risk of adverse effects and may increase mortality. Conversion to sinus rhythm does not necessarily eliminate the need for chronic anticoagulation.

For acute conversion, synchronized cardioversion or drugs can be used. Before conversion is attempted, the ventricular rate should be controlled to < 120 beats/min, and, if AF has been present > 48 h, patients should be given anticoagulants (conversion, regardless of method used, increases risk of thromboembolism). Anticoagulation with warfarin (see p. 2168) should be maintained for > 3 wk before conversion when possible and continued indefinitely because AF may recur. Alternatively, the patient can be anticoagulated with heparin, and transesophageal echocardiography done; if there is no intra-atrial clot, cardioversion can be done immediately.

Synchronized cardioversion (100 joules, followed by 200 and 360 joules as needed) converts AF to normal sinus rhythm in 75 to 90% of patients, although recurrence rate is high. Efficacy and maintenance of sinus rhythm after the procedure is improved with use of class Ia, Ic, or III drugs 24 to 48 h before the procedure. Cardioversion is more effective in patients with shorter duration of AF, lone AF, or AF with a reversible cause; it is less effective when the left atrium is enlarged (> 5 cm), atrial appendage flow is low, or a significant underlying structural heart disorder is present.

Drugs for conversion to sinus rhythm include class Ia (procainamide, quinidine, disopyramide), Ic (flecainide, propafenone), and III (amiodarone, dofetilide, ibutilide, sotalol) antiarrhythmics (see Table 213-2). All are effective in about 50 to 60% of patients, but adverse effects differ. These drugs should not be used until rate has been controlled by a βblocker or nondihydropyridine Ca channel blocker. These converting drugs are also used for long-term maintenance of sinus rhythm (with or without previous cardioversion). Choice depends on patient tolerance. However, for paroxysmal AF that occurs only or almost only at rest or during sleep when vagal tone is high, drugs with vagolytic effects (eg, disopyramide) may be particularly effective. Exercise-induced AF may be better prevented with a β-

blocker.

For certain patients with recurrent paroxysmal AF who also can identify its onset by symptoms, some clinicians provide a single oral loading dose of flecainide (300 mg for patients ≥ 70 kg otherwise 200 mg) or propafenone (600 mg for patients ≥ 70 kg, otherwise 450 mg) that patients carry and self-administer when palpitations develop ("pillin-the-pocket" approach). This approach must be limited to patients who have no sinoatrial or AV node dysfunction, bundle branch block, QT prolongation, Brugada syndrome, or structural heart disease. Its hazard (estimated at 1%) is the possibility of converting AF to a slowish atrial flutter that conducts 1:1 in the 200 to 240 beat/min range.

ACE inhibitors, angiotensin II receptor blockers, and aldosterone blockers may attenuate the myocardial fibrosis that provides a substrate for AF in patients with heart failure, but the role of these drugs in routine AF treatment has yet to be defined.

Ablation procedures: For patients who do not respond to or cannot take rate-controlling drugs, radiofrequency ablation of the AV node may be done to produce complete heart block; insertion of a permanent pacemaker is then necessary. Ablation of only one AV nodal pathway (AV node modification) reduces the number of atrial impulses reaching the ventricles and eliminates the need for a pacemaker, but this approach is considered less effective than complete ablation and is rarely used.

Ablation procedures that isolate the pulmonary veins from the left atrium can prevent AF without producing AV block. In comparison to other ablation procedures, pulmonary vein isolation has a lower success rate (60 to 80%) and a higher complication rate (1 to 5%). Accordingly, this procedure is often reserved for the best candidates—younger patients with drug-resistant AF who have no significant structural heart disease.

Prevention of thromboembolism: Measures to prevent thromboembolism are necessary at the time of cardioversion and during long-term treatment of most patients.

Warfarin titrated to an INR of 2 to 3 should be given for ≥ 3 wk before elective cardioversion of lone AF present for > 48 h and continued for 4 wk after successful cardioversion. Anticoagulants should be continued indefinitely for patients with recurrent paroxysmal, persistent, or permanent AF in the presence of risk factors for thromboembolism. Healthy patients with a single episode of lone AF are given anticoagulants for 4 wk.

Aspirin is less effective than warfarin but is used for patients with no risk factors for thromboembolism or those with contraindications to warfarin. Direct thrombin inhibitors that do not require INR monitoring may be equivalent to warfarin for stroke prevention in high-risk patients, but they require further study before being recommended for mainstream use. The left atrial appendage may be surgically ligated or closed with a transcatheter device when warfarin and antiplatelet drugs are absolutely contraindicated.

Atrial Flutter

Atrial flutter is a rapid regular atrial rhythm due to an atrial macro-reentrant circuit. Symptoms are mainly palpitations. Atrial thrombi may form and embolize. Diagnosis is by ECG. Treatment involves rate control with drugs, prevention of thromboembolism with anticoagulants, and often conversion to sinus rhythm with drugs or cardioversion.

Atrial flutter is much less common than atrial fibrillation, but its causes and hemodynamic consequences are similar. Many patients with atrial flutter also have periods of atrial fibrillation.

Classical atrial flutter is due to a large reentrant circuit involving most of the right atrium. The atria depolarize at a rate of 250 to 350/min (typically 300/min). Because the atrioventricular (AV) node cannot usually conduct at this rate, typically half of the impulses get through (2:1 block), resulting in a regular ventricular rate of 150 beats/min. Sometimes the block varies from moment to moment, causing an irregular ventricular rhythm. Less commonly, a fixed 3:1, 4:1, or 5:1 block may be present.

The probability of a thromboembolic event, once considered rare in atrial flutter, is now thought to be

about half of that in atrial fibrillation.

Symptoms and Signs

Symptoms depend primarily on ventricular rate and the nature of any underlying heart disorder. If ventricular rate is < 120 beats/min and regular, there are likely to be few or no symptoms. Faster rates and variable AV conduction usually cause palpitations, and decreased cardiac output may cause symptoms of hemodynamic compromise (eg, chest discomfort, dyspnea, weakness, syncope). Close inspection of the jugular venous pulse reveals flutter *a* waves.

Diagnosis

• ECG

The diagnosis is by ECG, which shows continuous and regular atrial activation with a sawtooth pattern, most obvious in leads II, III, and aVF (see Fig. 213-11).

Carotid sinus massage can increase AV block and better expose the typical flutter waves. A similar response may follow pharmacologic AV nodal blockade (eg, with adenosine), but such therapy does not terminate atrial flutter.

Treatment

• Rate control with drugs

• Rhythm control with cardioversion, drugs, or ablation

• Prevention of thromboembolism

As for atrial fibrillation, treatment focuses on ventricular rate control, rhythm control, and prevention of thromboembolism. However, pharmacologic rate control is more difficult to achieve in atrial flutter than in atrial fibrillation. Thus for most patients, electrical conversion (using synchronized cardioversion or overdrive pacing) is the treatment of choice for an initial episode and is mandatory with 1:1 AV conduction or hemodynamic compromise. Typically, low-energy (50 joules) conversion is effective. Anticoagulation, as in atrial fibrillation, is necessary before cardioversion.

If drugs are used to restore sinus rhythm, rate must first be controlled with β-blockers or nondihydropyridine Ca channel blockers (eg, verapamil, diltiazem). Many of the antiarrhythmics that can restore sinus rhythm (especially class Ia and Ic) can slow atrial flutter, shorten AV nodal refractoriness (by their vagolytic effects), or do both enough to allow 1:1 conduction with paradoxical increase in ventricular rate and hemodynamic compromise. These drugs may be used for long-term maintenance as required to prevent recurrence.

An antitachycardia pacing system is an alternative to long-term use of antiarrhythmics in selected patients. Also, ablation procedures designed to interrupt the atrial reentrant circuit may effectively prevent atrial flutter, particularly classic atrial flutter.

Patients with chronic or recurrent atrial flutter require warfarin (to maintain an INR of 2 to 3) or aspirin therapy long-term. The choice between the 2 therapies is based on the same considerations as for atrial fibrillation.

[**Fig. 213-11.** Atrial flutter with variable atrioventricular block.]

Reentrant Supraventricular Tachycardias

Reentrant supraventricular tachycardias involve reentrant pathways with a component above the bifurcation of the His bundle. Patients have sudden episodes of palpitations that begin and

terminate abruptly; some have dyspnea or chest discomfort. Diagnosis is clinical and by ECG. Treatment is with vagotonic maneuvers and, if they are ineffective, with IV adenosine or nondihydropyridine Ca channel blockers for narrow QRS rhythms, procainamide or amiodarone for wide QRS rhythms, or synchronized cardioversion for all cases.

Pathophysiology

The reentry pathway (see Fig. 213-1) in supraventricular tachycardia (SVT) is within the atrioventricular (AV) node in about 50%, involves an accessory bypass tract in 40%, and is within the atria or sinoatrial (SA) node in 10%.

AV nodal reentrant tachycardia occurs most often in otherwise healthy patients. It is most commonly triggered by an atrial premature beat.

Accessory pathway reentrant tachycardia involves tracts of conducting tissue that partially or totally bypass normal AV connections (bypass tracts). They run most commonly from the atria directly to the ventricles and less commonly from the atrium to a portion of the conduction system or from a portion of the conduction system to the ventricle. They can be triggered by atrial premature beats or ventricular premature beats.

Wolff-Parkinson-White (WPW) syndrome: WPW (preexcitation) syndrome is the most common accessory pathway SVT, occurring in about 1 to 3/1000 people. WPW syndrome is mainly idiopathic, although it is more common among patients with hypertrophic or other forms of cardiomyopathy, transposition of the great vessels, or Epstein's anomaly.

In classic (or manifest) WPW syndrome, antegrade conduction occurs over both the accessory pathway and the normal conducting system during sinus rhythm. The accessory pathway, being faster, depolarizes some of the ventricle early, resulting in a short PR interval and a slurred upstroke to the QRS complex (delta wave—see
Fig. 213-12).

The delta wave prolongs QRS duration to > 0.1 sec, although the overall configuration, apart from the delta wave, may appear normal. Depending on the orientation of the delta wave, a pseudoinfarction pattern Q-wave may be present. Because the early depolarized parts of the ventricle also repolarize early, the T-wave vector may be abnormal.

In concealed WPW syndrome, the accessory pathway does not conduct in an antegrade direction; consequently, the above ECG abnormalities do not appear. However, it conducts in a retrograde direction and thus can participate in reentrant tachycardia.

In the most common form of reentrant tachycardia (called orthodromic reciprocating tachycardia), the circuit uses the normal AV conduction pathway to activate the ventricles, returning to the atrium via the accessory AV connection. The resultant QRS complex is thus narrow (unless bundle branch block

[**Fig. 213-12.** Classic Wolff-Parkinson-White (WPW) syndrome.]

coexists) and without a delta wave. Orthodromic reciprocating tachycardia is typically a short RP tachycardia with the retrograde P wave in the ST segment.

Rarely, the reentrant circuit revolves in the opposite direction, from the atrium to the ventricle via the accessory AV connection, and returns from the ventricle in the retrograde direction up the normal AV conduction system (called antidromic reciprocating tachycardia). The QRS complex is wide because the ventricles are activated abnormally. In patients with 2 accessory AV connections (not uncommon), a reciprocating tachycardia using one accessory connection in the antegrade direction and the other in the retrograde direction may occur.

Tachycardias in WPW syndrome may begin as or degenerate into atrial fibrillation (AF), which can be very dangerous (see p. 2172). Enlarged atria due to hypertrophic and other forms of cardiomyopathy makes

patients with WPW syndrome more prone to AF.

Symptoms and Signs

Most patients present during young adulthood or middle age. They typically have episodes of sudden-onset, sudden-offset, rapid, regular palpitations often associated with symptoms of hemodynamic compromise (eg, dyspnea, chest discomfort, light-headedness). Attacks may last only a few seconds or persist for several hours (rarely, > 12 h).

Infants present with episodic breathlessness, lethargy, feeding problems, or rapid precordial pulsations. If the episode of tachycardia is protracted, they may present with heart failure.

Examination is usually unremarkable except for a heart rate of 160 to 240 beats/min.

Diagnosis

• ECG

Diagnosis is by ECG showing rapid, regular tachycardia. Previous tracings, if available, are reviewed for signs of manifest WPW syndrome.

P waves vary. In most cases of AV node re-entry, retrograde P waves are in the terminal portion of the QRS complex (often producing a pseudo-R′ deflection in lead V_1); about one third occur just after the QRS complex, and very few occur before. P waves always follow the QRS complex in orthodromic reciprocating tachycardia of WPW syndrome.

QRS complex is narrow except with coexisting bundle branch block, antidromic tachycardia, or dual accessory connection reciprocating tachycardia. Wide-complex tachycardia must be distinguished from ventricular tachycardia (see Table 213-5 and Figs. 213-12 and 213-13).

Treatment

• Vagotonic maneuvers

• Adenosine

• Verapamil or diltiazem if narrow QRS complex

• For frequent recurrence, radiofrequency ablation

Many episodes stop spontaneously before treatment. Vagotonic maneuvers (eg, Valsalva maneuver, unilateral carotid sinus massage, ice water facial immersion, swallowing of ice-cold water), particularly if used early, may terminate the tachyarrhythmia; some patients use these maneuvers at home.

If these maneuvers are ineffective and the QRS complex is narrow (indicating orthodromic conduction), AV node blockers are used;

[**Fig. 213-13.** Narrow QRS tachycardia: Orthodromic reciprocating tachycardia using an accessory pathway in Wolff-Parkinson-White syndrome.]

blocking conduction through the AV node for one beat interrupts the reentrant cycle. Adenosine is the first choice. Dose is 6 mg by rapid IV bolus (0.05 to 0.1 mg/kg in children), followed by a 20-mL saline bolus. If this dosage is ineffective, 2 subsequent 12-mg doses are given q 5 min. Adenosine sometimes causes a brief (2- to 3-sec) period of cardiac standstill, which may distress patient and physician. Verapamil 5 mg IV or diltiazem 0.25 to 0.35 mg/kg IV are alternatives.

For a regular, wide QRS complex tachycardia known to be an antidromic reciprocating tachycardia not

involving double accessory pathways (which must be identified by the history; they cannot be established acutely), AV nodal blockers may also be effective. However, if the mechanism of the tachycardia is unknown, ventricular tachycardia has not been excluded, and AV nodal blockers should be avoided because they may worsen ventricular tachycardias. In such cases (or those in which drugs are ineffective), IV procainamide or amiodarone can be used. Alternatively, synchronized cardioversion with 50 joules (0.5 to 2 joules/kg for children) is quick and safe and may be preferred to these more toxic drugs.

When episodes of AV nodal reentrant tachycardia are frequent or bothersome, options include long-term antiarrhythmics or transvenous catheter radiofrequency ablation. Generally, ablation is recommended, but if it is not acceptable, drug prophylaxis usually begins with digoxin and proceeds, as required, to β-blockers, nondihydropyridine Ca channel blockers, or both, then to one or more class Ia, class Ic, or class III antiarrhythmics.

Atrial Fibrillation and Wolff-Parkinson-White Syndrome

Atrial fibrillation (AF) is a medical emergency in the setting of antegrade conduction over an accessory pathway in Wolff-Parkinson-White (WPW) syndrome.

In manifest WPW syndrome, antegrade conduction occurs over the accessory pathway. If AF develops, the normal rate-limiting effects of the atrioventricular (AV) node are bypassed, and the resultant excessive ventricular rates (sometimes 200 to 240 beats/min) may lead to ventricular fibrillation (see Fig. 213-14) and sudden death. Patients with concealed WPW syndrome are not at risk because in them, antegrade conduction does not occur over the accessory connection.

[**Fig. 213-14.** Atrial fibrillation in Wolff-Parkinson-White syndrome.]

The treatment of choice is direct-current cardioversion. The usual rate-slowing drugs used in AF are not effective, and digoxin and the nondihydropyridine Ca channel blockers (eg, verapamil, diltiazem) are contraindicated because they may increase the ventricular rate and cause ventricular fibrillation. If cardioversion is impossible, drugs that prolong the refractory period of the accessory connection should be used. IV procainamide or amiodarone is preferred, but any class Ia, class Ic, or class III antiarrhythmic can be used.

Bundle Branch and Fascicular Block

Bundle branch block is partial or complete interruption of impulse conduction in a bundle branch; fascicular block is similar interruption in a hemifascicle of the bundle. The 2 disorders often coexist. There are usually no symptoms, but presence of either suggests a heart disorder. Diagnosis is by ECG. No specific treatment is indicated.

Conduction blocks can be caused by many heart disorders, including intrinsic degeneration without another associated heart disorder.

Right bundle branch block (RBBB—see Fig. 213-15) can occur in apparently normal people. It may also occur with anterior MI, indicating substantial myocardial injury. New appearance of RBBB should prompt a search for underlying cardiac pathology, but often, none is found. Transient RBBB may occur after pulmonary embolism. Although RBBB distorts the QRS complex, it does not significantly interfere with ECG diagnosis of MI.

Left bundle branch block (LBBB—see Fig. 213-16) is associated with a structural heart disorder more often than is RBBB. LBBB usually precludes use of ECG for diagnosis of MI.

Fascicular block involves the anterior or posterior fascicle of the left bundle branch. Interruption of the left anterior fascicle causes left anterior hemiblock characterized by modest QRS prolongation (< 120 msec) and a frontal plane QRS axis more negative than -30° (left axis deviation). Left posterior hemiblock is associated with a frontal plane QRS axis more positive than +120°. The associations between hemiblocks

and a structural heart disorder are the same as for LBBB.

Hemiblocks may coexist with other conduction disturbances: RBBB and left anterior or posterior hemiblock (bifascicular block); and left anterior or posterior hemiblock, RBBB, and 1st-degree atrioventricular (AV) block (incorrectly called trifascicular block; 1st-degree block is usually AV nodal in origin). Trifascicular block refers to RBBB with alternating left anterior and left posterior hemiblock or alternating LBBB and RBBB. Presence of bifascicular or trifascicular block after MI implies extensive cardiac damage. Bifascicular blocks require no direct treatment unless intermittent 2nd- or 3rd-degree AV block is present. True trifascicular blocks require immediate, then permanent pacing.

Nonspecific intraventricular conduction defects are diagnosed when the QRS complex is

[Fig. 213-15. Right bundle branch block.]

[Fig. 213-16. Left bundle branch block.]

prolonged (> 120 msec), but the QRS pattern is not typical of LBBB or RBBB. The conduction delay may occur beyond the Purkinje fibers and result from slow cell-to-cell myocyte conduction. No specific treatment is indicated.

Ventricular Premature Beats

Ventricular premature beats (VPBs) are single ventricular impulses caused by reentry within the ventricle or abnormal automaticity of ventricular cells. They are extremely common in healthy patients and in patients with a heart disorder. VPBs may be asymptomatic or cause palpitations. Diagnosis is by ECG. Treatment is usually not required.

VPBs, also called premature ventricular contractions (PVCs), may occur erratically or at predictable intervals (eg, every 3rd [trigeminy] or 2nd [bigeminy] beat). VPBs may increase with stimulants (eg, anxiety, stress, alcohol, caffeine, sympathomimetic drugs), hypoxia, or electrolyte abnormalities.

VPBs may be experienced as missed or skipped beats; the VPB itself is not sensed but rather the following augmented sinus beat. When VPBs are very frequent, particularly when they represent every 2nd heart beat, mild hemodynamic symptoms are possible because the sinus rate has been effectively halved. Existing ejection murmurs may be accentuated because of increased cardiac filling and augmented contractility after the compensatory pause.

Diagnosis

• ECG

Diagnosis is by ECG showing a wide QRS complex without a preceding P wave, typically followed by a fully compensatory pause.

Prognosis

VPBs are not significant in patients without a heart disorder, and no treatment is required beyond avoiding obvious triggers. β-Blockers are offered only if symptoms are intolerable. Other antiarrhythmics that suppress VPBs increase risk of more serious arrhythmias.

Treatment

• β-Blockers for patients with symptomatic heart failure and after MI

In patients with a structural heart disorder (eg, aortic stenosis, post MI), treatment is controversial even though frequent VPBs (> 10/h) correlate with increased mortality, because no studies have shown that pharmacologic suppression reduces mortality. In post-MI patients, mortality rate is higher with class I antiarrhythmics than with placebo. This finding probably reflects adverse effects of the antiarrhythmics. β-

Blockers are beneficial in symptomatic heart failure and post MI. If VPBs increase during exercise in a patient with coronary artery disease, evaluation for percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery should be considered.

Ventricular Tachycardia

Ventricular tachycardia (VT) is ≥ 3 consecutive ventricular beats at a rate ≥ 120 beats/min. Symptoms depend on duration and vary from none to palpitations to hemodynamic collapse and death. Diagnosis is by ECG. Treatment of more than brief episodes is with cardioversion or antiarrhythmics depending on symptoms. If necessary, long-term treatment is with an implantable cardioverter defibrillator.

Some experts use a cutoff rate of ≥ 100 beats/min for VT. Repetitive ventricular rhythms at slower rates are called accelerated idioventricular rhythms or slow VT; they are usually benign and are not treated unless associated with hemodynamic symptoms.

Most patients with VT have a significant heart disorder, particularly prior MI or a cardiomyopathy. Electrolyte abnormalities (particularly hypokalemia or hypomagnesemia), acidemia, hypoxemia, and adverse drug effects contribute. The long QT syndrome (congenital or acquired) is associated with a particular form of VT, torsades de pointes.

VT may be monomorphic or polymorphic and nonsustained or sustained. Monomorphic VT results from a single abnormal focus or reentrant pathway and has regular, identical-appearing QRS complexes. Polymorphic VT results from several different foci or pathways and is thus irregular, with varying QRS complexes. Nonsustained VT lasts < 30 sec; sustained VT lasts ≥ 30 sec or is terminated sooner because of hemodynamic collapse. VT frequently deteriorates to ventricular fibrillation and thus cardiac arrest (see p. 2255).

Symptoms and Signs

VT of short duration or slow rate may be asymptomatic. Sustained VT is almost always symptomatic, causing palpitations, symptoms of hemodynamic compromise, or sudden cardiac death.

Diagnosis

• ECG

Diagnosis is by ECG (see Fig. 213-17). Any wide QRS complex tachycardia (QRS ≥ 0.12 sec) should be considered VT until proved otherwise. Diagnosis is supported by ECG findings of dissociated P-wave activity, fusion or capture beats, uniformity of QRS vectors in the V leads (concordance) with discordant T-wave vector (opposite QRS vectors), and a frontal-plane QRS axis in the northwest quadrant. Differential diagnosis includes supraventricular tachycardia conducted with bundle branch block or via an accessory pathway (see Table 213-1). However, because some patients tolerate VT surprisingly well, concluding that a well-tolerated wide

[**Fig. 213-17.** Broad QRS ventricular tachycardia.]

QRS complex tachycardia must be of supraventricular origin is a mistake. Using drugs appropriate for supraventricular tachycardia (eg, verapamil, diltiazem) in patients with VT may cause hemodynamic collapse and death.

Treatment

• Acute: Sometimes synchronized direct-current cardioversion, sometimes lidocaine

• Long-term: Usually an implantable cardioverter-defibrillator

Acute: Treatment depends on symptoms and duration of VT. Hypotensive VT requires synchronized direct-current cardioversion with ≥ 100 joules. Stable sustained VT can be treated with IV drugs, usually lidocaine (see Table 213-2), which acts quickly but is frequently ineffective. If lidocaine is ineffective, IV procainamide may be given, but it may take up to 1 h to work. Failure of IV procainamide is an indication for cardioversion.

Nonsustained VT does not require immediate treatment unless the runs are frequent or long enough to cause symptoms. In such cases, antiarrhythmics are used as for sustained VT.

Long-term: The primary goal is preventing sudden death, rather than simply suppressing the arrhythmia. It is best accomplished by use of an implantable cardioverter-defibrillator (ICD—see p. 2159). However, the decision about whom to treat is complex and depends on the estimated probability of life-threatening VTs and the severity of underlying heart disorders (see Table 213-5).

Long-term treatment is not required when the index episode of VT resulted from a transient cause (eg, during the 48 h after onset of MI) or a reversible cause (acid-base disturbances, electrolyte abnormalities, proarrhythmic drug effect).

In the absence of a transient or reversible cause, patients who have had an episode of sustained VT typically require an ICD. Most patients with sustained VT and a significant structural heart disorder should also receive a β-blocker. If an ICD cannot be used, amiodarone may be the preferred antiarrhythmic for prevention of sudden death.

Because nonsustained VT is a marker for increased risk of sudden death in patients with a structural heart disorder, such patients (particularly those with an ejection fraction < 0.35) require further evaluation. Such patients should receive an ICD.

When prevention of VTs is important (usually in patients who have an ICD and are having frequent episodes of VT), antiarrhythmics or transcatheter radiofrequency or surgical ablation of the arrhythmogenic substrate is required. Any class Ia, Ib, Ic, II, or III drug can be used. Because β-blockers are safe, they are the first choice unless contraindicated. If an additional drug is required, sotalol is commonly used, then amiodarone.

Transcatheter radiofrequency ablation is used most commonly in patients who have VT with well-defined syndromes (eg, right ventricular outflow tract VT or left septal VT [Belhassen VT, verapamil-sensitive VT]) and otherwise healthy hearts.

Long QT Syndrome and Torsades de Pointes Ventricular Tachycardia

Torsades de pointes is a specific form of polymorphic VT in patients with a long QT interval. It is characterized by rapid, irregular QRS complexes, which appear to be twisting around the ECG baseline. This arrhythmia may cease spontaneously or degenerate into ventricular fibrillation. It causes significant hemodynamic compromise and often death. Diagnosis is by ECG. Treatment is with IV Mg, measures to shorten the QT interval, and often direct-current cardioversion.

The long QT interval responsible for torsades de pointes can be congenital or drug-induced. QT-interval prolongation predisposes to arrhythmia by prolonging repolarization, which induces early after-depolarizations and spatial dispersion of refractoriness.

Congenital: At least 10 distinct forms of congenital long QT syndrome have been described. Most cases fall into the first 3 subgroups:

- Long QT syndrome type 1 (LQT1), caused by a loss of function mutation of gene *KCNQ1*, which encodes an adrenergic-sensitive cardiac K current I_{Ks}

- Long QT syndrome type 2 (LQT2), caused by a loss of function mutation of gene *HERG*, which encodes another cardiac K channel (I_{Kr})

• Long QT syndrome type 3 (LQT3), caused by a mutation in gene *SCN5A*, which disrupts fast inactivation of the cardiac Na channel (I_{Na})

These forms are inherited as autosomal dominant disorders with incomplete penetrance and, in the past, were referred to as Romano-Ward syndrome. In rare patients with 2 abnormal copies of the genetic abnormality (particularly LQT1), the disorder is associated with congenital deafness and, in the past, was referred to as the Jervell and Lange-Nielsen syndrome. Patients with long QT syndrome are prone to recurrent syncope secondary to torsade de pointes and to sudden

[
Fig. 213-18. Torsades de pointes ventricular tachycardia.]

death secondary to torsade de pointes degenerating into ventricular fibrillation.

Drug-induced: More commonly, torsades de pointes results from a drug, usually a class Ia, Ic, or III antiarrhythmic. Other drugs that can induce torsades de pointes include tricyclic antidepressants, phenothiazines, and certain antivirals and antifungals (see www.torsades.org for an up-to-date list).

Symptoms and Signs

Patients often present with syncope because the underlying rate (200 to 250 beats/min) is nonperfusing. Palpitations are common among conscious patients. Sometimes the long QT interval is detected after resuscitation.

Diagnosis

• ECG

Diagnosis is by ECG showing an undulating QRS axis, with the polarity of complexes shifting around the baseline (see Fig. 213-18). ECG between episodes shows a long QT interval after correction for heart rate (QTc). Normal values average about 0.44 sec, although they vary among individuals and by sex. A family history may suggest a congenital syndrome.

Treatment

• Usually unsynchronized direct-current cardioversion

• Sometimes magnesium sulfate ($MgSO_4$) IV

An acute episode prolonged enough to cause hemodynamic compromise is treated with unsynchronized cardioversion, beginning with 100 joules. Nevertheless, early recurrence is the rule. Patients often respond to Mg: $MgSO_4$ 2 g IV over 1 to 2 min. If this treatment is unsuccessful, a 2nd bolus is given in 5 to 10 min, and an Mg infusion of 3 to 20 mg/min may be started in patients without renal insufficiency. Lidocaine (class Ib) shortens the QT interval and may be effective especially for drug-induced torsades de pointes. Class Ia, Ic, and III antiarrhythmics are avoided.

If a drug is the cause, it is stopped, but until drug clearance is complete, patients with frequent or long runs of torsades de pointes require treatment to shorten the QT interval. Because increasing the heart rate shortens the QT interval, temporary pacing, IV isoproterenol, or both are often effective. Long-term treatment is required for patients with a congenital long QT-interval syndrome. Treatment choices include β-blockers, permanent pacing, ICD, or a combination. Family members should be evaluated by ECG.

Patients with congenital long QT syndrome should clearly avoid drugs that prolong the QT interval, and patients with exercise-related symptoms (usually LQT1 or LQT2) should avoid strenuous exercise. Treatment options include β-blockers, pacing to maintain faster heart rates (which shortens the QT interval), and the ICD, alone or in combinations. Current guidelines recommend the ICD for patients resuscitated from cardiac arrest and those with syncope despite β-blocker treatment.

Brugada Syndrome

Brugada syndrome is an inherited disorder of cardiac electrophysiology causing an increased risk of syncope and sudden death.

Several different mutations are involved, most affecting the *SCN5A* gene that encodes the α-subunit of the voltage-dependent cardiac Na channel. Typically, patients have no structural heart disease. Nevertheless, relationships with other genetic and acquired structural heart diseases are increasingly being recognized, as are overlap syndromes with LQT3 and with arrhythmogenic right ventricular dysplasia (ARVD).

In some patients, Brugada syndrome has no clinical expression. However, in many patients it leads to syncope or sudden cardiac death due to polymorphic ventricular tachycardia and ventricular fibrillation. Events occur more often at night and are not usually related to exercise. Events may also be brought on by fever and by treatment with certain drugs including Na channel blockers,

[
Fig. 213-19. Type 1 Brugada syndrome.]

β-blockers, tricyclic antidepressants, lithium, and cocaine.

Initial diagnosis is based on a characteristic ECG pattern (type 1 Brugada ECG pattern—see Fig. 213-19) with prominent ST elevation in V_1 and V_2 (sometimes involving V_3) that causes the QRS complex in these leads to resemble right bundle branch block. The ST segment is coved and descends to an inverted T-wave. Lesser degrees of these patterns (type 2 and type 3 Brugada ECG patterns) are not considered diagnostic. The type 2 and type 3 patterns may change to a type 1 pattern spontaneously, with fever, or in response to drugs. The latter is the basis of a challenge diagnostic test usually using ajmaline or procainamide. Diagnosis should be considered in patients with unexplained cardiac arrest or syncope or a family history of such. Role of electrophysiologic testing is currently unclear and is the subject of onging study.

Patients presenting with syncope and patients resuscitated from arrest should receive an implantable cardioverter-defrillator. Best treatment of patients diagnosed based on ECG changes and family history is unclear, although they do have increased risk of sudden death.

Ventricular Fibrillation

Ventricular fibrillation (VF) causes uncoordinated quivering of the ventricle with no useful contractions. It causes immediate syncope and death within minutes. Treatment is with cardiopulmonary resuscitation, including immediate defibrillation.

VF is due to multiple wavelet reentrant electrical activity and is manifested on ECG by ultrarapid baseline undulations that are irregular in timing and morphology (see Fig. 213-14).

VF is the presenting rhythm for about 70% of patients in cardiac arrest and is thus the terminal event in many disorders. Overall, most patients with VF have an underlying heart disorder (typically ischemic, but also hypertrophic or dilated cardiomyopathies, arrhythmogenic right ventricular dysplasia [ARVD], or Brugada syndrome). Risk of VF in any disorder is increased by electrolyte abnormalities, acidosis, hypoxemia, or ischemia.

