15 Diseases of the Peripheral Vasculature

Sruthi Renati
Mark A. Creager

Chapter Outline

Peripheral vascular disease is an umbrella term that includes a number of diverse pathologic entities that affect arteries, veins, and lymphatics. Although this terminology makes a distinction between the "central" coronary and "peripheral" systemic vessels, the vasculature as a whole comprises a dynamic, integrated, and multifunctional organ system that does not naturally comply with this semantic division.

Blood vessels serve many critical functions. First, they regulate the differential distribution of blood and delivery of nutrients and oxygen to tissues. Second, blood vessels actively synthesize and secrete vasoactive substances that regulate vascular tone, and antithrombotic substances that maintain the fluidity of blood and vessel patency (see Chapters 6 and 7). Third, the vessels play an integral role in the transport and distribution of immune cells to traumatized or infected tissues. Disease states of the peripheral vasculature interfere with these essential functions.

Peripheral vascular diseases result from processes that can be grouped into three categories: (1) structural changes in the vessel wall secondary to degenerative conditions, infection, or inflammation that lead to dilatation, aneurysm, dissection, or rupture; (2) narrowing of the vascular lumen caused by atherosclerosis, thrombosis, or inflammation; and (3) spasm of vascular smooth muscle. These processes can occur in isolation or in combination.

DISEASES OF THE AORTA

The aorta is the largest conductance vessel of the vascular system. In adults, its diameter is approximately 3 cm at its origin at the base of the heart. The **ascending aorta**, 5 to 6 cm in length, leads to the **aortic arch**, from which arise three major branches: the brachiocephalic (which bifurcates into the right common carotid and subclavian arteries), the left common carotid, and the left subclavian arteries. As the **descending aorta** continues beyond the arch, its diameter narrows to approximately 2 to 2.5 cm in healthy adults. As the aorta pierces the diaphragm, it becomes the **abdominal aorta**, providing arteries to the abdominal viscera before bifurcating into the left and right common iliac arteries, which supply the pelvic organs and lower extremities.

The aorta, like other arteries, is composed of three layers (see Fig. 5-1). At the luminal surface, the intima is composed of endothelial cells overlying the internal elastic lamina. The endothelial layer is a functional interface between the vasculature and circulating blood cells and plasma. The media is composed of smooth muscle cells and a matrix that includes collagen and elastic fibers. Collagen provides tensile strength that enables the vessels to withstand high-pressure loads. Elastin is capable of stretching to 250% of its original length and confers a distensible quality on vessels that allows them to recoil under pressure. The adventitia is composed primarily of collagen fibers, perivascular nerves, and vasa vasorum, a rich vascular network that supplies oxygenated blood to the aorta.

The aorta is subject to injury from mechanical trauma because it is continuously exposed to high pulsatile pressure and shear stress. The predominance of elastin in the media (2:1 over collagen) allows the aorta to expand during systole and recoil during diastole. The recoil of the aorta against the closed aortic valve contributes to the distal propagation of blood flow during the phase of left ventricular relaxation. With advancing age, the elastic component of the aorta and its branches degenerates, and as collagen becomes more prominent, the arteries stiffen. Systolic blood pressure (SBP), therefore, tends to rise with age because less energy is dissipated into the aorta during left ventricular contraction.

Diseases of the aorta most commonly appear as one of three clinical conditions: aneurysm, dissection, or obstruction.

Aortic Aneurysms

An aneurysm is an abnormal localized dilatation of an artery. In the aorta, aneurysms are distinguished from diffuse ectasia, which is a generalized yet lesser increase of the aortic diameter. Ectasia develops in older patients as elastic fiber fragments, smooth muscle cells decrease in number, and acid mucopolysaccharide ground substance accumulates within the vessel wall.

The term aneurysm is applied when the diameter of a portion of the aorta has increased by at least 50% compared with normal. A **true aneurysm** represents a dilatation of all three layers of the aorta, creating a large bulge of the vessel wall. True aneurysms are characterized as either fusiform or saccular, depending on the extent of the vessel's circumference within the aneurysm. A fusiform aneurysm, the more common type, is characterized by symmetrical dilation of the entire circumference of a segment of the aorta. A saccular aneurysm is a localized outpouching involving only a portion of the circumference.

In contrast, a **pseudoaneurysm** (also termed **false aneurysm**) is a contained rupture of the vessel wall that develops when blood leaks out of the vessel lumen through a hole in the intimal and medial layers and is contained by a layer of adventitia or perivascular organized thrombus. Pseudoaneurysms develop at sites of vessel injury caused by infection or trauma, such as puncture of the vessel during surgery or percutaneous catheterization. They are very unstable and are prone to rupture completely.

Aneurysms may be confined to the abdominal aorta (most common), the thoracic aorta, or involve both locations. They may also appear in peripheral and cerebral arteries.

Etiology and Pathogenesis of True Aortic Aneurysms

The etiology of aortic aneurysm formation varies depending on the location of the lesion (Table 15-1). Ascending thoracic aortic aneurysms typically are characterized by **cystic medial degeneration** (also termed cystic medial necrosis), a condition of degeneration and fragmentation of elastic fibers, with subsequent accumulation of collagenous and mucoid material within the medial layer. Cystic medial degeneration occurs normally with aging but is also associated with hypertension. Additionally, it develops in certain inherited disorders of connective tissue that affect the structural integrity of the aortic wall, including Marfan syndrome, Loeys–Dietz syndrome, the vascular form of Ehlers–Danlos syndrome (type IV), and familial thoracic aortic aneurysms. Marfan syndrome is caused by missense mutations of the fibrillin-1 gene (FBN1), which impair formation of functional microfibrils in elastin. Abnormal fibrillin-1 also limits the binding and inactivation of transforming growth factor β (TGF-β), a signaling molecule that regulates cellular proliferation and differentiation. Loeys–Dietz syndrome is an autosomal dominant disorder caused by genetic mutations of TGF-β receptors. While thoracic aortic aneurysms have been associated with both increased activity of TGF-β and mutations of its receptors, the mechanism by which aberrant TGF-β signaling alters vascular integrity is not yet known. Ehlers–Danlos type IV syndrome results from mutations encoding type III procollagen. Familial thoracic aortic aneurysms are caused by mutations of the TGF-β receptor as well as of genes encoding the smooth muscle–specific alpha-actin (ACTA2) and beta-myosin heavy chain (MYH11), which are essential components of the contractile complex in vascular smooth muscle cells. Cystic medial degeneration also characterizes the form of thoracic aortic aneurysm often associated with bicuspid aortic valves.

Aneurysms of the descending thoracic and abdominal aorta are usually associated with **atherosclerosis** and its risk factors, including smoking, hypertension, dyslipidemia, male gender, and advanced age. However, it is unlikely that atherosclerosis alone is responsible for such aneurysm development. Rather, other important pathophysiologic mechanisms include a genetic predisposition, local vessel inflammation, and an imbalance between synthesis and degradation of extracellular matrix proteins. For example, specific proteases (e.g., elastase, collagenase) and matrix metalloproteinases derived from inflammatory cells and vascular endothelial and smooth muscle cells may contribute to the breakdown of elastin and collagen. Aneurysm formation is also associated with markers of inflammation, including C-reactive protein (CRP) and cytokines such as interleukin-6 (IL-6). Levels of both CRP and IL-6 have been shown to correlate with the size of aneurysms, and inflammatory cells such as B and T lymphocytes and macrophages are frequently found on histologic examination. Angiotensin II, via its effect on inflammation and oxidative stress, has also been implicated in experimental models of abdominal aortic aneurysms.

TABLE 15-1 Conditions Associated with True Aortic Aneurysms

1. Cystic medial degeneration (usually affects ascending thoracic aorta)
   - Marfan syndrome
   - Loeys–Dietz syndrome
   - Ehlers–Danlos syndrome (type IV)
   - Bicuspid aortic valve
   - Familial
2. Atherosclerosis/degenerative (usually affects descending thoracic and abdominal aorta)
3. Infections of arterial wall
4. Vasculitis
   - Takayasu arteritis
   - Giant cell arteritis

Infrequent causes of aortic aneurysms (Table 15-1) include weakness of the media from infections of the vessel wall by Salmonella species, staphylococci, streptococci, tuberculosis, syphilis, or fungi. Inf ammatory diseases such as Takayasu arteritis or giant cell arteritis (both described later in the chapter) may similarly weaken the vessel and result in aneurysm formation.

Clinical Presentation and Diagnosis

Most aneurysms are asymptomatic, though some patients, especially those with abdominal aortic aneurysms, may be aware of a pulsatile mass. Others present with symptoms related to compression of neighboring structures by an expanding aneurysm. Thoracic aortic aneurysms may compress the trachea or mainstem bronchus, resulting in cough, dyspnea, or pneumonia. Compression of the esophagus can result in dysphagia, and involvement of the recurrent laryngeal nerve may lead to hoarseness. Aneurysms of the ascending aorta may dilate the aortic ring, resulting in aortic regurgitation and symptoms of congestive heart failure. Abdominal aortic aneurysms may cause abdominal or back pain or nonspecific gastrointestinal symptoms.

Aortic aneurysms are often first suspected when dilatation of the vessel is observed on chest or abdominal radiographs, particularly if the wall is calcified. Aneurysms of the abdominal aorta or of the large peripheral arteries may also be discovered by careful palpation during physical examination. The diagnosis is confirmed by ultrasonography, contrast-enhanced computed tomography (CT), or magnetic resonance (MR) imaging (Fig. 15-1).

