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Pulmonary Vascular Disease

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The pulmonary vasculature is an anatomic compartment that is frequently overlooked in the histologic review of lung biopsy samples, other than those obtained specifically to assess pulmonary vascular disease.[1] Though often of a nonspecific nature, the histologic pattern of vascular remodeling may at times suggest its underlying pathogenesis and provide clues to the cause of pulmonary hypertension.[2] Disproportionately severe vascular pathology may further indicate alternate disease processes, such as congestive heart failure or thromboemboli, contributing to the patient's overall respiratory condition.

This chapter discusses pulmonary hypertension, which represents a final common pathway of pulmonary vascular disease.[3] Idiopathic pulmonary arterial hypertension (i.e., primary pulmonary hypertension) serves as a model of vascular reconfiguration formerly designated as "plexogenic arteriopathy."[4] The 2003 World Health Organization (WHO) classification of pulmonary hypertension, however, has shifted the primary emphasis from the plexiform lesion (now considered a generic marker of severe pulmonary hypertension) toward an integrated construct that incorporates clinical history, epidemiology, and morphology in the classification schema.[5]

Other major categories of pulmonary hypertension, including thromboembolic, hypoxic, and pulmonary venous hypertension, are each considered in separate sections that focus on morphologic patterns of recognition and the important underlying conditions that contribute to each category. The broad and complex topic of pulmonary vasculitis is discussed in Chapter 29, which serves as a companion chapter to this chapter.

It is, admittedly, artificial to segregate pulmonary vascular pathology in one or two isolated chapters since blood vessels are involved either primarily or secondarily across the vast spectrum of lung pathology. The reader is therefore liberally referred to other areas of the text where vascular pathology is considered in the context of parenchymal or airway diseases. For example, the important vascular changes of Langerhans cell histiocytosis, sarcoidosis, and amyloidosis are respectively addressed in Chapters 17, 18, and 21. Remodeling of the bronchial arteries is an important focus in the section on bronchiectasis in Chapter 5. Vascular malformations predominantly affecting the pediatric population are mainly discussed in Chapter 6, and intralobar sequestration, considered by many an acquired rearrangement of the pulmonary blood supply, is covered in Chapter 7. The topic of vasoformative neoplasms, including hemangiomas, lymphangiomatous proliferations, angiosarcoma, and pulmonary artery sarcoma, is covered in Chapter 40 on mesenchymal tumors. Although pulmonary capillary hemangiomatosis is considered by some to be a neoplastic proliferation, because of its close morphologic and (possibly) pathogenetic associations with pulmonary veno-occlusive disease, this entity is mainly discussed in this chapter.

Diseases of the lung vasculature, notably pulmonary embolism, are also frequently implicated as underlying, immediate, or contributory causes of death. It is a somber reality that fatalities secondary to clinically undiagnosed pulmonary embolism are a major source of medical malpractice claims. The forensic issues related to pulmonary embolism and the topics of air, amniotic fluid, and fat embolism are primarily addressed in Chapter 31 on pulmonary forensic pathology. Other forms of nonthrombotic emboli, such as parasites (Chapter 14), tumors (Chapter 44), soft tissue (Chapter 31) and pharmaceutical tablet filler materials (Chapter 26), are each primarily discussed in the context of the disease categories in which the emboli arise.

Finally, the reader is encouraged also to review the sections on lung vascular anatomy and histology (Chapter 2) and the various techniques relevant to the study of the pulmonary vasculature (Chapter 1), which serve as fundamental starting points in the morphologic assessment of pulmonary vascular disease.

Embryology

Pulmonary Arteries

In the embryonic period (4 to 6 weeks gestational age) the developing circulatory system consists of six pairs of aortic arches that join the dorsal and ventral aortas, which arise from the primitive heart (Fig. 28.1).[6] According to classical embryology, the right and left pulmonary arteries are derived mainly from the sixth aortic arches, which are formed by the 36th day of development.[7] The dorsolateral portion of the right sixth aortic arch ultimately disappears; the ventral part persists as the proximal right pulmonary artery. The dorsal portion of the left sixth arch persists as the ductus arteriosus joining the pulmonary artery and aorta, while the ventral left sixth aortic arch becomes the proximal portion of the left main pulmonary artery (Fig. 28.1). Recent evidence, however, suggests that the pulmonary arteries may initially arise from the fourth and later merge with the sixth aortic arch.[6] The right and left pulmonary arteries, by day 50, have joined the vascular plexus that surrounds and infiltrates the lung buds. Small vessels within the lung buds are formed in situ by the process of vasculogenesis.[8] The pulmonary trunk is formed as the aorticopulmonary septum divides the truncus arteriosus into two major channels—the aorta and the pulmonary artery (Fig. 28.1).[6] After birth, the ductus arteriosus closes to become the ligamentum arteriosum.

Veins

A single main pulmonary vein initially arises from the cardiac atrium around the 4th week. The vein rapidly branches into the right and left pulmonary veins, each of which further divides, producing a total of four pulmonary veins. The pulmonary veins connect with the venous plexus around the esophagus and developing lung buds. As the left atrium enlarges, it absorbs, by a process of intussusception, the main and then the right and left branches to just beyond the entry of their main tributaries. In this manner, four separate venous openings are found in the dorsal wall of the left atrium. Even in the adult, small connections persist between the pulmonary and esophageal veins near the lung hilum. During fetal life, the pulmonary veins carry little blood and are largely free of muscle. A continuous smooth muscle coat is only present near term.[9]

Bronchial Arteries

During the embryonic period, transient feeding vessels are thought to extend directly from the dorsal aorta to the developing lung buds, although this concept has been challenged.[8] Persistence of these vascular sprouts may result in aberrant systemic blood supply to the lung. Definitive bronchial arteries, which nourish the bronchi, pleura, and walls of vessels, arise from the aorta in the 9th to 12th week of gestation.[10] In the normal fetus, patent precapillary anastomoses between bronchial and