VF is much less common among infants and children, in whom asystole is the more common presentation of cardiac arrest.

Treatment is with cardiopulmonary resuscitation, including defibrillation (see p. 2260). The success rate for immediate (within 3 min) defibrillation is about 95%, provided that overwhelming pump failure does not preexist. When it does, even immediate defibrillation is only 30% successful, and most resuscitated patients die of pump failure before hospital discharge.

Patients who have VF without a reversible or transient cause are at high risk of future VF events and of sudden death. Most of these patients require an implantable cardioverterdefibrillator; many require concomitant antiarrhythmics to reduce the frequency of subsequent episodes of ventricular tachycardia and VF.

Chapter 214. Valvular Disorders

Introduction

Any heart valve can become stenotic or insufficient, causing hemodynamic changes long before symptoms. Most often, valvular stenosis or insufficiency occurs in isolation in individual valves, but multiple valvular disorders may coexist and a single valve may be both stenosed and insufficient.

Treatment depends on severity of disease but usually involves catheter-based valvuloplasty (eg, percutaneous balloon commissurotomy, valvotomy) or surgery (eg, surgical commissurotomy, valve repair, valve replacement). Two kinds of valve prosthesis are used: bioprosthetic (porcine) and mechanical (manufactured).

Traditionally, a mechanical valve has been used in patients < 65 and in older patients with a long life expectancy, because bioprosthetic valves deteriorate over 10 to 12 yr. Patients with a mechanical valve or bioprosthetic mitral valve require lifelong anticoagulation to an INR of 2.5 to 3.5 (to prevent thromboembolism) and antibiotics before some medical or dental procedures (to prevent endocarditis). An aortic bioprosthetic valve, which does not require anticoagulation beyond the immediate postoperative period, has been used in patients > 65, younger patients with a life expectancy < 10 yr, and those with some right-sided lesions. However, newer bioprosthetic valves may be more durable than 1st-generation valves; thus, patient preference regarding valve type can now be considered.

Women of childbearing age who require valve replacement and plan to become pregnant must balance the increased risk of teratogenicity from warfarin with mechanical valves against that of accelerated valve deterioration with bioprosthetic valves. These risks can be reduced by use of heparin instead of warfarin in the first 12 wk and last 2 wk of the pregnancy, but management is difficult and careful discussion is required before surgery.

Endocarditis prophylaxis is rarely indicated for patients with valvular heart disorders (see p. 2199).

Aortic Regurgitation

Aortic regurgitation (AR) is incompetency of the aortic valve causing flow from the aorta into the left ventricle during diastole. Causes include idiopathic valvular degeneration, rheumatic fever, endocarditis, myxomatous degeneration, congenital bicuspid aortic valve, aortic root dilatation or dissection, and connective tissue or rheumatologic disorders. Symptoms include exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, palpitations, and chest pain. Signs include widened pulse pressure and an early diastolic murmur. Diagnosis is by physical examination and echocardiography. Surgical treatment is aortic valve replacement.

Etiology

AR may be acute or chronic. The primary causes of acute AR are infective endocarditis and dissection of the ascending aorta. Mild chronic AR in adults is most often caused by a bicuspid or fenestrated aortic valve (2% of men and 1% of women), especially when severe diastolic hypertension (pressure ≥ 110 mm Hg) is present. Moderate to severe chronic AR in adults is most often caused by idiopathic degeneration of the aortic valves or root, rheumatic fever, infective endocarditis, myxomatous degeneration, or trauma. In children, the most common cause is a ventricular septal defect with aortic valve prolapse. Rarely, AR is caused by seronegative spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis), RA, SLE, arthritis associated with ulcerative colitis, luetic (syphilitic) aortitis, osteogenesis imperfecta, thoracic aortic aneurysm, aortic dissection, supravalvular aortic stenosis, Takayasu's arteritis, rupture of a sinus of Valsalva, acromegaly, and temporal (giant cell) arteritis. AR due to myxomatous degeneration may develop in patients with Marfan syndrome or EhlersDanlos syndrome.

Pathophysiology

In chronic AR, left ventricular (LV) volume and LV stroke volume gradually increase because the LV

receives aortic blood regurgitated in diastole in addition to blood from the pulmonary veins and left atrium. LV hypertrophy compensates for the increase in LV volume over years, but decompensation eventually develops. These changes may ultimately cause arrhythmias, LV impairment, and heart failure (HF).

Symptoms and Signs

Acute AR causes symptoms of HF and cardiogenic shock. Chronic AR is typically asymptomatic for years; progressive exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and palpitations develop insidiously. Symptoms of HF correlate poorly with objective measures of LV function. Chest pain (angina pectoris) affects only about 5% of patients who do not have coexisting coronary artery disease (CAD) and, when it occurs, is especially common at night. Patients may present with endocarditis (eg, fever, anemia, weight loss, embolic phenomena) because the abnormal aortic valve is predisposed to bacterial seeding.

Signs vary by severity. As chronic disease progresses, systolic BP increases while diastolic BP decreases, creating a widened pulse pressure. With time, the LV impulse may become enlarged, sustained, increased in amplitude, and displaced downward and laterally, with systolic depression of the entire left parasternal area, giving a rocking motion to the left chest.

A systolic apical or carotid thrill may become palpable in later stages of AR; it is caused by large forward stroke volumes and low aortic diastolic pressure.

Auscultatory findings include a normal 1st heart sound (S_1) and a nonsplit, loud, sharp or slapping 2nd heart sound (S_2) caused by increased elastic aortic recoil. The murmur of AR is often unimpressive. The murmur is blowing, high-pitched, diastolic, and decrescendo, beginning soon after the aortic component of S_2 (A_2); it is loudest at the 3rd or 4th left parasternal intercostal space. The murmur is heard best with the diaphragm of the stethoscope when the patient is leaning forward, with breath held at end-expiration. It increases in volume in response to maneuvers that increase afterload (eg, squatting, isometric handgrip). If AR is slight, the murmur may occur only in early diastole. If LV diastolic pressure is very high, the murmur is short because aortic and LV diastolic pressures equalize earlier in diastole.

Other abnormal sounds include a forward ejection and backward regurgitant flow (to-and-fro) murmur, an ejection click soon after the S_1, and an aortic ejection flow murmur. A diastolic murmur heard near the axilla or mid left thorax (Cole-Cecil murmur) is caused by fusion of the aortic murmur with the 3rd heart sound (S_3), which is due to simultaneous filling of LV from the left atrium and AR. A mid-to-late diastolic rumble heard at the apex (Austin Flint murmur) may result from rapid regurgitant flow into the LV, causing mitral valve leaflet vibration at the peak of atrial flow; this murmur mimics the diastolic murmur of mitral stenosis.

Other signs are unusual; sensitivity and specificity are low or unknown. Visible signs include head bobbing (Musset's sign) and pulsation of the fingernail capillaries (Quincke's sign, best seen with slight pressure) or uvula (Muller's sign). Palpable signs include a large-volume pulse with rapid rise and fall (slapping, water-hammer, or collapsing pulse) and pulsation of the carotid arteries (Corrigan's sign), retinal arteries (Becker's sign), liver (Rosenbach's sign), or spleen (Gerhard's sign). BP findings may include popliteal systolic pressure ≥ 60 mm Hg higher than brachial pressure (Hill's sign) and a fall in diastolic BP of > 15 mm Hg with arm elevation (Mayne's sign). Auscultatory signs include a sharp sound heard over the femoral pulse (pistol-shot sound, or Traube's sign) and a femoral systolic bruit distal and a diastolic bruit proximal to arterial compression (Duroziez's murmur).

Diagnosis

• Echocardiography

Diagnosis is suspected based on history and physical examination and confirmed by echocardiography. Doppler echocardiography is the test of choice to detect and quantify the magnitude of regurgitant blood flow. Two-dimensional echocardiography can quantify aortic root size and anatomy and LV function. An end-systolic LV volume > 60 mL/m^2, endsystolic LV diameter > 50 mm, and LV ejection fraction (LVEF) <

50% suggest decompensation. Echocardiography can also assess severity of pulmonary hypertension secondary to LV failure, detect vegetations or pericardial effusions (eg, in aortic dissection), and provide information about prognosis.

Radionuclide imaging may be used to determine LVEF if echocardiographic results are borderline abnormal or if echocardiography is technically difficult.

An ECG and chest x-ray should be obtained. ECG may show repolarization abnormalities with or without QRS voltage criteria of LV hypertrophy, left atrial enlargement, and T-wave inversion with ST-segment depression in precordial leads. Chest x-ray may show cardiomegaly and a prominent aortic root in patients with chronic progressive AR. If AR is severe, signs of pulmonary edema and HF may also be present. Exercise testing may help assess functional capacity and symptoms in patients with documented AR and equivocal symptoms.

Coronary angiography should be done before surgery, even if no angina is present, because about 20% of patients with severe AR have significant CAD, which may need concomitant coronary artery bypass graft surgery.

Prognosis

With treatment, the 10-yr survival for patients with mild to moderate AR is 80 to 95%. With appropriately timed valve replacement (ie, before HF and using criteria below), long-term prognosis for patients with moderate to severe AR is good. However, the prognosis for those with severe AR and HF is considerably poorer.

Treatment

• Aortic valve replacement

• Sometimes vasodilators, diuretics, and nitrates

Treatment of acute AR is aortic valve replacement. Treatment of chronic AR varies by symptoms and degree of LV dysfunction. Patients with symptoms precipitated by normal daily activity or during exercise testing require aortic valve replacement; patients who prefer to avoid surgery may be treated with vasodilators (eg, long-acting nifedipine 30 to 90 mg po once/day or ACE inhibitors). Also, diuretics or nitrates to reduce preload may be beneficial for severe AR. Asymptomatic patients with LVEF < 55%, an end-systolic diameter ≥ 55 mm (55 rule), or an end-diastolic diameter > 75 mm also require surgery; oral drugs are a 2nd-best option for this group. Additional surgical criteria have been proposed, including fractional shortening < 25 to 29%, end-diastolic radius to myocardial wall thickness ratio > 4.0, and cardiac index < 2.2 to 2.5 L/min/m^2.

Patients who do not meet these criteria should be reevaluated by physical examination, echocardiography, and possibly rest-exercise radionuclide cineangiography to measure LV contractility every 6 to 12 mo.

Antibiotic prophylaxis against endocarditis is no longer recommended except for patients who have had valve replacement (see
Table 215-4).

Aortic Stenosis

Aortic stenosis (AS) is narrowing of the aortic valve obstructing blood flow from the left ventricle to the ascending aorta during systole. Causes include a congenital bicuspid valve, idiopathic degenerative sclerosis with calcification, and rheumatic fever. Progressive untreated AS ultimately results in one or more of the classic triad of syncope, angina, and exertional dyspnea; heart failure and arrhythmias may develop. A carotid pulse with small amplitude and delayed upstroke and a crescendo-decrescendo ejection murmur are characteristic. Diagnosis is by physical examination and echocardiography. Asymptomatic AS often requires no

treatment. For progressive severe or symptomatic AS in children, balloon valvotomy is used; adults require valve replacement.

Etiology

Aortic sclerosis, a degenerative aortic valve disease with thickening of aortic valve structures by fibrosis and calcification initially without causing significant obstruction, is the most common cause of AS in elderly patients. Over years, aortic sclerosis progresses to stenosis in as many as 15% of patients. Aortic sclerosis resembles atherosclerosis, with deposition of lipoproteins, active inflammation, and calcification of the valves; risk factors are similar (see p. 2082).

The most common cause of AS in patients < 70 yr is a congenital bicuspid aortic valve. Congenital AS occurs in 3 to 5/1000 live births and affects more males.

In developing countries, rheumatic fever is the most common cause in all age groups. Supravalvular AS caused by a discrete, congenital membrane or hypoplastic constriction just above the sinuses of Valsalva is uncommon. A sporadic form of supravalvular AS is associated with a characteristic facies (high and broad forehead, hypertelorism, strabismus, upturned nose, long philtrum, wide mouth, dental abnormalities, puffy cheeks, micrognathia, low-set ears). When associated with idiopathic hypercalcemia of infancy, this form is known as Williams syndrome. Subvalvular AS caused by a congenital membrane or fibrous ring just beneath the aortic valve is uncommon.

Pathophysiology

Aortic regurgitation may accompany AS, and about 60% of patients > 60 yr with significant AS also have mitral annular calcification, which may lead to significant mitral regurgitation.

The left ventricle (LV) gradually hypertrophies in response to AS. Significant LV hypertrophy causes diastolic dysfunction and, with progression, may lead to decreased contractility, ischemia, or fibrosis, any of which may cause systolic dysfunction and heart failure (HF). LV chamber enlargement is a late finding unless there is coexisting MI. Patients with AS have a higher incidence of GI bleeding (called Heyde's syndrome) because the high shear stress of stenotic valves makes multimeric von Willebrand's factor more susceptible to cleavage by a plasma metalloprotease and may increase platelet clearance. GI bleeding may also be due to angiodysplasia.

Symptoms and Signs

Congenital AS is usually asymptomatic until at least age 10 or 20 yr, when symptoms may begin to develop insidiously. In all forms, progressive untreated AS ultimately results in exertional syncope, angina, and dyspnea (SAD triad). Other symptoms and signs may include those of HF and arrhythmias, including ventricular fibrillation leading to sudden death.

Exertional syncope occurs because cardiac output cannot increase enough to meet the demands of physical activity. Nonexertional syncope may result from altered baroreceptor responses or ventricular tachycardia. Exertional angina pectoris affects about two thirds of patients; about one half have significant coronary artery atherosclerosis, and one half have normal coronary arteries but have ischemia induced by LV hypertrophy, altered coronary flow dynamics, or both.

There are no visible signs of AS. Palpable signs include carotid and peripheral pulses that are reduced in amplitude and slow rising (pulsus parvus, mollus et tardus) and an apical impulse that is sustained (thrusts with the 1st heart sound [S_1] and relaxes with the 2nd heart sound [S_2]) because of LV hypertrophy. The LV impulse may become displaced when systolic dysfunction develops. A palpable 4th heart sound (S_4), felt best at the apex, and a systolic thrill, corresponding with the murmur of AS and felt best at the left upper sternal border, are occasionally present in severe cases. Systolic BP may be high with mild or moderate AS and falls as AS becomes more severe.

On auscultation, S_1 is normal and S_2 is single because aortic valve closing is delayed and merges with

the pulmonic (P_2) component of S_2. The aortic component may also be soft. Paradoxical splitting of S_2 may be heard. An S_4 may be audible. An ejection click may also be audible early after S_1 in patients with congenital bicuspid AS when valve leaflets are stiff but not completely immobile. The click does not change with dynamic maneuvers.

The hallmark finding is a crescendodecrescendo ejection murmur, heard best with the diaphragm of the stethoscope at the right and left upper sternal border when a patient who is sitting upright leans forward. The murmur typically radiates to the right clavicle and both carotid arteries (left often louder than right) and has a harsh or grating quality. But in elderly patients, vibration of the un-fused cusps of calcified aortic valve leaflets may transmit a louder, more high-pitched, "cooing" or musical sound to the cardiac apex, with softening or absence of the murmur parasternally (Gallavardin's phenomenon), thereby mimicking mitral regurgitation. The murmur is soft when stenosis is less severe, grows louder as stenosis progresses, and becomes longer and peaks in volume later in systole (ie, crescendo phase becomes longer and decrescendo phase becomes shorter) as stenosis becomes more severe. As LV contractility decreases in critical AS, the murmur becomes softer and shorter. The intensity of the murmur may therefore be misleading in these circumstances.

The murmur of AS typically increases with maneuvers that increase LV volume and contractility (eg, leg-raising, squatting, Valsalva release, after a ventricular premature beat) and decreases with maneuvers that decrease LV volume (Valsalva maneuver) or increase afterload (isometric handgrip). These dynamic maneuvers have the opposite effect on the murmur of hypertrophic cardiomyopathy, which can otherwise resemble that of AS. The murmur of mitral regurgitation due to prolapse of the posterior leaflet may also mimic AS.

Diagnosis

• Echocardiography

Diagnosis is suspected clinically and confirmed by echocardiography. Two-dimensional transthoracic echocardiography is used to identify a stenotic aortic valve and possible causes, to quantify LV hypertrophy and degree of diastolic or systolic dysfunction, and to detect coexisting valvular heart disorders (aortic regurgitation, mitral valve disorders) and complications (eg, endocarditis). Doppler echocardiography is used to quantify degree of stenosis by measuring aortic valve area, jet velocity, and transvalvular systolic pressure gradient.

A valve area of 0.5 to 1.0 cm^2 or a mean gradient > 45 to 50 mm Hg represents severe stenosis. The gradient may be overestimated in aortic regurgitation and underestimated in LV systolic dysfunction. The rate of progression of AS from mild to severe is quite variable and does not necessarily proceed in a linear fashion.

Cardiac catheterization is necessary to determine whether coronary artery disease (CAD) is the cause of angina and, occasionally, to resolve differences between clinical and echocardiographic findings.

An ECG and chest x-ray are obtained. ECG typically shows changes of LV hypertrophy with or without an ischemic ST- and T-wave pattern. Chest x-ray findings may include calcification of the aortic cusps (seen on the lateral projection or on fluoroscopy) and evidence of HF. Heart size may be normal or only mildly enlarged.

Prognosis

AS may progress slowly or quickly and thus requires regular follow-up to detect progression, particularly in sedentary elderly patients. In such patients, flow may become significantly compromised without triggering symptoms.

Overall, about 3 to 6% of asymptomatic patients with normal systolic function develop symptoms or LV ejection fraction depression every year. However, surgery is usually delayed until symptoms develop because the risk of surgery outweighs the survival benefit in asymptomatic patients. Surgery should not

be delayed once symptoms develop. Mean survival in untreated symptomatic patients is about 2 to 3 yr. Aortic valve replacement relieves symptoms and improves survival. Risk with surgery increases for patients who require simultaneous coronary artery bypass graft (CABG) and for those with depressed systolic LV function.

About 50% of deaths occur suddenly. While awaiting surgery, patients with severe AS should be advised to restrict physical exertion.

Treatment

• Sometimes aortic valve replacement

Asymptomatic patients with a maximum gradient ≤ 25 mm Hg and a valve area > 1.0 cm^2 have a low mortality and low overall risk of requiring surgery in the next 2 yr; annual evaluation for symptom progression, including echocardiography to determine gradient and valve area, is appropriate.

Asymptomatic patients with gradients of 25 to 50 mm Hg or valve area < 1.0 cm^2 are at higher risk of developing symptoms in the next 2 yr, but generally elective valve replacement is not required in the absence of symptoms. Valve replacement is indicated for patients who have moderate or severe AS and primarily require CABG. Surgery may be indicated for patients who become hypotensive during exercise treadmill testing and for those with LV ejection fraction < 50%. Patients with ventricular arrhythmias and severe LV hypertrophy are also often referred for surgery, but benefits are less clear. Recommendations for patients without any of these qualifying conditions include more frequent monitoring for progression of symptoms, LV hypertrophy, gradients, and valve area with medical management as needed. It is unclear whether statins reduce the progression of AS. Other drugs may be detrimental, especially those that can cause hypotension. Small studies suggest that perhexilene maleate may decrease symptoms. Nitroprusside has been used as a temporizing measure to reduce afterload in patients with decompensated HF in the hours before valve replacement, but because this drug can have the same effect as rapid-acting nitrates, it must be used cautiously and monitoring is required.

Symptomatic patients should undergo valve replacement or balloon valvotomy. Valve replacement is indicated for virtually all who can tolerate surgery. In younger patients, the patient's own pulmonic valve can be used, providing good durability; a bioprosthesis is then used to replace the pulmonic valve (Ross procedure). Most often, the aortic valve is replaced with a mechanical or bio-prosthetic valve. Preoperative evaluation for CAD is indicated so that CABG and valve replacement, if indicated, can be done during the same procedure.

Balloon valvotomy is used primarily in children and very young adults with congenital AS. In older patients who are unfit for surgery, balloon valvuloplasty can provide temporary relief of symptoms, perhaps for 6 to 12 mo, and can be repeated in selected patients. Minimally invasive percutaneous valve replacement is being used as an alternative procedure in very elderly or frail patients.

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is a billowing of mitral valve leaflets into the left atrium during systole. The most common cause is idiopathic myxomatous degeneration. MVP is usually benign, but complications include mitral regurgitation, endocarditis, valve rupture, and possibly thromboembolism. MVP is usually asymptomatic in the absence of important regurgitation, although there are reports that some patients experience chest pain, dyspnea, dizziness, and palpitations. Signs include a crisp mid-systolic click, followed by a late systolic murmur if regurgitation is present. Diagnosis is by physical examination and echocardiography. Prognosis is excellent in the absence of significant regurgitation, but chordal rupture and endocarditis may occur. No specific treatment is necessary unless mitral regurgitation is present.

MVP is common; prevalence is 1 to 3% in otherwise normal populations, depending on the echocardiographic criteria used. Women and men are affected equally; onset usually follows the adolescent growth spurt.

Etiology

MVP is most often caused by myxomatous degeneration of the mitral valve and chordae tendineae. Degeneration is usually idiopathic, although it may be inherited in an autosomal dominant or, rarely, in an X-linked recessive fashion. Myxomatous degeneration may also be caused by connective tissue disorders (eg, Marfan syndrome, Ehlers-Danlos syndrome, adult polycystic kidney disease, osteogenesis imperfecta, pseudoxanthoma elasticum, SLE, polyarteritis nodosa) and muscular dystrophies. MVP is more common among patients with Graves' disease, hypomastia, von Willebrand's syndrome, sickle cell disease, and rheumatic heart disease. Myxomatous degeneration may also affect the aortic or tricuspid valve, resulting in aortic or tricuspid prolapse. Tricuspid regurgitation is uncommon.

Mitral regurgitation (MR) may occur in patients with apparently normal mitral valve leaflets (ie, nonmyxomatous) if papillary muscle dysfunction is present or the mitral annulus is dilated (eg, in dilated cardiomyopathy). In hypertrophic cardiomyopathy with outflow obstruction, MR occurs due to interference with the closure of the mitral leaflets (which may also be abnormal). Transient MVP may occur when intravascular volume decreases significantly, as occurs in severe dehydration or sometimes during pregnancy (when the woman is recumbent and the gravid uterus compresses the inferior vena cava, reducing venous return).

MR is the most common complication of MVP. MR may be acute (due to ruptured chordae tendineae or flail mitral valve leaflets) or chronic; sequelae of chronic MR include heart failure and atrial fibrillation (AF) with thromboembolism. Whether MVP causes stroke independent of MR and AF is unclear. In addition, MR increases the risk of infective endocarditis.

Symptoms and Signs

Most patients are asymptomatic. Some experience nonspecific symptoms (eg, chest pain, dyspnea, palpitations, dizziness, near syncope, migraines, anxiety), thought to be due to poorly defined associated abnormalities in adrenergic signaling and sensitivity rather than to mitral valve pathology. In about one third of patients, emotional stress precipitates palpitations, which may be a symptom of benign arrhythmias (atrial premature beats, paroxysmal atrial tachycardia, ventricular premature beats, complex ventricular ectopy).

Occasionally, patients present with MR. Rarely, patients present with endocarditis (eg, fever, weight loss, thromboembolic phenomena) or stroke. Sudden death occurs in < 1%, most often resulting from ruptured chordae tendineae and flail mitral valve leaflets. Death due to a fatal arrhythmia is rare.

Typically, MVP causes no visible or palpable cardiac signs. MVP alone causes a crisp mid-systolic click heard best with the diaphragm of the stethoscope over the left apex when the patient is in the left lateral decubitus position. MVP with MR causes a click with a late-systolic MR murmur. The click becomes audible or moves closer to the 1st heart sound (S_1) and becomes louder with maneuvers that decrease left ventricle (LV) size (eg, sitting, standing, Valsalva maneuver); the same maneuvers cause an MR murmur to appear or become louder and last longer. These effects occur because decreasing LV size causes papillary muscles and chordae tendineae to pull together more centrally beneath the valve, resulting in quicker, more forceful prolapse with earlier, more severe regurgitation. Conversely, squatting or isometric handgrip delays the S_1 click and shortens the MR murmur. The systolic click may be confused with the click of congenital aortic stenosis, which can be distinguished because it occurs very early in systole and does not move with postural or LV volume changes. Other findings include a systolic honk or whoop, thought to be caused by valvular leaflet vibration; these findings are usually transient and may vary with respiratory phase. An early diastolic opening snap caused by return of the prolapsed valve to its normal position is rarely heard.

Other physical findings associated with but not diagnostic of MVP include hypomastia, pectus excavatum, straight back syndrome, and a narrow anteroposterior chest diameter.

Diagnosis

• Echocardiography

Diagnosis is suggested clinically and confirmed by 2-dimensional echocardiography. Holosystolic displacement of ≥ 3 mm or late systolic displacement of ≥ 2 mm identifies 95% of patients with MVP; the percentage is slightly higher if echocardiography is done while the patient is standing. Thickened, redundant mitral valve leaflets and displacement of ≥ 5 mm are thought to indicate more extensive myxomatous degeneration and greater risk of endocarditis and MR.

Holter monitoring and 12-lead ECG may be useful for documenting arrhythmias in patients with palpitations.

Prognosis

MVP is usually benign, but severe myxomatous degeneration of the valve can lead to MR. In patients with severe MR, incidence of LV or left atrium enlargement, arrhythmias (eg, AF), infective endocarditis, stroke, need for valve replacement, and death is about 2 to 4%/yr.

Treatment

• Usually none

• Sometimes β-blockers

MVP does not usually require treatment. β-Blockers may be used to relieve symptoms of excess sympathetic tone (eg, palpitations, migraines, dizziness) and to reduce risk of tachyarrhythmias, although no data support this practice. A typical regimen is atenolol 25 to 50 mg po once/day or propranolol 20 to 40 mg po bid. AF may require additional treatment (see p. 2166).

Treatment of MR depends on severity and associated left atrial and LV changes.

Antibiotic prophylaxis against endocarditis is no longer recommended. Anticoagulants to prevent thromboembolism are recommended only for patients with AF or prior transient ischemic attack or stroke.

Mitral Regurgitation

Mitral regurgitation (MR) is incompetency of the mitral valve causing flow from the left ventricle (LV) into the left atrium during systole. Common causes include mitral valve prolapse, ischemic papillary muscle dysfunction, rheumatic fever, and annular dilation secondary to LV systolic dysfunction and dilation. Complications include progressive heart failure, arrhythmias, and endocarditis. Symptoms and signs include palpitations, dyspnea, and a holosystolic apical murmur. Diagnosis is by physical examination and echocardiography. Prognosis depends on LV function and severity and duration of MR. Patients with mild, asymptomatic MR may be monitored, but progressive or symptomatic MR requires mitral valve repair or replacement.

Etiology

MR may be acute or chronic. Causes of acute MR include ischemic papillary muscle dysfunction or rupture; infective endocarditis; acute rheumatic fever; spontaneous, traumatic, or ischemic tears or rupture of the mitral valve leaflets or subvalvular apparatus; acute dilation of the LV due to myocarditis or ischemia; and mechanical failure of a prosthetic mitral valve.

Common causes of chronic MR include those of acute MR plus myxomatous degeneration of the mitral leaflets or chordae tendineae, mitral valve prolapse (MVP), mitral annular enlargement, and nonischemic papillary muscle dysfunction (eg, due to LV enlargement). Uncommon causes of chronic MR include a congenital endocardial cushion defect with a cleft anterior leaflet, SLE, acromegaly, myxoma involving the valve or chordae, and calcification of the mitral annulus (mainly in elderly women).

In infants, the most likely causes of MR are papillary muscle dysfunction, endocardial fibroelastosis, acute

myocarditis, cleft mitral valve with or without an endocardial cushion defect, and myxomatous degeneration of the mitral valve. MR may coexist with mitral stenosis when thickened valvular leaflets do not close.

Pathophysiology

Acute MR may cause acute pulmonary edema and biventricular failure with cardiogenic shock or sudden cardiac death. Complications of chronic MR include gradual enlargement of the left atrium (LA); LV enlargement and hypertrophy, which initially compensates for regurgitant flow (preserving forward stroke volume) but eventually decompensates (reducing forward stroke volume); atrial fibrillation (AF), which may be further complicated by thromboembolism; and infective endocarditis.

Symptoms and Signs

Acute MR causes the same symptoms and signs as acute heart failure and cardiogenic shock (see p. 2116). Most patients with chronic MR are initially asymptomatic and develop symptoms insidiously as the LA enlarges, pulmonary artery and venous pressure increases, and LV remodeling occurs. Symptoms include dyspnea, fatigue (due to heart failure), orthopnea, and palpitations (often due to AF). Rarely, patients present with endocarditis (eg, fever, weight loss, embolic phenomena).

Signs develop only when MR becomes moderate to severe. Inspection and palpation may detect a brisk apical impulse and sustained left parasternal movement due to systolic expansion of an enlarged LA. An LV impulse that is sustained, enlarged, and displaced downward and to the left suggests LV hypertrophy and dilation. A diffuse precordial lift occurs with severe MR because the LA enlarges, causing anterior cardiac displacement, and pulmonary hypertension causes right ventricular hypertrophy. A regurgitant murmur (or thrill) may also be palpable in severe cases.

On auscultation, the 1st heart sound (S_1) may be soft (or occasionally loud). A 3rd heart sound (S_3) at the apex reflects a dilated LV and important MR.

The cardinal sign of MR is a holosystolic (pansystolic) murmur, heard best at the apex with the diaphragm of the stethoscope when the patient is in the left lateral decubitus position. In mild MR, the systolic murmur may be abbreviated or occur late in systole. The murmur begins with S_1 in conditions causing leaflet incompetency throughout systole, but it often begins after S_1 (eg, when chamber dilation during systole distorts the valve apparatus or when myocardial ischemia or fibrosis alters dynamics). When the murmur begins after S_1, it always continues to the 2nd heart sound (S_2). The murmur radiates toward the left axilla; intensity may remain the same or vary. If intensity varies, the murmur tends to crescendo in volume up to S_2. MR murmurs increase in intensity with handgrip or squatting because peripheral vascular resistance to ventricular ejection increases, augmenting regurgitation into the LA; murmurs decrease in intensity with standing or the Valsalva maneuver. A short rumbling mid-diastolic inflow murmur due to torrential mitral diastolic flow may be heard following an S_3. In patients with posterior leaflet prolapse, the murmur may be coarse and radiate to the upper sternum, mimicking aortic stenosis.

MR murmurs may be confused with tricuspid regurgitation, which can be distinguished because its murmur is augmented during inspiration.

Diagnosis

• Echocardiography

Diagnosis is suspected clinically and confirmed by echocardiography. Doppler echocardiography is used to detect regurgitant flow and help quantify its severity; 2-dimensional or 3-dimensional echocardiography is used to determine the cause of MR and to detect pulmonary hypertension.

If endocarditis or valvular thrombi are suspected, transesophageal echocardiography (TEE) can provide a more detailed view of the mitral valve and LA. TEE is also indicated when mitral valve repair instead of replacement is being considered to confirm the anatomy in more detail.

An ECG and chest x-ray are usually obtained initially. ECG may show LA enlargement and LV hypertrophy with or without ischemia. Sinus rhythm is usually present when MR is acute because the atria have not had time to stretch and remodel.

Chest x-ray in acute MR may show pulmonary edema; abnormalities in cardiac silhouette are not evident unless an underlying chronic disorder is also present. Chest x-ray in chronic MR may show LA and LV enlargement. It may also show pulmonary vascular congestion and pulmonary edema with heart failure. Cardiac catheterization is done before surgery, mainly to determine whether coronary artery disease (CAD) is present. A prominent systolic *c-v* wave is seen on pulmonary artery occlusion pressure (pulmonary capillary wedge pressure) tracings during ventricular systole. Ventriculography can be used to quantify MR. Cardiac MRI can accurately measure regurgitant fraction and determine the underlying cause of dilated myopathy with MR.