The most devastating consequence of an aortic aneurysm is rupture, which can be fatal. An aneurysm may leak slowly or burst suddenly, resulting in profound blood loss

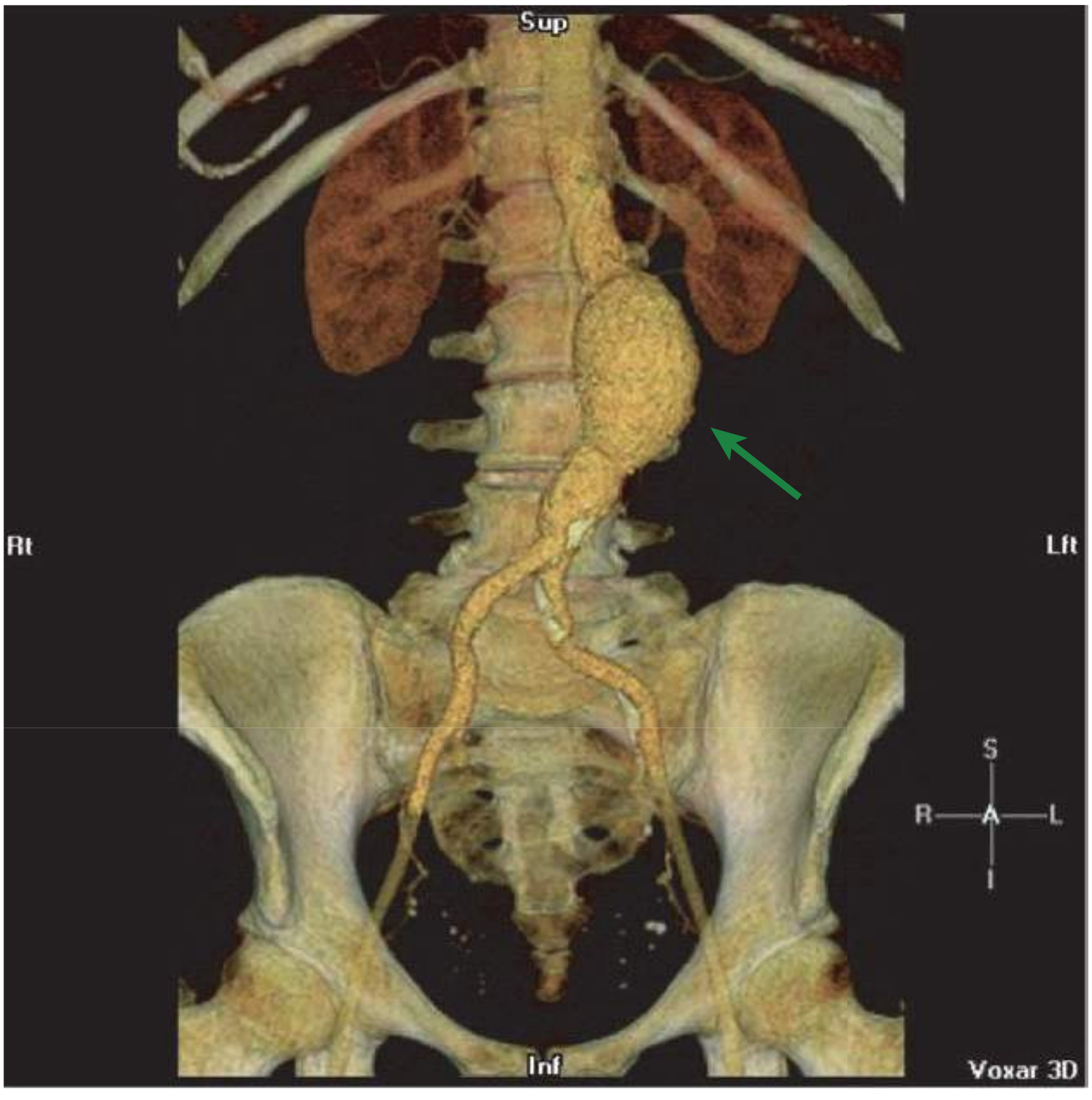

FIGURE 15-1. Abdominal aortic aneurysm. Computed tomographic angiogram (CTA) of an abdominal aortic aneurysm, indicated by the green arrow. (Courtesy of Frank Rybicki MD, Brigham and Women's Hospital, Boston, MA.)

and hypotension. Thoracic aortic aneurysms may rupture into the pleural space, mediastinum, or bronchi. Abdominal aortic aneurysms may rupture into the retroperitoneal space or abdominal cavity or erode into the intestines, resulting in massive gastrointestinal bleeding.

Natural history studies have shown that the risk of rupture is related to the size of the aneurysm, as predicted by the Laplace relationship (i.e., wall tension is proportional to the product of pressure and radius). The mean rates of thoracic and abdominal aortic aneurysms expansion are 0.1 and 0.4 cm/year, respectively. Thoracic aneurysms rupture at an annual rate of 2% for aneurysms less than 5 cm in diameter, 3% for aneurysms 5 to 5.9 cm, and 7% for aneurysms greater than 6 cm. Abdominal aneurysms less than 4 cm, 4 to 4.9 cm, and 5 to 5.9 cm have annual rates of rupture of 0.3%, 1.5%, and 6.5%, respectively. Abdominal aneurysms greater than 6 cm have a markedly higher risk of rupture.

Treatment

Treatment of an aortic aneurysm is based on its size and the patient's overall medical condition. Once an aneurysm is identified, its dimensions should be closely monitored through repeated imaging, typically every 6 to 12 months depending on size. In general, surgical treatment is considered for ascending aortic aneurysms greater than 5.5 to 6.0 cm. Ascending aortic aneurysms in patients with Marfan syndrome (in whom the risk of complications is greater) should be considered for surgical repair if the diameter is greater than 5 cm. Surgical repair is generally recommended for descending thoracic aortic aneurysms measuring 6.5 to 7.0 cm, for abdominal aortic aneurysms measuring 5.5 cm or more, and for smaller aneurysms that enlarge at a rate greater than 1.0 cm/year.

The mortality associated with elective surgical repair of thoracic aortic aneurysms is 3% to 5%. Patients are maintained on cardiopulmonary bypass as the aneurysm is resected and replaced with a prosthetic Dacron graft. Patients with aneurysms involving multiple aortic segments have staged repairs, in which one segment is corrected at a time. Some patients with thoracic aortic aneurysms may be candidates for minimally invasive repair, in which a transluminally placed endovascular stent graft is positioned across the aneurysm.

Surgical repair of abdominal aortic aneurysms involves placement of a prosthetic graft. The operative mortality for such procedures at high-volume institutions is 1% to 2%. Percutaneous endovascular repair of infrarenal abdominal aortic aneurysms with stent grafts can be performed in selected patients with less acute morbidity, and long-term results are similar to that of surgical repair.

Medical management, including risk-factor reduction (e.g., smoking cessation), is currently recommended for patients with small aneurysms. β-Blockers may reduce the expansion rate of thoracic aortic aneurysms in patients with Marfan syndrome; it is not clear whether they are effective for other causes or types of aneurysms. Angiotensin II receptor antagonists, which also inhibit TGF-β, are undergoing clinical trials in Marfan syndrome.

Aortic Dissection

Aortic dissection is a life-threatening condition in which blood from the vessel lumen passes through a tear in the intima into the medial layer and spreads along the artery. Other related acute syndromes include aortic intramural hematoma, penetrating aortic ulcer, and aortic rupture. Acute intramural hematoma is a variant of aortic dissection characterized by a hemorrhage in the wall of the aorta without evidence of an intimal tear. A penetrating atherosclerotic ulcer results from erosion of a plaque into the aortic wall. Aortic rupture may be a complication of aortic dissection, intramural hematoma, penetrating atherosclerotic ulcer, or result from trauma.

Etiology, Pathogenesis, and Classif cation

Aortic dissection arises from a circumferential or transverse tear in the intimal layer of the vessel wall that allows blood from the lumen, under the driving force of the systemic pressure, to enter into the media and propagate along the plane of the muscle layer. Another potential origin of aortic dissection is rupture of vasa vasorum with hemorrhage into the media, forming a hematoma in the arterial wall that subsequently tears through the intima and into the vessel's lumen.

Any condition that interferes with the normal integrity of the elastic or muscular components of the medial layer can predispose to aortic dissection. Such degeneration may arise from chronic hypertension, aging, and/or cystic medial degeneration (which, as described earlier, is a feature of certain hereditary connective tissue disorders, such as Marfan syndrome and Ehlers–Danlos syndrome). In addition, traumatic insult to the aorta (e.g., blunt chest trauma or accidental vessel damage during intra-arterial catheterization or cardiac surgery) can also initiate dissection.

Aortic dissection is most common in the sixth and seventh decades and occurs more frequently in men. More than two thirds of patients have a history of hypertension. Dissection most commonly involves the ascending thoracic aorta (65%) and descending thoracic aorta (20%), while the aortic arch (10%) and abdominal aortic (5%) segments are less commonly affected.

Dissections are commonly classif ed into two categories (Stanford types A and B), depending on their location and extent (Fig. 15-2). In a type A dissection (proximal), the ascending aorta and/or aortic arch is involved, regardless of the site of the primary tear. A type B dissection (distal) does not involve the ascending aorta or arch and is, therefore, conf ned to the descending thoracic and abdominal aorta. This distinction is important because treatment strategies and prognoses are determined by location. Proximal aortic involvement tends to be more devastating because of the potential for extension into the coronary and arch vessels, the support structures of the aortic valve, or the pericardial space. Approximately two thirds of dissections are type A and one third are type B. Dissections may also be classif ed as acute or chronic, with acute dissections presenting with symptoms of less than 2 weeks' duration.

Clinical Presentation and Diagnosis

The most common symptom of aortic dissection is sudden, severe pain with a "tearing" or "ripping" quality in the anterior chest (typical of type A dissections) or between the scapulae (type B dissections). The pain travels as the dissection propagates along the aorta and can radiate anywhere in the thorax or abdomen. Painless dissection is possible but uncommon (6.4% of cases).

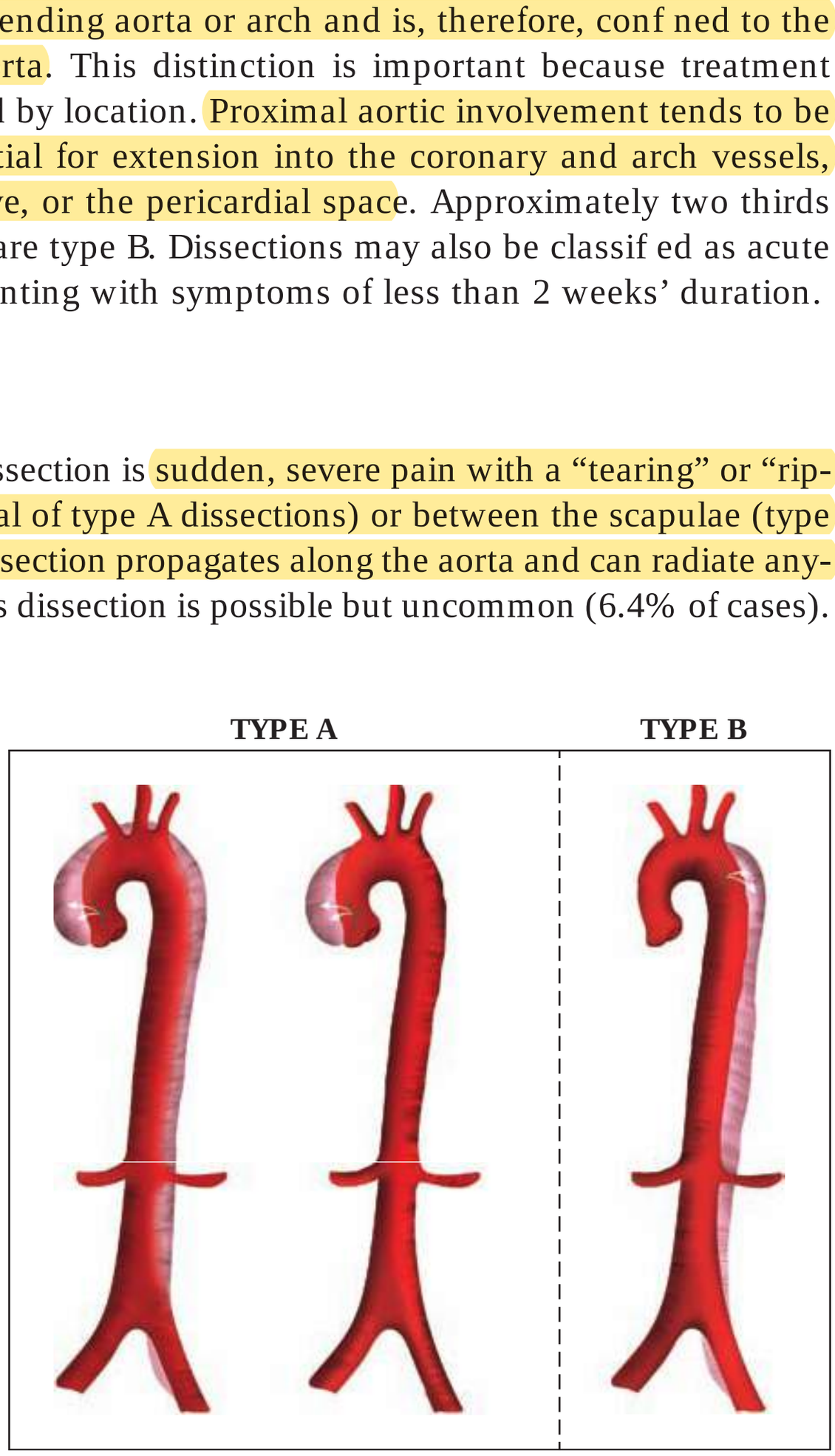

FIGURE 15-2. Aortic dissection. Type A involves the ascending aorta, whereas type B does not. (Reprinted from Braverman AC, Thompson R, Sanchez L. Diseases of the aorta. In: Bonow RO, Mann DL, Zipes DP, et al., eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 9th ed. Philadelphia, PA: Elsevier; 2012.)