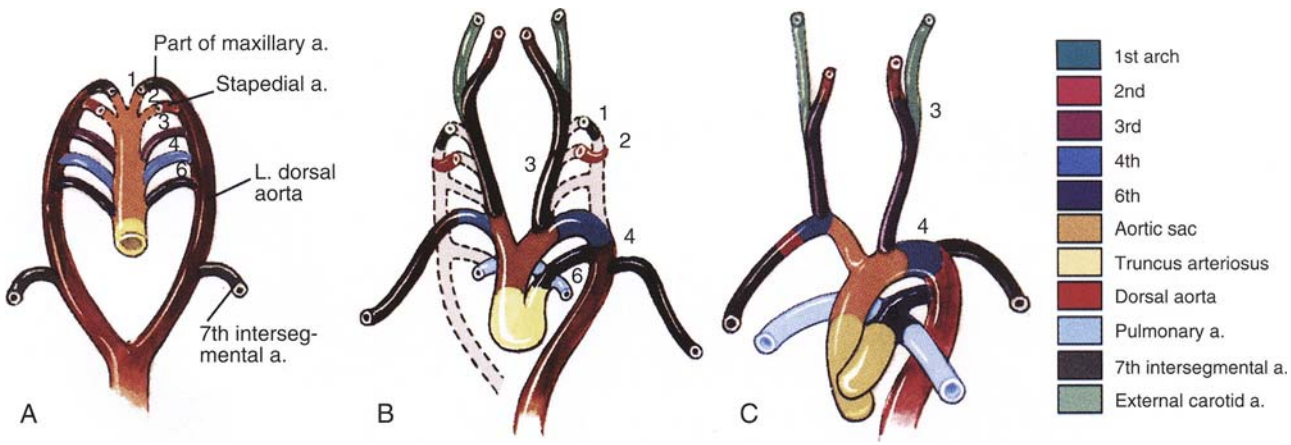


FIGURE 28.1. Embryologic development of the aortic system and pulmonary arteries. **A.** A 29-day embryo. Aortic arches joining dorsal and ventral aortas. The sixth aortic arch appears around day 29. **B.** A 7-week embryo. The pulmonary arteries may initially sprout from arch 4 and become secondarily connected to the sixth arch. The pulmonary trunk evolves from the division of the truncus arteriosus. **C.** An 8-week embryo. Further development of the pulmonary arteries. The dorsal right sixth aortic arch has disappeared. The dorsal left sixth arch persists as the ductus arteriosus. (From Larsen,[6] with permission from Elsevier.)

pulmonary circulations are infrequently observed. There is, however, free communications between the two circulations at the capillary level, and both systems drain into the pulmonary veins.[7,11]

Congenital Vascular Malformations

Congenital malformations of the pulmonary vasculature are rare lesions, usually seen in children, and often associated with congenital cardiac anomalies. Two of the more notable conditions in which anomalous lung vessels play a role are the scimitar syndrome (anomalous pulmonary venous return) and intralobar sequestration (aberrant aortic-derived blood supply). The scimitar syndrome is discussed in Chapter 6, and intralobar sequestration is considered in Chapter 7. Other anomalies of the pulmonary vasculature that can contribute to pulmonary hypertension include persistent truncus arteriosus, aorticopulmonary septal defect, and assorted anomalies of pulmonary veins. These exceedingly rare malformations are discussed in the textbook by Wagenvoort and Wagenvoort.[12] Some selected important anomalies of pulmonary vessels are discussed in detail below.

Congenital Unilateral Absence of the Pulmonary Artery

Unilateral absence of a main pulmonary artery is an infrequent congenital anomaly that may present as an isolated lesion or in association with other cardiac or vascular anomalies (combined anomaly) in children or (more frequently) adults. Absence of the left pulmonary artery has been particularly associated with tetralogy of Fallot (e.g., pulmonary stenosis, ventricular septal defect, overriding dextroposed aorta, and right ventricular hypertrophy), while an absent right pulmonary artery more frequently occurs with patent ductus arteriosus.[13,14] The blood supply to the affected lung may derive directly from the aorta as in some cases of absent right pulmonary artery, or from bronchial arteries or an aortic arch vessel in most cases of absent left pulmonary artery and other instances of absent right pulmonary artery. Collateral supply from the coronary arteries has also been described.[15]

Patients exhibit respiratory complaints of recurrent pneumonia or, less frequently, hemoptysis. Cardiovascular symptoms depend on whether the lesion is an isolated or a combined anomaly. Patients with an isolated absence of the pulmonary artery may have no cardiovascular symptoms. Approximately 85% of combined anomalies progress to pulmonary hypertension. The most important finding on the plane chest x-ray is ipsilateral pulmonary hypovascularity. Unilateral thrombotic or embolic occlusion of a pulmonary artery is the most difficult lesion to distinguish angiographically from unilateral absence of the pulmonary artery (Fig. 28.2) (see also Fig. 28.32).[16] Within the ipsilateral lung, intrapulmonary arteries may be either normal or exhibit features of pulmonary hypertension, such as medial hypertrophy, intimal fibrosis, or

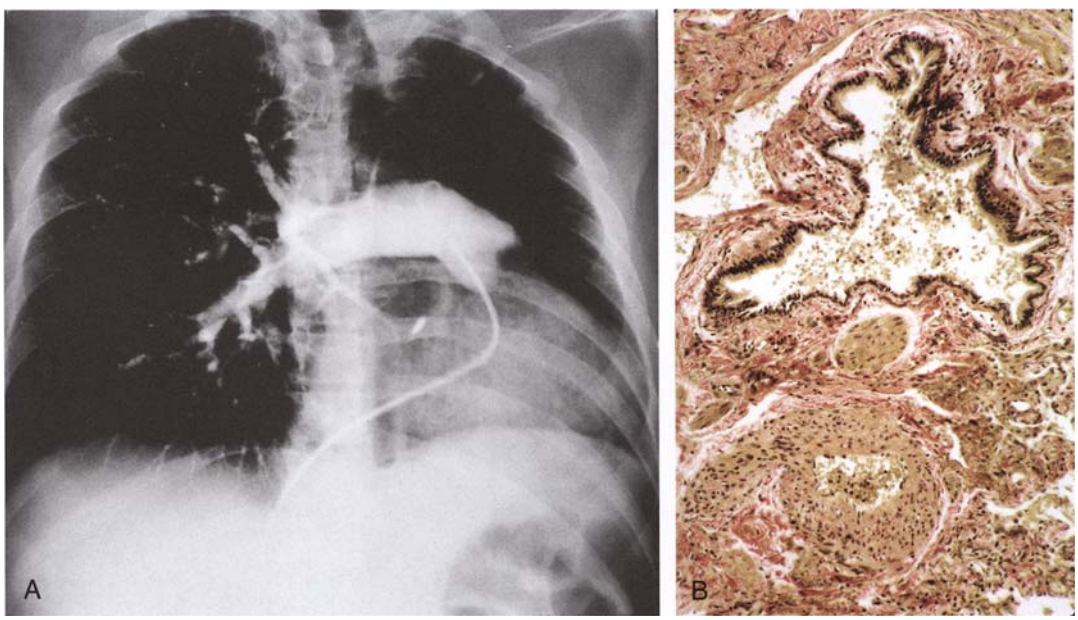


FIGURE 28.2. Congenital unilateral absence of left pulmonary artery. **A.** Pulmonary arteriogram demonstrates absence of flow of contrast into left lung. Compared to the right lung, there is hyperlucency and reduced lung volume on the left. **B.** Hypertrophic muscular artery is in the position of a normal intraparenchymal pulmonary artery. (Elastic van Gieson.) (Courtesy of Dr. Atul Mehta, Cleveland Clinic Foundation.)