Prognosis

Prognosis varies by acuity and cause of MR. Once MR becomes severe, about 10% of asymptomatic patients become symptomatic per year thereafter. About 10% of patients with chronic MR caused by MVP require surgical intervention.

Treatment

• Mitral valve repair or replacement

Acute MR requires emergency mitral valve repair or replacement; patients with ischemic papillary muscle rupture may also require coronary revascularization. Pending surgery, nitroprusside or nitroglycerin infusion may be used to reduce afterload, thus improving forward stroke volume and reducing ventricular and regurgitant volume.

Definitive treatment of chronic MR is also mitral valve repair or replacement, but patients with asymptomatic or mild chronic MR and no pulmonary hypertension or AF may do well with periodic monitoring. ACE inhibitors or angiotensin II receptor blockers are used to decrease left ventricular preload and afterload. They are used in patients with moderate mitral insufficiency to delay dilation of the LV. Loop diuretics such as furosemide are helpful in patients with exertional or nocturnal dyspnea. Digoxin may reduce symptoms in patients with AF or those in whom valve surgery is not appropriate. The ideal timing for surgery is uncertain, but intervention before ventricular decompensation (defined as echocardiographic end-diastolic dimension > 70 mm, end-systolic dimension > 45 mm, and ejection fraction < 60%) improves outcomes and decreases the chance of worsening LV function. After decompensation, ventricular function becomes dependent on the afterload reduction of MR, and in about 50% of decompensated patients, valve replacement causes a markedly depressed ejection fraction. For patients with moderate MR and significant CAD, perioperative mortality rate is 1.5% with bypass surgery alone and 25% with concomitant valve replacement. If technically feasible, valve repair instead of replacement is preferred; perioperative mortality rate is 2 to 4% (compared with 5 to 10% for replacement), and long-term prognosis is good (80 to 94% survival rate at 5 to 10 yr, compared with 40 to 60% for replacement).

New percutaneous procedures that tailor the mitral leaflets have been used in elderly and high-risk patients, and percutaneous placement of artificial valves is under trial.

Antibiotic prophylaxis is no longer recommended except for patients who have had valve replacement (see Table 215-4).

Anticoagulants are used to prevent thromboemboli (see p. 1920) in patients with heart failure or AF. Although severe MR without mitral stenosis or AF is less likely to be complicated by atrial thrombosis, most cardiologists still recommend anticoagulants.

Mitral Stenosis

Mitral stenosis (MS) is narrowing of the mitral orifice that impedes blood flow from the left atrium to the left ventricle. The (almost) invariable cause is rheumatic fever. Common complications are pulmonary hypertension, atrial fibrillation, and thromboembolism. Symptoms are those of heart failure; signs include an opening snap and a diastolic murmur. Diagnosis is by physical examination and echocardiography. Prognosis is good. Medical treatment includes diuretics, β-blockers or rate-limiting Ca channel blockers, and anticoagulants. Effective treatment for more severe disease consists of balloon valvotomy, surgical commissurotomy, or valve replacement.

In MS, mitral valve leaflets become thickened and immobile and the mitral orifice becomes narrowed due to fusion of the commissures. The chordae are usually thickened, matted, and shortened to a variable degree, contributing to the reduced mobility of the leaflets. The most common cause is rheumatic fever (see p. 2861), even though many patients do not recall the disorder. Less common causes include bacterial endocarditis, SLE, atrial myxoma, RA, malignant carcinoid syndrome with an atrial right-to-left shunt, and methysergide. Occasionally, MS is congenital. If the valve cannot close completely, mitral regurgitation (MR) may coexist with MS. Patients with MS due to rheumatic fever may also have lesions of the aortic or tricuspid valve or both.

The normal area of the mitral valve orifice is 4 to 5 cm^2. An area of 1 to 1.5 cm^2 reflects moderate MS and often causes exertional symptoms. An area < 1 cm^2 represents severe stenosis and may cause symptoms during rest. However, the relationship between the area of the valve orifice and symptoms is not always reliable. Left atrial (LA) size and pressure increase progressively to compensate for MS; pulmonary venous and capillary pressures also increase and may cause secondary pulmonary hypertension, leading to right ventricular (RV) heart failure and tricuspid and pulmonic regurgitation. Rate of progression varies.

LA enlargement predisposes to atrial fibrillation (AF), a risk factor for thromboembolism. The faster heart rate and loss of atrial contraction with onset of AF often leads to sudden worsening of symptoms.

Symptoms and Signs

Symptoms correlate poorly with disease severity because the disease often progresses insidiously and patients reduce their activity without being aware of it. Many patients are asymptomatic until they become pregnant or AF develops. Initial symptoms are usually those of heart failure (eg, exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue). They typically do not appear until 15 to 40 yr after an episode of rheumatic fever, but in developing countries, much younger children may become symptomatic because streptococcal infections may not be treated with antibiotics and recurrent infections are common. Paroxysmal or chronic AF exacerbates existing diastolic dysfunction, precipitating pulmonary edema and acute dyspnea when ventricular rate is poorly controlled. AF may also cause palpitations; in up to 15% of unanticoagulated patients, it causes systemic embolism with symptoms of stroke or other organ ischemia.

Less common symptoms include hemoptysis due to rupture of small pulmonary vessels and pulmonary edema, particularly during pregnancy when blood volume increases; hoarseness due to compression of the left recurrent laryngeal nerve by a dilated LA or pulmonary artery (Ortner's syndrome); and symptoms of pulmonary hypertension (see p. 1986) and RV failure (see p. 2120).

Inspection and palpation may detect palpable 1st and 2nd heart sounds (S_1 and S_2). S_1 is best palpated at the apex, and S_2 at the upper left sternal border. The pulmonic component of S_2 (P_2) is responsible for the impulse and results from pulmonary hypertension. An RV impulse (heave) palpable at the left sternal border may accompany jugular venous distention when pulmonary hypertension is present and RV diastolic dysfunction develops.

Auscultatory findings include a loud S_1 caused by the leaflets of a stenotic mitral valve closing abruptly (M_1), like a sail on "coming about"; it is heard best at the apex. A normally split S_2 with an exaggerated P_2 due to pulmonary hypertension is also heard. Most prominent is an early diastolic opening snap as the leaflets billow into the left ventricle (LV), which is loudest close to left lower sternal border; it is followed by a low-pitched decrescendo-crescendo rumbling diastolic murmur, heard best with the bell of the

stethoscope at the apex (or over the palpable apex beat) at end-expiration when the patient is in the left lateral decubitus position. The opening snap may be soft or absent if the mitral valve is calcified; the snap moves closer to S_2 (increasing duration of the murmur) as MS becomes more severe and LA pressure increases. The diastolic murmur increases after a Valsalva maneuver (when blood pours into the LA), after exercise, and in response to squatting and handgrip. The murmur may be softer or absent when an enlarged RV displaces the LV posteriorly and when other disorders (pulmonary hypertension, right-sided valve abnormalities, AF with fast ventricular rate) decrease blood flow across the mitral valve. The presystolic crescendo is caused by increased flow with atrial contraction. However, the closing mitral valve leaflets during LV contraction may also contribute to this finding but only at the end of short diastoles when LA pressure is still high.

Diastolic murmurs that may coexist with the MS murmur are the early diastolic murmur of coexisting aortic regurgitation (AR), which may be conducted to the apex; the Austin Flint murmur (a low-pitched mid-diastolic murmur heard at the apex due to AR); Graham Steell's murmur (a soft decrescendo diastolic murmur heard best along the left sternal border and caused by pulmonic regurgitation secondary to severe pulmonary hypertension); a diastolic flow murmur in the presence of severe MR; and (rarely) an obstructing left atrial myxoma or ball thrombus.

MS may cause signs of cor pulmonale (see p. 2132). The classic mitral facies, a plum-colored malar flush, occurs only when cardiac output is low and pulmonary hypertension is severe; cause is cutaneous vasodilation and chronic hypoxemia.

Occasionally, the initial symptoms and signs of MS are those of an embolic event such as stroke. Endocarditis is rare in MS unless MR is also present.

Diagnosis

• Echocardiography

Diagnosis is suspected clinically and confirmed by echocardiography. Two-dimensional echocardiography provides information about the degree of valvular calcification and stenosis and LA size. Doppler echocardiography provides information about the transvalvular gradient and pulmonary artery pressure. Transesophageal echocardiography can be used to detect or exclude small LA thrombi, especially those in the LA appendage, which usually cannot be seen transthoracically.

An ECG and chest x-ray are usually obtained. The ECG may show LA enlargement, manifest as a P wave lasting > 0.12 msec with prominent negative deflection of its terminal component (duration: > 0.04 msec; amplitude: > 0.10 mV) in V_1; broad, notched P waves in lead II; or both. Low voltage in V_1, right axis QRS deviation, and tall R waves in V_1 suggest RV hypertrophy.

Chest x-ray usually shows straightening of the left cardiac border due to a dilated LA appendage, and widening of the carina. With barium in the esophagus, the lateral chest x-ray will show the dilated LA displacing the esophagus posteriorly. The main pulmonary artery (trunk) may be prominent; the descending right pulmonary artery diameter is ≥ 16 mm if pulmonary hypertension is significant. The upper lobe pulmonary veins may be dilated. A double shadow of an enlarged LA may be seen along the right cardiac border. Horizontal lines in the lower posterior lung fields (Kerley B lines) indicate interstitial edema associated with high LA pressure.

Cardiac catheterization, indicated only for perioperative assessment of coronary artery disease (CAD) before surgical repair, can confirm elevated LA and pulmonary artery pressures, mitral gradient and valve area.

Prognosis

The natural history of MS varies, but the interval between onset of symptoms and severe disability is about 7 to 9 yr. Outcome is affected by the patient's preprocedural age and functional status, pulmonary hypertension, and degree of MR. Symptomatic results of balloon valvotomy and surgical commissurotomy

are equivalent in patients with noncalcified valves. However, after a variable period of time, function deteriorates in most patients due to restenosis, and valve replacement may become necessary. Risk factors for death are AF and pulmonary hypertension. Cause of death is most commonly heart failure or pulmonary or cerebrovascular embolism.

Treatment

• Diuretics and sometimes β-blockers or Ca channel blockers

• Valvotomy, commissurotomy, or valve replacement

Asymptomatic patients require no treatment.

Mildly symptomatic patients usually respond to diuretics and, if sinus tachycardia or AF is present, to β-blockers or Ca channel blockers, which can control ventricular rate. Anticoagulants are indicated to prevent thromboembolism. All patients should be encouraged to continue at least low levels of physical exercise despite exertional dyspnea.

More severely symptomatic patients and patients with evidence of pulmonary hypertension require valvotomy, commissurotomy, or valve replacement.

Percutaneous balloon valvotomy is the procedure of choice for younger patients and for patients without heavily calcified valves, subvalvular distortion, LA thrombi, or significant MR. In this fluoroscopic- and echocardiographic-guided procedure, a transvenous catheter with an inflatable distal balloon is passed transseptally from the right atrium to the LA and inflated to separate fused mitral valve leaflets. Outcomes are equivalent to those of more invasive procedures. Complications are uncommon but include MR, embolism, and tamponade.

Patients with severe subvalvular disease, valvular calcification, or LA thrombi may be candidates for surgical commissurotomy, in which fused mitral valve leaflets are separated using a dilator passed through the LV (closed commissurotomy) via a thoracotomy, or by direct vision (open commissurotomy) via a sternotomy. Choice of procedure is based on surgeon's experience and the morphology of the valve, although closed valvotomy is now done less frequently in Western countries.

Valve replacement is confined to patients with severe morphologic changes that make the valve unsuitable for balloon or surgical valvotomy.

Antibiotic prophylaxis against endocarditis is no longer recommended except for patients who have had valve replacement (see Table 215-4 on p. 2200).

Pulmonic Regurgitation

Pulmonic (pulmonary) regurgitation (PR) is incompetency of the pulmonic valve causing blood flow from the pulmonary artery into the right ventricle during diastole. The most common cause is pulmonary hypertension. PR is usually asymptomatic. Signs include a decrescendo diastolic murmur. Diagnosis is by echocardiography. Usually, no specific treatment is necessary except for management of conditions causing pulmonary hypertension.

Secondary pulmonary hypertension (see Table 202-1 on p. 1985) is by far the most common cause of PR. Less common causes are infective endocarditis, surgical repair of tetralogy of Fallot, idiopathic pulmonary artery dilation, and congenital valvular heart disease. Carcinoid syndrome, rheumatic fever and catheter-induced trauma are rare causes. Severe PR is rare and most often results from an isolated congenital defect involving dilation of the pulmonary artery and pulmonary valve annulus.

PR may contribute to development of right ventricular (RV) dilatation and eventually RV dysfunction-induced heart failure (HF), but in most cases, pulmonary hypertension contributes to this complication much more significantly. Rarely, acute RV dysfunction-induced HF develops when endocarditis causes

acute PR.

Symptoms and Signs

PR is usually asymptomatic. A few patients develop symptoms and signs of RV dysfunction-induced HF (see p. 2122).

Palpable signs are attributable to pulmonary hypertension and RV hypertrophy. They include a palpable pulmonic component (P_2) of the 2nd heart sound (S_2) at the left upper sternal border and a sustained RV impulse that is increased in amplitude at the left middle and lower sternal border.

On auscultation, the 1st heart sound (S_1) is normal. The S_2 may be split or single. When split, P_2 may be loud and audible shortly after the aortic component of S_2 (A_2) because of pulmonary hypertension, or P_2 may be delayed because of increased RV stroke volume. S_2 may be single because of prompt pulmonic valve closing with a merged A_2-P_2 or, rarely, because of congenital absence of the pulmonic valve. An RV 3rd heart sound (S_3), 4th heart sound (S_4), or both may be audible with RV dysfunction-induced HF or RV hypertrophy; these sounds can be distinguished from left ventricular heart sounds because they are located at the left parasternal 4th intercostal space and because they grow louder with inspiration.

The murmur of PR due to pulmonary hypertension is a high-pitched, early diastolic decrescendo murmur that begins with P_2 and ends before S_1 and that radiates toward the mid-right sternal edge (Graham Steell's murmur); it is heard best at the left upper sternal border with the diaphragm of the stethoscope while the patient holds the breath at end-expiration and sits upright. The murmur of PR without pulmonary hypertension is shorter, lower-pitched (rougher in quality), and begins after P_2. Both murmurs may resemble the murmur of aortic regurgitation but can be distinguished by inspiration (which makes the PR murmur louder) and by Valsalva release. After Valsalva release, the PR murmur immediately becomes loud (because of immediate venous return to the right side of the heart), but the aortic regurgitation murmur requires 4 or 5 beats to do so. Also, a soft PR murmur may sometimes become even softer during inspiration because this murmur is usually best heard at the 2nd left intercostal space, where inspiration pushes the stethoscope away from the heart.

Diagnosis

• Echocardiography

PR is usually incidentally detected during a physical examination or Doppler echocardiography done for other reasons. An ECG and chest x-ray are obtained. Either may show signs of RV hypertrophy; chest x-ray typically shows evidence of conditions underlying pulmonary hypertension.

Treatment

• Treatment of cause

• Rarely valve replacement

Treatment is management of the condition causing PR. Pulmonic valve replacement is an option if symptoms and signs of RV dysfunction-induced HF develop, but outcomes and risks are unclear because the need for replacement is so infrequent.

Pulmonic Stenosis

Pulmonic stenosis (PS) is narrowing of the pulmonary outflow tract causing obstruction of blood flow from the right ventricle to the pulmonary artery during systole. Most cases are congenital; many remain asymptomatic until adulthood. Signs include a crescendo-decrescendo ejection murmur. Diagnosis is by echocardiography. Symptomatic patients and those with large gradients require balloon valvuloplasty.

Etiology

PS is most often congenital and affects predominantly children; stenosis may be valvular or just below the valve in the outflow tract (infundibular). It commonly is a component of tetralogy of Fallot. Less common causes are Noonan's syndrome (a familial syndrome similar to Turner's syndrome but with no chromosomal defect) and carcinoid syndrome in adults.

Symptoms and Signs

Many children remain asymptomatic for years and do not present to a physician until adulthood. Even then many patients remain asymptomatic. When symptoms develop, they resemble those of aortic stenosis (syncope, angina, dyspnea). Visible and palpable signs reflect the effects of right ventricular (RV) hypertrophy and include a prominent jugular venous *a* wave (due to forceful atrial contraction against a hypertrophied RV), an RV precordial lift or heave, and a left parasternal systolic thrill at the 2nd intercostal space.

On auscultation, the 1st heart sound (S_1) is normal and the 2nd heart sound (S_2) splitting is widened because of prolonged pulmonic ejection (pulmonic component of S_2 [P_2] is delayed). In RV failure and hypertrophy, the 3rd and 4th heart sounds (S_3 and S_4) are rarely audible at the left parasternal 4th intercostal space. A click in congenital PS is thought to result from abnormal ventricular wall tension. The click occurs early in systole (very near S_1) and is not affected by hemodynamic changes. A harsh crescendodecrescendo ejection murmur is audible and is heard best at the left parasternal 2nd (valvular stenosis) or 4th (infundibular stenosis) intercostal space with the diaphragm of the stethoscope when the patient leans forward. Unlike the aortic stenosis murmur, a PS murmur does not radiate, and the crescendo component lengthens as stenosis progresses. The murmur grows louder immediately with Valsalva release and with inspiration; the patient may need to be standing for this effect to be heard.

Diagnosis

• Echocardiography

Diagnosis is confirmed by Doppler echocardiography, which can characterize the stenosis as mild (≤ 40 mm Hg peak gradient), moderate (41 to 79 mm Hg), or severe (≥ 80 mm Hg). ECG is often part of the evaluation; it may be normal or show RV hypertrophy or right bundle branch block. Right heart catheterization is indicated only when 2 levels of obstruction are suspected (valvular and infundibular), when clinical and echocardiographic findings differ, or before intervention is done.

Treatment

• Sometimes balloon valvuloplasty

Prognosis without treatment is generally good and improves with appropriate intervention. Treatment is balloon valvuloplasty, indicated for symptomatic patients and asymptomatic patients with normal systolic function and a peak gradient > 40 to 50 mm Hg.

Tricuspid Regurgitation

Tricuspid regurgitation (TR) is insufficiency of the tricuspid valve causing blood flow from the right ventricle to the right atrium during systole. The most common cause is dilation of the right ventricle. Symptoms and signs are usually absent, but severe TR can cause neck pulsations, a holosystolic murmur, and right ventricular-induced heart failure or atrial fibrillation. Diagnosis is by physical examination and echocardiography. TR is usually benign and does not require treatment, but some patients require annuloplasty or valve repair or replacement.

Etiology

TR is most commonly caused by dilation of the right ventricle (RV) with malfunction of a normal valve, as

occurs in pulmonary hypertension, RV dysfunction-induced heart failure (HF), and pulmonary outflow tract obstruction. TR results less commonly from infective endocarditis in IV drug abusers, carcinoid syndrome, chest or abdominal injury, rheumatic fever, idiopathic myxomatous degeneration, ischemic papillary muscle dysfunction, congenital defects (eg, cleft tricuspid valve, endocardial cushion defects), Ebstein's anomaly (downward displacement of a distorted tricuspid cusp into the RV), Marfan syndrome, and use of certain drugs (eg, ergotamine, fenfluramine, phentermine).

Long-standing severe TR may lead to RV dysfunction-induced HF and atrial fibrillation (AF).

Symptoms and Signs

TR usually causes no symptoms, but some patients experience neck pulsations due to elevated jugular pressures. Acute or severe TR may cause symptoms of RV dysfunction-induced HF. Patients may also develop symptoms of AF or atrial flutter.

Pedal edema or ascites can occur in severe TR.

The only visible sign of moderate to severe TR is jugular venous distention, with a prominent merged *c-v* wave and a steep *y* descent. In severe TR, a right jugular venous thrill may be palpable, as may systolic hepatic pulsation and an RV impulse at the left lower sternal border. On auscultation, the 1st heart sound (S_1) may be normal or barely audible if a TR murmur is present; the 2nd heart sound (S_2) may be split (with a loud pulmonic component [P_2] in pulmonary hypertension) or single because of prompt pulmonic valve closing with merger of P_2 and the aortic component (A_2). An RV 3rd heart sound (S_3) may be audible near the sternum with RV dysfunction-induced HF.

The murmur of TR is a holosystolic murmur heard best at the left middle or lower sternal border or at the epigastrium with the bell of the stethoscope when the patient is sitting upright or standing. The murmur may be high-pitched if TR is trivial and due to pulmonary hypertension, or it may be medium-pitched if TR is severe and has other causes. Sometimes the murmur is not present at all and the diagnosis is best made by the appearance of the jugular venous wave pattern and the presence of hepatic systolic pulsations. The murmur varies with respiration, becoming louder with inspiration (Carvallo's sign).

Diagnosis

• Echocardiography

Mild TR is most often detected on echocardiography done for other reasons. More moderate or severe TR may be suggested by history and physical examination and confirmed by Doppler echocardiography.

An ECG and chest x-ray are also often obtained. ECG is usually normal but, in advanced cases, may show tall peaked P waves caused by right atrial enlargement, a tall R or QR wave in V_1 characteristic of RV hypertrophy, or AF. Chest x-ray is usually normal but, in advanced cases with RV hypertrophy or RV dysfunction-induced HF, may show an enlarged superior vena cava, an enlarged right atrial or RV silhouette (behind the upper sternum in the lateral projection), or pleural effusion.

Cardiac catheterization is rarely indicated for evaluation of TR. When catheterization is indicated (eg, to evaluate coronary anatomy), findings include a prominent right atrial *c-v* wave during ventricular systole.

Prognosis

Few reliable data about prognosis exist because so few patients develop severe TR in isolation.

Treatment

• Treatment of cause

• Sometimes valve repair or replacement

TR is usually well tolerated and often does not require surgical treatment. Medical treatment of causes (eg, HF, endocarditis) is indicated. The tricuspid valve may be repaired during surgery for left-sided heart lesions, such as mitral stenosis or regurgitation. Surgery may also be indicated for TR alone when RV impairment or cirrhosis threatens.

Surgical options include annuloplasty, valve repair, and valve replacement. Annuloplasty, in which the tricuspid valve annulus is sutured to a prosthetic ring or a tailored reduction in annulus circumferential size is done, is indicated when TR is due to annular dilation. Valve repair or replacement is indicated when TR is due to primary valve abnormalities or when annuloplasty is not technically feasible. Tricuspid valve replacement is indicated when TR is due to carcinoid syndrome or Ebstein's anomaly. A bioprosthetic valve is used to reduce the risk of thromboembolism associated with the low pressures of the right heart; in the right heart, unlike the left heart, bioprosthetic valves last > 10 yr.

If endocarditis has damaged the tricuspid valve and cannot be cured with antibiotics, the valve may be totally excised and not replaced until 6 to 9 mo later; this procedure is well tolerated.

Tricuspid Stenosis

Tricuspid stenosis (TS) is narrowing of the tricuspid orifice that obstructs blood flow from the right atrium to the right ventricle. Almost all cases result from rheumatic fever. Symptoms include a fluttering discomfort in the neck, fatigue, cold skin, and right upper quadrant abdominal discomfort. Jugular pulsations are prominent, and a presystolic murmur is often heard at the left sternal edge in the 4th intercostal space and is increased during inspiration. Diagnosis is by echocardiography. TS is usually benign, requiring no specific treatment, but symptomatic patients may benefit from surgery.

TS is almost always due to rheumatic fever; tricuspid regurgitation is almost always also present, as is a mitral valve disorder (usually mitral stenosis). Rare causes of TS include SLE, right atrial (RA) myxoma, congenital malformations, and metastatic tumors. The RA becomes hypertrophied and distended, and sequelae of right heart disease-induced heart failure develop but without right ventricular (RV) dysfunction; the RV remains underfilled and small. Uncommonly, atrial fibrillation occurs.

Symptoms and Signs

The only symptoms of severe TS are fluttering discomfort in the neck (due to giant *a* waves in the jugular pulse), fatigue and cold skin (due to low cardiac output), and right upper quadrant abdominal discomfort (due to an enlarged liver).

The primary visible sign is a giant flickering *a* wave with gradual *y* descent in the jugular veins. Jugular venous distention may occur, increasing with inspiration (Kussmaul's sign). The face may become dusky and scalp veins may dilate when the patient is recumbent (suffusion sign). Hepatic congestion and peripheral edema may occur.

On auscultation, TS may produce a soft opening snap and a mid-diastolic rumble with presystolic accentuation. The murmur becomes louder and longer with maneuvers that increase venous return (exercise, inspiration, leg-raising, Muller's maneuver) and softer and shorter with maneuvers that decrease venous return (standing, Valsalva maneuver).

Findings of TS often coexist with those of mitral stenosis and are less prominent. The murmurs can be distinguished clinically (see
Table 214-1).

Diagnosis

• Echocardiography

Diagnosis is suspected based on history and physical examination and confirmed by Doppler

echocardiography showing a pressure gradient across the tricuspid valve. Two-dimensional echocardiography shows thickened leaflets with reduced movement and RA enlargement. An ECG and chest x-ray are often obtained. ECG may show RA enlargement out of proportion to RV hypertrophy and tall, peaked P waves in inferior leads and V_1. Chest x-ray may show a dilated superior vena

[**Table 214-1.** Distinguishing Murmurs of Tricuspid and Mitral Stenosis]

cava and RA enlargement, indicated by an enlarged right heart border. Liver enzymes are elevated because of passive hepatic congestion.

Cardiac catheterization (see p. 2048) is rarely indicated for evaluation of TS. When catheterization is indicated (eg, to evaluate coronary anatomy), findings include elevated RA pressure with a slow fall in early diastole and a diastolic pressure gradient across the tricuspid valve.

Treatment

• Diuretics and aldosterone antagonists

• Rarely valve repair or replacement

Evidence to guide treatment is scarce. For all symptomatic patients, treatment should include a low-salt diet, diuretics, and aldosterone antagonists. Patients with hepatic congestion leading to cirrhosis or severe systemic venous congestion and effort limitation may benefit from interventions such as balloon valvotomy or valve repair or replacement. Comparative outcomes are unstudied.

Chapter 215. Endocarditis

Introduction

Endocarditis usually refers to infection of the endocardium (ie, infective endocarditis). The term can also include noninfective endocarditis, in which sterile platelet and fibrin thrombi form on cardiac valves and adjacent endocardium. Noninfective endocarditis sometimes leads to infective endocarditis. Both can result in embolization and impaired cardiac function.

Infective Endocarditis

Infective endocarditis is infection of the endocardium, usually with bacteria (commonly, streptococci and staphylococci) or fungi. It causes fever, heart murmurs, petechiae, anemia, embolic phenomena, and endocardial vegetations. Vegetations may result in valvular incompetence or obstruction, myocardial abscess, or mycotic aneurysm. Diagnosis requires demonstration of microorganisms in blood and usually echocardiography. Treatment consists of prolonged antimicrobial treatment and sometimes surgery.

Endocarditis can occur at any age. Men are affected about twice as often. IV drug abusers and immunocompromised patients are at highest risk.

Etiology

The normal heart is relatively resistant to infection. Bacteria and fungi do not easily adhere to the endocardial surface, and constant blood flow helps prevent them from settling on endocardial structures. Thus, 2 factors are generally required for endocarditis: a predisposing abnormality of the endocardium and microorganisms in the bloodstream (bacteremia). Rarely, massive bacteremia or particularly virulent microorganisms cause endocarditis on normal valves.

Endocardial factors: Endocarditis usually involves the heart valves. Major predisposing factors are congenital heart defects, rheumatic valvular disease, bicuspid or calcific aortic valves, mitral valve prolapse, and hypertrophic cardiomyopathy. Prosthetic valves are a particular risk. Occasionally, mural thrombi, ventricular-septal defects, and patent ductus arteriosus sites become infected. The actual nidus for infection is usually a sterile fibrin-platelet vegetation formed when damaged endothelial cells release tissue factor.

Infective endocarditis occurs most often on the left side (eg, mitral or aortic valve). About 10 to 20% of cases are right-sided (tricuspid or pulmonic valve). IV drug abusers have a much higher incidence of right-sided endocarditis (about 30 to 70%).

Microorganisms: Microorganisms that infect the endocardium may originate from distant infected sites (eg, cutaneous abscess, inflamed or infected gums, UTI) or have obvious portals of entry such as a central venous catheter or a drug injection site. Almost any implanted foreign material (eg, ventricular or peritoneal shunt, prosthetic device) is at risk of bacterial colonization, thus becoming a source of bacteremia and hence endocarditis. Endocarditis also may result from asymptomatic bacteremia, such as typically occurs during invasive dental, medical, or surgical procedures. Even toothbrushing and chewing can cause bacteremia (usually due to viridans streptococci) in patients with gingivitis.

Causative microorganisms vary by site of infection, source of bacteremia, and host risk factors (eg, IV drug abuse), but overall, streptococci and *Staphylococcus aureus* cause 80 to 90% of cases. Enterococci, gram-negative bacilli, HACEK organisms (*Haemophilus* sp, *Actinobacillus actinomycetemcomitans, Cardio-bacterium hominis, Eikenella corrodens,* and *Kingella kingae*—see p. 1252), and fungi cause most of the rest. Why streptococci and staphylococci frequently adhere to vegetations and why gram-negative aerobic bacilli seldom adhere are unclear. However, the ability of *S. aureus* to adhere to fibronectin may play a role, as may dextran production by viridans streptococci.

After colonizing vegetations, microorganisms are covered by a layer of fibrin and platelets, which prevents

access by neutrophils, Ig, and complement and thus blocks host defenses.

Pathophysiology

Endocarditis has local and systemic consequences.

Local consequences: Local consequences include formation of myocardial abscesses with tissue destruction and sometimes conduction system abnormalities (usually with low septal abscesses). Severe valvular regurgitation may develop suddenly, causing heart failure and death (usually due to mitral or aortic valve lesions). Aortitis may result from contiguous spread of infection. Prosthetic valve infections are particularly likely to involve valve ring abscesses, obstructing vegetations, myocardial abscesses, and mycotic aneurysms manifested by valve obstruction, dehiscence, and conduction disturbances.

Systemic consequences: Systemic consequences are primarily due to embolization of infected material from the heart valve and, primarily in chronic infection, immune-mediated phenomena. Right-sided lesions typically produce septic pulmonary emboli, which may result in pulmonary infarction, pneumonia, or empyema. Left-sided lesions may embolize to any tissue, particularly the kidneys, spleen, and CNS. Mycotic aneurysms can form in any major artery. Cutaneous and retinal emboli are common. Diffuse glomerulonephritis may result from immune complex deposition.

Classification

Infective endocarditis may have an indolent, subacute course or a more acute, fulminant course with greater potential for rapid decompensation.

Subacute bacterial endocarditis (SBE), although aggressive, usually develops insidiously and progresses slowly (ie, over weeks to months). Often, no source of infection or portal of entry is evident. SBE is caused most commonly by streptococci (especially viridans, microaerophilic, anaerobic, and nonenterococcal group D streptococci and enterococci) and less commonly by *S. aureus, Staphylococcus epidermidis, Gemella morbillorum, Abiotrophia defectiva, Granulicatella* sp, and fastidious *Haemophilus* sp. SBE often develops on abnormal valves after asymptomatic bacteremia due to periodontal, GI, or GU infections.

Acute bacterial endocarditis (ABE) usually develops abruptly and progresses rapidly (ie, over days). A source of infection or portal of entry is often evident. When bacteria are virulent or bacterial exposure is massive, ABE can affect normal valves. It is usually caused by *S. aureus*, group A hemolytic streptococci, pneumococci, or gonococci.

Prosthetic valvular endocarditis (PVE) develops in 2 to 3% of patients within 1 yr after valve replacement and in 0.5%/yr thereafter. It is more common after aortic than after mitral valve replacement and affects mechanical and bioprosthetic valves equally. Early-onset infections (< 2 mo after surgery) are caused mainly by contamination during surgery with antimicrobial-resistant bacteria (eg, *S. epidermidis*, diphtheroids, coliform bacilli, *Candida* sp, *Aspergillus* sp). Late-onset infections are caused mainly by contamination with low-virulence organisms during surgery or by transient asymptomatic bacteremias, most often with streptococci; *S. epidermidis*; diphtheroids; and the fastidious gram-negative bacilli, *Haemophilus* sp, *Actinobacillus actinomycetemcomitans*, and *Cardiobacterium hominis*.