TABLE 15-2 Complications of Aortic Dissection

Rupture
Pericardial tamponade
Hemomediastinum
Hemothorax (usually left sided)
Occlusion of aortic branch vessels
Carotid (stroke)
Coronary (myocardial infarction)
Splanchnic (visceral infarction)
Renal (acute renal failure)
Iliac, brachiocephalic, subclavian (limb ischemia)
Distortion of aortic annulus
Aortic regurgitation

Other symptoms relate to the catastrophic complications that can occur at the time of presentation or thereafter (Table 15-2) and include (1) rupture through the adventitia anywhere along the aorta (often into the left pleural space or pericardium); (2) occlusion of major branches of the aorta by the propagating hematoma within the vessel wall, which compresses the lumen and can result in myocardial infarction (coronary artery involvement), stroke (carotid artery involvement), visceral ischemia, renal failure, or loss of pulse in an extremity; and (3) extension into the aortic root, with disruption of the aortic valve support apparatus causing aortic regurgitation.

Several important physical findings may be present. Hypertension is frequently detected, either as an underlying cause of dissection, a result of the sympathetic nervous system response to the severe pain, or because of diminished renal vascular flow, with activation of the renin–angiotensin system. If the dissection has occluded one of the subclavian arteries, a difference in SBP between the arms is noted. Neurologic deficits may accompany dissection into the carotid vessels. If a type A dissection results in aortic regurgitation, an early diastolic murmur can be detected on auscultation. Leakage from a type A dissection into the pericardial sac may produce signs of cardiac tamponade (see Chapter 14).

The diagnosis of aortic dissection must not be delayed, because catastrophic complications or death may rapidly ensue. The confirmatory imaging techniques most useful in detecting dissection include contrast-enhanced CT, transesophageal echocardiography (TEE), MR angiography, and contrast angiography. Each of these techniques has specific advantages and disadvantages, and the decision of which to employ is often guided by a hospital's local expertise. In emergency situations, CT scanning or TEE can generally be obtained rapidly and offer excellent sensitivity and specificity for the diagnosis.

Treatment

The goal of acute treatment is to arrest progression of the dissecting channel. Suspicion of acute aortic dissection warrants immediate medical therapy to reduce SBP (aiming for a systolic pressure of 100 to 120 mm Hg) and to decrease the force of left ventricular contraction and thus minimize aortic wall shear stress. Useful pharmacologic agents in this regard include β-blockers (to reduce the force of contraction and heart rate as well as to lower blood pressure) and vasodilators such as sodium nitroprusside (to rapidly reduce blood pressure). In proximal (type A) dissections, early surgical correction has been shown to improve outcomes compared with medical therapy alone. Surgical therapy involves repairing the intimal tear, suturing the edges of the false channel, and if necessary, inserting a synthetic aortic graft.

In contrast, patients with uncomplicated type B dissections are initially managed with aggressive medical therapy alone; early surgical intervention does not further improve the outcome in these patients. Surgery is indicated, however, if there is clinical evidence of propagation of the dissection, compromise of major branches of the aorta, impending rupture, or continued pain. Percutaneous catheter-based repair with endovascular stent grafts has been used successfully in selected stable patients with type B dissections. The graft seals the entry site of the dissection, resulting in thrombosis of the false lumen.

PERIPHERAL ARTERY DISEASES

Peripheral artery disease (PAD) is defined by the presence of a flow-limiting lesion in an artery that provides blood supply to the limbs. The major causes of such arterial stenosis or occlusion are atherosclerosis, thromboembolism, and vasculitis. The clinical presentation of these disorders results from decreased perfusion to the affected extremity.

Peripheral Atherosclerotic Vascular Disease

Etiology and Pathogenesis

The most common cause of PAD is atherosclerosis. It is a prevalent vascular disorder, affecting approximately 4% of persons over the age of 40 and 15% to 20% of those over the age of 70. The pathology of atherosclerotic PAD is identical to that of coronary artery disease (CAD), and the major coronary risk factors (e.g., cigarette smoking, diabetes mellitus, dyslipidemia, and hypertension) are also associated with PAD. Approximately 40% of patients with PAD actually have clinically significant CAD. As a consequence of the systemic nature of atherosclerosis, patients with PAD have a twofold to fivefold increased risk of cardiovascular death compared with patients who do not have this condition. Thus, detection of PAD is useful in identifying patients at increased risk of adverse cardiovascular events.

The pathophysiology of atherosclerotic PAD is also similar to that of CAD. Ischemia of the affected region occurs when the balance between oxygen supply and demand is upset; exercise raises the demand for blood flow in the limbs' skeletal muscle, and a stenosed or obstructed artery cannot provide an adequate supply. Rest improves symptoms as the balance between oxygen supply and demand is restored.

Recall from Chapter 6 that the degree of blood flow reduction relates closely to the extent of vessel narrowing, the length of the stenosis, and blood viscosity. The Poiseuille equation describes this relationship:

$$Q = \frac{\Delta P \pi r^4}{8 \eta L}$$

in which Q = flow, ΔP = pressure drop across the stenosis, r = vessel radius, η = blood viscosity, and L = length of stenosis. Thus, the degree of vessel narrowing by the stenosis (i.e., the change in r) has the greatest impact on flow. For example, if the radius is reduced by one half, the flow will be reduced to 1/16th of its baseline. The equation also indicates that for stenoses of the same length and radius, higher flow rates correspond to greater pressure drops across the stenoses. That is, as the flow velocity increases across a stenotic vessel, the blood turbulence results in a loss of kinetic energy. The result is a decline in perfusion pressure distal to the stenosis.

During exercise, products of skeletal muscle metabolism (e.g., adenosine) act locally to dilate arterioles. The resulting decrease in vascular resistance serves to increase blood flow to the active muscle (recall that flow = pressure/resistance). In turn, the increased flow stimulates healthy arterial endothelium to release vasodilating factors such as nitric oxide, thereby increasing the radii of upstream conduit vessels. However, in PAD, obstructed arteries cannot respond to the vasodilating stimuli, thereby limiting flow increases. In addition,

dysfunctional atherosclerotic endothelium does not release normal amounts of vasodilating substances (see Chapter 6). Thus, the physical properties of a stenosis and the reduced vasodilator activity imposed by diseased endothelium prevent adequate blood f ow from reaching distal tissues and contribute to ischemia.

Hemodynamic changes alone cannot account for the dramatic reductions in exercise capacity experienced by PAD patients; changes in muscle structure and function are also seen. One such change is the denervation and dropout of muscle fibers, which is thought to occur as an adaptation to intermittent ischemia. The loss of such fibers can explain the reduced muscle strength and atrophy that occur in PAD patients. Even viable muscle fibers in affected limbs may show abnormalities of mitochondrial oxidative metabolism.

In summary, atherosclerotic lesions produce stenoses in peripheral conduit vessels and limit blood f ow to the affected extremity. Mechanisms normally in place to compensate for increased demand, such as endogenous release of vasodilators during exercise and recruitment of microvessels, fail in the face of endothelial dysfunction and diminished f ow velocity. Thus, states of increased oxygen demand are not met with adequate supply, producing limb ischemia. Adaptations to ischemia include changes in muscle fiber metabolism and muscle fiber dropout. Together, these physical and biochemical changes result in weak lower limbs that suffer ischemic discomfort during exercise. Severe peripheral atherosclerosis may reduce limb blood f ow to such an extent that it cannot satisfy resting metabolic requirements. This results in critical limb ischemia, which may progress to tissue necrosis and gangrene that may threaten viability of the extremity.

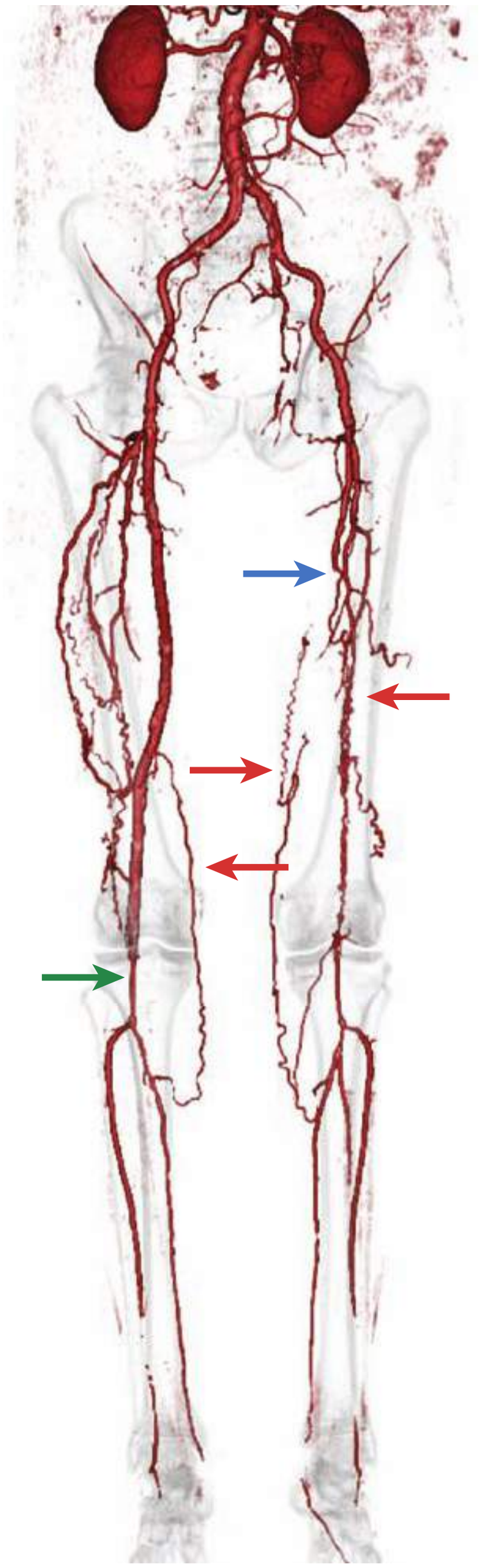

FIGURE 15-3. An angiogram demonstrating peripheral artery disease. There is occlusion of the left femoral artery (blue arrow) and stenosis of the right popliteal artery (green arrow). Collateral vessels that circumvent areas of stenosis and occlusion are present (red arrows). (Courtesy of Michael L. Steigner MD, Brigham and Women's Hospital, Boston, MA.)