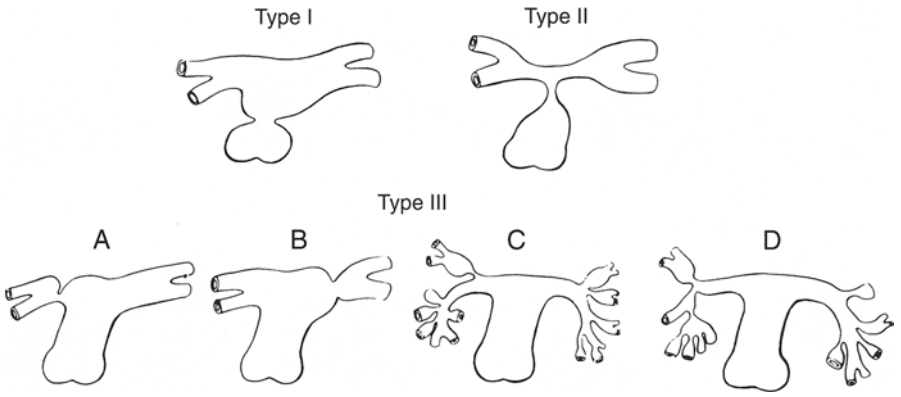


FIGURE 28.3. Types and locations of major pulmonary artery stenoses. Type I involves the main pulmonary artery in the form of a supravalvular membrane or hypoplastic segment. In type II, the entire bifurcation is stenosed and may involve varying lengths of pulmonary branches. Type III includes multiple strictures in lobar, segmental, and/or peripheral branches. (From Goor DA, Lillehei CW. Congenital malformations of the heart. New York: Grune & Stratton, 1975, with permission from Elsevier. Copyright © 1975.)

plexiform lesions, depending on the size of the systemic arterial supply (Fig. 28.2B). Pleural collateral vessels may be prominent.[14,17,18] The lung on the affected slide is often hypoplastic.[17,19]

Congenital Pulmonary Stenosis/Atresia and Tetralogy of Fallot: Vascular Remodeling in Low-Flow States

Diminution of the pulmonary arterial pulse pressures and blood flow occurs in a variety of congenital cardiac malformations that impede right ventricular outflow, especially pulmonary artery stenosis, pulmonic valve stenosis or atresia, and tetralogy of Fallot. In tetralogy of Fallot, the pulmonary trunk is narrower than the aorta, while the main pulmonary arteries may be normal or hypoplastic. Stenosis of the distal pulmonary trunk and bilateral main pulmonary arteries may be diffuse or localized (Fig. 28.3).[20] Saccular dilatation may occur distal to strictures. Intraparenchymal pulmonary arteries have a normal anatomic distribution.[8]

The most constant finding in the elastic pulmonary arteries of any of these disorders is thinning of the media, often to a marked degree (Fig. 28.4).[21] In tetralogy of Fallot mural thinning may extend to the level of muscular arteries, which, along with capillaries and pulmonary veins, may be markedly dilated. When mural thinning is extreme, medial muscle may be focally absent. Similar changes have also been described in pulmonic atresia.[22] Medial atrophy and widened vascular lumina tend to be more pronounced in isolated pulmonic stenosis than in tetralogy of Fallot.[21] Other associated findings include intimal fibrosis and thrombotic lesions (including web lesions), which are more frequently seen in tetralogy of Fallot than in isolated pulmonic stenosis.[21] Rich[23] in 1948 had recognized the increased tendency toward pulmonary arterial and venous thrombosis in tetralogy of Fallot and had ascribed these changes to the influence of polycythemia and sluggish flow. This concept was later supported by Heath et al.[24] In commemoration, recanalized

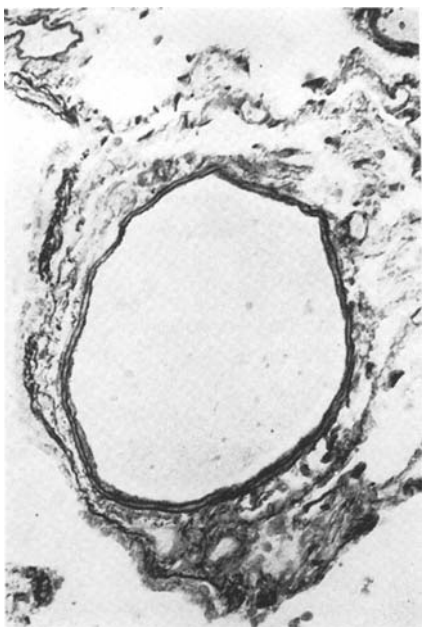


FIGURE 28.4. Wide lumen and thin wall in a pulmonary artery in a case of pulmonic stenosis. (Elastic van Gieson.) (From Wagenvoort et al.,[21] with permission from Lippincott Williams & Wilkins.)

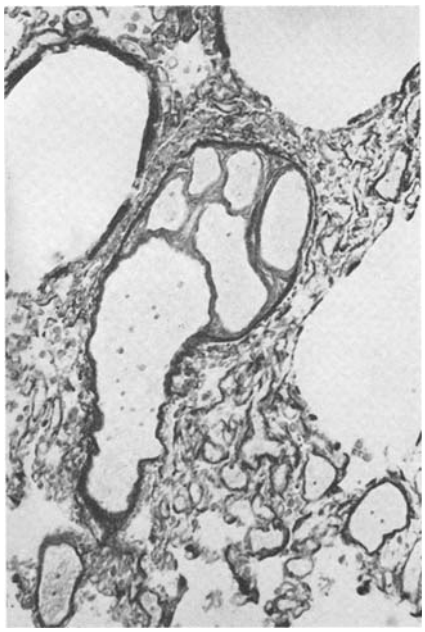


FIGURE 28.5. Pulmonary artery in a case of tetralogy of Fallot with multiple thin septa. (Elastic van Gieson.) (From Wagenvoort et al.,[21] with permission from Lippincott Williams & Wilkins.)

thrombi in dilated arteries and veins have been designated Arnold Rich lesions (Fig. 28.5).[20]

In cases of pulmonic atresia with tetralogy of Fallot, the lungs are sustained by systemic blood flow. The systemic collateral supply to the lung (not including the ductus arteriosus) may be one of three types: Type I, seen in most instances of tetralogy of Fallot, consists of hypertrophied bronchial arteries that anastomose with intrapulmonary arteries. Type II anastomoses, most common in pulmonary atresia, represent aortic vessels that anastomose to the junction of interlobar and intralobar pulmonary arteries near the hilum. Type III anastomoses originate from aortic branch vessels to supply the central pulmonary artery.[8,20,25] Pulmonary hypertensive changes infrequently occur in uncorrected tetralogy as a result of direct systemic arterial supply. The repair of tetralogy of Fallot involves surgical construction of a systemic-pulmonary shunt. In cases of large shunts, pulmonary hypertensive changes, including plexiform lesions and necrotizing arteritis, may result from the systemic flow. Complete correction of tetralogy of Fallot rarely results in postsurgical pulmonary hypertension.[20,26]