Symptoms and Signs

Symptoms and signs vary based on the classification but are nonspecific.

SBE: Initially, symptoms are vague: low-grade fever (< 39° C), night sweats, fatigability, malaise, and weight loss. Chills and arthralgias may occur. Symptoms and signs of valvular insufficiency may be a first clue. Initially, ≤ 15% of patients have fever or a murmur, but eventually almost all develop both. Physical examination may be normal or include pallor, fever, change in a preexisting murmur or development of a new regurgitant murmur, and tachycardia.

Retinal emboli can cause round or oval hemorrhagic retinal lesions with small white centers (Roth's

spots). Cutaneous manifestations include petechiae (on the upper trunk, conjunctivae, mucous membranes, and distal extremities), painful erythematous subcutaneous nodules on the tips of digits (Osler's nodes), nontender hemorrhagic macules on the palms or soles (Janeway lesions), and splinter hemorrhages under the nails. About 35% of patients have CNS effects, including transient ischemic attacks, stroke, toxic encephalopathy, and, if a mycotic CNS aneurysm ruptures, brain abscess and subarachnoid hemorrhage. Renal emboli may cause flank pain and, rarely, gross hematuria. Splenic emboli may cause left upper quadrant pain. Prolonged infection may cause splenomegaly or clubbing of fingers and toes.

ABE and PVE: Symptoms and signs are similar to those of SBE, but the course is more rapid. Fever is almost always present initially, and patients appear toxic; sometimes septic shock develops. Heart murmur is present initially in about 50 to 80% and eventually in > 90%. Rarely, purulent meningitis occurs.

Right-sided endocarditis: Septic pulmonary emboli may cause cough, pleuritic chest pain, and sometimes hemoptysis. A murmur of tricuspid regurgitation is typical.

Diagnosis

• Blood cultures

• Echocardiography

• Clinical criteria

Because symptoms and signs are nonspecific, vary greatly, and may develop insidiously, diagnosis requires a high index of suspicion. Endocarditis should be suspected in patients with fever and no obvious source of infection, particularly if a heart murmur is present. Suspicion of endocarditis should be very high if blood cultures are positive in patients who have a history of a heart valve disorder, who have had certain recent invasive procedures, or who abuse IV drugs. Patients with documented bacteremia should be examined thoroughly and repeatedly for new valvular murmurs and signs of emboli.

If endocarditis is suspected, 3 blood cultures (20 mL each) should be obtained within 24 h (if presentation suggests ABE, 2 cultures within the first 1 to 2 h). When endocarditis is present and no prior antibiotic therapy was given, all 3 blood cultures usually are positive because the bacteremia is continuous; at least one culture is positive in 99%. Premature use of empiric antibiotic therapy should be avoided in patients with acquired or congenital valvular or shunt lesions to avoid culture-negative endocarditis. If prior antimicrobial therapy was given, blood cultures should still be obtained, but they may be negative.

Echocardiography, typically transthoracic (TTE) rather than transesophageal (TEE), should be done. Although TEE is somewhat more accurate (ie, capable of revealing vegetations too small to be seen on TTE), it is invasive and more costly. TEE should be done when endocarditis is suspected in patients with prosthetic valves, when TTE is nondiagnostic, and when diagnosis of infective endocarditis has been established clinically.

Other than positive blood cultures, there are no specific laboratory findings. Established infections often cause a normocytic-normochromic anemia, elevated WBC count, increased ESR, increased Igs, circulating immune complexes, and rheumatoid factor, but these findings are not diagnostically helpful. Urinalysis often shows microscopic hematuria and, occasionally, RBC casts, pyuria, or bacteriuria.

Identification of the organism and its antimicrobial susceptibility is vital to guide treatment. Blood cultures may require 3 to 4 wk incubation for certain organisms; however, some proprietary, automated culture monitoring systems can identify positive cultures within a week. Other organisms (eg, *Aspergillus* sp) may not produce positive cultures. Some organisms (eg, *Coxiella burnetii, Bartonella* sp, *Chlamydia psittaci, Brucella* sp) require serodiagnosis; others (eg, *Legionella pneumophila*) require special culture media or PCR (eg, *Tropheryma whippelii*). Negative blood culture results may indicate suppression due to prior antimicrobial therapy, infection with organisms that do not grow in standard culture media, or another diagnosis (eg, non-infective endocarditis, atrial myxoma with embolic phenomena, vasculitis).

Infective endocarditis is definitively diagnosed when microorganisms are seen histologically in (or cultured from) endocardial vegetations obtained during cardiac surgery, embolectomy, or autopsy. Because vegetations are not usually available for examination, clinical criteria for establishing a diagnosis (with a sensitivity and specificity > 90%) have been developed (see Table 215-1).

Prognosis

Untreated, infective endocarditis is always fatal. Even with treatment, death is more likely and the prognosis is generally poorer for older people and people who have infection with resistant organisms, an underlying disorder, or a long delay in treatment. The prognosis is also poorer for people with aortic or multiple valve involvement, large vegetations, polymicrobial bacteremia, prosthetic valve infections, mycotic aneurysms, valve ring abscess, and major embolic events. The mortality rate for viridans streptococcal endocarditis without major complications is < 10% but is virtually 100% for *Aspergillus* endocarditis after prosthetic valve surgery.

The prognosis is better with right-sided than left-sided endocarditis because tricuspid valve dysfunction is tolerated better, systemic emboli are absent, and right-sided *S. aureus* endocarditis responds better to antimicrobial therapy.

Treatment

• IV antibiotics (based on the organism and its susceptibility)

• Sometimes valve debridement, repair, or replacement

Treatment consists of a prolonged course of antimicrobial therapy. Surgery may be needed for mechanical complications or resistant organisms. Typically, antimicrobials are given IV. Because they must be given for 2 to 8 wk, home IV therapy is often used.

Any apparent source of bacteremia must be managed: necrotic tissue debrided, abscesses drained, and foreign material and infected devices removed. Existing IV catheters (particularly central venous ones) should be changed. If endocarditis persists in a patient

[**Table 215-1.** Revised Duke Clinical Diagnostic Criteria for Infective Endocarditis]

with a newly inserted central venous catheter, that catheter should also be removed. Organisms within biofilms adherent to catheters and other devices may not respond to antimicrobial therapy, leading to treatment failure or relapse. If continuous infusions are used instead of intermittent boluses, infusions should not be interrupted for long periods.

Antibiotic regimens: Drugs and dosages depend on the microorganism and its antimicrobial susceptibility (for typical regimens, see Table 215-2). Initial therapy before organism identification (but after adequate blood cultures have been obtained) should be broad spectrum to cover all likely organisms. Typically, patients with native valves and no IV drug abuse receive ampicillin 500 mg/h continuous IV infusion plus nafcillin 2 g IV q 4 h plus gentamicin 1 mg/kg IV q 8 h. Patients with a prosthetic valve receive vancomycin 15 mg/kg IV q 12 h plus gentamicin 1 mg/kg q 8 h plus rifampin 300 po q 8 h. IV drug abusers receive nafcillin 2 g IV q 4 h. In all regimens, penicillin-allergic patients require substitution of vancomycin 15 mg/kg IV q 12 h.

IV drug abusers frequently do not adhere to treatment, abuse IV access lines, and tend to leave the hospital too soon. For such patients, short-course IV or (less preferably) oral therapy may be used. For right-sided endocarditis caused by methicillin-sensitive *S. aureus*, nafcillin 2 g IV q 4 h plus gentamicin 1 mg/kg IV q 8 h for 2 wk is effective, as is a 4-wk oral regimen of ciprofloxacin 750 mg po bid plus rifampin 300 mg po bid. Left-sided endocarditis does not respond to 2-wk courses.

Cardiac valve surgery: Surgery (debridement, valve repair or replacement) is frequently required for abscess, persistent infection despite antimicrobial therapy (ie, persistent positive blood cultures or

recurrent emboli), or severe valvular regurgitation.

Timing of surgery requires experienced clinical judgment. If heart failure caused by a correctable lesion is worsening (particularly when the organism is *S. aureus*, a gram-negative bacillus, or a fungus), surgery may be required after only 24 to 72 h of antimicrobial therapy. In patients with prosthetic valves, surgery may be required when TEE shows

[**Table 215-2.** Antibiotic Regimens for Endocarditis]

valve dehiscence on a paravalvular abscess, when valve dysfunction precipitates heart failure, when recurrent emboli are detected, or when the infection is caused by an antimicrobial-resistant organism.

Response to treatment: After starting therapy, patients with penicillin-susceptible streptococcal endocarditis usually feel better, and fever is reduced within 3 to 7 days. Fever may continue for reasons other than persistent infection (eg, drug allergy, phlebitis, infarction due to emboli). Patients with staphylococcal endocarditis tend to respond more slowly. Diminution of vegetation size can be followed by serial echocardiography.

Relapse usually occurs within 4 wk. Antibiotic retreatment may be effective, but surgery may also be required. In patients without prosthetic valves, recrudescence of endocarditis after 6 wk usually results from a new infection rather than a relapse. Even after successful antimicrobial therapy, sterile emboli and valve rupture may occur up to 1 yr later.

Prevention

Preventive dental examination and therapy before surgery to repair heart valves or congenital heart lesions is recommended.

Patients: The American Heart Association (AHA) recommends antimicrobial prophylaxis for patients at high risk of an adverse outcome from infective endocarditis (see AHA guidelines). Such patients include those with

- Prosthetic heart valves
- Previous infective endocarditis
- Certain congenital heart diseases (CHD): Unrepaired cyanotic CHD (including palliative shunts and conduits), completely repaired CHD during the first 6 mo after surgery if prosthetic material or device was used, repaired CHD that has residual defects at or adjacent to the site of repair
- Heart transplant recipients with valvulopathy

Procedures: Most procedures for which prophylaxis is required for high-risk patients are oral-dental procedures that manipulate the gingiva or the periapical region of teeth or perforate the oral mucosa. Other procedures include those respiratory tract procedures in which mucosa is incised, and GI, GU, or musculo-skeletal procedures that involve an area with an established infection (see Table 215-3).

Antibiotic regimens: For most patients and procedures, a single dose shortly before the procedure is effective.

For oral-dental and respiratory procedures, a drug effective against viridans group streptococci is used (see Table 215-4).

For GI, GU, and musculoskeletal procedures on areas involving infected tissue, antibiotics should be selected based on the known organism and its sensitivities. If infection is present but the infecting organism has not been identified, antibiotics for GI and GU prophylaxis should be effective against

enterococci (eg, amoxicillin or ampicillin, and vancomycin for patients who are allergic to penicillin). Antibiotics for skin and musculoskeletal

[Table 215-3. Procedures Requiring Antimicrobial Endocarditis Prophylaxis in High-Risk Patients]

[Table 215-4. Recommended Endocarditis Prophylaxis During Oral-Dental or Respiratory Tract Procedures*]

prophylaxis should be effective against staphylococci and β-hemolytic streptococci (eg, a cephalosporin or vancomycin or clindamycin if infection with methicillin-resistant staphylococci is possible).

Noninfective Endocarditis

Noninfective endocarditis (nonbacterial thrombotic endocarditis) refers to formation of sterile platelet and fibrin thrombi on cardiac valves and adjacent endocardium in response to trauma, circulating immune complexes, vasculitis, or a hypercoagulable state. Symptoms are those of systemic arterial embolism. Diagnosis is by echocardiography and negative blood cultures. Treatment consists of anticoagulants.

Etiology

Vegetations are caused by physical trauma, not infection. They may be clinically undetectable or become a nidus for infection (leading to infective endocarditis), produce emboli, or impair valvular function.

Catheters passed through the right side of the heart may injure the tricuspid and pulmonic valves, resulting in platelet and fibrin attachment at the site of injury. In disorders such as SLE, circulating immune complexes may result in friable platelet and fibrin vegetations along a valve leaflet closure (Libman-Sacks lesions). These lesions do not usually cause significant valvular obstruction or regurgitation. Antiphospholipid syndrome (lupus anticoagulants, recurrent venous thrombosis, stroke, spontaneous abortions, livdo reticularis) also can lead to sterile endocardial vegetations and systemic emboli. Rarely, Wegener's granulomatosis leads to noninfective endocarditis.

Marantic endocarditis: In patients with chronic wasting diseases, disseminated intravascular coagulation, mucin-producing metastatic carcinomas (of lung, stomach, or pancreas), or chronic infections (eg, TB, pneumonia, osteomyelitis), large thrombotic vegetations may form on valves and produce significant emboli to the brain, kidneys, spleen, mesentery, extremities, and coronary arteries. These vegetations tend to form on congenitally abnormal cardiac valves or those damaged by rheumatic fever.

Symptoms and Signs

Vegetations themselves do not cause symptoms. Symptoms result from embolization and depend on the organ affected (eg, brain, kidneys, spleen). Fever and a heart murmur are sometimes present.

Diagnosis

• Blood cultures

• Echocardiography

Noninfective endocarditis should be suspected when chronically ill patients develop symptoms suggesting arterial embolism. Serial blood cultures (see p. 2195) and echocardiography should be done. Negative blood cultures and valvular vegetations (but not atrial myxoma) suggest the diagnosis. Examination of embolic fragments after embolectomy can help make the diagnosis. Differentiation from culture-negative infective endocarditis may be difficult but is important. An anticoagulant is often needed in noninfective endocarditis but is contraindicated in infective endocarditis.

Prognosis

Prognosis is generally poor, more because of the seriousness of predisposing disorders than the cardiac lesion.

Treatment

• Anticoagulation

Treatment consists of anticoagulation with heparin or warfarin, although results of such treatment have not been evaluated. Predisposing disorders should be treated whenever possible.

Chapter 216. Pericarditis

Introduction

Pericarditis is inflammation of the pericardium, often with fluid accumulation. Pericarditis may be caused by many disorders (eg, infection, MI, trauma, tumors, metabolic disorders) but is often idiopathic. Symptoms include chest pain or tightness, often worsened by deep breathing. Cardiac output may be greatly reduced. Diagnosis is based on symptoms, a friction rub, ECG changes, and evidence of pericardial fluid accumulation on x-ray or echocardiogram. Finding the cause requires further evaluation. Treatment depends on the cause, but general measures include analgesics, anti-inflammatory drugs, and sometimes surgery.

Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare.

Anatomy

The pericardium has 2 layers. The visceral pericardium is a single layer of mesothelial cells that is attached to the myocardium, folds back (reflects) on itself over the origin of the great vessels, and joins with a tough, fibrous layer to envelop the heart as the parietal pericardium. The sac created by these layers contains a small amount of fluid (< 25 to 50 mL), composed mostly of an ultrafiltrate of plasma. The pericardium limits distention of the cardiac chambers and increases the heart's efficiency.

The pericardium is richly innervated with sympathetic and somatic afferents. Stretch-sensitive mechanoreceptors sense changes in cardiac volume and tension and may be responsible for transmitting pericardial pain. The phrenic nerves are embedded in the parietal pericardium and are vulnerable to injury during surgery on the pericardium.

Pathophysiology

Pericarditis may be

• Acute

• Chronic

Acute pericarditis develops quickly, causing an inflammatory reaction. Chronic pericarditis (defined as persisting > 6 mo) develops more slowly; its prominent feature is effusion. Acute disease may become chronic. Adverse hemodynamic effects and rhythm disturbance are rare, although cardiac tamponade is possible. Occasionally, pericarditis causes a marked thickening and stiffening of the pericardium (constrictive pericarditis). Pericarditis can lead to inflammation of the epicardial myocardium.

Pericardial effusion is accumulation of fluid in the pericardium. The fluid may be serous fluid (sometimes with fibrin strands), serosanguineous fluid, blood, pus, or chyle.

Cardiac tamponade occurs when a large pericardial effusion impairs cardiac filling, leading to low cardiac output and sometimes shock and death. If fluid (usually blood) accumulates rapidly, even small amounts (eg, 150 mL) may cause tamponade because the pericardium cannot stretch quickly enough to accommodate it. Slow accumulation of up to 1500 mL may not cause tamponade. Loculated effusion may cause localized tamponade on the right or left side of the heart.

Constrictive pericarditis, which is uncommon, results from marked inflammatory, fibrotic thickening of the pericardium. Sometimes the visceral and parietal layers adhere to each other or to the myocardium. The fibrotic tissue often contains Ca deposits. The stiff, thickened pericardium markedly impairs ventricular filling, decreasing stroke volume and cardiac output. Significant pericardial fluid accumulation is rare. Rhythm disturbance is common. The diastolic pressures in the ventricles, atria, and venous beds become virtually the same. Systemic venous congestion occurs, causing considerable transudation of fluid from systemic capillaries, with dependent edema and, later, ascites. Chronic elevation of systemic venous and hepatic venous pressure may lead to cardiac cirrhosis. Constriction of the left atrium, the left

ventricle, or both may elevate pulmonary venous pressure.

Etiology

Acute pericarditis may result from infection, autoimmune and inflammatory disorders, uremia, trauma, MI, or certain drugs (see Table 216-1). Infectious pericarditis is most often viral. Purulent bacterial pericarditis is uncommon but may follow infective endocarditis, pneumonia, septicemia, penetrating trauma, or cardiac surgery. Often, the cause cannot be identified (called nonspecific or idiopathic pericarditis), but many of these cases are probably viral. Overall, the most common causes are viral and idiopathic. Acute MI causes 10 to 15% of cases of acute pericarditis. Post-MI syndrome (Dressler's syndrome) is a less common cause now, occurring mainly when reperfusion with percutaneous transluminal coronary angioplasty (PTCA) or thrombolytic drugs is ineffective in patients with transmural infarction. Pericarditis occurs after pericardiotomy (called postpericardiotomy syndrome) in 5 to 30% of cardiac operations.

[**Table 216-1.** Causes of Acute Pericarditis]

Chronic pericardial effusion or constrictive pericarditis may follow almost any disorder that causes acute pericarditis, as well as TB, a tumor, irradiation, rheumatoid disease, and cardiac surgery. Sometimes no cause of chronic pericarditis is identified. Pericarditis with large effusion (serous, serosanguineous, or bloody) is most commonly caused by metastatic tumors, most often by lung or breast carcinoma, sarcoma, melanoma, leukemia, or lymphoma.

Fibrosis of the pericardium may follow purulent pericarditis or myocardial infection (myocarditis—a common cause in young people) or accompany a connective tissue disorder. In elderly patients, common causes are malignant tumors, MI, and TB. Hemopericardium (accumulation of blood within the pericardium) may lead to pericarditis or pericardial fibrosis; common causes include chest trauma, iatrogenic injury (eg, from cardiac catheterization, pacemaker insertion, or central venous line placement), and rupture of a thoracic aortic aneurysm.

Symptoms and Signs

Some patients present with symptoms and signs of inflammation (acute pericarditis); others present with those of fluid accumulation (pericardial effusion). Symptoms and signs vary depending on the severity of inflammation and the amount and rate of fluid accumulation. Even a large amount of pericardial fluid may be asymptomatic if it develops slowly (eg, over months).

Acute pericarditis: Acute pericarditis tends to cause chest pain and a pericardial rub, sometimes with dyspnea. The first evidence can be tamponade, with hypotension, shock, or pulmonary edema.

Because the innervation of the pericardium and myocardium is the same, the chest pain of pericarditis is sometimes similar to that of myocardial inflammation or ischemia: Dull or sharp precordial or substernal pain may radiate to the neck, trapezius ridge (especially the left), or shoulders. Pain ranges from mild to severe. Unlike ischemic chest pain, pain due to pericarditis is usually aggravated by thoracic motion, cough, breathing, or swallowing food; it may be relieved by sitting up and leaning forward. Tachypnea and nonproductive cough may be present; fever, chills, and weakness are common. In 15 to 25% of patients with idiopathic pericarditis, symptoms recur intermittently for months or years.

The most important physical finding is a triphasic or a systolic and diastolic precordial friction rub. However, the rub is often intermittent and evanescent; it may be present only during systole or, less frequently, only during diastole. If no rub is heard with the patient seated and leaning forward, auscultation may be attempted by listening with the diaphragm of the stethoscope while the patient is on all fours. Sometimes, a pleural component to the rub is noted during breathing, which is due to inflammation of the pleura adjacent to the pericardium. Considerable amounts of pericardial fluid may muffle heart sounds, increase the area of cardiac dullness, and change the size and shape of the cardiac silhouette.

Pericardial effusion: Pericardial effusion is often painless, but when it occurs with acute pericarditis,

pain may be present. Typically, heart sounds are muffled. A pericardial rub may be heard. With large effusions, compression of the base of the left lung can decrease breath sounds (heard near the left scapula) and cause crackles. Arterial pulse, jugular venous pulse, and BP are normal unless intrapericardial pressure increases substantially, causing tamponade.

In the post-MI syndrome, pericardial effusion can occur with fever, friction rub, pleurisy, pleural effusions, and joint pain. This syndrome usually occurs within 10 days to 2 mo after MI. It is usually mild but may be severe. Occasionally, the heart ruptures post-MI, causing hemopericardium and tamponade, usually 1 to 10 days post-MI and more commonly in women.

Cardiac tamponade: The clinical findings are similar to those of cardiogenic shock: decreased cardiac output, low systemic arterial pressure, tachycardia, and dyspnea. Neck veins are markedly dilated. Severe cardiac tamponade is nearly always accompanied by a fall of > 10 mm Hg in systolic BP during inspiration (pulsus paradoxus—see p. 2018). In advanced cases, pulse may disappear during inspiration. (However, pulsus paradoxus can also occur in COPD, bronchial asthma, pulmonary embolism, right ventricular infarction, and noncardiogenic shock.) Heart sounds are muffled unless the effusion is small.

Constrictive pericarditis: Fibrosis or calcification rarely causes symptoms unless constrictive pericarditis develops. The only early abnormalities may be elevated ventricular diastolic, atrial, pulmonary, and systemic venous pressures. Symptoms and signs of peripheral venous congestion (eg, peripheral edema, neck vein distention, hepatomegaly) may appear with an early diastolic sound (pericardial knock), often best heard during inspiration. This sound is due to abrupt slowing of diastolic ventricular filling by the rigid pericardium. Ventricular systolic function (based on ejection fraction) is usually preserved. Prolonged elevation of pulmonary venous pressure results in dyspnea (particularly during exertion) and orthopnea. Fatigue may be severe. Distention of neck veins with a rise in venous pressure during inspiration (Kussmaul's sign) is present; it is absent in tamponade. Pulsus paradoxus is rare and is usually less severe than in tamponade. Lungs are not congested unless severe left ventricular constriction develops.

Diagnosis

• ECG and chest x-ray

• Echocardiography

• Tests to identify cause (eg, pericardial fluid aspiration, pericardial biopsy)

Acute pericarditis: If acute pericarditis is suspected, hospitalization is sometimes required for initial evaluation. ECG and chest x-ray are done. If symptoms or signs of elevated right-sided pressure, tamponade, or an enlarged cardiac silhouette are present, echocardiography to check for effusion and cardiac filling abnormalities is also done. Blood tests may detect leukocytosis and an elevated ESR, but these findings are nonspecific.

The diagnosis is based on the presence of typical clinical findings and ECG abnormalities. Serial ECGs may be needed to show abnormalities.

The ECG in acute pericarditis may show abnormalities confined to ST segments and T waves, usually in most leads (see Fig. 216-1). The ST segments in 2 or 3 of the standard leads become elevated but subsequently return to baseline. Unlike MI, acute pericarditis does not cause reciprocal depression in ST segments (except in leads aVR and V_1), and there are no pathologic Q waves. The PR segment may be depressed. After several days or longer, T waves may become flattened and then inverted throughout the ECG, except in lead aVR; T wave-inversion occurs after the ST segment has returned to baseline and thus differs from the pattern of acute ischemia or MI.

Because the pain of pericarditis may resemble that of acute MI or pulmonary infarction, additional tests (eg, serum cardiac marker measurement, lung scan) may be required if the history and ECG findings are atypical for pericarditis. Troponin is almost always elevated in acute pericarditis due to epicardial

inflammation so it cannot discriminate between acute infarction and pulmonary embolism. The CK level is usually normal in acute pericarditis unless myocarditis is also present.

Postpericardiotomy and post-MI syndromes may be difficult to identify and must be distinguished from recent MI, pulmonary embolism, and pericardial infection after surgery. Pain, friction rub, and fever appearing 2 wk to several months after surgery and a rapid response to aspirin, NSAIDs, or corticosteroids aid diagnosis.

Pericardial effusion: Diagnosis is suggested by clinical findings but often is suspected only after finding an enlarged cardiac silhouette on chest x-ray. On ECG, QRS voltage is often decreased, and sinus rhythm remains in about 90% of patients. With large, chronic effusions, the ECG may show electrical alternans (ie, P, QRS, or T wave amplitude increases and decreases on alternate beats). Electrical alternans is associated with variation in cardiac position (swinging heart). Echocardiography has a high degree of sensitivity and specificity for detecting pericardial fluid.

Patients with a normal ECG, small (< 0.5 L) effusion, and no suspicious findings from the history and examination may be observed with serial examination and echocardiography. Other patients must be evaluated further to determine etiology.

Constrictive pericarditis: Diagnosis may be suspected based on ECG, chest x-ray, and Doppler echocardiography findings, but cardiac catheterization and CT (or MRI) are usually required. Because ventricular filling is restricted, ventricular pressure tracings show a sudden dip followed by a plateau (resembling a square root sign) in early diastole. Rarely, right heart biopsy is needed to exclude restrictive cardiomyopathy.

ECG changes are nonspecific. QRS voltage is usually low. T waves are usually non-specifically abnormal. Atrial fibrillation occurs in about one third of patients; atrial flutter is less common.

Lateral chest x-rays often show pericardial calcification best, but the finding is nonspecific.

The changes on echocardiogram are also nonspecific. When the right and left ventricular filling pressures are equally elevated, Doppler echocardiography helps distinguish constrictive pericarditis from restrictive cardiomyopathy. During inspiration, mitral diastolic flow velocity usually falls > 25% in

[**Fig. 216-1.** Acute pericarditis: Stage 1 ECG.]

constrictive pericarditis but < 15% in restrictive cardiomyopathy. In constrictive pericarditis, inspiratory tricuspid flow velocity increases more than it normally does, but it does not do so in restrictive cardiomyopathy. Determining tissue velocities at the mitral annulus may be helpful when excessively high left atrial pressure blunts respiratory variation in transvalvular velocities.

If clinical and echocardiographic findings suggest constrictive pericarditis, right heart cardiac catheterization is done. It helps confirm and quantify the abnormal hemodynamics that define constrictive pericarditis: Mean pulmonary artery occlusion pressure (pulmonary capillary wedge pressure), pulmonary artery diastolic pressure, right ventricular end-diastolic pressure, and mean right atrial pressure are all at about 10 to 30 mm Hg. The pulmonary artery and right ventricular systolic pressures are normal or modestly elevated, so that pulse pressures are small. In the atrial pressure curve, *x* and *y* descents are typically accentuated; in the ventricular pressure curve, a diastolic dip occurs at the time of rapid ventricular filling. These changes almost always occur with significant constrictive pericarditis.

Right ventricular systolic pressure of > 50 mm Hg often occurs in restrictive cardiomyopathy but less often in constrictive pericarditis. When the pulmonary artery occlusion pressure equals the right atrial mean pressure and an early diastolic dip in the ventricular pressure curve occurs with large *x* and *y* waves in the right atrial curve, either disorder may be present.

CT or MRI can identify pericardial thickening > 5 mm. Such thickening with typical hemodynamic changes can confirm a diagnosis of constrictive pericarditis. When no pericardial thickening or fluid is seen, the diagnosis of restrictive cardiomyopathy is favored but not proved; a normal pericardial thickness does not

exclude the diagnosis of constrictive pericarditis.

Cardiac tamponade: Low voltage and electrical alternans on the ECG suggest cardiac tamponade, but these findings lack sensitivity and specificity. When tamponade is suspected, echocardiography is done unless even a brief delay might be life threatening. Then pericardiocentesis is done immediately for diagnosis and treatment. On an echocardiogram, respiratory variation of transvalvular and venous flows and compression or collapse of right cardiac chambers in the presence of a pericardial effusion support the diagnosis.

If tamponade is suspected, right heart (Swan-Ganz) catheterization may be done. In cardiac tamponade, there is no early diastolic dip in the ventricular pressure record. In the atrial pressure curve, *x* descent is preserved and *y* descent is lost. In contrast, in severe congestive states due to dilated cardiomyopathy, pulmonary artery occlusion or left ventricular diastolic pressure usually exceeds right atrial mean pressure and right ventricular diastolic pressure by ≥ 4 mm Hg.

Diagnosis of cause: After pericarditis is diagnosed, tests to determine etiology and the effect on cardiac function are done. In a young, previously healthy adult who presents with a viral infection and pericarditis, an extensive evaluation is usually unnecessary. Differentiating viral from idiopathic pericarditis is difficult, expensive, and generally of little practical importance.

A biopsy of pericardial tissue or aspiration of pericardial fluid may be needed to establish a diagnosis. Acid-fast stains and cultures of pericardial fluid help identify infectious causes. Samples are examined for malignant cells. However, complete drainage of a newly identified pericardial effusion is usually unnecessary for diagnosis. Persistent (usually > 3 mo) or progressive effusion, particularly when the etiology is uncertain, also warrants pericardiocentesis.

The choice between needle pericardiocentesis and surgical drainage depends on institutional resources and physician experience, the etiology of the effusion, the need for diagnostic tissue samples, and the prognosis of the patient. Needle pericardiocentesis is often best when the etiology is known or the presence of tamponade is in question. Surgical drainage is best when the presence of tamponade is certain but the etiology is unclear.

Laboratory tests of pericardial fluid other than culture and cytology are usually nonspecific. But specific diagnoses are sometimes possible using newer visual, cytologic, and immunologic analysis of fluid obtained via pericardioscopic-guided biopsy.

Cardiac catheterization may be useful for evaluating pericarditis and identifying the cause of reduced cardiac function.

CT or MRI can help identify metastases, although echocardiography is usually sufficient.

Other tests include CBC, acute-phase reactants, routine chemistries, cultures, autoimmune tests, and, when appropriate, tests for HIV, histoplasmosis complement fixation (in endemic areas), streptozyme, and neutralizing antibodies for coxsackievirus, influenza virus, and echovirus. Anti-DNA and anti-RNA antibody tests may be useful. A PPD skin test is done.

Treatment

- Varies by cause
- NSAIDs and sometimes colchicine or corticosteroids for pain and inflammation
- Pericardiocentesis for tamponade and some large effusions
- Sometimes intrapericardial drugs (eg, triamcinolone)
- Sometimes pericardial resection for constrictive pericarditis

• Treatment of cause

Hospitalization to watch for complications is often advisable. Possible causative drugs (eg, anticoagulants, procainamide, phenytoin) are stopped. For cardiac tamponade, immediate pericardiocentesis (see Fig. 216-2) is done; removal of even a small volume of fluid may be lifesaving.

Pain can usually be controlled with aspirin 325 to 650 mg po q 4 to 6 h or other NSAIDs (eg, ibuprofen 600 to 800 mg po q 6 to 8 h); duration of therapy varies, and patients should be treated until an effusion, if present, has resolved. Colchicine 1 mg/day (for 3 mo), added to NSAIDs or given alone, is effective for the initial episode of pericarditis and helps prevent recurrences. The intensity of therapy is dictated by the patient's distress. Severe pain may require opioids and corticosteroids (eg, prednisone 60 to 80 mg po once/day for 1 wk, followed by rapid tapering of the dose). Corticosteroids are particularly useful in acute pericarditis due to uremia or a connective tissue disorder, but tuberculous and pyogenic pericarditis should be excluded before corticosteroid therapy is initiated. Intrapericardial instillation of triamcinolone (300 mg/m^2)

[**Fig. 216-2.** Pericardiocentesis.]

avoids systemic adverse effects and is highly effective. Anticoagulants are usually contraindicated in acute pericarditis because they may cause intrapericardial bleeding and even fatal tamponade; however, they can be given in early pericarditis complicating acute MI. Uncommonly, pericardial resection is required.