Clinical Presentation and Diagnosis

PAD may affect the aorta or the iliac, femoral, popliteal, and tibioperoneal arteries (Fig. 15-3). Patients with PAD may therefore develop buttock, thigh, or calf discomfort precipitated by walking and relieved by rest. This classic symptom of exertional limb fatigue and pain is known as **claudication.** In severe PAD, patients may experience pain at rest, usually affecting the feet or toes. The chronically reduced blood f ow in this case predisposes the extremity to ulceration, infection, and skin necrosis (Fig. 15-4). Patients who smoke or have diabetes mellitus are at high risk of these complications.

The location of claudication corresponds to the diseased artery, with the femoral and popliteal arteries being the most common sites (Table 15-3). The arteries of the upper extremities are less frequently affected, but brachiocephalic or subclavian artery disease can cause arm claudication.

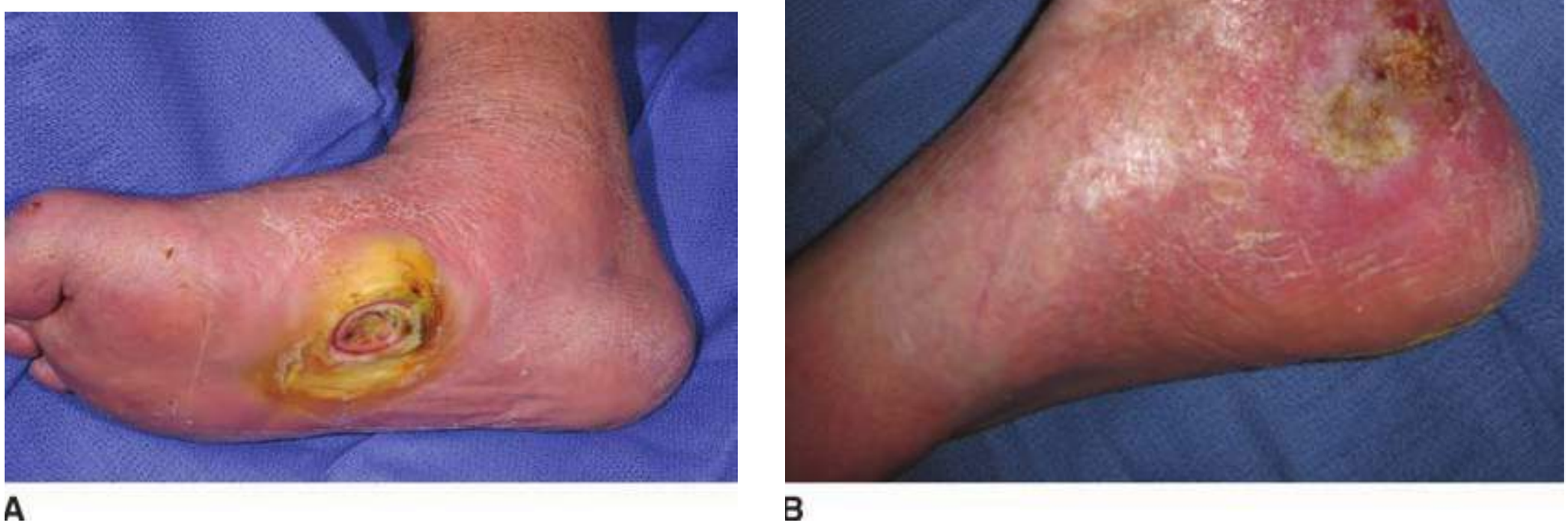

FIGURE 15-4. Leg ulcers. A. Ulceration affecting the foot in a patient with diabetes and peripheral artery disease. (Courtesy of Christian E. Sampson MD, Brigham and Women's Hospital, Boston, MA.) **B.** Venous insuff ciency ulcer near the medial malleolus of the right leg. Notice the venous stasis pigmentation of the surrounding skin. (Courtesy of Lauren R. Bayer PA, Brigham and Women's Hospital, Boston, MA.)

Physical examination generally reveals loss of pulses distal to the stenotic segment. Bruits (swishing sounds auscultated over a region of turbulent blood f ow) may be audible in the abdomen (because of stenoses within the mesenteric or renal arteries) or over iliac, femoral, or subclavian arterial stenoses. In patients with chronic severe ischemia, the lack of blood perfusion results in muscle atrophy, pallor, cyanotic discoloration, hair loss, and occasionally gangrene and necrosis of the foot and digits.

Ischemic ulcers resulting from PAD often begin as small traumatic wounds in areas of increased pressure or in regions prone to injury, such as the tips of the toes and the volar surface of the foot (see Fig. 15-4A). These often painful ulcers fail to heal owing to the inadequate blood supply. Diabetic patients with peripheral sensory neuropathies are particularly susceptible to ulcers at sites of trauma or pressure from ill-fitting footwear. Ischemic ulcers can be distinguished from venous insufficiency ulcers, which develop more proximally and on the medial portion of the leg. Venous ulcers are also associated with reddish-brown pigmentation and varicose veins (see Fig. 15-4B).

In the evaluation of PAD, it is helpful to measure the ratio of blood pressure in the ankles to that in the arms (termed the ankle–brachial index [ABI]) using a blood pressure cuff and a Doppler instrument to detect blood f ow (Box 15-1). Other testing to assess peripheral

TABLE 15-3 Relation of Stenotic Site to Claudication Symptoms

Site	Location of Claudication Symptoms
Distal aorta or iliac arteries	Buttocks, hips, thighs, or calves
Femoral or popliteal arteries	Calves
Subclavian or axillary arteries	Arms

BOX 15-1 Measurement and Interpretation of the Ankle–Brachial Index

The ABI is the ratio of the SBP measured at the ankle to that measured at the brachial artery. To determine the ABI, the patient should lie supine for 10 minutes with the head and heels fully supported. A Doppler ultrasound probe is used to detect flow in the brachial, posterior tibial (PT), and dorsalis pedis (DP) arteries. A blood pressure cuff is placed on each arm to measure the SBP at the brachial arteries and on each of the lower calves, just above the malleoli, to measure the SBP at the PT and DP arteries. Use the higher of the PT and DP values on each side as the ankle pressure measurement. Finally, divide the ankle pressure measurement by the higher of the two brachial artery pressure measurements to determine the ABI.

A normal ABI is ≥ 1.0. An index < 0.9 is diagnostic of PAD. Patients with PAD may be asymptomatic or have symptoms of intermittent claudication or rest pain. An index < 0.5 is found in patients with severe PAD and critical limb ischemia.

Ankle Pressure Measurement using a Doppler Probe at the Right Dorsalis Pedis Artery

perfusion includes limb segmental systolic pressure measurements (using pneumatic cuffs placed along the extremity) and pulse volume recordings (i.e., graphical measurement of volume changes in segments of the extremity with each pulse). Duplex ultrasonography is a commonly used noninvasive method to visualize and assess the extent of arterial stenoses and the corresponding reductions in blood flow. Other more advanced imaging studies (e.g., MR angiography, CT angiography, or intra-arterial contrast angiography) are obtained when revascularization procedures are planned.

Treatment

For patients with PAD, antiplatelet therapy and risk factor modification (including smoking cessation, lipid lowering, and control of diabetes and hypertension) are important in reducing the likelihood of coronary events. Platelet inhibitors, such as aspirin and clopidogrel, reduce cardiovascular morbidity and mortality in patients with PAD. It has not been established if antiplatelet agents reduce symptoms or prevent thrombotic complications of PAD itself.

Specific treatment of PAD includes supportive care of the feet to prevent trauma or restriction of blood flow. Exercise, particularly walking, improves endurance in part by increasing metabolic efficiency in the skeletal muscle of the legs. A formal exercise program is considered first-line therapy in the management of PAD.

Certain medical therapies are sometimes useful in the treatment of claudication. Cilostazol is a selective phosphodiesterase inhibitor that increases cyclic adenosine monophosphate

and has vasodilator and platelet-inhibiting properties; it has been shown to improve exercise capacity in patients with PAD. Pentoxifylline is a drug purported to improve the deformability of red and white blood cells and may improve claudication symptoms in some patients. Conversely, most vasodilator drugs (see Chapter 17) are not helpful in relieving claudication.

More effective medical therapies for PAD are on the horizon. Advances in angiogenesis research and clinical trials provide hope that revascularization through delivery of angiogenic growth factors (e.g., vascular endothelial growth factor and basic fibroblast growth factor), and regenerative cell-based therapies, including use of endothelial progenitor cells, may be possible.

Mechanical revascularization is indicated when medical therapy has failed for patients with disabling claudication and as first-line therapy in cases of critical limb ischemia. In advanced cases, therapy is directed at healing ischemic ulcerations and preventing limb loss. Catheter-based interventions, such as percutaneous transluminal angioplasty and stent implantation, can be performed on selected patients with low morbidity. Surgical procedures include bypass operations to circumvent the occluded arteries using saphenous vein or prosthetic grafts. However, amputation may be necessary if blood flow cannot be satisfactorily reestablished to maintain limb viability.

Acute Arterial Occlusion

Acute arterial occlusion is caused either by embolization from a cardiac or proximal vascular site or by thrombus formation in situ. The origin of arterial emboli is most often the heart, usually resulting from disorders involving intracardiac stasis of flow (Table 15-4). Emboli may also originate from thrombus or atheromatous material overlying a segment of the aorta. Rarely, arterial emboli originate from the venous circulation. If a venous clot travels to the right-heart chambers and is able to pass through an abnormal intracardiac communication (e.g., an atrial septal defect), it then enters the systemic arterial circulation (a condition known as a **paradoxical embolism**). Primary arterial thrombus formation may appear at sites of endothelial damage or atherosclerotic stenoses, or within bypass grafts.

The extent of tissue damage from thromboembolism depends on the site of the occluded artery, the duration of occlusion, and the degree of collateral circulation serving the tissue beyond the obstruction. Common symptoms and signs that may develop from abrupt reduction in blood supply include pain, pallor, paralysis, paresthesia, and pulselessness (termed the “five Ps”). A sixth P, poikilothermia (coolness), is also often manifest.