Anomalies of Intraparenchymal Vessels

Medial Defects

In contrast to tetralogy of Fallot or pulmonic stenosis, in which medial thinning is diffuse, Wagenvoort[27] has reported on two patients, one a 20-year-old woman with pulmonary hypertension, and the other an 11-year-old girl with pulmonary arteriovenous fistulas and preportal hypertension, in whom muscular pulmonary arteries exhibited focal thinning or focal absence of the media immediately adjacent to medial hypertrophy (Fig. 28.6). Marked intimal fibrosis was present overlying the thickened portion of the media but not over the defective media. The veins also exhibited arterialization immediately adjacent to zones in which muscle was deficient. Medial defects can be easily misdiagnosed as embolic pulmonary hypertension or veno-occlusive disease in lung biopsies. It is uncertain if medial defects predispose to arteriovenous aneurysms.

Misalignment of Lung Vessels

Misalignment of lung vessels is a fatal anomaly and a cause of persistent pulmonary hypertension of the newborn, in which dilated, thin-walled veins are juxtaposed to thickened muscular arteries in the peribronchiolar connective tissue (see Fig. 6.32 in Chapter 6).[28] From the earliest descriptions, misalignment of lung vessels has been associated with alveolar underdevelopment and interstitial fibrosis.[28] This constellation of histologic features is also known as alveolar capillary dysplasia and is further discussed in Chapter 6 on pediatric congenital malformations.[29–33]

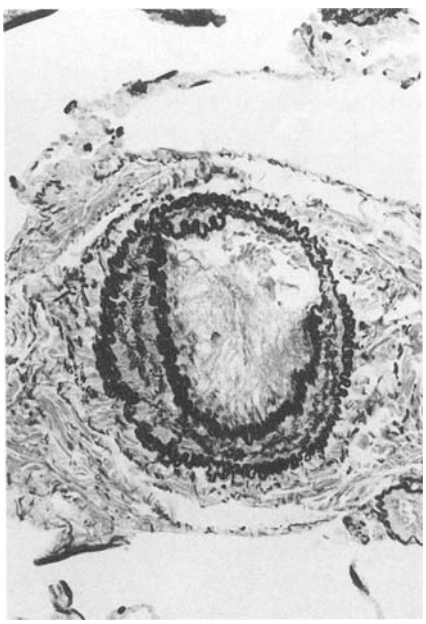


FIGURE 28.6. Muscular pulmonary artery showing severe medial hypertrophy with abrupt transition to a thin medial segment. Severe intimal fibrosis is limited to the hypertrophied portion of the wall. (Elastic van Gieson.) (From Wagenvoort,[27] with permission from Elsevier.)

Pulmonary Hypertensive Vascular Disease

Pulmonary vascular disorders encompass a wide range of clinical and pathologic entities affecting every compartment of the pulmonary vasculature. Lesions of the pulmonary arteries, arterioles, capillaries, and veins, while histologically distinct, may all result in an elevation of pulmonary pressure, and present with similar symptoms such as dyspnea with exertion, fatigue, syncope, and lower extremity edema. While many cases of pulmonary vascular disease are diagnosed by clinical setting, radiologic findings, and hemodynamic measurements, lung biopsy is undertaken in patients for whom the diagnosis remains elusive.[1] The evaluation of lung biopsies for vascular disease requires careful consideration of subtle, and often overlooked, changes within the pulmonary vasculature.

Analytical Methods (Morphometry)

In hypertensive pulmonary vascular disease, intimal and medial hypertrophy can often be estimated by eye. However, analytic methods such as morphometry are valuable in comparative studies. There are several approaches to morphometry; a simple yet reliable approach proposed by Reid and colleagues[34] is to measure the thickness of the media and to express this as a percentage of the external vascular diameter. The intimal thickness is measured as a percentage of the internal vascular diameter, since this gives an indication of the degree of luminal obstruction. To minimize errors in sampling, 25 to 50 arteries are randomly selected for measurement. To accurately measure a vessel, cross sections should be circular or nearly circular.

With a calibrated eyepiece, measurements are made along a horizontal line traversing the diameter if the vascular cross section is circular, or along the shortest axis if the cross section is oval. Media (M1 and M2) and intima (I1 and I2) traversed by this line on either side of the vessel are respectively measured using the elastic laminae as a boundary (Fig. 28.7). The sum of the two measured values is divided by the external (ED) or internal (ID) vascular diameter to calculate the percentage medial (%MT) or intimal (%IT) thickness respectively:

$$\%MT = [(M1 + M2)/ ED] \times 100 \quad \text{and}$$
$$\%IT = [(I1 + I2)/ID] \times 100$$

Normal values for %MT range from 3% to 7%; a thickness greater than 7% is considered to represent medial hypertrophy.[35]

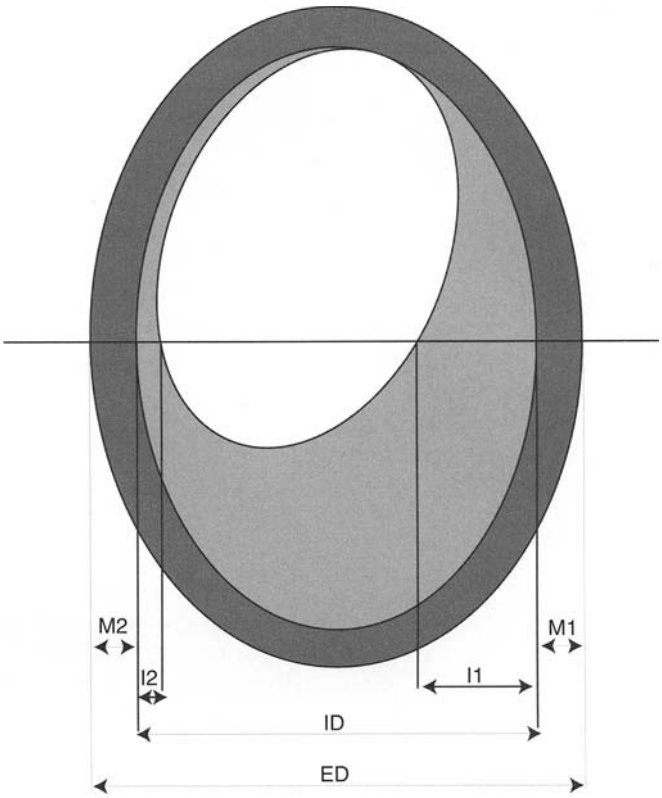


FIGURE 28.7. Vessel wall dimensions for quantitative assessment of medial and intimal thickness. M1, M2, medial thickness; I1, I2, intimal thickness; ED, external vessel diameter; ID, internal vessel diameter.