Infections are treated with specific antimicrobials. Complete drainage is often necessary.

In postpericardiotomy syndrome, post-MI syndrome, or idiopathic pericarditis, antibiotics are not indicated. An NSAID at full doses may control pain and effusion. When required to control pain, fever, and effusion, prednisone 20 to 60 mg po once/day may be given for 3 to 4 days. If the response is satisfactory, the dose is gradually reduced, and the drug may be stopped in 7 to 14 days. But sometimes many months of treatment are needed.

For pericarditis due to rheumatic fever, another connective tissue disorder, or tumor, therapy is directed at the underlying process.

For pericardial effusion due to trauma, surgery is sometimes required to repair the injury and evacuate blood from the pericardium.

Pericarditis due to uremia may respond to increased frequency of hemodialysis, aspiration, or systemic or intrapericardial adrenal corticosteroids. Intrapericardial triamcinolone may be useful.

Chronic effusions are best treated by treating the cause, if known. Recurrent or persistent symptomatic effusions may be treated with balloon pericardiotomy or a surgical pericardial window. Recurrent effusion due to malignant tumor invasion may be treated with sclerosing drugs. Asymptomatic effusions of unknown cause may require only observation.

Congestion in chronic constrictive pericarditis may be alleviated with bed rest, salt restriction, and diuretics. Digoxin is indicated only if atrial arrhythmias or ventricular systolic dysfunction is present. Symptomatic constrictive pericarditis usually requires pericardial resection. However, patients with mild symptoms, heavy calcification, or extensive myocardial damage may be poor surgical candidates. The mortality rate for pericardial resection may approach 40% in New York Heart Association (NYHA) functional class IV patients. Patients who have constrictive pericarditis due to irradiation or a connective tissue disorder are especially likely to have severe myocardial damage and may not benefit from pericardial resection.

Chapter 217. Diseases of the Aorta and Its Branches

Introduction

The aorta originates at the left ventricle above the aortic valve (aortic root), travels upward (ascending thoracic aorta) to the first branch of the aorta (brachiocephalic or innominate artery), arches up and behind the heart (aortic arch), then turns downward distal to the left subclavian artery (descending aorta) through the thorax (thoracic aorta) and abdomen (abdominal aorta). The abdominal aorta ends by dividing into the 2 common iliac arteries.

Aneurysms

Aneurysms are abnormal dilations of arteries caused by weakening of the arterial wall. Common causes include hypertension, atherosclerosis, infection, trauma, and hereditary or acquired connective tissue disorders. Aneurysms are usually asymptomatic but can cause pain and lead to ischemia, thromboembolism, spontaneous dissection, and rupture, which may be fatal. Diagnosis is by imaging tests (eg, ultrasonography, CT angiography, magnetic resonance angiography, aortography). Treatment of unruptured aneurysms is with risk factor modification (eg, strict BP control) plus surveillance imaging or with open or endovascular stent-graft surgery, depending on size and location of the aneurysm and presence of symptoms. Treatment of ruptured aneurysms is immediate repair by either an open surgical synthetic graft or an endovascular stent-graft.

Aneurysms, defined as a ≥ 50% increase in arterial diameter compared with normal segments, result from localized weakening of an arterial wall. True aneurysms involve all 3 layers of the artery (intima, media, and adventitia). A pseudoaneurysm (false aneurysm) is a communication between the arterial lumen and overlying connective tissue resulting from arterial rupture; a blood-filled cavity forms outside the vessel wall and seals the leak as it thromboses. Aneurysms are classified as fusiform (circumferential widening of the artery) or saccular (localized outpouchings of the artery wall). Thrombi that develop in layers (laminated thrombi) may line the walls of either type and are a sign that blood flow beyond the aneurysm is normal or near normal.

Aneurysms may occur in any artery. Abdominal and thoracic aortic aneurysms are most common and significant; aneurysms of the major branches (subclavian and splanchnic arteries) are much less common. Aneurysms of the cerebrovascular system are discussed in Sidebar 173-1 on p. 1653.

Abdominal Aortic Aneurysms

Abdominal aortic aneurysms (AAAs) account for three fourths of aortic aneurysms and affect 0.5 to 3.2% of the population. Prevalence is 3 times greater in men. AAAs typically begin below the renal arteries but may include renal arterial ostia; about 50% involve the iliac arteries. Generally, aortic diameter ≥ 3 cm constitutes an AAA. Most AAAs are fusiform; some are saccular. Many are lined with laminated thrombi. AAAs involve all layers of the aorta and do not involve dissection; however, a thoracic aortic dissection may extend to the distal abdominal aorta.

Etiology

The most common cause is weakening of the arterial wall, usually associated with atherosclerosis. Other causes include trauma, vasculitis, cystic medial necrosis, and post-surgical anastomotic disruption. Uncommonly, syphilis and localized bacterial or fungal infection, typically due to sepsis or infective endocarditis, weaken the arterial wall and cause infected (mycotic) aneurysms.

Smoking is the strongest risk factor. Other risk factors include hypertension, older age (peak incidence at age 70 to 80), family history (in 15 to 25%), race (more common in whites than in blacks), and male sex.

Symptoms and Signs

Most AAAs are asymptomatic; symptoms and signs, when they do occur, may not be specific. As AAAs

expand, they may cause pain, which is steady, deep, boring, visceral, and felt most prominently in the lumbosacral region; patients may be aware of an abnormally prominent abdominal pulsation. Rapidly enlarging aneurysms that are about to rupture are frequently tender, but most aneurysms grow slowly without symptoms.

The aneurysm may or may not be palpable as a pulsatile mass, depending on its size and patient habitus. The probability that a patient with a pulsatile palpable mass has an aneurysm > 3 cm is about 40% (positive predictive value). A systolic bruit may be audible over the aneurysm.

If an AAA ruptures, patients who do not die immediately typically present with abdominal or back pain, hypotension, and tachycardia. They may have a history of recent upper abdominal trauma, often minimal, or isometric straining (eg, lifting a heavy object).

Patients with an occult AAA sometimes present with symptoms of complications (eg, extremity pain due to embolization of mural thrombi) or of the cause (eg, fever, malaise, or weight loss due to infection or vasculitis). Uncommonly, large AAAs cause disseminated intravascular coagulation, perhaps because large areas of abnormal endothelial surface trigger rapid thrombosis and consumption of coagulation factors.

Diagnosis

• Often incidental

• Confirmation by ultrasonography or CT

• Sometimes CT angiography or magnetic resonance angiography

Most AAAs are diagnosed incidentally when they are detected during physical examination or when abdominal ultrasonography, CT, or MRI is done for other reasons. An AAA should be considered in elderly patients who present with acute abdominal or back pain whether a palpable pulsatile mass is present or not.

When symptoms or physical examination findings suggest AAA, abdominal ultra-sonography or CT is usually the test of choice. Symptomatic patients should have immediate testing to make the diagnosis before catastrophic rupture. For hemodynamically unstable patients with presumed rupture, ultrasonography provides bedside results more rapidly, but intestinal gas and distention may limit its accuracy. Laboratory tests, including CBC, electrolytes, BUN, creatinine, PT, PTT, blood type and cross-match, are done in preparation for possible surgery.

If rupture is not suspected, CT angiography (CTA) or magnetic resonance angiography (MRA) can more precisely characterize aneurysm size and anatomy. If thrombi line the aneurysm wall, CTA may underestimate true size; noncontrast CT may provide a more accurate estimate. Aortography is essential if renal artery or aortoiliac disease is suspected or if correction with endovascular stent-grafts (endografts) is being considered.

Plain abdominal x-rays are neither sensitive nor specific; however, if obtained for other purposes, aortic calcification may outline the aneurysm wall. If a mycotic aneurysm is suspected, bacterial and fungal blood cultures should be done.

Treatment

• Surgery or endovascular stent grafting

Some AAAs enlarge at a steady rate (2 to 3 mm/yr), some enlarge exponentially, and, for unknown reasons, about 20% remain the same size indefinitely. The need for treatment is related to size, which is linked to risk of rupture (see
Table 217-1).

Ruptured AAAs require immediate open surgery or endovascular stent grafting. Without treatment, mortality rate approaches 100%. With open surgical treatment, mortality rate is about 50%; mortality with endovascular stent grafting is generally lower (20 to 30%). The mortality remains high because many patients have coexisting coronary, cerebrovascular, and peripheral atherosclerosis. Patients who present in hemorrhagic shock require fluid resuscitation (see p. 2297) and blood transfusions, but mean arterial pressure should not be elevated to > 70 to 80 mm Hg because bleeding may increase. Preoperative control of hypertension is important.

Elective surgical repair is recommended for aneurysms > 5 to 5.5 cm (when risk of rupture increases to > 5 to 10%/yr), unless coexisting medical conditions contraindicate surgery. Additional indications for elective surgery include increase in aneurysm size by > 0.5 cm within 6 mo regardless of size, chronic abdominal pain, thromboembolic complications, and an iliac or femoral artery aneurysm that causes lower-limb ischemia. Before elective repair, clinical recognition of coronary artery disease (CAD) is essential (see
Table 207-1 on p. 2049) because many patients with an AAA have generalized atherosclerosis and surgical repair poses a major risk of cardiovascular events. Aggressive medical treatment and risk factor control are essential, and revascularization should be considered only in patients with unstable CAD. Routine preoperative coronary angioplasty or bypass surgery has not been shown to be necessary in most patients who can be prepared with good medical management before aneurysm repair.

[**Table 217-1.** Abdominal Aortic Aneurysm Size and Rupture Risk*]

Surgical repair consists of replacing the aneurysmal portion of the abdominal aorta with a synthetic graft. If the iliac arteries are involved, the graft must be extended to include them. If the aneurysm extends above the renal arteries, the renal arteries must be reimplanted into the graft, or bypass grafts must be created.

Placement of an endovascular stent-graft within the aneurysmal lumen via the femoral artery is a less invasive alternative and is indicated when risk of perioperative complications is high. This procedure excludes the aneurysm from systemic blood flow and reduces risk of rupture. The aneurysm eventually thromboses, and 50% of aneurysms decrease in diameter. Short-term results are good, but long-term results are unknown. Complications include angulation, kinking, thrombosis, migration of the stent-graft, and endoleak (persistent flow of blood into the aneurysm sac after endovascular stent-graft placement). Thus, follow-ups must be more frequent after endovascular stent-graft placement than after a traditional repair. If no complications occur, imaging tests are recommended at 1 mo, 6 mo, 12 mo, and every year thereafter. Complex anatomy (eg, short aneurysm neck below renal arteries, severe arterial tortuosity) makes endovascular stent grafting difficult in 30 to 40% of patients.

Repair of aneurysms < 5 cm does not appear to improve survival. These aneurysms should be monitored with ultrasonography every 6 to 12 mo for expansion that warrants treatment. Control of atherosclerotic risk factors, especially smoking cessation and use of antihypertensives as appropriate, is important. If a small or moderate-sized aneurysm becomes > 5.5 cm and if risk of perioperative complications is lower than estimated risk of rupture, AAA repair is indicated; risk of rupture vs that of perioperative complications should be discussed frankly with the patient.

Treatment of a mycotic aneurysm consists of vigorous antimicrobial therapy directed at the pathogen, followed by excision of the aneurysm. Early diagnosis and treatment improve outcome.

Thoracic Aortic Aneurysms

Thoracic aortic aneurysms (TAAs) account for one fourth of aortic aneurysms. Men and women are affected equally. About 40% of TAAs occur in the ascending thoracic aorta (between the aortic valve and brachiocephalic, or innominate, artery), 10% occur in the aortic arch (including the brachiocephalic, carotid, and subclavian arteries), 35% occur in the descending thoracic aorta (distal to the left subclavian artery), and 15% occur in the upper abdomen (as thoracoabdominal aneurysms).

Etiology

Most TAAs result from atherosclerosis. Risk factors for both include prolonged hypertension, dyslipidemia, and smoking; additional risk factors for TAAs include presence of aneurysms elsewhere and older age (peak incidence at age 65 to 70).

Congenital connective tissue disorders (eg, Marfan syndrome, Ehlers-Danlos syndrome) cause cystic medial necrosis, a degenerative change that leads to TAAs complicated by aortic dissection (see p. 2212) and by widening of the proximal aorta and aortic valve (annuloaortic ectasia), which causes aortic regurgitation. Marfan syndrome causes 50% of cases of annuloaortic ectasia, but cystic medial necrosis and its complications can occur in young people even if no congenital connective tissue disorder is present.

Infected (mycotic) TAAs result from hematogenous spread of systemic or local infections (eg, sepsis, pneumonia), lymphangitic spread (eg, in TB), or direct extension (eg, in osteomyelitis or pericarditis). Bacterial endocarditis and tertiary syphilis are uncommon causes. TAAs occur in some connective tissue disorders (eg, temporal arteritis, Takayasu's arteritis, Wegener's granulomatosis).

Blunt chest trauma causes pseudoaneurysms (extramural hematomas due to blood that has leaked through the torn aortic wall).

TAAs may dissect, compress or erode into adjacent structures, lead to thromboembolism, leak, or rupture.

Symptoms and Signs

Most TAAs are asymptomatic until complications (eg, thromboembolism, rupture, aortic regurgitation, dissection) develop. However, compression of adjacent structures can cause chest or back pain, cough, wheezing, dysphagia, hoarseness (due to left recurrent laryngeal or vagus nerve compression), chest pain (due to coronary artery compression), and superior vena cava syndrome. Erosion of aneurysms into the lungs causes hemoptysis or pneumonitis; erosion into the esophagus (aortoesophageal fistula) causes massive hematemesis. Dissection manifests with tearing pain, often radiating to the back. Thromboembolism may cause stroke, abdominal pain (due to mesenteric embolism), or extremity pain. Patients who do not immediately die of a ruptured TAA present with severe chest or back pain and hypotension or shock; exsanguination most commonly occurs into the pleural or pericardial space.

Additional signs include Horner syndrome due to compression of sympathetic ganglia, palpable downward pull of the trachea with each cardiac contraction (tracheal tug), and tracheal deviation. Visible or palpable chest wall pulsations, occasionally more prominent than the left ventricular apical impulse, are unusual but may occur.

Syphilitic aneurysms of the aortic root classically lead to aortic regurgitation and inflammatory stenosis of the coronary artery ostia, which may manifest as chest pain due to myocardial ischemia. Syphilitic aneurysms do not dissect.

Diagnosis

• Incidental x-ray finding

• Confirmation by CTA, MRA, or transesophageal echocardiography (TEE)

TAAs are usually first suspected when a chest x-ray incidentally shows a widened mediastinum or enlargement of the aortic knob. These findings or symptoms and signs suggesting an aneurysm should be followed up with a 3-dimensional imaging test. CTA can delineate aneurysm size and proximal or distant extent, detect leakage, and identify coincident pathology. MRA may provide similar detail. TEE can delineate size and extent and detect leakage of aneurysms of the ascending but not descending aorta; TEE is especially useful for detecting aortic dissection. Contrast angiography provides the best image of the arterial lumen but no information on extraluminal structures, is invasive, and has a significant risk of renal and extremity atheroembolism and contrast nephropathy. Choice of imaging test is based on availability and local experience; however, if rupture is suspected, TEE or CTA, depending on availability, is done immediately.

Aortic root dilation or unexplained ascending aorta aneurysms warrant serologic testing for syphilis. If a mycotic aneurysm is suspected, bacterial and fungal blood cultures are done.

Prognosis

TAAs enlarge an average of 3 to 5 mm/yr; risk factors for rapid enlargement include larger size of aneurysm, location in the descending aorta, and presence of mural thrombi. Median diameter at aneurysm rupture is 6 cm for ascending aneurysms and 7 cm for descending aneurysms, but rupture of smaller aneurysms may occur in patients with Marfan syndrome. Survival rate of patients with untreated large TAAs is 65% at 1 yr and 20% at 5 yr.

Treatment

• Endovascular stent grafting or open surgical repair

• Control of hypertension

Treatment is endovascular stent grafting when anatomically possible and open surgical repair for more complex aneurysms. Immediate control of hypertension is essential.

Ruptured TAAs, if untreated, are universally fatal; they require immediate intervention, as do leaking aneurysms and those that cause acute dissection or acute valvular regurgitation. Surgery involves a median sternotomy (for ascending and aortic arch aneurysms) or left thoracotomy (for descending and thoracoabdominal aneurysms) and subsequent excision of the aneurysm and replacement with a synthetic graft. Transcatheter-placed endovascular stent-grafts (endografts) for descending TAAs are being used more frequently as a less invasive alternative to open surgery. With emergency surgery, 1-mo mortality rate is about 40 to 50%. In patients who survive, incidence of serious complications (eg, renal failure, respiratory failure, severe neurologic damage) is high.

Elective surgery is indicated for large aneurysms (diameter > 5 to 6 cm in the ascending aorta, > 6 to 7 cm in the descending aorta, and, for patients with Marfan syndrome, > 5 cm in any location) and also for those that rapidly enlarge (> 1 cm/yr). Elective surgery is also indicated for symptomatic, traumatic, or syphilitic aneurysms. For syphilitic aneurysms, benzathine penicillin 2.4 million units once/wk IM is given for 3 wk afterward. For patients allergic to penicillin, tetracycline or erythromycin 500 mg po qid for 30 days is acceptable.

Although surgical repair of an intact TAA improves outcome, mortality rate may still exceed 5 to 10% at 30 days and is 40 to 50% at 10 yr. Risk of death increases greatly if aneurysms are complicated (eg, in the aortic arch or thoracoabdominal aorta) or if patients have CAD, are older, are symptomatic, or have preexisting renal insufficiency. Perioperative complications (eg, stroke, spinal injury, renal failure) occur in about 10 to 20%.

Asymptomatic aneurysms that do not meet criteria for elective surgical or endovascular repair are treated with aggressive BP control using a β-blocker and other antihypertensives if necessary. Smoking cessation is essential. Patients require frequent follow-ups to check for symptoms and serial CT every 6 to 12 mo.

Aortic Branch Aneurysms

Aneurysms may occur in any major aortic branch; such aneurysms are much less common than abdominal or thoracic aortic aneurysms. Risk factors include atherosclerosis, hypertension, cigarette smoking, and older age. Localized infection can cause mycotic aneurysms.

Subclavian artery aneurysms are sometimes associated with cervical ribs or thoracic outlet syndrome.

Splanchnic artery aneurysms are uncommon. About 60% occur in the splenic artery, 20% in the hepatic artery, and 5.5% in the superior mesenteric artery. Splenic artery aneurysms occur in more women than

men (4:1). Causes include medial fibromuscular dysplasia, portal hypertension, multiple pregnancies, penetrating or blunt abdominal trauma, pancreatitis, and infection. Hepatic artery aneurysms occur in more men than women (2:1). They may result from previous abdominal trauma, illicit IV drug use, medial degeneration of the arterial wall, or periarterial inflammation. Renal artery aneurysms may dissect or rupture, causing acute occlusion (see p. 2430).

Symptoms and Signs

Symptoms vary. Subclavian aneurysms can cause local pain, a pulsating sensation, venous thrombosis or edema (due to compression of adjacent veins), distal ischemic symptoms, transient ischemic attacks, stroke, or hoarseness or impaired motor and sensory function (due to compression of the recurrent laryngeal nerve or brachial plexus). Superior mesenteric aneurysms may cause abdominal pain and ischemic colitis.

Regardless of location, mycotic or inflammatory aneurysms may cause local pain and sequelae of systemic infection (eg, fever, malaise, weight loss).

Diagnosis

• Ultrasonography or CT

Most aortic branch aneurysms are not diagnosed before rupture, although calcified asymptomatic or occult aneurysms may be seen on x-rays or other imaging tests done for other reasons. Ultrasonography or CT is typically used to detect or confirm aortic branch aneurysms. Angiography can be used as needed to evaluate distal symptoms thought to be due to the aneurysm or embolism.

Treatment

• Open repair or sometimes endovascular stent grafting

Treatment is surgical removal and replacement with a graft. Endovascular repair is an option for some patients. The decision to repair asymptomatic aneurysms is based on risk of rupture, extent and location of the aneurysm, and perioperative risk.

Surgery for subclavian artery aneurysms may involve removal of a cervical rib (if present) before repair and replacement.

For splanchnic aneurysms, risk of rupture and death is as high as 10% and is particularly high for women of childbearing age and for patients with hepatic aneurysms (> 35%). Elective repair of splanchnic aneurysms is therefore indicated for women of childbearing age, for symptomatic aneurysms in other age groups, and for hepatic aneurysms. For splenic aneurysms, repair may consist of ligation without arterial reconstruction or aneurysm exclusion and vascular reconstruction. Depending on location of the aneurysm, splenectomy may be necessary.

Treatment of mycotic aneurysms is aggressive antibiotic therapy directed at the specific pathogen. Generally, these aneurysms must also be surgically repaired.

Aortic Dissection

Aortic dissection is the surging of blood through a tear in the aortic intima with separation of the intima and media and creation of a false lumen. The intimal tear may be a primary event or secondary to hemorrhage within the media. The dissection may occur anywhere along the aorta and extend proximally or distally into other arteries. Hypertension is an important contributor. Symptoms and signs include abrupt onset of tearing chest or back pain, and dissection may result in aortic regurgitation and compromised circulation in branch arteries. Diagnosis is by imaging tests (eg, transesophageal echocardiography, CT angiography, MRI, contrast aortography). Treatment always involves aggressive BP control and serial imaging to monitor progression of dissection; surgical repair of the aorta and placement of a synthetic graft are

needed for ascending aortic dissection and for certain descending aortic dissections. Endovascular stent-grafts are used for certain patients, especially when dissection involves the descending thoracic aorta. One fifth of patients die before reaching the hospital, and up to one third die of operative or perioperative complications.

Evidence of dissection is found in 1 to 3% of all autopsies. African-Americans, men, the elderly, and people with hypertension are especially at risk. Peak incidence occurs at age 50 to 65 or, for patients with congenital connective tissue disorders (eg, Marfan syndrome, Ehlers-Danlos syndrome), at age 20 to 40.

Aortic dissections are classified anatomically. The DeBakey classification system is most widely used.

- Type I (50% of dissections): These dissections start in the ascending aorta and extend at least to the aortic arch and sometimes beyond.

- Type II (35%): These dissections start in and are confined to the ascending aorta.

- Type III (15%): These dissections start in the descending thoractic aorta just beyond the origin of the left subclavian artery and extend distally or, less commonly, proximally.

The Stanford system is simpler.

- Type A: These dissections involve the ascending aorta.

- Type B: These dissections are confined to the descending thoracic aorta.

Although dissection may originate anywhere along the aorta, it occurs most commonly at the proximal ascending aorta (within 5 cm of the aortic valve) or the descending thoracic aorta (just beyond the origin of the left subclavian artery). Rarely, dissection is confined to individual arteries (eg, coronary or carotid arteries), typically in pregnant or postpartum women.

Etiology

Aortic dissection always occurs in the setting of preexisting degeneration of the aortic media. Causes include connective tissue disorders and injury (see Table 217-2).

Atherosclerotic risk factors, notably hypertension, contribute in more than two thirds of patients. After rupture of the intima, which is a primary event in some patients and secondary to hemorrhage within the media in others, blood flows into the media, creating a false channel that extends distally or, less commonly, proximally along the artery.

Pathophysiology

Dissections may communicate back with the true aortic lumen through intimal rupture at a distal site, maintaining systemic blood flow. But serious consequences are common:

- Compromise of the blood supply of tributary arteries (including coronary arteries)

- Aortic valvular dilation and regurgitation

- Heart failure

- Fatal rupture of the aorta through the adventitia into the pericardium, right atrium, or left pleural space

Acute dissections and those present < 2 wk are most likely to cause these complications. Risk decreases at ≥ 2 wk if evidence indicates thrombosis of the false lumen and loss of communication between the true and false lumina.

Variants of aortic dissection include separation of the intima and media by intramural hematoma without a clear intimal tear or flap, intimal tear and bulge without hematoma or false lumen, and dissection or hematoma caused by ulceration of atherosclerotic plaque. These variants are thought to be precursors of classic aortic dissection.

Symptoms and Signs

Typically, excruciating precordial or inter-scapular pain, often described as tearing or ripping, occurs abruptly. The pain frequently migrates from the original location as the dissection extends along the aorta. Up to 20% of patients present with syncope due to severe pain, aortic baroreceptor activation, extracranial cerebral artery obstruction, or cardiac tamponade.

Occasionally, patients present with symptoms of stroke, MI, intestinal infarction, paraparesis or paraplegia due to interruption of the blood supply to the spinal cord, or ischemic limb due to acute distal arterial occlusion.

About 20% of patients have partial or complete deficits of major arterial pulses, which may wax and wane. Limb BPs may differ, sometimes by > 30 mm Hg; this finding suggests a poor prognosis. A murmur of aortic regurgitation is heard in about 50% of patients with proximal dissection. Peripheral signs of aortic regurgitation may be present. Rarely, heart failure results from severe acute aortic regurgitation. Leakage of blood or inflammatory serous fluid into the left pleural space may lead to signs of pleural effusion; occlusion of a limb artery may cause signs of peripheral ischemia or neuropathy. Renal artery occlusion may cause oliguria or anuria. Cardiac tamponade may cause pulsus paradoxus and jugular venous distention.

[**Table 217-2.** Conditions Contributing to Aortic Dissection]

Diagnosis

- Transesophageal echocardiography (TEE), CT angiography (CTA), or magnetic resonance angiography (MRA)

Aortic dissection must be considered in any patient with chest pain, thoracic back pain, unexplained syncope or abdominal pain, stroke, or acute-onset heart failure, especially when pulses or BPs in the limbs are unequal. Such patients require a chest x-ray; in 60 to 90%, the mediastinal shadow is widened, usually with a localized bulge signifying the site of origin. Left pleural effusion is common.

If chest x-ray suggests dissection, TEE, CTA, or MRA is done immediately after the patient is stabilized. Findings of an intimal flap and double lumina confirm dissection.

Multiplanar TEE is 97 to 99% sensitive and, with M-mode echocardiography, is nearly 100% specific. It can be done at the bedside in < 20 min and does not require contrast agents. If TEE is unavailable, CTA is recommended; it has a positive predictive value of 100% and a negative predictive value of 86%.

MRA has nearly 100% sensitivity and specificity for aortic dissection. But it is time-consuming and ill-suited for emergencies. It is probably best used for stable patients with sub-acute or chronic chest pain when dissection is suspected.

Contrast aortography is an option if surgery is being considered. In addition to identifying the origin and extent of dissection, severity of aortic regurgitation, and extent of involvement of the aorta's major branches, aortography helps determine whether simultaneous coronary artery bypass surgery is needed. Echocardiography should also be done to check for aortic regurgitation and thus determine whether the aortic valve should be repaired or replaced concomitantly.

ECG is nearly universally done. However, findings range from normal to markedly abnormal (in acute coronary artery occlusion or aortic regurgitation), so the test is not diagnostically helpful. Assays for soluble elastin compounds and smooth-muscle myosin heavy-chain protein are being studied; they look promising but are not routinely available. Serum CK-MB and troponin may help distinguish aortic

dissection from MI, except when dissection causes MI.

Routine laboratory tests may detect slight leukocytosis and anemia if blood has leaked from the aorta. Increased LDH may be a non-specific sign of celiac or mesenteric arterial trunk involvement.

A cardiothoracic surgeon should be consulted early during the diagnostic evaluation.

Prognosis

About 20% of patients with aortic dissection die before reaching the hospital. Without treatment, mortality rate is 1 to 3%/h during the first 24 h, 30% at 1 wk, 80% at 2 wk, and 90% at 1 yr.

Hospital mortality rate for treated patients is about 30% for proximal dissection and 10% for distal. For treated patients who survive the acute episode, survival rate is about 60% at 5 yr and 40% at 10 yr. About one third of late deaths are due to complications of the dissection; the rest are due to other disorders.

Treatment

• β-Blockers and other drugs to control BP

• Surgery

Patients who do not immediately die of aortic dissection should be admitted to an ICU with intra-arterial BP monitoring; an in-dwelling urethral catheter is used to monitor urine output. Blood should be typed and cross-matched for 4 to 6 units of packed RBCs when surgery is likely. Hemodynamically unstable patients should be intubated.

Drugs to decrease arterial pressure, arterial shear stress, ventricular contractility, and pain are started immediately to maintain systolic BP at ≤ 110 mm Hg or the lowest level compatible with adequate cerebral, coronary, and renal perfusion. A β-blocker is usually used first. Options include metoprolol 5 mg IV up to 4 doses 15 min apart, esmolol 50 to 200 µg/kg/min in a constant IV infusion, and labetalol (an α- and β-adrenergic blocker) 1 to 2 mg/min in a constant IV infusion or 5 to 20 mg IV initial bolus with additional doses of 20 to 40 mg given q 10 to 20 min until BP is controlled or a total of 300 mg has been given, followed by additional 20- to 40-mg doses q 4 to 8 h prn. Alternatives to β-blockers include Ca channel blockers (eg, verapamil 0.05 to 0.1 mg/kg IV bolus or diltiazem 0.25 mg/kg [up to 25 mg] IV bolus or 5 to 10 mg/h by continuous infusion).

If systolic BP remains > 110 mm Hg despite use of β-blockers, nitroprusside in a constant IV infusion can be started at 0.2 to 0.3 µg/kg/min and titrated upward (often to 200 to 300 µg/min) as necessary to control BP. Nitroprusside should not be given without a β-blocker or Ca channel blocker, because reflex sympathetic activation in response to vasodilation can increase ventricular inotropy and aortic shear stress, worsening the dissection.

A trial of drug therapy alone is appropriate for uncomplicated, stable dissection confined to the descending aorta (type B) and for stable, isolated dissection of the aortic arch. Surgery is virtually always indicated if dissection involves the proximal aorta. Surgery is also indicated for limb or visceral ischemia, uncontrolled hypertension, continued aortic enlargement, extension of the dissection, and evidence of aortic rupture, regardless of dissection type. Surgery may also be best for acute distal dissections in patients with Marfan syndrome.

The goal of surgery is to obliterate entry into the false channel and reconstitute the aorta with a synthetic graft. If present, significant aortic regurgitation must be treated by resuspending the aortic leaflets or replacing the valve. Surgical outcomes are best with early, aggressive intervention; mortality rate ranges from 7 to 36%. Predictors of poor outcome include hypotension, renal failure, age > 70, abrupt onset of chest pain, pulse deficit, and ST-segment elevation on ECG.

Stent-grafts that seal entry to the false lumen and improve patency of the true lumen, balloon fenestration (in which an opening is made in the dissection flap that separates the true and false lumina), or both may

be less invasive alternatives for patients with type B dissection if peripheral ischemic complications develop.

All patients, including those treated by surgery or endovascular methods, are given long-term antihypertensive drug therapy, usually including β-blockers, Ca channel blockers, and ACE inhibitors. Almost any combination of antihypertensives is acceptable; exceptions are those that act mainly by vasodilation (eg, hydralazine, minoxidil) and β-blockers that have intrinsic sympathomimetic action (eg, acebutolol, pindolol). Avoidance of strenuous physical activity is often recommended. MRI may be done before discharge and repeated at 6 mo and 1 yr, then every 1 to 2 yr.

The most important late complications include redissection, formation of localized aneurysms in the weakened aorta, and progressive aortic regurgitation. These complications may require surgical or endovascular repair.

Aortitis

Aortitis is inflammation of the aorta, sometimes causing aneurysm or occlusion.

Aortitis is caused by several connective tissue disorders (eg, Takayasu's arteritis, temporal arteritis, ankylosing spondylitis, relapsing polychondritis) and infections (eg, bacterial endocarditis, syphilis, Rocky Mountain spotted fever, fungal infections). It is also a feature of Cogan's syndrome (inflammatory keratitis, vestibular and auditory dysfunction, and aortitis).