Patients with a proven acute arterial occlusion should be treated with a parenteral anticoagulant such as heparin (followed by oral warfarin) to prevent propagation of the clot

TABLE 15-4 Origins of Arterial Emboli

Cardiac origin
Stagnant left atrial flow (e.g., atrial fibrillation, mitral stenosis)
Left ventricular mural thrombus (e.g., dilated cardiomyopathy, myocardial infarction, ventricular aneurysm)
Valvular lesions (endocarditis, thrombus on prosthetic valve)
Left atrial myxoma (mobile tumor in left atrium)
Aortic origin
Thrombus material overlying atherosclerotic segment
Venous origin
Paradoxical embolism travels through intracardiac shunt

and to reduce the likelihood of additional embolic events. A revascularization procedure (catheter-based thrombolysis or thrombectomy, surgical embolectomy, or bypass surgery) is indicated if limb viability is at risk.

Atheroembolism is the condition of peripheral arterial occlusion by atheromatous material (i.e., cholesterol, platelets, and fibrin) derived from more proximal vascular sites, such as atherosclerotic lesions or aneurysms. The emboli lodge distally, resulting in occlusion of small arteries in the muscle and skin. Patients typically present with acute pain and tenderness at the involved site. Occlusion of digital vessels may result in the "blue toe" syndrome, culminating in gangrene and necrosis. Other findings may include livedo reticularis (purplish mottling of involved skin), kidney failure (caused by renal atheroembolism), and intestinal ischemia. Although an estimated 50% to 60% of cases are spontaneous, atheroembolism may occur after intra-arterial procedures (e.g., cardiac catheterization) when atherosclerotic material is unintentionally dislodged from the proximal vasculature. Ischemia resulting from atheroemboli is difficult to manage because the heterogeneous composition and distribution of emboli often precludes surgical removal or thrombolytic therapy. Surgical intervention to remove or bypass the source of emboli may be necessary to prevent recurrences.

Vasculitic Syndromes

Vasculitis (vessel wall inf ammation) results from immune complex deposition or cell-mediated immune reactions directed against the vessel wall. Immune complexes activate the complement cascade with subsequent release of chemoattractants and anaphylatoxins that direct neutrophil migration to the vessel wall and increase vascular permeability. Neutrophils injure the vessel by releasing lysosomal contents and producing toxic oxygen-derived free radicals. In cell-mediated immune reactions, T lymphocytes bind to vascular antigens and release lymphokines that attract additional lymphocytes and macrophages to the vessel wall. These inf ammatory processes can cause end-organ ischemia through vascular necrosis or local thrombosis.

The cause of most of the vasculitic syndromes is unknown, but they often can be distinguished from one another by the pattern of involved vessels and by histologic characteristics. Three important examples of vasculitic syndromes are Takayasu arteritis, giant cell arteritis, and thromboangiitis obliterans.

Takayasu arteritis is a chronic vasculitis of unknown etiology that targets the aorta and its major branches. The estimated annual incidence is 1.2 to 2.6 cases per million. Between 80% and 90% of affected persons are women, with onset typically between the ages of 10 and 40. Most reported cases have been from Asia and Africa, but it is a worldwide disease. Patients typically present with systemic complaints such as malaise and fever; focal symptoms are related to inf ammation of the affected vessel and include cerebrovascular ischemia (brachiocephalic or carotid artery involvement), myocardial ischemia (coronary artery), arm claudication (brachiocephalic or subclavian artery), or hypertension (renal artery). The carotid and limb pulses are diminished or absent in nearly 85% of patients at the time of diagnosis; hence, this condition is often termed "pulseless" disease. Takayasu arteritis is also an uncommon cause of aortic aneurysm or aortic dissection. Histologic examination of affected vessels reveals continuous or patchy granulomatous inf ammation with lymphocytes, histiocytes, and multinucleated giant cells, resulting in intimal proliferation, disruption of the elastic lamina, and fibrosis. Antiendothelial antibodies may also play a role in the disease. Steroid and cytotoxic drugs may reduce vascular inf ammation and alleviate symptoms of Takayasu arteritis. Surgical bypass of obstructed vessels may be helpful in severe cases. The 5-year survival rate is 80% to 90%.

Giant cell arteritis (also termed **temporal arteritis**) is a chronic vasculitis of medium-sized to large arteries that most commonly involves the cranial vessels or the aortic arch and its branches. It is an uncommon disease, with an incidence of 24 per 100,000, and the typical onset is after age 50; 65% of patients are female. Giant cell arteritis may be associated with the inf ammatory condition known as polymyalgia rheumatica. Histologic findings in affected

vessels include lymphocyte and macrophage infiltration, intimal fibrosis, and focal necrosis, with granulomas containing multinucleated giant cells.

Symptoms and signs of giant cell arteritis depend on the distribution of affected arteries and may include diminished temporal pulses, prominent headache (temporal artery involvement), or facial pain and claudication of the jaw while chewing (facial artery involvement). Ophthalmic artery arteritis leads to impaired vision, with permanent partial or complete loss in 15% to 20% of patients. Serum markers of inf ammation (e.g., erythrocyte sedimentation rate and CRP) are invariably elevated in patients with giant cell arteritis. Ultrasound examination can support the diagnosis by demonstrating a hypoechoic halo around the involved arterial lumen with vessel stenosis and/or occlusion. The diagnosis can be confirmed by biopsy of an involved vessel, usually a temporal artery, but treatment should not wait for biopsy results. High-dose systemic steroids are effective in treating vasculitis and preventing visual complications. Giant cell arteritis usually has a self-limited course of 1 to 5 years.

Thromboangiitis obliterans (Buerger disease) is a segmental inf ammatory disease of small and medium-sized arteries, veins, and nerves involving the distal vessels of the upper and lower extremities. It is most prevalent in the Far and Middle East and has a very strong association with cigarette smoking. It is most common in men younger than age 45; only 10% to 25% of patients are female. There is an increased incidence of human leukocyte antigen A9 (HLA-A9) and HLA-B5 in affected persons.

Thromboangiitis obliterans presents with a triad of symptoms and signs: distal arterial occlusion, Raynaud phenomenon (described in the next section), and migrating superficial vein thrombophlebitis. Arterial occlusion results in arm and foot claudication as well as ischemia of the digits. Traditional laboratory markers of inf ammation and autoimmune disease are usually not detected. Arteriographic features of involved arteries include areas of stenosis interspersed with normal-appearing vessels with more severe disease distally, collateral vessels with a "corkscrew" appearance around the stenotic regions, and lack of atherosclerosis in proximal arteries. The diagnosis can be established by tissue biopsy, although this is rarely needed. Biopsy specimens of affected vessels reveal an occlusive, highly cellular, inf ammatory thrombus, with limited involvement of the vessel wall and preservation of the internal elastic lamina (Fig. 15-5). The most important treatment for thromboangiitis obliterans is smoking cessation, which usually prevents progression of the disease and its complications. Debridement of necrotic tissue may be necessary in advanced cases. Revascularization is not usually an option because of the distal location of the arterial lesions.

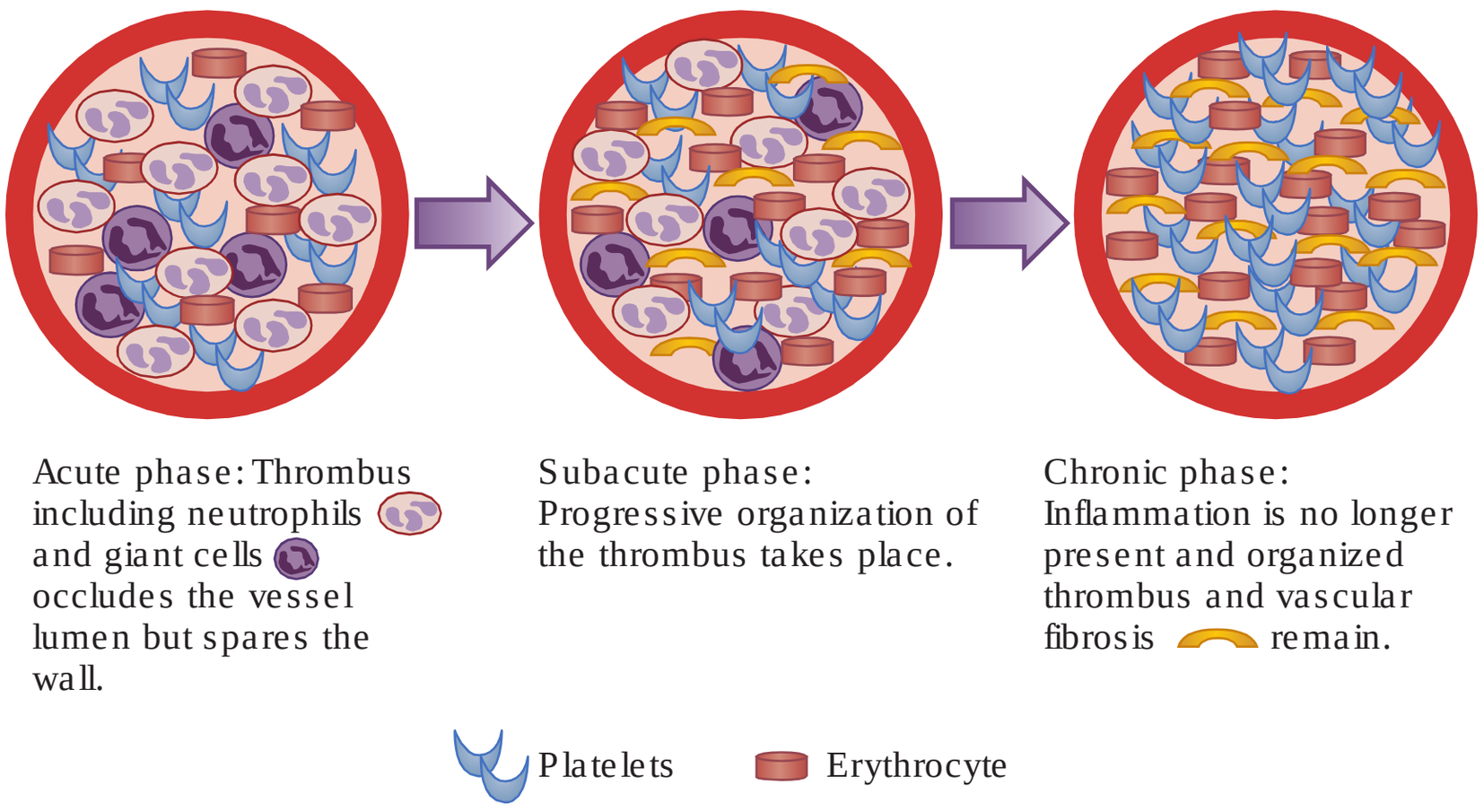

FIGURE 15-5. Pathophysiologic phases of thromboangiitis obliterans. (Reprinted from Piazza G, Creager MA. Thromboangiitis obliterans. Circulation. 2010;121(16):1858–1861.)

VASOSPASM: RAYNAUD PHENOMENON

Raynaud phenomenon is a vasospastic disease of the digital arteries that occurs in susceptible people when exposed to cool temperatures or sometimes during emotional stress. Vasospasm is an extreme vasoconstrictor response that temporarily obliterates the vascular lumen, inhibiting blood flow. Typically, such episodes are characterized by a triphasic color response. First, the fingers and/or toes blanch to a distinct white as blood flow is interrupted (Fig. 15-6). The second phase is characterized by cyanosis, related to local accumulation of desaturated hemoglobin, followed by a third phase of ruddy color as blood flow resumes. The color response may be accompanied by numbness, paresthesias, or pain of the affected digits.