Historical Approaches to Pulmonary Hypertensive Disease: Plexogenic Arteriopathy and Congenital Heart Disease

The earliest classification system of pulmonary hypertension, the Heath and Edwards schema (Table 28.1), was based on studies of patients with congenital heart disease.[4] In this system, disease severity was graded by histologic assessment alone. Since the schema is still widely used, it will be reviewed here. However, it is important to note that this approach only applies to pulmonary hypertension in the context of congenital heart disease, and attempts to extrapolate this grading system to other settings of pulmonary hypertension prove to be problematic.

Medial hypertrophy is the earliest and most widespread lesion that develops. The thickening of the media is attributed both to an increased number of smooth muscle cells, and to an increase in the size of those cells.[36] The normally nonmuscularized small arterioles (15 to 150 μm in diameter) also develop a layer of smooth muscle in a process referred to as muscularization of arterioles. The intima also undergoes a cellular proliferation of myofibroblasts and smooth muscle cells, with little or no deposition of

TABLE 28.1. Heath and Edwards Classification

Grade 1	Medial hypertrophy of pulmonary arteries and muscularization of arterioles
Grade 2	Intimal proliferation in arteries
Grade 3	Intimal concentric laminar fibrosis becomes prominent in muscular arteries
Grade 4	Dilation of small arteries occurs with development of plexiform lesions
Grade 5	Plexiform and angiomatoid lesions become prominent; hemosiderin deposition present
Grade 6	Necrotizing arteritis

Source: Modified from Heath and Edwards.[4]

elastin or collagen. Later the cellular intimal proliferation deposits collagen and elastin to form an onion-skin concentric laminar intimal fibrosis with a strong tendency to obliterate the central lumen. Dilation of arterial segments, thought to be the result of muscular incompetence and rising luminal pressure, results in large angiomatoid/dilatation lesions.

In advanced disease, fibrinoid necrosis may be seen particularly following bifurcation points in the arterial tree. A small segment of arterial wall becomes swollen with fibrin, followed by destruction of the smooth muscle layer and elastic laminae. Thrombus often forms within the lumen of the vessel. In addition, frank vasculitis with inflammatory exudates in the vessel wall and surrounding lung parenchyma may be seen.

A late-stage alteration in the sequence of changes is the development of the plexiform lesion itself. Like fibrinoid necrosis, these lesions typically develop distal to the bifurcation point of small pulmonary arteries. The artery is dilated and the lumen filled by a plexus of capillary-sized vascular channels that are separated by cells with hyperchromatic nuclei.

The term *plexogenic arteriopathy* was proposed at a WHO meeting in 1975 to describe this characteristic morphologic pattern of hypertensive vascular changes in the lung.[37] This common morphologic progression is seen in relation to a number of etiologies including congenital heart disease with a left-to-right shunt, such as atrial and ventricular septal defects, patent ductus arteriosus, and persistent truncus arteriosus[38,39] (Table 28.2). In addition, patients with tetralogy of Fallot may develop plexogenic arteriopathy as the result of large surgical shunts between the systemic and pulmonary circulation.[40–42]

In addition to cardiac abnormalities, whether congenital or surgical, plexogenic arteriopathy is encountered most frequently in portal hypertension, collagen vascular diseases, drug use, familial disease, and idiopathic disease. Historically, the idiopathic and familial cases of the disease have been called primary pulmonary hypertension, while those cases attributable to another disease have been called secondary pulmonary hypertension.

As described at the 1975 WHO meeting, the plexiform lesion is not a defining characteristic, but rather is a late step in a sequence of progressively more severe vascular changes.[37] It is therefore possible to have a biopsy that, while representing a disease process that falls under the auspice of plexogenic arteriopathy, does not contain the requisite plexiform lesion. Thus, finding even a single plexiform lesion imparts tremendous diagnostic significance. However, the term *plexogenic arteriopathy* was questioned by many pulmonary hypertension experts, as "plexogenic" implies a cause and effect, which may not necessarily exist. It was therefore deemed necessary to reclassify pulmonary hypertension in a way that provides meaningful clinical and prognostic data without placing excessive importance on the finding of a single histologic entity.

Current Classification of Pulmonary Hypertension by the World Health Organization

The WHO in 1998 adopted a revised classification for pulmonary hypertension that combines our understanding of clinical history, epidemiology, and pathology in an attempt to create a system that provides meaningful diagnostic and prognostic information across a wide range of disease entities.[43] In this classification scheme, the term *secondary pulmonary hypertension* was dropped in favor of *pulmonary arterial hypertension related to [related condition].*

In 2003, the nomenclature and classification were once again revised at the Third World Conference on Pulmo-

TABLE 28.2. Congenital heart malformations that may be associated with pulmonary hypertension

Pretricuspid shunts
Atrial septal defect
Communication between coronary sinus and left atrium
Anomalous pulmonary venous drainage to the right atrium or superior vena cava
Post-tricuspid shunts
Ventricular septal defect
Atrioventricular septal defect
Transposition of the great arteries with ventricular septal defect
Truncus arteriosus
Patent ductus arteriosus
Aortopulmonary window
Transposition of the great arteries with intact ventricular septum
Surgically induced systemic pulmonary shunt
Obstruction to pulmonary venous flow
Congenital mitral stenosis
Cor triatriatum
Hypoplastic left heart syndrome

Source: Drut,[38] with permission from Lippincott Williams & Wilkins.

TABLE 28.3. 2003 revised nomenclature and classification of pulmonary hypertension

Pulmonary arterial hypertension (PAH)
1. Idiopathic (IPAH)
2. Familial (FPAH)
3. Associated with:
   a. Collagen vascular disease
   b. Congenital systemic to pulmonary shunts (large, small, repaired, or nonrepaired)
   c. Portal hypertension
   d. HIV infection
   e. Drugs and toxins
   f. Other (glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
4. Associated with significant venous or capillary involvement:
   a. Pulmonary veno-occlusive disease
   b. Pulmonary capillary hemangiomatosis

Pulmonary venous hypertension
1. Left-sided atrial or ventricular heart disease
2. Left-sided valvular heart disease

Pulmonary hypertension associated with hypoxemia
1. Chronic obstructive pulmonary disease
2. Interstitial lung disease
3. Sleep-disordered breathing
4. Alveolar hypoventilation disorders
5. Chronic exposure to high altitude