Inflammation usually involves all layers of the aorta (intima, media, adventitia) and may lead to occlusion of the aorta or its branches or weakening of the arterial wall, resulting in aneurysms. Pathogenesis, symptoms and signs, diagnosis, and treatment differ by etiology.

Abdominal Aortic Branch Occlusion

Various branches of the aorta can be occluded by atherosclerosis, fibromuscular dysplasia, or other conditions, causing symptoms and signs of ischemia or infarction. Diagnosis is by imaging tests. Treatment is with embolectomy, angioplasty, or sometimes surgical bypass grafting.

Acute occlusion of branches of the abdominal aorta may result from embolism, atherothrombosis, or dissection; chronic occlusion may result from atherosclerosis, fibromuscular dysplasia, or external compression by mass lesions. Common sites of occlusion include

• Superior mesenteric arteries

• Celiac axis

• Renal arteries

• Aortic bifurcation

Chronic occlusion of the celiac axis is more common among women for unclear reasons.

Symptoms and Signs

Clinical manifestations (eg, pain, organ failure, necrosis) result from ischemia or infarction and vary depending on artery involved and acuity.

Acute mesenteric occlusion (see p. 109) causes intestinal ischemia and infarction, resulting in severe, diffuse abdominal pain typically out of proportion to the minimal physical findings. Acute occlusion of the celiac axis may cause liver or spleen infarction.

Chronic mesenteric vascular insufficiency rarely causes symptoms unless both the superior mesenteric artery and celiac axis are substantially narrowed or occluded, because collateral circulation between the major splanchnic trunks is extensive. Symptoms of chronic mesenteric vascular insufficiency typically occur postprandially (as intestinal angina) because digestion requires increased mesenteric blood flow; pain begins about 30 min to 1 h after eating and is steady, severe, and usually periumbilical and may be relieved by sublingual nitroglycerin. Patients become fearful of eating; weight loss, often extreme, is common. Rarely, malabsorption develops and contributes to weight loss. Patients may have an abdominal bruit, nausea, vomiting, diarrhea or constipation, and dark stools.

Acute renal artery embolism causes sudden flank pain, followed by hematuria (see p. 2430). Chronic occlusion may be asymptomatic or result in new or hard-to-control hypertension and other sequelae of renal insufficiency or failure.

Acute occlusion of the aortic bifurcation or distal branches can cause sudden onset of pain at rest, pallor, paralysis, absence of peripheral pulses, and coldness in the legs (see p. 2221). Chronic occlusion can cause intermittent claudication in the legs and buttocks and erectile dysfunction (Leriche syndrome). Femoral pulses are absent. A limb may be jeopardized.

Diagnosis

• Imaging tests

Diagnosis is based primarily on history and physical examination and is confirmed by duplex ultrasonography, CT angiography, magnetic resonance angiography, or traditional angiography.

Treatment

• Embolectomy or percutaneous angioplasty for acute occlusion

• Surgery or angioplasty for chronic occlusion

Acute occlusion is a surgical emergency requiring embolectomy or percutaneous transluminal angioplasty (PTA) with or without stent placement. Chronic occlusion, if symptomatic, may require surgery or angioplasty. Risk factor modification and antiplatelet drugs may help.

Acute mesenteric occlusion (eg, in the superior mesenteric artery), which causes significant morbidity and mortality, requires prompt revascularization. Prognosis is poor if the intestine is not revascularized within 4 to 6 h.

For chronic occlusion of the superior mesenteric artery and celiac axis, dietary modifications may temporarily relieve symptoms. If symptoms are severe, surgical bypass from the aorta to the splanchnic arteries distal to the occlusion usually results in revascularization. Long-term patency of the grafts exceeds 90%. In appropriately selected patients (particularly among older patients who may be poor candidates for surgery), revascularization by PTA with or without stent placement may be successful. Symptoms may resolve rapidly, and weight may be regained.

Acute renal artery occlusion requires embolectomy; sometimes PTA can be done. Initial treatment of chronic occlusion involves antihypertensives. If BP is not controlled adequately or if renal function deteriorates, PTA with stent placement or, when PTA is impossible, open surgical bypass or endarterectomy can improve blood flow.

Occlusion of the aortic bifurcation requires urgent embolectomy, usually done transfemorally. If chronic occlusion of the aortic bifurcation causes claudication, an aortoiliac or aortofemoral graft can be used to surgically bypass the occlusion. PTA is an alternative for selected patients.

Chapter 218. Peripheral Arterial Disorders

Introduction

Peripheral arterial disorders include acrocyanosis, erythromelalgia, fibromuscular dysplasia, peripheral arterial aneurysms, peripheral arterial disease (caused by atherosclerosis), Raynaud's syndrome, and thromboangiitis obliterans.

Acrocyanosis

Acrocyanosis is persistent, painless, symmetric cyanosis of the hands, feet, or face caused by vasospasm of the small vessels of the skin in response to cold.

Acrocyanosis usually occurs in women and is not associated with occlusive arterial disease. The digits and hands or feet are persistently cold and bluish, sweat profusely, and may swell. In acrocyanosis, unlike Raynaud's syndrome, cyanosis persists and is not easily reversed, trophic changes and ulcers do not occur, and pain is absent. Pulses are normal.

Treatment, other than reassurance and avoidance of cold, is usually unnecessary. Vasodilators may be tried but are usually ineffective.

Erythromelalgia

Erythromelalgia is distressing paroxysmal vaso-dilation of small arteries in the feet and hands and, less commonly, in the face, ears, or knees; it causes burning pain, increased skin temperature, and redness.

This rare disorder may be primary (cause unknown) or secondary to myeloproliferative disorders (eg, polycythemia vera, thrombocythemia), hypertension, venous insufficiency, diabetes mellitus, SLE, RA, lichen sclerosus, gout, spinal cord disorders, or multiple sclerosis. Less commonly, the disorder is related to the use of some drugs (eg, nifedipine, bromocriptine). A rare hereditary form of erythromelalgia starts at birth or during childhood.

Burning pain, heat, and redness in the feet or hands last a few minutes to several hours. In most patients, symptoms are triggered by warmth (temperatures of 29 to 32° C) and are typically relieved by immersion in ice water. Trophic changes do not occur. Symptoms may remain mild for years or become severe enough to cause total disability. Generalized vasomotor dysfunction is common, and Raynaud's syndrome may occur.

Diagnosis is clinical. Testing is done to detect causes. Because erythromelalgia may precede a myeloproliferative disorder by several years, repeated blood counts may be indicated. Differential diagnosis includes posttraumatic reflex dystrophies, shoulder-hand syndrome, peripheral neuropathy, causalgia, Fabry's disease, and bacterial cellulitis.

Treatment is warmth avoidance, rest, elevation of the extremity, and application of cold. For primary erythromelalgia, gabapentin may be of benefit. For secondary erythromelalgia, the underlying disorder is treated; aspirin may be helpful when a myeloproliferative disorder is involved.

Fibromuscular Dysplasia

Fibromuscular dysplasia includes a heterogenous group of nonatherosclerotic, noninflammatory arterial changes, causing some degree of vascular stenosis, occlusion, or aneurysm.

Fibromuscular dysplasia usually occurs in women aged 40 to 60. The cause is unknown. However, there may be a genetic component, and smoking may be a risk factor. Fibromuscular dysplasia is more common among people with certain connective tissue disorders (eg, Ehlers-Danlos syndrome type 4, cystic medial necrosis, hereditary nephritis, neurofibromatosis).

Medial dysplasia, the most common type, is characterized by alternating regions of thick and thin fibromuscular ridges containing collagen along the media. In perimedial dysplasia, extensive collagen deposition occurs in the outer half of the media. Fibromuscular dysplasia may affect the renal arteries (60 to 75%), carotid and intracranial arteries (25 to 30%), intra-abdominal arteries (9%), or external iliac arteries (5%).

Fibromuscular dysplasia is usually asymptomatic regardless of location. Symptoms, when they occur, vary by location:

- Claudication in the thighs and calves, femoral bruits, and decreased femoral pulses when leg arteries are affected
- Secondary hypertension when renal arteries are affected
- Transient ischemic attack or stroke symptoms when carotid arteries are affected
- Aneurysmal symptoms when intracranial arteries are affected
- Rarely, mesenteric ischemic symptoms when intra-abdominal arteries are affected

Ultrasonography may suggest the diagnosis, but definitive diagnosis is made by angiography showing a beaded appearance (in medial or perimedial dysplasia) or a concentric band or long, smooth narrowing (in other forms).

Treatment varies by location. It may involve percutaneous transluminal angioplasty, bypass surgery, or aneurysm repair. Smoking cessation is important. Control of other risk factors for atherosclerosis (hypertension, dyslipidemia, diabetes) helps prevent accelerated development of flow-limiting arterial stenoses.

Peripheral Arterial Aneurysms

Peripheral arterial aneurysms are abnormal dilations of the peripheral arteries caused by weakening of the arterial wall (see also p. 2207).

About 70% of peripheral arterial aneurysms are popliteal aneurysms; 20% are iliofemoral aneurysms. Aneurysms at these locations frequently accompany abdominal aortic aneurysms, and > 50% are bilateral. Rupture is relatively infrequent, but these aneurysms may lead to thromboembolism. They occur in men much more often than women (> 20:1); mean age at presentation is 65. Aneurysms in arm arteries are relatively rare; they may cause limb ischemia, distal embolism, and stroke.

Infectious (mycotic) aneurysms may occur in any artery but are most common in the femoral. They are usually due to salmonellae, staphylococci, or *Treponema pallidum* (which causes syphilitic aneurysm).

Common causes include atherosclerosis, popliteal artery entrapment, and septic emboli (which cause mycotic aneurysms).

Peripheral arterial aneurysms are usually asymptomatic at the time of detection. Thrombosis or embolism (or rarely, aneurysm rupture) causes extremities to be painful, cold, pale, paresthetic, or pulseless. Infectious aneurysms may cause local pain, fever, malaise, and weight loss.

Diagnosis is by ultrasonography, magnetic resonance angiography, or CT. Popliteal aneurysms may be suspected when physical examination detects an enlarged, pulsatile artery; the diagnosis is confirmed by imaging tests.

Risk of rupture of extremity aneurysms is low (< 5% for popliteal and 1 to 14% for iliofemoral aneurysms). For leg artery aneurysms, surgical repair is therefore often elective. It is indicated when the arteries are twice normal size or when the patient is symptomatic. However, surgical repair is indicated for all arm

artery aneurysms because serious complications (eg, thromboembolism) are a greater risk. The affected segment of artery is excised and replaced with a graft. Limb salvage rate after surgical repair is 90 to 98% for asymptomatic patients and 70 to 80% for symptomatic patients.

In certain patients, an endovascular-covered stent-graft is another option for repair.

Peripheral Arterial Disease

(Peripheral Vascular Disease)

Peripheral arterial disease (PAD) is atherosclerosis of the extremities (virtually always lower) causing ischemia. Mild PAD may be asymptomatic or cause intermittent claudication; severe PAD may cause rest pain with skin atrophy, hair loss, cyanosis, ischemic ulcers, and gangrene. Diagnosis is by history, physical examination, and measurement of the ankle-brachial index. Treatment of mild PAD includes risk factor modification, exercise, antiplatelet drugs, and cilostazol or possibly pentoxifylline as needed for symptoms. Severe PAD usually requires angioplasty or surgical bypass and may require amputation. Prognosis is generally good with treatment, although mortality rate is relatively high because coronary artery or cerebrovascular disease often coexists.

Etiology

PAD affects about 12% of people in the US; men are affected more commonly. Risk factors are the same as those for atherosclerosis: hypertension, diabetes, dyslipidemia (high low-density lipoprotein [LDL] cholesterol, low high-density lipoprotein [HDL] cholesterol), cigarette smoking (including passive smoking) or other forms of tobacco use, diabetes, and a family history of atherosclerosis. Obesity, male sex, and a high homocysteine level are also risk factors.

Atherosclerosis is a systemic disorder; 50 to 75% of patients with PAD also have clinically significant coronary artery disease (CAD) or cerebrovascular disease. However, CAD may be silent because PAD may prevent patients from exerting themselves enough to trigger angina.

Symptoms and Signs

Typically, PAD causes intermittent claudication, which is a painful, aching, cramping, uncomfortable, or tired feeling in the legs that occurs during walking and is relieved by rest. Claudication usually occurs in the calves but can occur in the feet, thighs, hips, buttocks, or, rarely, arms. Claudication is a manifestation of exercise-induced reversible ischemia, similar to angina pectoris. As PAD progresses, the distance that can be walked without symptoms may decrease, and patients with severe PAD may experience pain during rest, reflecting irreversible ischemia. Rest pain is usually worse distally, is aggravated by leg elevation (often causing pain at night), and lessens when the leg is below heart level. The pain may be burning, tightening, or aching, although this finding is nonspecific. About 20% of patients with PAD are asymptomatic, sometimes because they are not active enough to trigger leg ischemia. Some patients have atypical symptoms (eg, nonspecific exercise intolerance, hip or other joint pain).

Mild PAD often causes no signs. Moderate to severe PAD commonly causes diminished or absent peripheral (popliteal, tibialis posterior, dorsalis pedis) pulses; Doppler ultra-sonography can often detect blood flow when pulses cannot be palpated.

When below heart level, the foot may appear dusky red (called dependent rubor). In some patients, elevating the foot causes loss of color and worsens ischemic pain; when the foot is lowered, venous filling is prolonged (> 15 sec). Edema is usually not present unless the patient has kept the leg immobile and in a dependent position to relieve pain. Patients with chronic PAD may have thin, pale (atrophic) skin with hair thinning or loss. Distal legs and feet may feel cool. The affected leg may sweat excessively and become cyanotic, probably because of sympathetic nerve overactivity.

As ischemia worsens, ulcers may appear (typically on the toes or heel, occasionally on the leg or foot), especially after local trauma. The ulcers tend to be surrounded by black, necrotic tissue (dry gangrene).

They are usually painful, but people with peripheral neuropathy due to diabetes or alcoholism may not feel them. Infection of ischemic ulcers (wet gangrene) occurs readily, causing rapidly progressive cellulitis.

The level of arterial occlusion influences location of symptoms. Aortoiliac PAD may cause buttock, thigh, or calf claudication; hip pain; and, in men, erectile dysfunction (Leriche syndrome). In femoropopliteal PAD, claudication typically occurs in the calf; pulses below the femoral artery are weak or absent. In PAD of more distal arteries, femoropopliteal pulses may be present, but foot pulses are absent.

Arterial occlusive disease occasionally affects the arms, especially the left proximal subclavian artery, causing arm fatigue with exercise and occasionally embolization to the hands.

Diagnosis

• Ankle-brachial BP index

• Ultrasonography

• Angiography before surgery

PAD is suspected clinically but is under-recognized because many patients have atypical symptoms or are not active enough to have symptoms. Spinal stenosis may also cause leg pain during walking but can be distinguished because the pain (called pseudo-claudication) requires sitting, not just rest, for relief, and distal pulses remain intact.

Diagnosis is confirmed by noninvasive testing. First, bilateral arm and ankle systolic BP is measured; because ankle pulses may be difficult to palpate, a Doppler probe may be placed over the dorsalis pedis or posterior tibial arteries. Doppler ultrasonography is often used, because pressure gradients and pulse volume waveforms can help distinguish isolated aortoiliac PAD from femoropopliteal PAD and below-the-knee PAD.

A low (≤ 0.90) ankle-brachial index (ratio of ankle to arm systolic BP) indicates PAD, which can be classified as mild (0.71 to 0.90), moderate (0.41 to 0.70), or severe (≤ 0.40). If the index is normal (0.91 to 1.30) but suspicion of PAD remains high, the index is determined after exercise stress testing. A high index (> 1.30) may indicate noncompressible leg vessels (as occurs in Monckeberg's arteriosclerosis with calcification of the arterial wall). If the index is > 1.30 but suspicion of PAD remains high, additional tests (eg, Doppler ultrasonography, measurement of BP in the first toe using toe cuffs) are done to check for arterial stenoses or occlusions. Ischemic lesions are unlikely to heal when systolic BP is < 55 mm Hg in patients without diabetes or < 70 mm Hg in patients with diabetes; below-the-knee amputations usually heal if BP is ≥ 70 mm Hg. Peripheral arterial insufficiency can also be assessed by transcutaneous oximetry (TcO_2). A TcO_2 level < 40 mm Hg is predictive of poor healing, and a value < 20 mm Hg is consistent with critical limb ischemia.

Angiography provides details of the location and extent of arterial stenoses or occlusion; it is a prerequisite for surgical correction or percutaneous transluminal angioplasty (PTA). It is not a substitute for noninvasive testing because it provides no information about the functional significance of abnormal findings. Magnetic resonance angiography and CT angiography are noninvasive tests that may eventually supplant contrast angiography.

Treatment

• Risk factor modification

• Exercise

• Antiplatelet drugs

• Sometimes pentoxifylline or cilostazol for claudication

• PTA or surgery for severe disease

All patients require aggressive risk factor modification, including smoking cessation and control of diabetes, dyslipidemia, hypertension, and hyperhomocysteinemia. β-Blockers are safe unless PAD is very severe.

Exercise—35 to 50 min of treadmill or track walking in an exercise-rest-exercise pattern 3 to 4 times/wk—is an important but underused treatment. It can increase symptom-free walking distance and improve quality of life. Mechanisms probably include increased collateral circulation, improved endothelial function with microvascular vasodilation, decreased blood viscosity, improved RBC filterability, decreased ischemia-induced inflammation, and improved O_2 extraction.

Patients are advised to keep the legs below heart level. For pain relief at night, the head of the bed can be elevated about 10 to 15 cm (4 to 6 inches) to improve blood flow to the feet.

Patients are also advised to avoid cold and drugs that cause vasoconstriction (eg, pseudoephedrine, contained in many sinus and cold remedies).

Preventive foot care is crucial, especially for patients with diabetes. It includes daily foot inspection for injuries and lesions; treatment of calluses and corns by a podiatrist; daily washing of the feet in lukewarm water with mild soap, followed by gentle, thorough drying; and avoidance of thermal, chemical, and mechanical injury, especially that due to poorly fitting footwear. For foot ulcer management, see also p. 740.

Antiplatelet drugs may modestly lessen symptoms and improve walking distance; more importantly, these drugs modify atherogenesis and help prevent acute coronary syndromes (see p. 2109) and transient ischemic attacks (see p. 1651). Options include aspirin 81 to 162 mg once/day, aspirin 25 mg plus dipyridamole 200 mg po once/day, and clopidogrel 75 mg po once/day or ticlopidine 250 mg po bid with or without aspirin. Aspirin is typically used alone first, followed by addition or substitution of other drugs if PAD progresses.

For relief of claudication, pentoxifylline 400 mg po tid with meals or cilostazol 100 mg po bid may be used to relieve intermittent claudication by improving blood flow and enhancing tissue oxygenation in affected areas; however, these drugs are no substitute for risk factor modification and exercise. Use of pentoxifylline is controversial because evidence of its effectiveness is mixed. A trial of ≥ 2 mo may be warranted, because adverse effects are uncommon and mild. The most common adverse effects of cilostazol are headache and diarrhea. Cilostazol is contraindicated by severe heart failure.

Other drugs that may relieve claudication are being studied; they include L-arginine (the precursor of endothelium-dependent vasodilator), nitric oxide, vasodilator prostaglandins, and angiogenic growth factors (eg, vascular endothelial growth factor [VEGF], basic fibroblast growth factor [bFGF]). Gene therapy for PAD is also being studied. In patients with severe limb ischemia, long-term parenteral use of vasodilator prostaglandins may decrease pain and facilitate ulcer healing, and intramuscular gene transfer of DNA encoding VEGF may promote collateral blood vessel growth.

Percutaneous transluminal intervention: PTA with or without stent insertion is the primary nonsurgical method for dilating vascular occlusions. PTA with stent insertion may keep the artery open better than balloon compression alone, with a lower rate of reocclusion. Stents work best in large arteries with high flow (iliac and renal); they are less useful for smaller arteries and for long occlusions.

Indications for PTA are similar to those for surgery: intermittent claudication that inhibits daily activities, rest pain, and gangrene. Suitable lesions are flow-limiting, short iliac stenoses (< 3 cm) and short, single or multiple stenoses of the superficial femoropopliteal segment. Complete occlusions (up to 10 or 12 cm long) of the superficial femoral artery can be successfully dilated, but results are better for occlusions ≤ 5 cm. PTA is also useful for localized iliac stenosis proximal to a bypass of the femoropopliteal artery.

PTA is less useful for diffuse disease, long occlusions, and eccentric calcified plaques. Such lesions are particularly common in patients with diabetes, often affecting small arteries.

Complications of PTA include thrombosis at the site of dilation, distal embolization, intimal dissection with occlusion by a flap, and complications related to heparin use.

With appropriate patient selection (based on complete and adequate angiography), the initial success rate approaches 85 to 95% for iliac arteries and 50 to 70% for thigh and calf arteries. Recurrence rates are relatively high (25 to 35% at ≤ 3 yr); repeat PTA may be successful.

Surgery: Surgery is indicated for patients who can safely tolerate a major vascular procedure and whose severe symptoms do not respond to noninvasive treatments. The goal is to relieve symptoms, heal ulcers, and avoid amputation. Because many patients have underlying CAD, which places them at risk of acute coronary syndromes during surgical procedures for PAD, patients usually undergo cardiac evaluation prior to surgery.

Thromboendarterectomy (surgical removal of an occlusive lesion) is used for short, localized lesions in the aortoiliac, common femoral, or deep femoral arteries.

Revascularization (eg, femoropopliteal bypass grafting) uses synthetic or natural materials (often the saphenous or another vein) to bypass occlusive lesions. Revascularization helps prevent limb amputation and relieve claudication.

In patients who cannot undergo major vascular surgery, sympathectomy may be effective when a distal occlusion causes severe ischemic pain. Chemical sympathetic blocks are as effective as surgical sympathectomy, so the latter is rarely done.

Amputation is a procedure of last resort, indicated for uncontrolled infection, unrelenting rest pain, and progressive gangrene. Amputation should be as distal as possible, preserving the knee for optimal use with a prosthesis.

External compression therapy: External pneumatic compression of the lower limb to increase distal blood flow is an option for limb salvage in patients who have severe PAD and are not candidates for surgery. Theoretically, it controls edema and improves arterial flow, venous return, and tissue oxygenation, but data supporting its use are lacking. Pneumatic cuffs or stockings are placed on the lower leg and inflated rhythmically during diastole, systole, or part of both periods for 1 to 2 h several times/wk.

Acute Peripheral Arterial Occlusion

Peripheral arteries may be acutely occluded by a thrombus, an embolus, aortic dissection, or acute compartment syndrome.

Acute peripheral arterial occlusion may result from rupture and thrombosis of an atherosclerotic plaque, an embolus from the heart or thoracic or abdominal aorta, an aortic dissection, or acute compartment syndrome (see p. 3213).

Symptoms and signs are sudden onset in an extremity of the 5 P's: severe pain, polar sensation (coldness), paresthesias (or anesthesias), pallor, and pulselessness. The occlusion can be roughly localized to the arterial bifurcation just distal to the last palpable pulse (eg, at the common femoral bifurcation when the femoral pulse is palpable; at the popliteal bifurcation when the popliteal pulse is palpable). Severe cases may cause loss of motor function. After 6 to 8 h, muscles may be tender when palpated.

Diagnosis is clinical. Immediate angiography is required to confirm location of the occlusion, identify collateral flow, and guide therapy.

Treatment consists of embolectomy (catheter or surgical), thrombolysis, or bypass surgery. The decision to do surgical thromboembolectomy vs thrombolysis is based on the severity of ischemia, the extent or location of the thrombus, and the general medical condition of the patient.

A thrombolytic (fibrinolytic) drug, especially when given by regional catheter infusion, is most effective for patients with acute arterial occlusions of < 2 wk and intact motor and sensory limb function. Tissue plasminogen activator and urokinase are most commonly used. A catheter is threaded to the occluded area, and the thrombolytic drug is given at a rate appropriate for the patient's size and the extent of thrombosis. Treatment is usually continued for 4 to 24 h, depending on severity of ischemia and signs of thrombolysis (relief of symptoms and return of pulses or improved blood flow shown by Doppler ultrasonography). About 20 to 30% of patients with acute arterial occlusion require amputation within the first 30 days.

Raynaud's Syndrome

Raynaud's syndrome is vasospasm of parts of the hand in response to cold or emotional stress, causing reversible discomfort and color changes (pallor, cyanosis, erythema, or a combination) in one or more digits. Occasionally, other acral parts (eg, nose, tongue) are affected. The disorder may be primary or secondary. Diagnosis is clinical; testing focuses on distinguishing primary from secondary disease. Treatment of uncomplicated cases includes avoidance of cold, biofeedback, smoking cessation, and, as needed, vasodilating Ca channel blockers (eg, nifedipine) or prazosin.

Overall prevalence is about 3 to 5%; women are affected more than men, and younger people are affected more than older people. Raynaud's syndrome is probably due to an exaggerated α_2-adrenergic response that triggers vasospasm; the mechanism is not defined.

Primary Raynaud's syndrome is much more common (> 80% of cases) than secondary; it occurs without symptoms or signs of other disorders. In the remaining 20% of patients with Raynaud's symptoms, a causative underlying disease (eg, systemic sclerosis) will be evident at initial presentation or diagnosed subsequently.

Secondary Raynaud's syndrome accompanies various disorders and conditions, mostly connective tissue disorders (see Table 218-1).

Nicotine commonly contributes to it but is often overlooked. Raynaud's syndrome may accompany migraine headaches, variant angina, and pulmonary hypertension, suggesting that these disorders share a common vasospastic mechanism.

Symptoms and Signs

Sensations of coldness, burning pain, paresthesias, or intermittent color changes of one or more digits are precipitated by exposure to cold, emotional stress, or vibration. All can be reversed by removing the stimulus. Re-warming the hands accelerates restoration of normal color and sensation.

Color changes are clearly demarcated across the digit. They may be triphasic (pallor, followed by cyanosis and after warming by erythema due to reactive hyperemia), biphasic (cyanosis, erythema), or uniphasic (pallor or cyanosis only). Changes are often symmetric. Raynaud's syndrome does not occur proximal to the metacarpophalangeal joints; it most commonly affects the middle 3 fingers and rarely affects the thumb. Vasospasm may last minutes to hours but is rarely severe enough to cause tissue loss.

[**Table 218-1.** Causes of Secondary Raynaud's Syndrome]

Raynaud's syndrome secondary to a connective tissue disorder may progress to painful digital gangrene; Raynaud's syndrome secondary to systemic sclerosis tends to cause extremely painful, infected ulcers on the fingertips.

Diagnosis

• Clinical criteria

• Examination and testing for underlying disorder

Raynaud's syndrome itself is diagnosed clinically. Acrocyanosis (see p. 2216) also causes color change of the digits in response to cold but differs from Raynaud's in that it is persistent, not easily reversed, and does not cause trophic changes, ulcers, or pain.

Primary and secondary forms are distinguished clinically, supported by vascular laboratory studies and blood testing. Vascular laboratory testing includes digital pulse wave forms and pressures. The primary blood testing is the panel for collagen vascular diseases.

Clinical findings: A thorough history and physical examination directed at identifying a causative disorder are helpful but rarely diagnostic.

Findings suggesting primary Raynaud's syndrome are the following:

• Age at onset < 40 (in two thirds of cases)

• Mild symmetric attacks affecting both hands

• No tissue necrosis or gangrene

• No history or physical findings suggesting another cause

Findings suggesting secondary Raynaud's syndrome are the following:

• Age at onset > 30

• Severe painful attacks that may be asymmetric and unilateral

• Ischemic lesions

• History and findings suggesting an accompanying disorder

Laboratory testing: Blood tests (eg, measurement of ESR, antinuclear antibodies, rheumatoid factor, anticentromere antibody, anti-SCL-70 antibody) are done to detect accompanying disorders.

Treatment

• Trigger avoidance

• Smoking cessation

• Ca channel blockers or prazosin

Treatment of the primary form involves avoidance of cold, smoking cessation, and, if stress is a triggering factor, relaxation techniques (eg, biofeedback) or counseling. Drugs are used more often than behavioral treatments because of convenience. Vasodilating Ca channel blockers (extended-release nifedipine 60 to 90 mg po once/day, amlodipine 5 to 20 mg po once/day, felodipine 2.5 to 10 mg po bid, or isradipine 2.5 to 5 mg po bid) are most effective, followed by prazosin 1 to 5 mg po once/day or bid. Topical nitroglycerine paste, pentoxifylline 400 mg po bid or tid with meals, or both may be effective, but no evidence supports routine use. β-Blockers, clonidine, and ergot preparations are contraindicated because they cause vasoconstriction and may trigger or worsen symptoms.

Treatment of the secondary form focuses on the underlying disorder. Ca channel blockers or prazosin is also indicated. Antibiotics, analgesics, and, occasionally, surgical debridement may be necessary for ischemic ulcers. Low-dose aspirin may prevent thrombosis but theoretically may worsen vasospasm via prostaglandin inhibition. IV prostaglandins (alprostadil, epoprostenol, iloprost) appear to be effective and may be an option for patients with ischemic digits. However, these drugs are not yet widely available, and

their role is yet to be defined. Cervical or local sympathectomy is controversial; it is reserved for patients with progressive disability unresponsive to all other measures, including treatment of underlying disorders. Sympathectomy often abolishes the symptoms, but relief may last only 1 to 2 yr.

Thromboangiitis Obliterans

(Buerger's Disease)

Thromboangiitis obliterans is inflammatory thrombosis of small and medium-sized arteries and some superficial veins, causing arterial ischemia in distal extremities and superficial thrombophlebitis. Tobacco use is the primary risk factor. Symptoms and signs include claudication, nonhealing foot ulcers, rest pain, and gangrene. Diagnosis is by clinical findings, noninvasive vascular testing, angiography, and exclusion of other causes. Treatment is cessation of tobacco use. Prognosis is excellent when tobacco use is stopped, but when it is not, the disorder inevitably progresses, often requiring amputation.

Thromboangiitis obliterans occurs almost exclusively in tobacco users (nearly all of them smokers) and predominantly affects men aged 20 to 40; it rarely occurs in women. It occurs more commonly in people with HLAA9 and HLA-B5 genotypes. Prevalence is highest in Asia and the Far and Middle East.

Thromboangiitis obliterans produces segmental inflammation in small and medium-sized arteries and, frequently, in superficial veins of the extremities. In acute thromboangiitis obliterans, occlusive thrombi accompany neutrophilic and lymphocytic infiltration of the intima; endothelial cells proliferate, but the internal elastic lamina remains intact. In an intermediate phase, thrombi organize and recanalize incompletely; the media is preserved but may be infiltrated with fibroblasts. In older lesions, periarterial fibrosis may occur, sometimes affecting the adjacent vein and nerve.

The cause is unknown, although cigarette smoking is a primary risk factor. The mechanism may involve delayed hypersensitivity or toxic angiitis. According to another theory, thromboangiitis obliterans may be an autoimmune disorder caused by cell-mediated sensitivity to types I and III human collagen, which are constituents of blood vessels.

Symptoms and Signs

Symptoms and signs are those of arterial ischemia and superficial thrombophlebitis. Some patients have a history of migratory phlebitis, usually in the superficial veins of a foot or leg.

Onset is gradual, starting in the most distal vessels of the upper and lower extremities with coldness, numbness, tingling, or burning. These symptoms may develop before objective evidence of disease. Raynaud's syndrome is common. Intermittent claudication occurs in the affected extremity (usually in the arch of the foot or in the leg; rarely in the hand, arm, or thigh) and may progress to rest pain. Frequently, if pain is severe and persistent, the affected leg feels cold, sweats excessively, and becomes cyanotic, probably because of sympathetic nerve overactivity. Later, ischemic ulcers develop in most patients and may progress to gangrene.