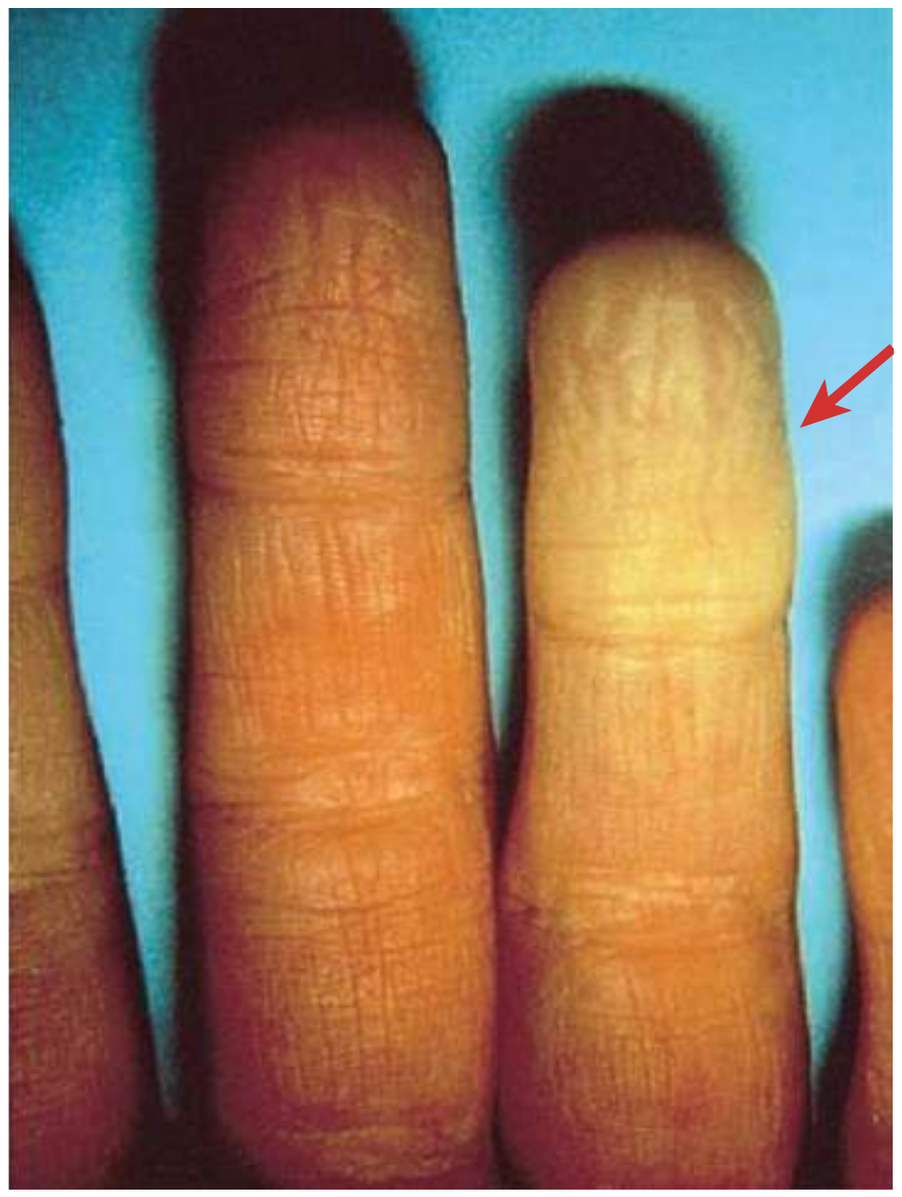

FIGURE 15-6. Raynaud phenomenon. Blanching of the fourth digit (red arrow) is evident (phase 1 of the tricolor response).

This condition may occur as an isolated disorder, termed primary Raynaud phenomenon or Raynaud disease. Patients are predominantly women between the ages of 20 and 40. Primary Raynaud phenomenon most often manifests in the fingers, but 40% of patients also have involvement of the toes. The prognosis of primary Raynaud phenomenon is relatively benign, with only a minority reporting a worsening of symptoms over time.

Secondary Raynaud phenomenon may appear as a component of other conditions. Common causes include connective tissue diseases (e.g., scleroderma and systemic lupus erythematosus) and arterial occlusive disorders. Other causes of secondary Raynaud phenomenon include carpal tunnel syndrome, thoracic outlet syndrome, blood dyscrasias, certain drugs, and thermal or vibration injury.

Even in healthy vessels, cold exposure normally produces a vasoconstrictor response. Cooling stimulates the sympathetic nervous system, resulting in local discharge of norepinephrine, which binds to vascular adrenergic receptors. In the fingers and toes, only vasoconstricting α receptors are present; other regional circulations have both constrictor and dilator adrenergic responses. Thus, a modest vasoconstriction of the digits results when healthy people are exposed to cooling. In contrast, in Raynaud phenomenon, cold exposure induces severe vasoconstriction.

A variety of mechanisms have been proposed to explain the vasospastic response to cold and stress in patients with primary Raynaud phenomenon, including an exaggerated sympathetic discharge in response to cold, heightened vascular sensitivity to adrenergic stimuli, or excessive release of vasoconstrictor stimuli, such as serotonin, thromboxane, and endothelin. In patients with secondary Raynaud phenomenon caused by connective tissue diseases or arterial occlusive disease, the digital vascular lumen is largely obliterated by sclerosis or inflammation, resulting in lower intraluminal pressure and greater susceptibility to sympathetically mediated vasoconstriction.

Treatment of Raynaud phenomenon involves avoiding cold environments, dressing in warm clothes, and wearing insulated gloves or footwear. There has also been some success in preventing vasospasm with pharmacologic agents that relax vascular tone, including calcium channel blockers, α-adrenergic blockers, and phosphodiesterase type 5 inhibitors such as sildenafil (see Chapter 17), but such therapies are reserved for severe cases.

VENOUS DISEASE

Veins are high-capacitance vessels that contain more than 70% of the total blood volume. In contrast to the muscular structure of arteries, the subendothelial layer of veins is thin, and the tunica media comprises fewer, smaller bundles of smooth muscle cells intermixed with reticular and elastic f bers. While veins of the extremities possess intrinsic vasomotor activity, transport of blood back to the heart relies greatly on external compression by the surrounding skeletal muscles and on a series of one-way endothelial valves.

Veins of the extremities are classif ed as either deep or superf cial. In the lower extremities, where most peripheral venous disorders occur, the deep veins generally course along the arteries, whereas the superf cial veins are located subcutaneously. The superf cial vessels drain into deeper veins through a series of perforating connectors, ultimately returning blood to the heart.

Varicose Veins

Varicose veins (Fig. 15-7) are dilated, tortuous superf cial vessels that often develop in the lower extremities. Clinically apparent varicose veins occur in 10% to 20% of the general population. They affect women two to three times more frequently than men, and roughly half of patients have a family history of this condition. Varicosities can occur in any vein in the body but are most common in the saphenous veins of the leg and their tributaries. They may also develop in the anorectal area (hemorrhoids), in the lower esophageal veins (esophageal varices), and in the spermatic cord (varicocele).

Varicosity is thought to result from intrinsic weakness of the vessel wall, from increased intraluminal pressure, or from congenital defects in the structure and function of venous valves. Varicose veins in the lower extremities are classif ed as either primary or secondary. Primary varicose veins originate in the superf cial system, and factors that lead to their development include pregnancy, prolonged standing, and obesity. During pregnancy or prolonged standing, the high venous pressure within the legs contributes to varicosities when there is underlying weakness of the vessel walls. In obese patients, the adipose tissue surrounding vessel walls offers less structural support to veins than does lean mass. Secondary varicose veins occur when an abnormality in the deep venous system is the cause of superf cial varicosities. These may develop in the setting of deep venous insuff ciency or occlusion or when the perforating veins are incompetent. In such cases, deep venous blood is shunted retrogradely through perforating channels into superf cial veins, increasing intraluminal pressure and volume and causing dilatation and varicosity formation.

Many people with varicose veins are asymptomatic but seek treatment for cosmetic reasons. When symptoms do develop,

FIGURE 15-7. A patient with varicose veins of the left leg (arrow**)**. (Courtesy of Marie Gerhard-Herman MD, Brigham and Women's Hospital, Boston, MA.)

they include a dull ache, “heaviness,” or a pressure sensation in the legs after prolonged standing. Superficial venous insufficiency may result when venous valves are unable to function normally in the dilated veins. This can cause swelling and skin ulceration that is particularly severe near the ankle. Stasis of blood within varicose veins can promote superficial vein thrombosis, and varicosities can also rupture, causing a localized hematoma.

Varicose veins are usually treated conservatively. Patients should elevate their legs while supine, avoid prolonged standing, and wear external compression stockings that counterbalance the increased venous hydrostatic pressure. Varicose veins that are symptomatic, or associated with signs of venous insufficiency, may be treated with more advanced techniques, including sclerotherapy, thermal ablation, or surgery. Sclerotherapy involves the localized intravenous administration of an irritating chemical agent to fibrose varicose veins. Endovenous thermal ablation procedures use laser or radiofrequency catheters to deliver heat energy, which induces thromboses and is used to obliterate varicose great saphenous veins. Surgical therapy involves direct vein ligation and removal.

Chronic Venous Insuff ciency

Chronic venous insufficiency (CVI) is characterized by elevated venous pressure with extravasation of edema into the tissues of the lower extremities. CVI develops when venous blood return to the heart is impaired by mechanisms that include valvular incompetence of deep or superficial veins, venous obstruction, and calf muscle pump dysfunction. A secondary form of CVI is postphlebitic syndrome, resulting from venous valvular damage or persistent venous occlusion after deep vein thrombosis (described below).

Patients with CVI may experience pain or achiness in the legs, particularly when standing for prolonged periods. Physical findings include varicose veins, edema, skin inf ammation and hyperpigmentation, and ulcerations. Noninvasive testing with duplex ultrasound is useful to detect the cause of CVI, such as venous obstruction. Compression stockings are the mainstay of treatment. Associated venous ulcerations are treated with compression bandages and absorbent dressings. Venous ablation techniques as described in the previous section are used to treat varicose veins that contribute to CVI.

Venous Thromboembolism

The term venous thrombosis or thrombophlebitis is used to describe thrombus formation within a superficial or deep vein and the inf ammatory response in the vessel wall that it incites. Thrombi in the lower extremities are classified by location as either deep venous thrombi or superficial venous thrombi.

Initially, the venous thrombus is composed principally of platelets and fibrin. Later, red blood cells become interspersed within the fibrin, and the thrombus tends to propagate in the direction of blood f ow. The changes in the vessel wall can be minimal or can include granulocyte infiltration, loss of endothelium, and edema. Thrombi may diminish or obstruct vascular f ow, or they may dislodge and form thromboemboli.