Pulmonary hypertension due to chronic thrombotic or embolic disease
1. Thromboembolic obstruction of proximal pulmonary arteries
2. Thromboembolic obstruction of distal pulmonary arteries
3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Source: Adapted from Simonneau et al.[5]

nary Hypertension, held in Venice[44] (Table 28.3). The revision was undertaken not only to address shortcomings in the WHO classification, but also to reflect the rapid advances that have been made in elucidating the pathogenesis of some pulmonary hypertensive states. The most recent recommendation is that the term *primary pulmonary hypertension* (PPH) be replaced with *idiopathic pulmonary arterial hypertension* (IPAH). Undoubtedly, as additional advances are made in understanding the pathogenesis and etiologies of the various forms of pulmonary hypertension, the nomenclature will undergo further changes. Both terms will be used here, as much of the literature is replete with the term *primary pulmonary hypertension*. Because vascular lesions can be overlooked in histologic sections, the WHO pathology working group also recommended a systematic approach to the evaluation of blood vessels as well as the surrounding lung tissue. This recommended approach is outlined in Table 28.4.[43]

TABLE 28.4. Protocol for evaluation of lung biopsies for pulmonary hypertension

Vasculature
Vessels
Vessel type: Elastic, preacinar, and intraacinar arteries, microvessels, postacinar and intraacinar veins, capillaries, lymphatics, and bronchial vessels
The vessel lumen should be commented on with respect to thrombi (recent or old) and abnormal cellular and matrix components

Components
Endothelium/intima
  Cellular components (endothelial cells and smooth muscle cells)
  Matrix (elastin, collagen, mucopolysaccharides)
Media
  Pattern (eccentric or concentric)
  Cellular components (smooth muscle and/or other cells)
  Matrix
Adventitia
  Cellular components (fibroblasts)
  Matrix
Complex vascular lesions
  Dilatation
  Plexiform
  Presence of granulomas
  Fibrinoid necrosis
  Vasculitis
Inflammatory cells
  Types (neutrophils and mononuclear cells)
  Sites (perivascular or vascular wall)

Quantification
Identify arteries by type of accompanying airways. An assessment of the number of affected vessels in proportion to total vessels at a given airway level should be given. The number of vessels in relation to the alveoli should be determined.

Lung tissue
Components
To include airways, alveoli, interstitium, and pleura
The description should include:
a. Source of tissue (postmortem, explant, or open lung biopsy) with a comment on size
b. Sample site:
   Lobe, central, or peripheral (avoid the lingula)
c. Preparation of tissue (e.g., inflated, formalin-fixed, frozen)
d. Stains
   Hematoxylin and eosin (H&E)
   Pentachrome (Movat) or other elastic tissue stain for assessment of elastic tissue and collagen
   Smooth muscle marker for assessment of smooth muscle involvement
   Endothelial cell marker for assessment of endothelial cell involvement
   Iron stain for assessment of hemosiderin

Comments: Description of state of inflation and adequacy of sample size, airway, and parenchyma including evidence of associated parenchymal disease, other abnormalities or hemorrhage.

Source: Travis WD, Colby TV, Koss MN, Rosado-de-Christenson ML, Muller NL, King TE. Pulmonary hypertension and other vascular disorders. In: King DW, ed. Non-neoplastic disorders of the lower respiratory tract. Bethesda, MD: American Registry of Pathology and Armed Forces Institute of Pathology, 2002, with permission from the American Registry of Pathology.

Clinical Features of Pulmonary Arterial Hypertension and Cor Pulmonale

Pulmonary arterial hypertension is defined clinically as a mean resting pulmonary artery pressure greater than 25 mm Hg, or a systolic pulmonary artery pressure greater than 30 mm Hg.[45] Mild elevations in pulmonary artery pressure are usually asymptomatic, and most cases are only diagnosed as the pulmonary artery pressure exceeds 60 mm Hg. Symptoms of pulmonary hypertension are related to right ventricular failure, or cor pulmonale, and include dyspnea, fatigue, syncope, lower extremity edema, and atypical chest pain. Clinical findings in cor pulmonale include right ventricular hypertrophy, manifested as a left parasternal or subxiphoid heave, split second heart sound, distended neck veins, peripheral edema, and pulsatile liver. Pleural effusions and ascites are uncommon. While death secondary to slowly progressive cor pulmonale is common in patients with severe pulmonary hypertension, some patients experience sudden death. Mechanisms of sudden death in these patients include arrhythmias, pulmonary hemorrhage, pulmonary embolism, and right ventricular ischemia.[46]

The definition of cor pulmonale is problematic and varies within the medical literature from simple pulmonary hypertension to florid right heart failure due to underlying lung disease.[47] The morphologic definition of cor pulmonale espoused by the WHO expert committee is that of "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart, as in congenital heart disease."[47,48] As reviewed in Chapter 1, the morphologic standard for determining right ventricular hypertrophy is to separately measure and compare ventricular weights.[49]

Sporadic Pulmonary Hypertension

Sporadic cases are inclusively one of the forms of pulmonary hypertension formerly known as primary pulmonary hypertension. By definition, these are cases that are idiopathic despite extensive clinical evaluation for known associated diseases and exposures. The overall incidence of the sporadic form of the disease is not known, but is estimated to be 1 to 2 per million. While more common in young females (mean age, 36.4 years; male-to-female ratio, 1.0:1.7), sporadic pulmonary hypertension can occur at any age.[50] The disease can be seen in children and infants, and appears to have a similar sex ratio to that in adult patients, although the overall median survival appears to be lower in children.[51] There is an increased incidence of pulmonary arterial hypertension in children with Down syndrome that may be attributable both to the associated cardiac defects and the decreased number and size of pulmonary arteries in those affected by Down syndrome.[52–54]

The current model for pulmonary hypertension is based on endothelial damage, followed by inappropriate cellular proliferation.[45] Endothelial damage can occur through a variety of mechanisms, and may explain the diverse associations of pulmonary hypertension with viral infections, autoimmune diseases, and drug exposure. Human herpes virus-8 (the causative agent in Kaposi sarcoma) has been reported to occur in the lungs of at least 62% of patients with primary pulmonary hypertension.[55] The virus leads to endothelial injury via the lytic phase of viral replication. In addition, p16 protein, which is associated with human papilloma virus infection and subsequent dysplasia,[56] is expressed in plexiform lesions.

Inflammation triggering endothelial cell apoptosis, as described in scleroderma, may explain the association of collagen vascular disease with the development of pulmonary hypertension.[57] Irrespective of the mechanism of initial vascular damage, there is a complex reparative response involving the liberation of growth factors, alterations in receptor expression, and changes to the basic growth-regulatory machinery of cells. Serotonin and endothelin contribute to smooth muscle hyperplasia within pulmonary arteries.[58,59] Altered expression of hypoxia inducible factor-1 (HIF-1), vascular endothelial growth factor (VEGF) receptor II, and endothelin receptors have all been reported within the plexiform lesions of pulmonary hypertension.[60] Microarray studies of gene expression in lung tissue from patients with PPH demonstrate the loss of expression of tumor suppressor caveolin-1 and peroxisome proliferation-activated receptor-γ (PPAR-γ).[61,62] It is postulated that the dysregulation of cell growth leads to an oligoclonal evolution of endothelial cells, in a process that closely parallels neoplasia.[63]

Familial Pulmonary Hypertension

Familial pulmonary arterial hypertension (FPAH) is rare and accounts for less than 6% of all primary pulmonary hypertension patients. The disease presents at an earlier age as compared with spontaneous cases, and appears to have an autosomal dominant inheritance pattern with incomplete penetrance.[64] Only 10% to 20% of family members develop the disease. Despite the autosomal dominant inheritance, the disease shows a female predominance, similar to the spontaneous form of the disease.