Pulses are impaired or absent in one or more pedal arteries and often at the wrist. In young men who smoke and have extremity ulcers, a positive Allen's test (the hand remains pale after the examiner simultaneously compresses the radial and ulnar arteries, then alternately releases them) suggests the disorder. Pallor with elevation and rubor with dependency frequently occur in affected hands, feet, or digits. Ischemic ulceration and gangrene, usually of one or more digits, may occur early in the disorder but not acutely. Noninvasive tests show greatly decreased blood flow and pressure in the affected toes, feet, and fingers.

Diagnosis

• Other causes of ischemia excluded by testing

• Angiography

History and physical examination suggest the diagnosis. It is confirmed when the ankle-brachial index (ratio of ankle to arm systolic BP) for legs or segmental pressures for arms indicates distal ischemia, when echocardiography excludes cardiac emboli, when blood tests (eg, measurement of antinuclear antibody, rheumatoid factor, complement, anticentromere antibody, anti-SCL-70 antibody) exclude vasculitis, when tests for antiphospholipid antibodies exclude antiphospholipid antibody syndrome (although these levels may be slightly elevated in thromboangiitis obliterans), and when angiography shows characteristic findings (segmental occlusions of the distal arteries in the hands and feet, tortuous, corkscrew collateral vessels around occlusions, and no atherosclerosis).

Treatment

• Smoking cessation

• Local measures

• Sometimes drug therapy

Treatment is cessation of tobacco use (see p. 3432). Continuing to use tobacco inevitably leads to disease progression and severe ischemia, often requiring amputation.

Other measures include avoiding cold; avoiding drugs that can cause vasoconstriction; and avoiding thermal, chemical, and mechanical injury, especially that due to poorly fitting footwear. For patients in the first phase of smoking cessation, iloprost 0.5 to 3 ng/kg/min IV infusion over 6 h may help prevent amputation. Pentoxifylline, Ca channel blockers, and thromboxane inhibitors may be tried empirically, but no data support their use. Use of antiendothelial cell antibody measurements to follow the course of disease is being studied. When these options fail, lumbar sympathetic chemical ablation or surgical sympathectomy can alleviate ischemic pain and enhance ulcer healing in about 70% of patients with an ankle-brachial pressure index ≥ 0.35 and no diabetes mellitus.

Chapter 219. Peripheral Venous and Lymphatic Disorders

Introduction

Venous and lymphatic disorders usually involve impairment of flow, abnormal vessel dilation, or both.

Deep Venous Thrombosis

Deep venous thrombosis (DVT) is clotting of blood in a deep vein of an extremity (usually calf or thigh) or the pelvis. DVT is the primary cause of pulmonary embolism. DVT results from conditions that impair venous return, lead to endothelial injury or dysfunction, or cause hypercoagulability. DVT may be asymptomatic or cause pain and swelling in an extremity. Diagnosis is by history, physical examination, and duplex ultrasonography, with D-dimer or other testing as necessary. Treatment is with anticoagulants. Prognosis is generally good with prompt, adequate treatment. Common long-term complications include venous insufficiency with or without postphlebitic syndrome.

DVT occurs most commonly occurs in the lower extremities, or pelvis (see Fig. 219-1). It can also develop in deep veins of the upper extremities (4 to 13% of DVT cases).

Lower extremity DVT is much more likely to cause pulmonary embolism (PE), possibly because of the higher clot burden. The superficial femoral and popliteal veins in the thighs and the posterior tibial veins in the calves are most commonly affected. Calf vein DVT is less likely to be a source of large emboli but can cause repeated showers of small emboli or propagate to the proximal thigh veins and from there cause PE. About 50% of patients with DVT have occult PE, and at least 30% with PE have demonstrable DVT.

Etiology

Many factors can contribute to DVT (see Table 219-1). Cancer is a risk factor for DVT, particularly in elderly patients and in patients with recurrent thrombosis. The association is strongest for mucin-secreting endothelial cell tumors. Occult cancers may be present in patients with apparently idiopathic DVT, but extensive workup of patients for tumors is not recommended.

Pathophysiology

Lower extremity DVT most often results from impaired venous return (eg, in immobilized patients), endothelial injury or dysfunction (eg, after leg fractures), or hypercoagulability.

Upper extremity DVT most often results from endothelial injury due to central venous catheters, pacemakers, or injection drug use. Upper extremity DVT occasionally occurs as part of superior vena cava (SVC) syndrome or results from a hypercoagulable state or subclavian vein compression at the thoracic outlet. The compression may be due to a normal or an accessory first rib or fibrous band (thoracic outlet syndrome) or occur during strenuous arm activity (effort thrombosis, or Paget Schroetter syndrome, which accounts for 1 to 4% of upper extremity DVT cases).

[**Fig. 219-1.** Deep veins of the legs.]

DVT usually begins in venous valve cusps. Thrombi consist of thrombin, fibrin, and RBCs with relatively few platelets (red thrombi); without treatment, thrombi may propagate proximally or travel to the lungs.

Complications: Common complications include chronic venous insufficiency and postphlebitic syndrome, as well as PE.

Much less commonly, acute DVT leads to phlegmasia alba dolens or phlegmasia cerulea dolens, both of which, unless promptly diagnosed and treated, can result in venous gangrene.

In **phlegmasia alba dolens**, a rare complication of DVT during pregnancy, the leg turns milky white. Pathophysiology is unclear, but edema may increase soft-tissue pressure beyond capillary perfusion pressures, resulting in tissue ischemia and wet gangrene.

In **phlegmasia cerulea dolens**, massive iliofemoral venous thrombosis causes near-total venous occlusion; the leg becomes ischemic, extremely painful, and cyanotic. Pathophysiology may involve complete stasis of venous and arterial blood flow in the lower extremity because venous return is occluded or massive edema cuts off arterial blood flow. Venous gangrene may result.

Rarely, venous clots can become infected. Jugular vein suppurative thrombophlebitis (Lemierre syndrome), a bacterial (usually anaerobic) infection of the internal jugular vein and surrounding soft tissues, may follow tonsillopharyngitis and is often complicated

[**Table 219-1.** Risk Factors for Venous Thrombosis]

by bacteremia and sepsis. In septic pelvic thrombophlebitis, pelvic thromboses develop postpartum and become infected, causing intermittent fever. Suppurative (septic) thrombophlebitis, a bacterial infection of a superficial peripheral vein, is infection and clotting usually caused by venous catheterization.

Symptoms and Signs

DVT may occur in ambulatory patients or as a complication of surgery or major medical illness. Among high-risk hospitalized patients, most deep vein thrombi occur in the small calf veins, are asymptomatic, and are never detected.

When present, symptoms and signs (eg, vague aching pain, tenderness along the distribution of the veins, edema, erythema) are nonspecific, vary in frequency and severity, and are similar in arms and legs. Dilated collateral superficial veins may become visible or palpable. Calf discomfort elicited by ankle dorsiflexion with the knee extended (Homans' sign) occasionally occurs with distal leg DVT but is neither sensitive nor specific. Tenderness, swelling of the whole leg, > 3 cm difference in circumference between calves, pitting edema, and collateral superficial veins may be most specific; DVT is likely with a combination of ≥ 3 in the absence of another likely diagnosis (see Table 219-2).

Low-grade fever may be present; DVT may be the cause of fever without an obvious source, especially in postoperative patients. If PE occurs, symptoms may include shortness of breath and pleuritic chest pain (see p. 1909).

Common causes of asymmetric leg swelling that mimic DVT are soft-tissue trauma, cellulitis, pelvic venous or lymphatic obstruction, and popliteal bursitis (Baker's cyst) that obstructs venous return. Abdominal or pelvic tumors that obstruct venous or lymphatic return are less common causes. Use of drugs that cause dependent edema (eg, dihydropyridine Ca channel blockers, estrogen, high-dose opioids), venous hypertension (usually due to right heart failure), and hypoalbuminemia cause symmetric bilateral leg swelling; swelling may be asymmetric if venous insufficiency coexists and is worse in one leg.

Common causes of calf pain that mimic acute DVT include venous insufficiency and postphlebitic syndrome; cellulitis that causes painful erythema of the calf; ruptured popliteal (Baker's) cyst (pseudo-DVT), which causes calf swelling, pain, and sometimes bruising in the region of the medial malleolus; and partial or complete tears of the calf muscles or tendons.

[**Table 219-2.** Probability of Deep Venous Thrombosis Based on Clinical Factors]

Diagnosis

• Ultrasonography

• Sometimes D-dimer testing

History and physical examination help determine probability of DVT before testing (see Table 219-2). Diagnosis is typically by ultrasonography with Doppler flow studies (duplex ultrasonography). The need for additional tests (eg, D-dimer testing) and their choice and sequence depend on pretest probability and sometimes ultrasonography results. No single testing protocol is best; one approach is described in Fig. 219-2.

Ultrasonography: Ultrasonography identifies thrombi by directly visualizing the venous lining and by demonstrating abnormal vein compressibility or, with Doppler flow studies, impaired venous flow. The test is > 90% sensitive and > 95% specific for femoral and popliteal vein thrombosis but is less accurate for iliac or calf vein thrombosis.

D-Dimer: D-Dimer is a byproduct of fibrinolysis; elevated levels suggest recent presence

[**Fig. 219-2.** One approach to testing for suspected deep venous thrombosis.]

and lysis of thrombi. D-dimer assays vary in sensitivity and specificity; however, most are sensitive and not specific. Only the most accurate tests should be used. For example, a highly sensitive test is enzyme-linked immunosorbent assay (ELISA), which has a sensitivity of about 95%.

If pretest probability of DVT is low, DVT can be safely excluded in patients with a normal D-dimer level on a sensitive test. Thus, a negative D-dimer test can identify patients who have a low probability of DVT and do not require ultrasonography. However, a positive test result is nonspecific; because levels can be elevated by other conditions (eg, liver disease, trauma, pregnancy, positive rheumatoid factor, inflammation, recent surgery, cancer), further testing is necessary.

If pretest probability of DVT is moderate or high, D-dimer testing can be done at the same time as duplex ultrasonography. A positive ultrasound result confirms the diagnosis regardless of the D-dimer level. If ultrasonography does not reveal evidence of DVT, a normal D-dimer level helps exclude DVT. Patients with an elevated D-dimer level should have repeat ultrasonography in a few days or possibly immediate venography depending on clinical suspicion. Newer latex qualitative assays are highly specific (up to about 99%) but should not yet be used to confirm DVT without ultrasonography.

Venography: Contrast venography was the definitive test for the diagnosis of DVT but has been largely replaced by ultrasonography, which is noninvasive, more readily available, and almost equally accurate for detecting DVT. Venography may be indicated when ultrasonography results are normal but pretest suspicion for DVT is high. The complication rate is 2%, mostly because of contrast dye allergy.

Other testing: Noninvasive alternatives to contrast venography are being studied. They include magnetic resonance venography and direct MRI of thrombi using T1-weighted gradient-echo sequencing and a water-excitation radiofrequency pulse; theoretically, the latter test can provide simultaneous views of thrombi in deep veins and subsegmental pulmonary arteries (for diagnosis of PE).

If symptoms and signs suggest PE, additional imaging (eg, ventilation/perfusion [V/Q] scanning or helical CT) is required.

Determination of cause: Patients with confirmed DVT and an obvious cause (eg, immobilization, surgical procedure, leg trauma) need no further testing. Testing to detect hypercoagulability is controversial but is sometimes done in patients who have idiopathic recurrent DVT, in patients who have a personal or family history of other thromboses, and in young patients with no obvious predisposing factors. Some evidence suggests that presence of hypercoagulability does not predict DVT recurrence as well as clinical risk factors.

Screening patients with DVT for cancer has a low yield. Selective testing guided by complete history and physical examination aimed at detecting cancer is probably adequate.

Prognosis

Without adequate treatment, lower extremity DVT has a 3% risk of fatal PE; death due to upper extremity

DVT is very rare. Risk of recurrent DVT is lowest for patients with transient risk factors (eg, surgery, trauma, temporary immobility) and greatest for patients with persistent risk factors (eg, heart failure, cancer), idiopathic DVT, or incomplete resolution of past DVT (residual thrombus). A normal D-dimer level obtained after warfarin is stopped may help predict a relatively low risk of DVT or PE recurrence. Risk of venous insufficiency is impossible to predict. Risk factors for post-phlebitic syndrome include proximal thrombosis, recurrent ipsilateral DVT, and body mass index (BMI) ≥ 22 kg/m^2.

Treatment

• Anticoagulation

Treatment is aimed primarily at PE prevention (see also p. 1920) and secondarily at symptom relief and prevention of DVT recurrence, chronic venous insufficiency, and post-phlebitic syndrome. Treatment of lower and upper extremity DVT is generally the same.

All patients with DVT are given anticoagulants, initially an injectable heparin (unfractionated or low molecular weight), followed by warfarin started within 24 to 48 h. Inadequate anticoagulation in the first 24 h may increase risk of recurrence or PE. Acute DVT can be treated on an outpatient basis unless severe symptoms require parenteral analgesics, other disorders preclude safe outpatient discharge, or other factors (eg, functional, socioeconomic) might prevent the patient from adhering to prescribed treatments. General supportive measures include pain control with analgesics other than aspirin and NSAIDs (because of their antiplatelet effects) and, during periods of inactivity, elevation of legs (supported by a pillow or other soft surface to avoid venous compression). Patients may be as physically active as they can tolerate; there is no evidence that early activity increases risk of clot dislodgement and PE.

Anticoagulants: The anticoagulants most often used are the following:

• Low molecular weight heparins (LMWHs)

• Unfractionated heparin (UFH)

• Fondaparinux

• Warfarin

LMWHs (eg, enoxaparin, dalteparin, tinzaparin—see Table 194-3 on p. 1917) are the initial treatment of choice because they can be given on an outpatient basis. LMWHs are as effective as UFH for reducing DVT recurrence, thrombus extension, and risk of death due to PE. Like UFH, LMWHs catalyze the action of antithrombin (which inhibits coagulation factor proteases), leading to inactivation of coagulation factor Xa and, to a lesser degree, factor IIa. LMWHs also have some antithrombin-mediated anti-inflammatory properties, which facilitate clot organization and resolution of symptoms and inflammation.

LMWHs are typically given sc in a standard weight-based dose (eg, enoxaparin 1.5 mg/kg sc once/day or 1 mg/kg sc q 12 h or dalteparin 200 units/kg sc once/day). Patients with renal insufficiency may be treated with UFH or with reduced doses of LMWH. Monitoring is not reliable because LMWHs do not significantly prolong the results of global tests of coagulation. Furthermore, they have a predictable dose response, and there is no clear relationship between LMWH overdose and bleeding. Treatment is continued until full anticoagulation is achieved with warfarin. However, evidence suggests that LMWH is effective for long-term DVT treatment in high-risk patients, such as those with cancer. Thus, LMWH may become an acceptable alternative to warfarin for some patients, although warfarin is likely to be the treatment of choice for most patients because of its low cost and oral route of administration.

UFH may be used instead of LMWH for hospitalized patients and for patients who have renal insufficiency or failure (creatinine clearance 10 to 30 mL/min) because UFH is not cleared by the kidneys. UFH is given as a bolus and infusion (see Fig. 194-2 on p. 1916) to achieve full anticoagulation, (eg, activated PTT [aPTT] 1.5 to 2.5 times that of the reference range). UFH 333 units/kg initial bolus, then 250 units/kg sc q 12 h can be substituted for IV

UFH to facilitate mobility in outpatients; the dose does not appear to need adjustment based on aPTT. Treatment is continued until full anticoagulation has been achieved with warfarin.

Complications of heparin include bleeding, thrombocytopenia (less common with LMWHs), urticaria, and, rarely, thrombosis and anaphylaxis. Long-term use of UFH causes hypokalemia, liver enzyme elevations, and osteoporosis. Rarely, UFH given sc causes skin necrosis. Inpatients and possibly outpatients should be screened for bleeding with serial CBCs and tests for occult blood in stool. Bleeding due to overheparinization can be stopped with protamine sulfate. The dose is 1 mg protamine for each milligram of LMWH given as 1 mg in 20 mL of normal saline infused slowly over 10 to 20 min. If a 2nd dose is required, it should be at one half the first dose. However, the precise dose is undefined because protamine only partially neutralizes LMWH inactivation of factor Xa. With all infusions, the patient should be observed for hypotension and a reaction similar to an anaphylactic reaction. Because UFH given IV has a half-life of 30 to 60 min, protamine is not given to patients receiving UFH (eg, if UFH was given > 60 min beforehand) or is given at a dose based on the amount of heparin estimated to be remaining in plasma, based on the half-life of UFH.

Fondaparinux, a selective factor Xa inhibitor, may be used as an alternative to UFH or LMWH for the initial treatment of DVT or PE. It is given in a fixed dose of 7.5 mg sc once/day (10 mg for patients > 100 kg, 5 mg for patients < 50 kg). It has the advantage of fixed dosing and is less likely to cause thrombocytopenia.

Vitamin K antagonists, including warfarin, are the drugs of choice for long-term anticoagulation for all patients except pregnant women (who should continue to take heparin) and patients who have had new or worsening venous thromboembolism during warfarin treatment (who may be candidates for an inferior vena cava filter). Warfarin 5 to 10 mg can be started immediately with heparin. The elderly and patients with a liver disorder typically require lower warfarin doses. Therapeutic goal is an INR of 2.0 to 3.0. INR is monitored weekly for the first 1 to 2 mo of warfarin treatment and monthly thereafter; the dose is increased or decreased by 0.5 to 3 mg to maintain the INR within this range. Patients taking warfarin should be informed of possible drug interactions, including interactions with foods and nonprescription medicinal herbs (see
Table 194-4 on p. 1917).

Patients with transient risk factors for DVT (eg, immobilization, surgery) can stop taking warfarin after 3 to 6 mo. Patients with non-modifiable risk factors (eg, hypercoagulability), spontaneous DVT with no known risk factors, or recurrent DVT should take warfarin for at least 6 mo and probably for life unless complications occur.

Bleeding is the most common complication. Risk factors for severe bleeding (defined as life-threatening hemorrhage or loss of ≥ 2 units of blood in ≤ 7 days) include age ≥ 65; history of prior GI bleeding or stroke; recent MI; and coexisting anemia (Hct < 30%), renal insufficiency (serum creatinine > 1.5 mg/dL), or diabetes. Anticoagulation can be reversed with vitamin K; the dose is 1 to 4 mg po if INR is 5 to 9, 5 mg po if INR is > 9, and 10 mg IV (given slowly to avoid anaphylaxis) if hemorrhage occurs. If hemorrhage is severe, a transfusion of coagulation factors, fresh frozen plasma, or prothrombin complex concentrate should also be given. Overanticoagulation (INR > 3 or 4) without bleeding can be managed by omitting several warfarin doses and more frequent INR monitoring, then giving warfarin at a lower dose. Rarely, warfarin causes skin necrosis in patients with protein C or S deficiency or factor V Leiden mutations.

Other anticoagulants, such as direct thrombin inhibitors (DTIs, eg, hirudin given sc; lepirudin, bivalirudin, desirudin, argatroban, given parenterally; dabigatran given po) and oral factor Xa inhibitors (eg, rivaroxaban and apixaban) are being evaluated for the treatment of DVT (see
Table 194-6 on p. 1921).

Inferior vena cava filter (IVCF): An IVCF may help prevent PE in patients with lower extremity DVT and contraindications to anticoagulants or with recurrent DVT (or emboli) despite adequate anticoagulation. An IVCF is placed in the inferior vena cava just below the renal veins via catheterization of an internal jugular or femoral vein. Some IVCFs are removable and can be used temporarily (eg, until contraindications to anticoagulation subside or resolve). IVCFs reduce risk of acute and subacute thrombotic complications but can have longer-term complications (eg, venous collaterals can develop,

providing a pathway for emboli to circumvent the IVCF). Also, IVCFs can dislodge or become obstructed by clot. Thus, patients with recurrent DVT or nonmodifiable risk factors for DVT may still require anticoagulation. A clotted filter may cause bilateral lower extremity venous congestion (including acute phlegmasia cerulea dolens), lower body ischemia, and acute renal failure. Treatment for a dislodged filter is removal, using angiographic, or, if necessary, surgical methods. Despite widespread use of IVCFs, efficacy in preventing PE is unstudied and unproved.

Thrombolytic (fibrinolytic) drugs: Streptokinase, urokinase, and alteplase lyse clots and appear to more effectively prevent post-phlebitic syndrome than heparin alone, but risk of bleeding is higher. Their use is under study. Thrombolytics may be indicated for large proximal thrombi, especially those in the iliofemoral veins, and for phlegmasia alba or cerulea dolens. Local perfusion with an indwelling catheter may be preferable to IV administration.

Surgery: Surgery is rarely needed. However, thrombectomy, fasciotomy, or both are mandatory for phlegmasia alba or cerulea dolens unresponsive to thrombolytics to try to prevent limb-threatening gangrene.

Prevention

• Prevention of immobility

• Assessment of risk

• Anticoagulation (eg, LMWH, fondaparinux, adjusted-dose warfarin)

• Intermittent pneumatic compression

• IVCF

Patients at low risk of DVT (eg, those who are undergoing minor surgery but have no clinical risk factors for DVT; those who must be temporarily inactive for long periods, as during an airplane flight) should be encouraged to walk or otherwise move their legs periodically; no medical treatment is needed. Dorsiflexion 10 times/h is probably sufficient.

Patients at higher risk of DVT (eg, those undergoing minor surgery if they have clinical risk factors for DVT; those undergoing major surgery, especially orthopedic surgery, even without risk factors; bedbound patients with major medical illnesses) require additional preventive treatment (see Table 194-5 on p. 1920). Most of these patients can be identified and should receive thrombosis prophylaxis.

After surgery, elevating the legs and avoiding sitting in chairs (which, by placing the legs in a dependent position, impedes venous return) can help. Additional treatment may involve low-dose UFH, LMWH, warfarin, newer anticoagulants such as fondaparinux, compression devices or stockings, or a combination, depending on patient's risk level, type of surgery (if applicable), projected duration of preventive treatment, contraindications, adverse effects, relative cost, ease of use, and local practice. Low-dose UFH 5000 units sc is given 2 h before surgery and q 8 to 12 h thereafter for 7 to 10 days or until patients are fully ambulatory. Bedbound patients who are not undergoing surgery are given 5000 units sc q 12 h until risk factors are reversed.

LMWHs are more effective than low-dose UFH for preventing DVT and PE, but widespread use is limited by cost. For example, enoxaparin 30 mg sc q 12 h, dalteparin 2500 units once/day, and tinzaparin 3500 units once/day are equally effective. Fondaparinux, 2.5 mg once/day, is equal to or more effective than LMWH depending on the surgical setting (eg, orthopedic surgery).

Warfarin, using a target INR of 2.0 to 3.0, is proven to be effective in orthopedic surgery.

Newer anticoagulants (eg, hirudin, lepirudin) are effective for preventing DVT and PE, but their cost-effectiveness and safety compared with heparin and warfarin require further study. Aspirin is better than

placebo but worse than all other available drugs for preventing DVT and PE and is not recommended as the sole method of prevention (see Table 194-5 on p. 1920).

Intermittent pneumatic compression (IPC) uses a pump to cyclically inflate and deflate hollow plastic leggings, providing external compression to the lower legs and sometimes thighs. IPC may be used instead of or with anticoagulants before and during surgery. IPC is recommended after knee surgery. IPC is probably more effective for preventing calf than proximal DVT. IPC is usually contraindicated in obese patients and can theoretically trigger PE in immobilized patients who, without preventive treatment, develop occult DVT.

The benefit of graded compression stockings is questionable except for low-risk surgical patients. However, combining stockings with other preventive measures may be more protective than any single approach.

For elective neurosurgery, spinal cord injury, or multiple trauma, low-dose UFH (q 8 h), LMWH, or adjusted-dose warfarin is recommended. For hip and other lower extremity orthopedic surgery, LMWH, fondaparinux, or adjusted-dose warfarin is recommended. For patients undergoing total knee replacement and some other high-risk patients, IPC is also beneficial. For orthopedic surgery, preventive treatment may be started before or after surgery and continued for at least 14 days. Fondaparinux 2.5 mg once/day is more effective than LMWH for orthopedic surgery. For neurosurgery patients, physical measures (IPC, elastic stockings) have been used because intracranial bleeding is a concern; however, LMWH appears to be an acceptable alternative. Limited data support the combination of IPC, elastic stockings, and LMWH in patients with spinal cord injury or multiple trauma.

For patients who are at very high risk of venous thromboembolism and bleeding and are taking anticoagulants, IVCF placement is an option.

Preventive treatment is also indicated for patients who have a major medical illnesses requiring bed rest (eg, MI, ischemic stroke). Low-dose UFH is effective in patients who are not already receiving IV heparin or thrombolytics; IPC, elastic stockings, or both may be used when anticoagulants are contraindicated. After a stroke, low-dose UFH or LMWH can be used; IPC, elastic stockings, or both may be beneficial. Other recommendations include low-dose UFH for patients with heart failure, warfarin (target INR 2.0 to 3.0) for those with metastatic breast cancer, and warfarin 1 mg once/day for those with cancer and an indwelling central venous catheter. Fondaparinux 2.5 mg once/day is also recommended in patients with major medical illnesses.

In patients with symptomatic DVT, primary prevention of venous insufficiency and postphlebitic syndrome is recommended; knee-high compression stockings providing 30 to 40 mm Hg pressure are used.

Chronic Venous Insufficiency and Postphlebitic Syndrome

Chronic venous insufficiency is impaired venous return, sometimes causing lower extremity discomfort, edema, and skin changes. Postphlebitic (postthrombotic) syndrome is symptomatic chronic venous insufficiency after deep venous thrombosis (DVT). Causes of chronic venous insufficiency are disorders that result in venous hypertension, usually through venous damage or incompetence of venous valves, as occurs (for example) after DVT. Diagnosis is by history, physical examination, and duplex ultrasonography. Treatment is compression, wound care, and, rarely, surgery. Prevention requires adequate treatment of DVT and compression stockings.

Chronic venous insufficiency affects up to 5% of people in the US. Postphlebitic syndrome may affect one fifth to two thirds of patients with DVT, usually within 1 to 2 yr after acute DVT.

Etiology

Venous return from the lower extremities relies on contraction of calf muscles to push blood from intramuscular (soleal) sinusoids and gastrocnemius veins into and through deep veins. Venous valves direct blood proximally to the heart. Chronic venous insufficiency occurs when venous obstruction (eg, in DVT), venous valvular insufficiency, or decreased contraction of muscles surrounding the veins (eg, due

to immobility) decrease forward venous flow and increase venous pressure (venous hypertension). Fluid accumulation in the lower extremities (eg, in right heart failure) can also contribute by causing venous hypertension. Prolonged venous hypertension causes tissue edema, inflammation, and hypoxia, leading to symptoms. Pressure may be transmitted to superficial veins if valves in perforator veins, which connect deep and superficial veins, are ineffective.

DVT is the most common identifiable risk factor for chronic venous insufficiency, followed by trauma, age, and obesity. Idiopathic cases are often attributed to a history of occult DVT.

Symptomatic chronic venous insufficiency that follows DVT is referred to as postphlebitic (or postthrombotic) syndrome. Risk factors for postphlebitic syndrome in patients with DVT include proximal thrombosis, recurrent ipsilateral DVT, and body mass index (BMI) ≥ 22 kg/m^2. Age, female sex, and estrogen therapy are also associated with the syndrome but are probably nonspecific. Use of compression stockings after DVT decreases risk.

Symptoms and Signs

Clinically evident chronic venous insufficiency may not cause any symptoms but always causes signs; postphlebitic syndrome always causes symptoms. Both disorders are a concern because their symptoms can mimic those of acute DVT and both can lead to substantial reductions in physical activity and quality of life.

Symptoms include a sense of fullness, heaviness, aching, cramps, pain, tiredness, and paresthesias in the legs; these symptoms worsen with standing or walking and are relieved by rest and elevation. Pruritus may accompany skin changes. Signs occur along a continuum: no changes to varicose veins (rare) to stasis dermatitis on the lower legs and at the ankles, with or without ulceration (see Table 219-3). The calf may be painful when compressed.

Venous stasis dermatitis consists of reddish brown hyperpigmentation, induration, venous ectasia, lipodermatosclerosis (fibrosing subcutaneous panniculitis), and venous stasis ulcers.

Venous stasis ulcers may develop spontaneously or after affected skin is scratched or injured. They typically occur around the medial malleolus, tend to be shallow and moist, and may be malodorous (especially when poorly cared for) or painful. They do not penetrate the deep fascia. In contrast, ulcers due to peripheral arterial disease eventually expose tendons or bone.

Leg edema tends to be unilateral or asymmetric; bilateral symmetric edema is more likely to result from a systemic disorder (eg, heart failure, hypoalbuminemia) or certain drugs (eg, Ca channel blockers).

In general, unless the lower extremities are adequately cared for, patients with any manifestation of chronic venous insufficiency or postphlebitic syndrome are at risk of progression to more advanced forms.

[**Table 219-3.** Clinical Classification of Chronic Venous Insufficiency]

Diagnosis

• Clinical diagnosis

• Ultrasonography to exclude DVT

Diagnosis is usually based on history and physical examination. A clinical scoring system that ranks 5 symptoms (pain, cramps, heaviness, pruritus, paresthesia) and 6 signs (edema, hyperpigmentation, induration, venous ectasia, blanching hyperemia, pain with calf compression) on a scale of 0 (absent or minimal) to 3 (severe) is increasingly recognized as a standard diagnostic tool of disease severity. Scores of 5 to 14 on 2 visits separated by ≥ 6 mo indicate mild-to-moderate disease, and scores of ≥ 15 indicate severe disease.

Lower-extremity duplex ultrasonography helps exclude DVT. Absence of edema and a reduced ankle-

brachial index suggest peripheral arterial disease rather than chronic venous insufficiency and postphlebitic syndrome.

Treatment

• Elevation

• Compression

• Topical treatments

Treatment involves leg elevation; compression using bandages, stockings, and pneumatic devices; topical wound care; and surgery, depending on the disorder's severity. Some experts believe that weight loss, regular exercise, and reduction of dietary sodium may benefit patients with bilateral chronic venous insufficiency. However, all interventions may be difficult to implement.

Elevating the leg above the level of the right atrium decreases venous hypertension and edema, is appropriate for all patients, and should be done a minimum of 3 times/day for ≥ 30 min. However, most patients cannot adhere to this schedule during the day.

Compression is effective for treatment and prevention of the effects of chronic venous insufficiency and postphlebitic syndrome and is indicated for all patients. Elastic bandages are used initially until edema and ulcers resolve and leg size stabilizes; commercial compression stockings are then used. Stockings that provide 20 to 30 mm Hg of distal circumferential pressure are indicated for smaller varicose veins and mild chronic venous insufficiency; 30 to 40 mm Hg is indicated for larger varicose veins and moderate disease; and 40 to > 60 mm Hg is indicated for severe disease. Stockings should be put on when patients awaken, before leg edema worsens with activity, and should exert maximal pressure at the ankles and gradually less pressure proximally. Adherence to this treatment varies; many younger or more active patients consider stockings irritating, restricting, or cosmetically undesirable; elderly patients may have difficulty putting them on.

Intermittent pneumatic compression (IPC) uses a pump to cyclically inflate and deflate hollow plastic leggings. IPC provides external compression, squeezing blood and fluid out of the lower legs. It effectively treats severe post-phlebitic syndrome and venous stasis ulcers but may be no more effective than compression stockings alone and is much less practical for patients to adhere to on an ongoing basis.

Topical wound care is important in venous stasis ulcer management (see p. 740 for full discussion). When an Unna boot (zinc oxide-impregnated bandages) is properly applied, covered by compression bandages, and changed weekly, almost all ulcers heal. Occlusive interactive dressings (eg, hydrocolloids such as aluminum chloride) provide a moist environment for wound healing and promote growth of new tissue; they may be used for ulcers with light to moderate exudate, but they probably add little to simple Unna bandaging and are expensive. Passive dressings are absorptive, making them most appropriate for heavier exudate.