Deep Venous Thrombosis

Epidemiology, Etiology, and Pathophysiology

Deep venous thrombosis (DVT) occurs most commonly in the veins of the calves but may also develop initially in more proximal veins such as the popliteal, femoral, and iliac vessels. If left untreated, 20% to 30% of DVTs that arise in the calves propagate to these proximal veins. The two major consequences of DVT are pulmonary embolism (PE) (also termed venous thromboembolism) and postphlebitic syndrome.

TABLE 15-5 Conditions that Predispose to DVT and Pulmonary Embolism

Stasis of blood flow
Prolonged inactivity (following surgery, prolonged travel)
Immobilized extremity (following bone fracture)
Heart failure (with systemic venous congestion)
Hyperviscosity syndromes (e.g., polycythemia vera)
Hypercoagulable states
Inherited disorders of coagulation
Resistance to activated protein C (factor V Leiden)
Prothrombin gene mutation (PTG20210A)
Antithrombin deficiency
Deficiency of protein C or protein S
Antiphospholipid antibodies/lupus anticoagulant
Neoplastic disease (e.g., pancreatic, lung, stomach, or breast cancers)
Pregnancy and oral contraceptive use
Myeloproliferative diseases
Smoking
Vascular damage
Instrumentation (e.g., intravenous catheters)
Trauma

In 1856, Virchow described a triad of factors that predispose to venous thrombosis: (1) stasis of blood flow, (2) hypercoagulability, and (3) vascular damage. Stasis disrupts laminar flow and brings platelets into contact with the endothelium. This allows coagulation factors to accumulate and retards the influx of clotting inhibitors. Factors that slow venous flow and induce stasis include immobilization (e.g., prolonged bed rest after surgery or sitting in a car or an airplane for a long trip), cardiac failure, and hyperviscosity syndromes (Table 15-5).

Various clinical disorders cause systemic hypercoagulability, including resistance of coagulation factor V to activated protein C, a prothrombin gene mutation, and inherited deficiencies of antithrombin, protein C, and protein S. Pancreatic, lung, stomach, breast, and genitourinary tract adenocarcinomas are associated with a high prevalence of venous thrombosis. This is thought to occur in part because necrotic tumor cells release thrombogenic factors. Other conditions that contribute to hypercoagulability are listed in Table 15-5.

Vascular damage, either by external injury or by intravenous catheters, can denude the endothelium and expose subendothelial collagen. Exposed collagen acts as a substrate for the binding of von Willebrand factor and platelets and initiates the clotting cascade, leading to clot formation. Less severe damage can cause endothelial dysfunction that contributes to thrombosis by disrupting the production of vasodilating and antiplatelet substances (e.g., nitric oxide and prostacyclin, as explained in Chapter 6) and antithrombotic molecules such as thrombomodulin and heparan sulfate (described in Chapter 7). Recent evidence indicates that atherosclerotic risk factors, such as hyperlipidemia and diabetes, are also associated with DVT formation.

The risk of venous thrombosis is particularly high after fractures of the spine, pelvis, and bones of the lower extremities. The risk following bone fracture may be related to stasis of blood flow, increased coagulability, and possibly traumatic endothelial damage. In addition, venous thrombosis may arise in patients following surgical procedures, particularly major orthopedic operations.

Women have a several-fold increase in the incidence of venous thrombus formation during late pregnancy and the early postpartum period. In the third trimester, the fetus compresses the inferior vena cava and can cause stasis of blood flow, and high levels of circulating estrogen may induce a hypercoagulable state. Oral contraceptives and other pharmacologic estrogen products also predispose to thrombus formation.

Clinical Presentation

Patients with DVT may be asymptomatic, may describe calf or thigh discomfort when standing or walking, or may report unilateral leg swelling. The physical signs of proximal DVT include edema of the involved leg and occasionally localized warmth and erythema. Tenderness may be present over the course of the phlebitic vein, and a deep venous cord (induration along the thrombosed vessel) is occasionally palpable. Calf pain produced by dorsiflexion of the foot (the Homan sign) is a nonspecific and unreliable marker of DVT.

Diagnosis

The primary laboratory tests for the diagnosis of DVT include measurement of the serum d-dimer level and venous compression ultrasonography. d-dimer, a by-product of fibrin degradation that can be measured in a peripheral blood sample, is highly sensitive for the diagnosis of DVT and/or acute PE. Because d-dimer may also be elevated in many other conditions (such as cancer, inflammation, infection, and necrosis), a positive test result is not specific for DVT. Thus, a normal d-dimer value helps exclude the presence of DVT, but an elevated level does not definitively confirm the diagnosis.

Venous compression duplex ultrasonography is a readily available noninvasive technique that is 95% sensitive for the diagnosis of symptomatic DVT in a proximal vein but only 75% sensitive for diagnosing symptomatic calf vein thrombi. This technique uses real-time ultrasound scanning to image the vein and pulsed Doppler ultrasound to assess blood flow within it (Fig. 15-8). Criteria used for diagnosis of DVT with duplex ultrasonography include the inability to compress the vein with direct pressure (suggesting the presence of an intraluminal thrombus), direct visualization of the thrombus, and absence of blood flow within the vessel.

Other diagnostic techniques are sometimes used. For example, MR venography can aid in the diagnosis of proximal DVT, particularly pelvic vein thrombi, which are difficult to detect by ultrasound. Contrast venography is now a rarely used invasive imaging technique that can provide a definitive diagnosis. Radiocontrast material is injected into a foot vein, and images are obtained as the contrast ascends through the venous system of the leg. DVT is diagnosed by the presence of a filling defect (see Fig. 15-8).

Treatment

In patients with proximal DVT, elevation of the affected extremity above the level of the heart helps reduce edema and tenderness, and anticoagulation prevents extension of the thrombus and PE. Initial anticoagulation typically consists of subcutaneous low molecular weight heparin (LMWH). Intravenous unfractionated heparin is a cost-effective alternative that has been used successfully for this purpose for many years, but LMWH is more convenient to administer. Warfarin, an oral anticoagulant, is then prescribed for long-term management and is continued for several months, depending on the underlying cause of DVT. Newer oral anticoagulants, such as the factor Xa inhibitors rivaroxaban and apixaban (see Chapter 17), allow a broader range of options for acute and long-term treatment of DVT. Catheter-based thrombolysis may be useful for selected patients with iliofemoral deep vein thrombosis.

Treatment of patients with calf DVT (i.e., thrombus confined to below the knee) is more controversial because pulmonary emboli from that site are uncommon. Some experts advocate

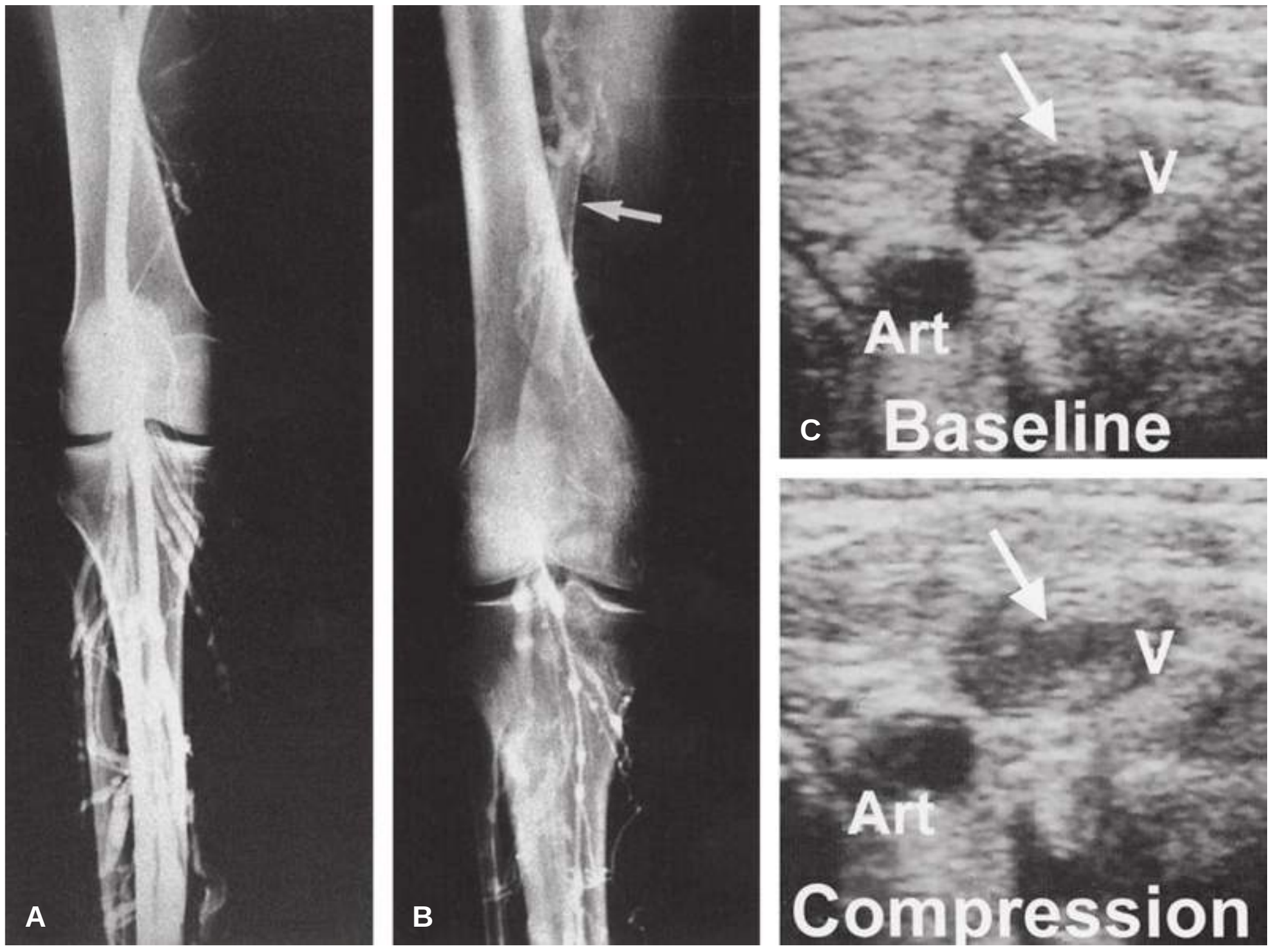

FIGURE 15-8. Diagnostic imaging of deep venous thrombosis. A. Normal venogram. Contrast material was injected into a foot vein and fills the leg veins in this radiograph. **B.** Venogram demonstrating extensive thrombosis of the deep calf veins, popliteal vein, and femoral vein. Arrow indicates a filling defect in the femoral vein due to the presence of thrombus. The deep calf veins are filled with thrombus and cannot be visualized. **C.** Ultrasound indicating deep venous thrombosis. The thrombus appears as an echogenic area (arrow) within the femoral vein (V). A healthy vein would be easily compressible by the ultrasound transducer. This vein, however, has the same diameter at baseline **(top panel)** and after compression **(bottom panel)**, confirming the presence of thrombus within it. Art, artery.

serial noninvasive monitoring to determine if the thrombus propagates into proximal veins, whereas others treat such thrombosis with heparin (unfractionated or low molecular weight) followed by warfarin for 3 to 6 months.