The familial form of pulmonary arterial hypertension has provided a rare opportunity to investigate the genetic basis of pulmonary hypertension predisposition. Germline mutations in bone morphogenetic protein receptor-II (BMPR2 [chromosome 2q31-32]), a gene that encodes a receptor in the transforming growth factor-β (TGF-β)

superfamily, have been identified in patients with FPAH.[65] Interestingly, 26% of a series of 50 patients with IPAH were also found to carry the BMPR2 mutation.[66] It is clear, however, that genetic susceptibility does not explain all cases of severe IPAH.

Collagen Vascular Disease

All forms of collagen vascular disease have been seen in association with pulmonary hypertension.[67] However, there is a wide range of risk based on the clinical classification of collagen vascular disease. CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), a variant form of systemic sclerosis, has a very high incidence of pulmonary hypertension with up to 10% to 30% of patients affected, and over 50% with evidence of pulmonary hypertension at autopsy.[68] A similar incidence has been reported in patients with mixed connective tissue disease.[69] Systemic lupus erythematosus has a somewhat lower risk, with approximately 5% to 10% of individuals affected.[70] Sjögren's disease, rheumatoid arthritis, and polymyositis/dermatomyositis rarely develop associated pulmonary hypertension.[71]

The pathogenesis of pulmonary hypertension in the setting of collagen vascular disease is not well established. Inflammation is believed to play a pivotal role in the development of pulmonary hypertension. Clustering of T cells and macrophages around vessels has been reported and may be linked to vascular remodeling.[72] The liberation of cytokines such as VEGF and platelet-derived growth factor (PDGF) in an inflammatory response may drive endothelial proliferation in these patients.[73,74] In patients with collagen vascular disease–associated hypercoagulable states, such as lupus anticoagulant or antiphospholipid antibodies, in situ thrombosis may play a role in the development of arteriopathy and pulmonary hypertension (see Chapter 20).[75,76]

Portal Hypertension

Portal hypertension, most commonly in the setting of liver disease, can be associated with pulmonary hypertension. Typically, pulmonary hypertension develops 4 to 7 years after the initial diagnosis of portal hypertension.[77] Portopulmonary hypertension (PPHTN) is seen in 0.25% to 0.73% of patients with liver cirrhosis irrespective of the cause of cirrhosis. A higher percentage (2%) was reported in a cardiac catheterization-based study.[78,79] Furthermore, the risk of pulmonary hypertension is associated with the duration of portal hypertension, but does not correlate well with the degree of portal hypertension.

It is believed that circulating factors and cytokines are responsible for the development of pulmonary hypertension in this setting. Endothelin-1 (ET-1), a vasoconstrictor and endothelial mitogen, has increased synthesis and reduced metabolism in cirrhotic patients, resulting in increased plasma concentrations.[80,81]

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) appears to be a potent risk factor for the development of pulmonary hypertension, with an incidence of approximately 0.5% in the HIV-positive population—at least a 2000-fold increase in risk as compared with the general population.[82] Unlike many of the complications of HIV, pulmonary hypertension appears to correlate poorly with CD4 counts or stage of infection. The mean CD4 count for those with HIV and pulmonary hypertension is 300/mm^3, with a range of 0 to 900/mm^3, and less than one third of these patients meet the clinical definition of AIDS.[83,84]

The development of pulmonary hypertension in HIV-positive patients with no other risk factors initially led researchers to suspect a direct mechanism via viral infection of endothelial cells. However, HIV viral sequences have not been recovered from endothelial cells of affected patients, nor have viral particles been identified by electron microscopy.[85] Therefore, the current models of HIV-associated pulmonary hypertension have focused on the role of cytokines in the mediation of HIV's effect. Platelet-derived growth factor may, at least in part, mediate some of the endothelial proliferation in response to HIV infection.[86] In addition, ET-1, a potent vasoconstrictor and mitogen produced by macrophages, appears to be increased by the HIV gp120 protein.[87] Furthermore, there does appear to be correlation between ET-1 immunostaining and the overall pulmonary vascular resistance.[88] While virally mediated cytokines may facilitate the development of pulmonary hypertension, the majority of HIV-positive patients do not have elevated pressures. This would suggest, therefore, that there are other host factors involved in the development of disease. Of particular interest is the association of HIV-associated pulmonary hypertension with specific human leukocyte antigen (HLA) DR alleles.[89]

Drugs

Fen-Phen

The diet drug combination of fenfluramine (Pondimin) or dexfenfluramine (Redux) in combination with phentermine (commonly referred to as Fen-Phen) was a popular diet regimen in the 1990s, with over 18 million prescriptions written by 1996. On September 15, 1997, American Home Products (AHP) Corporation, now known as Wyeth, withdrew the drugs Pondimin and Redux from the marketplace after the *New England Journal of Medicine* published a report of 24 patients

who had developed valvular heart disease.[90] The Food and Drug Administration (FDA) acted rapidly, issuing a warning on September 17, 1997, that cardiovascular symptoms could be seen in up to 30% of patients taken Fen-Phen. In addition to valvular heart disease, the drugs had been previously also linked to a 28-fold increase in incidence of pulmonary hypertension, resulting in a purported incidence of 28 per million, as opposed to 1 per million for the general population.[91] However, in absolute numbers, the number of patients developing pulmonary hypertension was dwarfed by the number who reported heart valve disease.

The legal response to the newly found associations was brisk, resulting in thousands of lawsuits and class actions, finally culminating in a settlement on September 1, 2000, establishing the AHP Settlement Trust, which accepted new claims for benefits up to the date of August 1, 2002 (also referred to as Date 1). By January 31, 2005, Wyeth had estimated the litigation costs to be $21.1 billion, making it one of the most expensive settlements in history.