Drugs have no role in routine treatment of chronic venous insufficiency, although many patients are given aspirin, topical corticosteroids, diuretics for edema, or antibiotics. Surgery (eg, venous ligation, stripping, valve reconstruction) is also generally ineffective. Grafting autologous skin or skin created from epidermal keratinocytes or dermal fibroblasts may be an option for patients with stasis ulcers when all other measures are ineffective, but the graft will reulcerate unless underlying venous hypertension is managed.

Prevention

Primary prevention involves adequate anticoagulation after DVT and use of compression stockings for up to 2 yr after DVT or lower extremity venous trauma. Lifestyle changes (eg, weight loss, regular exercise, reduction of dietary sodium) can decrease risk by decreasing lower extremity venous pressure.

Superficial Venous Thrombosis

Superficial venous thrombosis is a blood clot in a superficial vein of the upper or lower extremities or, less commonly, in one or more veins of the chest or breast (Mondor's disease).

Superficial venous thrombosis in the upper extremity most commonly results from IV infusions or catheterization; varicose veins seem to be the main risk factor for the lower extremity, especially among women. Superficial venous thrombi rarely cause serious complications and rarely become emboli.

Typically, patients present with pain, tenderness, or an indurated cord along a palpable superficial vein. The overlying skin is usually warm and erythematous. Migratory superficial venous thrombosis, which develops, resolves, and recurs in normal veins of the arms, legs, and torso at various times, is a possible harbinger of pancreatic cancer and other adenocarcinomas (Trousseau's syndrome).

Diagnosis is based on history and physical examination. Patients with superficial phlebitis above the knee have an increased risk of deep venous thrombosis and should probably have ultrasonography. Treatment traditionally involves warm compresses and NSAIDs, but local thrombectomy with a local anesthetic is very effective. In patients with extensive superficial phlebitis, heparin is often beneficial.

Varicose Veins

Varicose veins are dilated superficial veins in the lower extremities. Usually, no cause is obvious. Varicose veins are typically asymptomatic but may cause a sense of fullness, pressure, and pain or hyperesthesia in the legs. Diagnosis is by physical examination. Treatment may include compression, wound care, sclerotherapy, and surgery.

Varicose veins may occur alone or with chronic venous insufficiency.

Etiology is usually unknown, but varicose veins may result from primary venous valvular insufficiency with reflux or from primary dilation of the vein wall due to structural weakness. In some people, varicose veins result from chronic venous insufficiency and venous hypertension. Most people have no obvious risk factors. Varicose veins are common within families, suggesting a genetic component. Varicose veins are more common among women because estrogen affects venous structure, pregnancy increases pelvic and leg venous pressures, or both. Rarely, varicose veins are part of Klippel-Trenaunay-Weber syndrome, which includes congenital arteriovenous fistulas and diffuse cutaneous capillary angiomas.

Symptoms and Signs

Varicose veins may initially be tense and palpable but are not necessarily visible. Later, they may progressively enlarge, protrude, and become obvious; they can cause a sense of fullness, fatigue, pressure, and superficial pain or hyperesthesia in the legs. Varicose veins are most visible when the patient stands. For unclear reasons, stasis dermatitis and venous stasis ulcers are uncommon. When skin changes (eg, induration, pigmentation, eczema) occur, they typically affect the medial malleolar region. Ulcers may develop after minimal trauma to an affected area; they are usually small, superficial, and painful. Varicose veins occasionally thrombose, causing pain. Superficial varicose veins may cause thin venous bullae in the skin, which may rupture and bleed after minimal trauma. Very rarely, such bleeding, if undetected during sleep, is fatal.

Diagnosis

• Clinical evaluation

Diagnosis is usually obvious from the physical examination. Trendelenburg's test (comparing venous filling before and after release of a thigh tourniquet) is no longer commonly used to identify retrograde blood flow past incompetent saphenous valves. Duplex ultra-sonography is an accurate test, but it is not clear whether it is routinely necessary. Ultra-sonography can be done to assess the function of the deep veins prior to surgery.

Treatment

• Compression stockings

• Sometimes sclerotherapy or surgery

Treatment aims to relieve symptoms, improve the leg's appearance, and, in some cases, prevent complications. Treatment includes compression stockings and local wound care as needed.

Injection therapy (sclerotherapy) and surgery are indicated for prevention of recurrent variceal thrombosis and for skin changes; these procedures are also commonly used for cosmetic reasons. Sclerotherapy uses an irritant (eg, Na tetradecyl sulfate) to induce a thrombophlebitic reaction that fibroses and occludes the vein; however, many varicose veins recannulate. Surgery involves ligation or stripping of the long and sometimes the short saphenous veins. These procedures provide good short-term symptom relief, but long-term efficacy is poor (ie, patients often develop recurrent varicose veins). Laser therapy is being used experimentally by some surgeons.

Regardless of treatment, new varicose veins develop, and treatment often must be maintained indefinitely.

Idiopathic Telangiectasias

Idiopathic telangiectasias are fine, dilated intracutaneous veins that are not clinically significant but may be extensive and unsightly.

Telangiectasias are usually asymptomatic. However, some patients report a burning sensation or pain, and many people consider even the smallest telangiectasias cosmetically unacceptable.

Telangiectasias can usually be eliminated by intracapillary injections of 0.3% solution of Na tetradecyl sulfate through a fine-bore needle. Hypertonic saline 23.4% is sometimes used but causes fairly severe, temporary, localized pain; therefore, large areas of spider veins (multiple telangiectasias) may require several treatments. Pigmentation may develop but usually subsides, often completely. Skin ulceration may result if the injection is extravascular or too large. Laser treatment is effective, but large areas require several treatments. Small telangiectasias may persist or recur after initial treatment.

Arteriovenous Fistula

An arteriovenous fistula is an abnormal communication between an artery and a vein.

An arteriovenous fistula may be congenital (usually affecting smaller vessels) or acquired as a result of trauma (eg, a bullet or stab wound) or erosion of an arterial aneurysm into an adjacent vein.

The fistula may cause symptoms and signs of arterial insufficiency (eg, ulceration due to reduced arterial flow or ischemia) or chronic venous insufficiency due to high-pressure arterial flow in the affected veins (eg, peripheral edema, varicose veins, stasis pigmentation). Emboli (eg, causing ulceration) may pass from the venous to the arterial circulation, although pressure differences make this unlikely. If the fistula is near the surface, a mass can be felt, and the affected area is usually swollen and warm with distended, often pulsating superficial veins. A thrill can be palpated over the fistula, and a continuous loud, to-and-fro (machinery) murmur with accentuation during systole can be heard during auscultation. Rarely, if a significant portion of cardiac output is diverted through the fistula to the right heart, high-output heart failure develops.

Congenital fistulas need no treatment unless significant complications develop (eg, leg lengthening in a growing child). When necessary, percutaneous vascular techniques can be used to place coils or plugs into the vessels to occlude the fistula. Treatment is seldom completely successful, but complications are often controlled. Acquired fistulas usually have a single large connection and can be effectively treated by surgery.

Lymphedema

Lymphedema is edema of a limb due to lymphatic hypoplasia (primary) or to obstruction or disruption (secondary) of lymphatic vessels. Symptoms and signs are brawny, fibrous, nonpitting edema in one or more limbs. Diagnosis is by physical examination. Treatment consists of exercise, pressure gradient dressings, massage, and sometimes surgery. Cure is unusual, but treatment may lessen symptoms, slow progression, and prevent complications. Patients are at risk of cellulitis, lymphangitis, and, rarely, lymphangiosarcoma.

Etiology

Lymphedema may be primary (due to lymphatic hypoplasia) or secondary (due to obstruction or disruption of lymphatic vessels).

Primary lymphedemas: Primary lymphedemas are inherited and uncommon. They vary in phenotype and patient age at presentation.

Congenital lymphedema appears before age 2 and is due to lymphatic aplasia or hypoplasia. Milroy's disease is an autosomal dominant familial form of congenital lymphedema attributed to vascular endothelial growth factor receptor-3 (*VEGFR-3*) gene mutations and sometimes associated with cholestatic jaundice and edema or diarrhea due to a protein-losing enteropathy caused by intestinal lymphangiectasia.

Lymphedema praecox appears between ages 2 and 35, typically in women at the onset of menses or pregnancy. Meige's disease is an autosomal dominant familial form of lymphedema praecox attributed to mutations in a transcription factor gene (*FOXC2*) and associated with extra eyelashes (distichiasis); cleft palate; and leg, arm, and sometimes facial edema.

Lymphedema tarda occurs after age 35. Familial and sporadic forms exist; the genetic basis of both is unknown. Clinical findings are similar to those of lymphedema praecox but may be less severe.

Lymphedema is prominent in some other genetic syndromes, including Turner's syndrome; yellow nail syndrome, characterized by pleural effusions and yellow nails; and Hennekam syndrome, a rare congenital syndrome of intestinal and other lymphangiectases, facial anomalies, and intellectual disability.

Secondary lymphedema: Secondary lymphedema is far more common than primary. It is most commonly caused by surgery (especially lymph node dissection, typically for breast cancer), radiation therapy (especially axillary or inguinal), trauma, lymphatic obstruction by a tumor, and, in developing countries, lymphatic filariasis. Mild lymphedema may also result from leakage of lymph into interstitial tissues in patients with chronic venous insufficiency.

Symptoms and Signs

Symptoms of secondary lymphedema include aching discomfort and a sensation of heaviness or fullness.

The cardinal sign is soft-tissue edema, graded in 3 stages:

• In stage 1, the edema is pitting, and the affected area often returns to normal by morning.

• In stage 2, the edema is nonpitting, and chronic soft-tissue inflammation causes early fibrosis.

• In stage 3, the edema is brawny and irreversible, largely because of soft-tissue fibrosis.

The swelling is most often unilateral and may worsen when the weather is warm, before menstruation occurs, and after the limb remains for a long time in a dependent position. It can affect any part of the limb (isolated proximal or distal) or the entire extremity; it can restrict range of motion when swelling is periarticular. Disability and emotional distress can be significant, especially when lymphedema results from medical or surgical treatment.

Skin changes are common and include hyperkeratosis, hyperpigmentation, verrucae, papillomas, and

fungal infections.

Complications: Lymphangitis (see p. 700) may develop, most often when bacteria enter through skin cracks between the toes as a result of fungal infections or through cuts to the hand. Lymphangitis is almost always streptococcal, causing erysipelas; sometimes it is staphylococcal. The affected limb becomes red and feels hot; red streaks may extend proximally from the point of entry, and lymphadenopathy may develop. Rarely, the skin breaks down. Rarely, long-standing lymphedema leads to lymphangiosarcoma (Stewart-Treves syndrome), usually in postmastectomy patients and in patients with filariasis.

Diagnosis

• Clinical diagnosis

• CT or MRI if cause not apparent

Primary lymphedema is usually obvious, based on characteristic soft-tissue edema throughout the body and other information from the history and physical examination. Diagnosis of secondary lymphedema is usually obvious from physical examination. Additional tests are indicated when secondary lymphedema is suspected unless the diagnosis and cause are obvious. CT and MRI can identify sites of lymphatic obstruction; radionuclide lymphoscintigraphy can identify lymphatic hypoplasia or sluggish flow. Progression can be monitored by measuring limb circumference, measuring water volume displaced by the submerged limb, or using skin or soft-tissue tonometry; these tests have not been validated. In developing countries, tests for lymphatic filariasis should be done (see p. 1346). If lymphedema seems much greater than expected (eg, on the basis of lymph node dissection) or appears after a delay in a woman treated for breast cancer, cancer recurrence should be considered.

Prognosis

Cure is unusual once lymphedema occurs. Meticulous treatment and possibly preventive measures can lessen symptoms, slow or halt disease progression, and prevent complications.

Treatment

• Sometimes surgical reconstruction for primary lymphedema

• Mobilizing fluid (eg, by elevation and compression, massage, pressure bandages, intermittent pneumatic compression)

Treatment of primary lymphedema may include surgical soft-tissue reduction (removal of subcutaneous fat and fibrous tissue) and reconstruction if quality of life is significantly reduced.

Treatment of secondary lymphedema involves managing its cause. For lymphedema itself, several interventions to mobilize fluid (complex decongestive therapy) can be used. They include manual lymphatic drainage, in which the limb is elevated and compressed ("milked") toward the heart; gradient pressure bandages or sleeves; limb exercises; and limb massage, including intermittent pneumatic compression. Surgical soft-tissue reduction, lymphatic reanastomoses, and formation of drainage channels are sometimes tried but have not been rigorously studied.

Preventive measures include avoiding heat, vigorous exercise, and constrictive garments (including blood pressure cuffs) around the affected limb. Skin and nail care require meticulous attention; vaccination, phlebotomy, and IV catheterization in the affected limb should be avoided.

Cellulitis and lymphangitis are treated with β-lactamase-resistant antibiotics that are effective against gram-positive organisms (eg, oxacillin, cloxacillin, dicloxacillin).

Chapter 220. Sports and the Heart

Introduction

Exercise and athletic training are of significant overall cardiovascular benefit, but occasionally they have adverse consequences.

Sudden Cardiac Death in Athletes

An estimated 1/200,000 apparently healthy young athletes develops abrupt-onset ventricular tachycardia or fibrillation and dies suddenly during exercise. Males are affected 10 times more often than females. Basketball and football players in the US and soccer players in Europe may be at highest risk.

In **young athletes**, sudden cardiac death has many causes (see Table 220-1) but the most common is

• Undetected hypertrophic cardiomyopathy

Athletes with thin, compliant chest walls are at risk of commotio cordis (sudden ventricular tachycardia or fibrillation after a blow to the precordium) even when no cardiovascular disorder is present. The blow may involve a moderate-force projectile (eg, baseball, hockey puck, lacrosse ball) or impact

[**Table 220-1.** Causes of Sudden Cardiovascular Death in Young Athletes*]

with another player during a vulnerable phase of myocardial repolarization. Other causes include inherited arrhythmia syndromes (eg, long QT syndrome, Brugada syndrome). Some young athletes die of aortic aneurysm rupture (in Marfan syndrome).

In **older athletes**, sudden cardiac death is typically caused by

• Coronary artery disease

Occasionally, hypertrophic cardiomyopathy, mitral valve prolapse, or acquired valvular disease is involved.

In other conditions underlying sudden death in athletes (eg, asthma, heatstroke, illicit or performance-enhancing drug-related complications), ventricular tachycardia or fibrillation is a terminal, not a primary event.

Symptoms and signs are those of cardiovascular collapse; diagnosis is obvious. Immediate treatment with advanced cardiac life support is successful in < 20%; the percentage may increase as distribution of community-based, automated external defibrillators expands. For survivors, treatment is management of the underlying condition. In some cases, an implanted cardioverter-defibrillator may ultimately be required.

Screening

Athletes are commonly screened to identify risk before participation in sports, and they are reevaluated every 2 yr (if high school age) or every 4 yr (if college age or older).

Screening recommendations for all children, adolescents, and college-age young adults include

• Medical, family, and drug history (including use of performance-enhancing drugs and drugs that predispose to long QT syndrome)

• Physical examination (including BP and supine and standing cardiac auscultation)

• Selected testing based on findings on history and physical examination

Screening for older adults also includes incremental symptom-limited exercise testing.

Athletes with a family history or symptoms or signs of hypertrophic cardiomyopathy (see p. 2138), long QT syndrome (see p. 2176), or Marfan syndrome (see p. 2908) require further evaluation, typically with ECG, echocardiography, or both. Confirmation of any of these disorders may preclude sports participation. Athletes with presyncope or syncope should also be evaluated for anomalous coronary arteries (eg, by cardiac catheterization). If ECG reveals Mobitz type II heart block, complete heart block, true right bundle branch block, or left bundle branch block, a search for cardiac disease is required. Athletes should be counseled against use of illicit and performance-enhancing drugs.

History and examination are neither sensitive nor specific; false-negative and false-positive findings are common because prevalence of cardiac disorders in an apparently healthy population is very low. Use of screening ECG or echocardiography would improve disease detection but would produce even more false-positive diagnoses and is impractical at a population level.

Genetic testing for hypertrophic cardiomyopathy or long QT syndrome is not recommended or even feasible for the screening of athletes.

Athlete's Heart

Athlete's heart is a constellation of structural and functional changes that occur in the heart of people who train for > 1 h most days. The changes are asymptomatic; signs include bradycardia, a systolic murmur, and extra heart sounds. ECG abnormalities are common. Diagnosis is clinical or by echocardiography. No treatment is necessary. Athlete's heart is significant because it must be distinguished from serious cardiac disorders.

Intensive, prolonged endurance and strength training causes many physiologic adaptations. Volume and pressure loads in the left ventricle (LV) increase, which, over time, increase LV muscle mass, wall thickness, and chamber size. Maximal stroke volume and cardiac output increase, contributing to a lower resting heart rate and longer diastolic filling time. Lower heart rate results primarily from increased vagal tone, but decreased sympathetic activation and other nonautonomic factors that decrease intrinsic sinus node activity may play a role. Bradycardia decreases myocardial O_2 demand; at the same time, increases in total Hb and blood volume enhance O_2 transport. Despite these changes, systolic function and diastolic function remain normal. Structural changes in women are typically less than those in men of the same age, body size, and training.

Symptoms and Signs

There are no symptoms. Signs vary but may include bradycardia; an LV impulse that is laterally displaced, enlarged, and increased in amplitude; a systolic ejection (flow) murmur at the left lower sternal border; a 3rd heart sound (S_3) due to early, rapid diastolic ventricular filling; a 4th heart sound (S_4), heard best during resting bradycardia because diastolic filling time is increased; and hyperdynamic carotid pulses. These signs reflect structural cardiac changes that are adaptive for intense exercise.

Diagnosis

• Clinical evaluation

• Usually ECG

• Sometimes echocardiography

• Rarely stress testing

Findings are typically detected during routine screening or during evaluation of unrelated symptoms. Most athletes do not require extensive testing, although ECG is often warranted. If symptoms suggest a cardiac disorder (eg, palpitations, chest pain), ECG, echocardiography, and exercise stress testing are done.

Athlete's heart is a diagnosis of exclusion; it must be distinguished from disorders that cause similar findings but are life threatening (eg, hypertrophic or dilated cardiomyopathies, ischemic heart disease, arrhythmogenic right ventricular dysplasia).

ECG: Numerous changes in rhythm and ECG morphology can occur; they correlate poorly with level of training and cardiovascular performance. The most common ECG finding is

• Sinus bradycardia

Rarely, heart rate is < 40 beats/min. Sinus arrhythmia often accompanies the slow heart rate. Resting bradycardia may also predispose to

• Atrial or ventricular ectopy (including couplets and bursts of nonsustained ventricular tachycardia); pauses after ectopic beats do not exceed 4 sec

• Wandering supraventricular pacemaker

• Atrial fibrillation

Other ECG findings that may occur include

• First-degree atrioventricular (AV) block (in up to one third of athletes)

• Second degree AV block (mainly type I); this finding occurs during rest and disappears with exercise

• High voltage QRS with inferolateral T-wave changes (reflecting LV hypertrophy)

• Deep anterolateral T-wave inversion

• Incomplete right bundle branch block

However, 3rd-degree AV block is abnormal and should be investigated thoroughly.

These ECG and rhythm changes have not been associated with adverse clinical events, suggesting that various arrhythmias are not abnormal in athletes. The arrhythmias are usually abolished or substantially reduced after a relatively brief period of deconditioning.

Echocardiography: Echocardiography can usually distinguish athlete's heart from cardiomyopathies (see Table 220-2), but the distinction is not always clear because there is a continuum from physiologic to pathologic cardiac enlargement. The zone of overlap between the athlete's heart and cardiomyopathy is left ventricular septal thickness between 13 to 15 mm in men and 11 to 13 mm in women. In this overlap area, the presence of mitral valve systolic anterior motion strongly suggests hypertrophic cardiomyopathy. In general, echocardiographic changes correlate poorly with level of training and cardiovascular performance. Trace mitral

[**Table 220-2.** Features Distinguishing Athlete's Heart from Cardiomyopathy]

regurgitation and tricuspid regurgitation are commonly detected.

Stress testing: During exercise stress testing, heart rate remains lower than normal at submaximal stress and increases appropriately and comparably to nonathletes at maximal stress; it rapidly recovers after exercise. BP response is normal: Systolic BP increases, diastolic BP falls, and mean BP stays relatively constant. Many resting ECG changes decrease or disappear during exercise; this finding is unique to athlete's heart, distinguishing it from pathologic conditions. However, pseudonormalization of T-wave inversions could reflect myocardial ischemia and thus warrants further investigation in older athletes.

Prognosis

Although gross structural changes resemble those in some cardiac disorders, no adverse effects are apparent. In most cases, structural changes and bradycardia regress with detraining, although up to 20% of elite athletes have residual chamber enlargement, raising questions, in the absence of long-term data, about whether athlete's heart is truly benign.

Treatment

No treatment is required, although 3 mo of deconditioning may be needed to monitor LV regression as a way of distinguishing this syndrome from cardiomyopathy. Such deconditioning can greatly interfere with an athlete's life and may meet with resistance.

Chapter 221. Cardiac Tumors

Introduction

Cardiac tumors may be primary (benign or malignant) or metastatic (malignant). Myxoma, a benign primary tumor, is the most common type. Cardiac tumors may occur in any cardiac tissue. They can cause valvular or inflow-outflow tract obstruction, thromboembolism, arrhythmias, or pericardial disorders. Diagnosis is by echocardiography followed by biopsy. Treatment of benign tumors is usually surgical resection; tumors may recur. Treatment of metastatic cancer depends on tumor type and origin; prognosis is generally poor.

Primary cardiac tumors are found in < 1/2000 people at autopsy. Metastatic tumors are 30 to 40 times more common. Usually, primary cardiac tumors originate in the myocardium or endocardium; they may also originate in valve tissue, cardiac connective tissue, or the pericardium.

Classification

Some of the more common primary and secondary cardiac tumors are listed (see Table 221-1).

Benign primary tumors: Examples are myxomas, papillary fibroelastomas, rhabdomyomas, fibromas, hemangiomas, teratomas, lipomas, paragangliomas, and pericardial cysts.

Myxoma is most common, accounting for 50% of all primary cardiac tumors. Incidence in women is 2 to 4 times that in men. In uncommon familial forms (Carney complex), men are affected more often. About 75% of myxomas occur in the left atrium, and the rest occur in the other chambers as a solitary tumor or, less commonly, at several sites. About 75% are pedunculated and may prolapse through the mitral valve and obstruct ventricular filling during diastole; the remainder are broad-based and sessile. Myxomas may be myxoid and gelatinous; smooth, firm, and lobular; or friable and irregular. Friable irregular myxomas increase risk of systemic embolism.

Carney complex is a familial, autosomal dominant syndrome of recurrent cardiac myxomas with some combination of cutaneous myxomas, myxoid mammary fibroadenomas, pigmented skin lesions (lentigines, ephelides, blue nevi), multiple endocrine neoplasia (primary pigmented nodular adreno-cortical disease causing Cushing's syndrome, growth hormone and prolactin-producing pituitary adenoma, testicular tumors, thyroid adenoma or carcinoma, and ovarian cysts), psammomatous melanotic schwannoma, breast ductal adenoma, and osteochondromyxoma. Patients are often younger at presentation (median age, 20 yr), have multiple myxomas (particularly in the ventricles), and have a higher risk of myxoma recurrence.

[**Table 221-1.** Types of Cardiac Tumors]

Papillary fibroelastomas are the 2nd most common benign primary tumor. They are avascular papillomas that predominantly occur on the aortic and mitral valves. Men and women are affected equally. They have papillary fronds branching from a central core, resembling sea anemones. About 45% are pedunculated. They do not cause valvular dysfunction but increase risk of embolism.

Rhabdomyomas account for 20% of all primary cardiac tumors and 90% of those in children. Rhabdomyomas affect mainly infants and children, 50% of whom also have tuberous sclerosis. Rhabdomyomas are usually multiple and located intramurally in the septum or free wall of the left ventricle, where they affect the cardiac conduction system. They are firm white lobules that typically regress with age. A minority of patients develop tachyarrhythmias and heart failure due to left ventricular outflow tract obstruction.

Fibromas occur mainly in children and are associated with adenoma sebaceum of the skin and kidney tumors. They occur primarily on valve tissue and may develop in response to inflammation. They can compress or invade the cardiac conduction system, causing arrhythmias and sudden death. Some fibromas occur as part of a syndrome with generalized body overgrowth, jaw keratocytes, skeletal

abnormalities, and various benign and malignant tumors (Gorlin's or basal cell nevus syndrome).

Hemangiomas account for 5 to 10% of benign tumors. They cause symptoms in a minority of patients. Most often, they are incidentally detected during examinations done for other reasons.

Teratomas of the pericardium affect mainly infants and children. They are often attached to the base of the great vessels. About 90% are located in the anterior mediastinum; the rest, mainly in the posterior mediastinum.

Lipomas can develop at a wide range of ages. They originate in the endocardium or epicardium and have a large pedunculated base. Many are asymptomatic, but some obstruct flow or cause arrhythmias.

Paragangliomas, including pheochromocytomas, rarely occur in the heart; when they do, they are usually localized to the base of the heart near vagus nerve endings. They may manifest with symptoms due to catecholamine secretion.

Pericardial cysts may resemble a cardiac tumor or pericardial effusion on chest x-ray. They are usually asymptomatic, although some cause compressive symptoms (eg, chest pain, dyspnea, cough).

Malignant primary tumors: Malignant primary tumors include sarcomas, pericardial mesothelioma, and primary lymphomas.

Sarcoma is the most common malignant and 2nd most common primary cardiac tumor (after myxoma). Sarcomas affect mainly middle-aged adults (mean, 41 yr). Almost 40% are angiosarcomas, most of which originate in the right atrium and involve the pericardium, causing right ventricular inflow tract obstruction, pericardial tamponade, and lung metastasis. Other types include undifferentiated sarcoma (25%), malignant fibrous histiocytoma (11 to 24%), leiomyosarcoma (8 to 9%), fibrosarcoma, rhabdomyosarcoma, liposarcoma, and osteosarcoma; these types are more likely to originate in the left atrium, causing mitral valve obstruction and heart failure.

Pericardial mesothelioma is rare. It affects all ages, males more than females. It causes tamponade and can metastasize to the spine, adjacent soft tissues, and brain.

Primary lymphoma is extremely rare. It usually occurs in AIDS patients or other people with immunodeficiency. These tumors grow rapidly and cause heart failure, arrhythmias, tamponade, and superior vena cava (SVC) syndrome.

Metastatic tumors: Lung and breast carcinoma, soft-tissue sarcoma, and renal cancer are the most common sources of metastases to the heart. Malignant melanoma, leukemia, and lymphoma often metastasize to the heart, but the metastases may not be clinically significant. When Kaposi's sarcoma spreads systemically in immunodeficient (usually AIDS) patients, it may spread to the heart, but clinical cardiac complications are uncommon.

Symptoms and Signs

Cardiac tumors cause symptoms and signs typical of much more common disorders (eg, heart failure, stroke, coronary artery disease). Symptoms and signs of benign primary cardiac tumors depend on tumor type, location, size, and friability and can be classified as extracardiac, intramyocardial, or intracavitary.

Extracardiac symptoms and signs may be constitutional or mechanical. Constitutional symptoms of fever, chills, lethargy, arthralgias, and weight loss are caused exclusively by myxomas, perhaps as a result of cytokine (eg, IL-6) release. Petechiae may also occur. These and other findings may erroneously suggest bacterial endocarditis, connective tissue disorders, and occult cancer. Mechanical symptoms (eg, dyspnea, chest discomfort) result from compression of cardiac chambers or coronary arteries or from pericardial irritation or tamponade caused by growth or hemorrhage within the pericardium. Pericardial tumors may produce pericardial friction rubs.

Intramyocardial symptoms and signs are caused by arrhythmias, usually atrioventricular or intraventricular

block or paroxysmal supraventricular or ventricular tachycardias due to compression or encroachment on the conduction system (notably rhabdomyomas and fibromas).

Intracavitary symptoms and signs are due to tumors that obstruct valvular function, blood flow, or both (causing valvular stenosis, valvular insufficiency, or heart failure) or to tumors (especially gelatinous myxomas) that cause thrombus or tumor fragments to embolize into the systemic circulation (brain, coronary arteries, kidneys, spleen, extremities) or the lungs. Intracavitary symptoms and signs may vary with body position, which can alter hemodynamics and physical forces associated with the tumor.

Myxomas usually cause some combination of constitutional and intracavitary symptoms and signs. Myxomas may cause a diastolic murmur that mimics that of mitral stenosis but whose loudness and location vary from beat to beat with body position. About 15% of pedunculated left atrial myxomas produce an audible "tumor plop" as they drop into the mitral orifice during diastole. Myxomas may also cause arrhythmias. Raynaud's syndrome and finger clubbing are less typical but may occur.

Fibroelastomas, often discovered incidentally at autopsy, are usually asymptomatic; however, they may be a source of systemic emboli. Rhabdomyomas are usually asymptomatic. Fibromas cause arrhythmias and sudden death. Hemangiomas are usually asymptomatic but may cause any of the extracardiac, intramyocardial, or intracavitary symptoms. Teratomas cause respiratory distress and cyanosis due to compression of the aortic and pulmonary artery or SVC syndrome.

Symptoms and signs of malignant cardiac tumors are more acute in onset and progress more rapidly. Cardiac sarcomas most commonly cause symptoms of ventricular inflow tract obstruction and pericardial tamponade. Mesothelioma causes symptoms of pericarditis or tamponade. Primary lymphoma causes refractory progressive heart failure, tamponade, arrhythmias, and SVC syndrome. Metastatic cardiac tumors may manifest as sudden cardiac enlargement, tamponade (due to rapid accumulation of hemorrhagic pericardial effusion), heart block, other arrhythmias, or sudden unexplained heart failure. Fever, malaise, weight loss, night sweats, and loss of appetite may also be present.

Diagnosis

• Echocardiography

• Biopsy (during catheterization or thoracotomy)

Diagnosis, which is often delayed because symptoms and signs mimic those of much more common disorders, is confirmed by echocardiography and is tissue-typed by biopsy. Transesophageal echocardiography is better for visualizing atrial tumors, and transthoracic echocardiography is better for ventricular tumors. If results are equivocal, MRI is useful as are gated radionuclide imaging and CT. Infrequently, contrast ventriculography during cardiac catheterization is required. Biopsy is done during catheterization or open thoracotomy.

Extensive testing often precedes echocardiography in patients with myxomas because their symptoms are nonspecific. Anemia; thrombocytopenia; and elevation of WBC count, ESR, C-reactive protein, and γ-globulins are common. ECG may show left atrial enlargement. Routine chest x-ray may show Ca deposits in right atrial myxomas or in teratomas seen as anterior mediastinal masses. Myxomas are sometimes diagnosed when tumor cells are found in a surgically removed embolus.

Arrhythmias and heart failure with features of tuberous sclerosis suggest rhabdomyomas or fibromas. New cardiac symptoms and signs in a patient with a known extracardiac cancer suggest cardiac metastases. Chest x-ray may show bizarre changes in the cardiac silhouette.

Treatment

• Benign primary: Excision

• Malignant primary: Palliation

• Metastatic: Depends on tumor origin

Treatment of benign primary tumors is surgical excision followed by serial echocardiography over 5 to 6 yr to monitor for recurrence. Tumors are excised unless another disorder (eg, dementia) contraindicates surgery. Surgery is usually curative (95% survival at 3 yr). Exceptions are rhabdomyomas, most of which regress spontaneously and do not require treatment, and pericardial teratoma, which may require urgent pericardiocentesis. Patients with fibroelastoma may also require valvular repair or replacement. When rhabdomyomas or fibromas are multi-focal, surgical excision is usually ineffective, and prognosis is poor after the first year of life; survival at 5 yr may be as low as 15%.

Treatment of malignant primary tumors is usually palliative (eg, radiation therapy, chemotherapy, management of complications) because prognosis is poor.

Treatment of metastatic cardiac tumors depends on tumor origin. It may include systemic chemotherapy or palliation.