Prophylaxis against DVT is appropriate in clinical situations in which the risk of developing the condition is high, such as during bed rest following surgery. Prophylactic measures may include subcutaneous unfractionated heparin, LMWH, low-dose oral warfarin, or one of the newer oral anticoagulants, as well as compression stockings, and/or intermittent external pneumatic compression of the legs to prevent venous stasis.

Pulmonary Embolism

Epidemiology, Etiology, and Pathophysiology

PE supervenes when a clot, most often derived from DVT in a proximal vein of the lower extremities, dislodges and travels through the inferior vena cava and right heart chambers, finally reaching and obstructing a portion of the pulmonary vasculature. PE is common (incidence of approximately 600,000 per year in the United States) and is often fatal, with an untreated mortality rate of 30% to 40%. In patients with PE, gas exchange is often impaired because of the associated anatomic dead space and ventilation–perfusion mismatches that ensue in the lungs. As

a result, the alveolar–arterial oxygen gradient increases and hypoxemia may occur. Pulmonary vascular resistance may rise as a consequence of the mechanical obstruction and because vasoactive and bronchoconstrictive mediators released by platelets within emboli induce constriction of the pulmonary vasculature and bronchospasm, respectively. The increased pulmonary vascular resistance may lead to elevation of right ventricular (RV) wall stress, dilatation, and contractile failure, compromising cardiac output. Recurrent and chronic PE can cause remodeling of the pulmonary vasculature with pulmonary hypertension leading to right-sided heart failure.

Clinical Presentation

Patients with PE may experience dyspnea, pleuritic chest pain (due to pleural irritation), hemoptysis, cough, or syncope (due to reduced cardiac output). Signs may include tachypnea, bronchospasm, and evidence of elevated pulmonary artery pressure, including an accentuated pulmonic component of the second heart sound and jugular venous distention.

Diagnosis

Many of the diagnostic tests used for DVT are also useful for PE. Additional tests are useful in the evaluation of suspected PE. The most common electrocardiographic abnormality is sinus tachycardia; there may be evidence of RV strain (e.g., inverted T waves in leads V_1–V_4 or an "S1–Q3–T3" pattern: a prominent S wave in lead I, Q wave in lead III, inverted T wave in lead III). RV strain may also produce elevated serum levels of cardiac-specific troponins or B-type natriuretic peptide (described in Chapters 7 and 9, respectively). Arterial blood gas analysis may show decreased arterial oxygenation but is insensitive to the diagnosis of PE. The preferred test to confirm the diagnosis is computed tomographic angiography (CTA; Fig. 15-9). For patients who cannot tolerate CTA, such as those with renal insufficiency or hypersensitivity to radioiodinated contrast agents, radionuclide ventilation–perfusion (V/Q) lung scanning may be obtained instead but is less precise for the diagnosis. Catheter-based pulmonary angiography is rarely necessary for confirmation.

Treatment

In patients with established PE, urgent anticoagulation is instituted to prevent recurrent embolism. Anticoagulation measures are similar to those used for DVT. In patients with proximal DVT or established PE who cannot be treated with anticoagulants (e.g., because of a bleeding

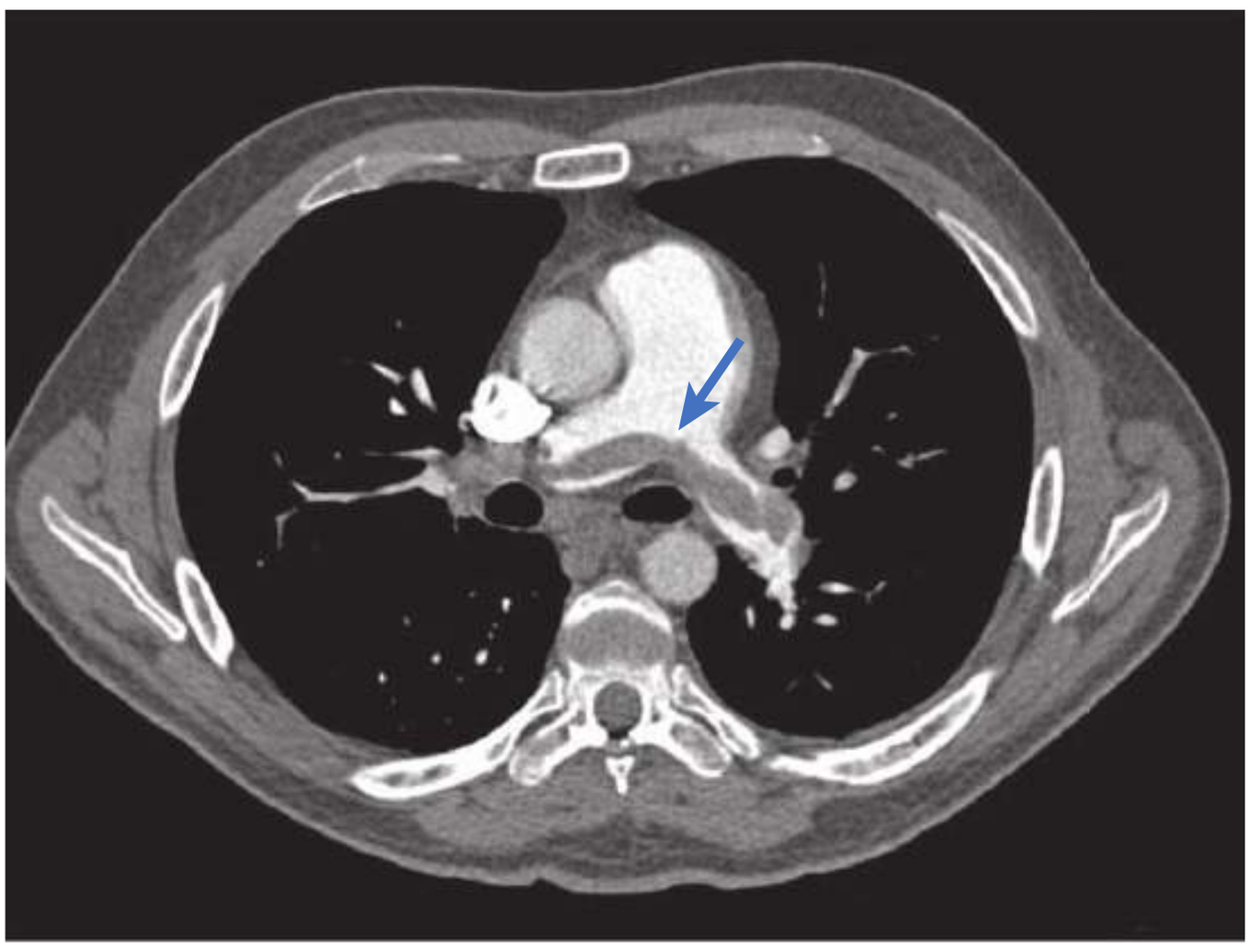

FIGURE 15-9. CT angiogram displaying a massive pulmonary embolism. There is a large filling defect in the main pulmonary artery that extends into branches of both left and right pulmonary arteries (blue arrow). (Courtesy of Andetta Hunsaker MD, Brigham and Women's Hospital, Boston, MA.)

disorder), an intravascular filter can be percutaneously inserted into the inferior vena cava to prevent emboli from reaching the lungs. Occasionally, systemic thrombolytic therapy or surgical pulmonary embolectomy is undertaken for patients with massive PE.

Superf cial Thrombophlebitis

Superficial thrombophlebitis is a benign disorder associated with inf ammation and thrombosis of a superficial vein, just below the skin. It may occur, for example, as a complication of an in-dwelling intravenous catheter. It is characterized by erythema, tenderness, and edema over the involved vein. Treatment consists of local heat and rest of the involved extremity. Aspirin or other anti-inf ammatory medications may relieve the associated discomfort. Unlike DVT, superficial thrombophlebitis does not lead to PE.

SUMMARY

- True aneurysms are caused by degenerative changes in the aortic wall; cystic medial degeneration is associated with ascending thoracic aortic aneurysms, and atherosclerosis is commonly found in descending thoracic and abdominal aortic aneurysms.
- A false aneurysm (pseudoaneurysm) represents a hole in the arterial intima and media contained by a layer of adventitia or perivascular clot.
- Symptoms of aortic aneurysms relate to compression of adjacent structures (back pain, dysphagia, respiratory symptoms) or blood leakage, with the most severe consequence being aneurysm rupture.
- Aortic dissection results from a tear in the intima that allows blood to enter into the medial layer, often in the setting of advanced age, hypertension, or cystic medial degeneration.
- Type A (proximal) aortic dissections involve the ascending aorta, are life threatening, and require surgical repair.
- Type B dissections are confined to the descending aorta and are often managed by pharmacologic therapy alone.
- PAD is a common atherosclerotic disease of large and medium-sized arteries, often resulting in claudication of the limbs.
- PAD is treated by risk factor modification, exercise, antiplatelet agents, and sometimes cilostazol, a selective phosphodiesterase inhibitor.
- Arterial embolism arises from thrombus within the heart, from proximal arterial sites, or paradoxically from the systemic veins in the presence of an intracardiac shunt (e.g., atrial septal defect).
- Therapeutic options for acute arterial occlusion include anticoagulation, thrombolysis, and surgical or endovascular interventions.
- Vasculitic syndromes are inf ammatory diseases of blood vessels that impair arterial f ow and result in localized and systemic symptoms; such syndromes are distinguished from one another by the pattern of vessel involvement and morphologic findings.
- Raynaud phenomenon is an episodic vasospasm of arteries that supply the digits of the upper and lower extremities; it may be a primary condition (Raynaud disease) or may appear in association with other disorders such as connective tissue diseases or blood dyscrasias.
- Varicose veins are dilated tortuous vessels that may present cosmetic problems; they may cause discomfort, become thrombosed, or lead to venous insufficiency.
- Initial management of varicose veins is conservative, with periodic leg elevation and compression stockings; severe symptomatic varicose veins can be treated with sclerotherapy, radiofrequency or laser ablation, or surgical ligation and removal.
- CVI develops when venous pressure is increased and return of blood f ow is impaired by venous valvular ref ux, resulting in chronic lower extremity edema, varicosities, and skin ulceration.

- Venous thrombosis results from stasis of blood f ow, hypercoagulability, and vascular damage; the major complication is PE.
- d-dimer assay and venous compression ultrasonography are the primary tools used to diagnose DVT.
- Anticoagulation therapy with LMWH or unfractionated intravenous heparin (UFH), followed by oral warfarin, is the usual treatment for DVT; newer targeted oral anticoagulant therapies are also available.
- PE can be confirmed by CT angiography or ventilation–perfusion scintigraphy.
- Anticoagulant agents (LMWH or UFH followed by warfarin or a newer oral anticoagulant) constitute usual PE therapy; however, if anticoagulants are contraindicated, an inferior vena cava filter is inserted to prevent recurrent PE.

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