Histopathologically, plexiform lesions have been described as the main vascular alteration in fenfluramine-phentermine–associated pulmonary hypertension,[92,93] although the case reported by Strothers et al.[94] was suggestive of thrombotic arteriopathy. It has been postulated that the serotonergic activity of these drugs, in combination with an underlying polymorphism in the gene encoding a serotonin transporter, is responsible for the development of pulmonary hypertension in patients taking Fen-Phen (see Fig. 22.6 in Chapter 22).[91,95,96]

Aminorex

Aminorex fumarate was a powerful appetite suppressant popular in the late 1960s in West Germany, Austria, and Switzerland, although it was never approved for use in the United States.[97] The drug was responsible for an epidemic of pulmonary hypertension, beginning in 1967 and ending by 1972. Half of the affected patients were alive in a 10-year follow up, with most dying of right-sided heart failure.[91,98] In a later analysis, it appears that aminorex is more highly correlated with the development of pulmonary hypertension than is dexfenfluramine, and was responsible for a fivefold increase in the number of pulmonary hypertension cases, as compared with the number expected for the same time period.[99]

Toxic Oil Syndrome

Toxic oil syndrome was described in Spain in 1981 following the illegal sale of rapeseed oil containing aniline. The syndrome involved liver disease, motor neuropathy, eosinophilia, pulmonary infections, and pulmonary hypertension. It is estimated that 20,000 people were affected, and over 2500 deaths have been attributed to the ingestion of toxic rapeseed oil.[100] Pulmonary hypertension was seen in up to 20% of patients following ingestion, although many cases appeared to spontaneously resolve.[101] However, some cases progressed, and were clinically and pathologically analogous to the idiopathic form of the disease, with right ventricular failure seen as early as 2 months following ingestion of the tainted oil.[102] Although the mechanism of the development of pulmonary hypertension in these patients is not known, it is suspected to involve direct endothelial toxicity by aniline.[101]

Amphetamines, Methamphetamines, and Cocaine

Stimulants such as amphetamine, methamphetamine, and cocaine have been associated with the development of pulmonary hypertension.[103,104] While these drugs do have structural similarity to fenfluramine and aminorex, it has been proposed that it is contaminants in the preparation of these substances, rather than the drug itself, that causes pulmonary hypertension.[104] Studies of patients with pulmonary hypertension associated with use of these drugs have often found foreign-body granulomas and microembolization in pulmonary arteries.[105] Drug additives believed to play a role, whether inhaled, smoked, or injected, include talc, corn starch, ascorbic acid, boric acid, plaster of Paris, phencyclidine, heroin, lidocaine, and phenytoin.[106,107] It remains unclear whether the stimulants themselves play a role in the development of pulmonary hypertension, although it has been proposed.[108]

L-Tryptophan

The dietary supplement L-tryptophan has been associated with an eosinophilia-myalgia syndrome that includes pulmonary manifestations including pulmonary hypertension.[109] Finding at lung biopsy in these patients have included vasculitis, perivasculitis, follicular bronchiolitis, chronic interstitial pneumonia, pulmonary eosinophilia, and fibrointimal hyperplasia of pulmonary vasculature.[110,111] High-dose steroids provided only partial resolution of the pulmonary symptoms in one small series.[111]

Phenylpropanolamine

Phenylpropanolamine was commonly found in over-the-counter antiobesity medications as well as some cold remedies until its removal from the market in 2000 due to increased risks of hemorrhagic stroke.[112] The Study of Pulmonary Hypertension in America (SOPHIA) incidentally discovered an association between phenylpropanolamine and the development of pulmonary

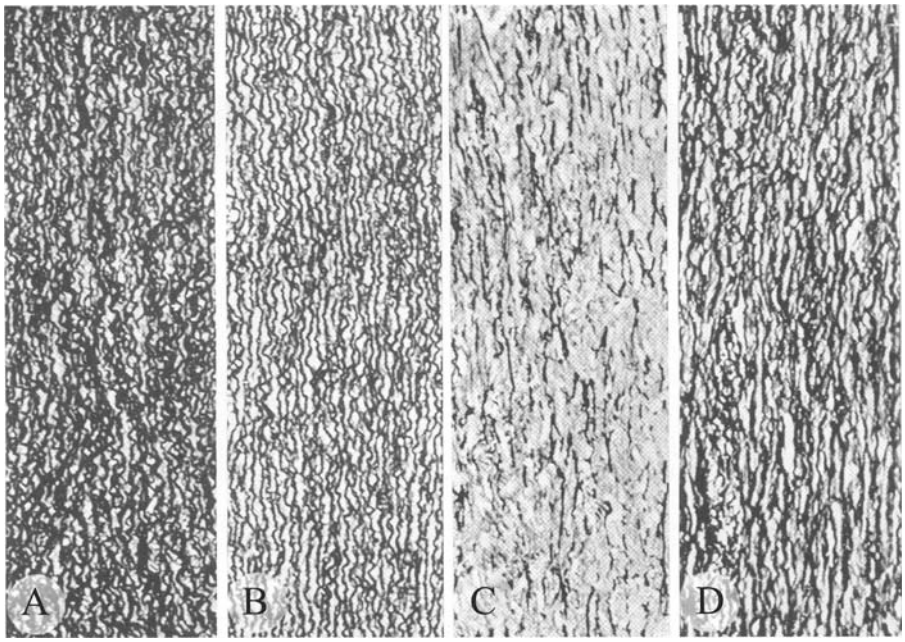


FIGURE 28.8. Elastic patterns of pulmonary artery vs. aorta. **A.** Pulmonary trunk, 7.5-month fetus. Aortic configuration. **B.** Aorta (same case as **A**). **C.** Pulmonary trunk. Normal adult elastic pattern. **D.** Pulmonary trunk of a 13-year-old with corrected transposition of the great vessels with large ventricular septal defect and pulmonary hypertension since birth. Aortic configuration. (From Heath et al.,[115] with permission.)

hypertension. In addition, there are case reports of children as young as 7 who developed pulmonary arterial hypertension following the ingestion of large quantities of phenylpropanolamine.[113]

Morphology

Pulmonary Trunk and Elastic Arteries

The pulmonary trunk and main pulmonary arteries in the fetus and newborn resemble the aorta in diameter, mural thickness, and elastic configuration (Fig. 28.8). Long continuous elastic fibers are circumferentially arranged in a parallel fashion within the pulmonary arterial wall.[114–116] After birth, as the pulmonary circuit assumes a lower pressure and resistance, the central elastic pulmonary arteries acquire a wall thickness less than that of the aorta with a postnatal "adult" configuration of interrupted, irregular elastic fibers (Fig. 28.8).[115] Lobar and more distal arteries, however, retain a circumferential elastic pattern. In patients with low-flow states, such as tetralogy of Fallot, the pulmonary artery may be further thinned and the interrupted pattern of elastic fibers accentuated.[114] However, when pulmonary hypertension persists from birth, as in certain congenital heart defects with left to right shunt, the normal transformation of elastic pattern in the central pulmonary arteries does not occur, and the arteries retain a fetal or "aortic" configuration of dense continuous mural elastic fibers (Fig. 28.8D).[115]

With sustained pulmonary hypertension, elastic pulmonary arteries undergo myxoid degeneration and accumulate intramural mucopolysaccharides stainable with Movat or Alcian blue stains (Fig. 28.9).[117] Intimal fibrosis or fibro-intimal atheromas are also frequently a sign of

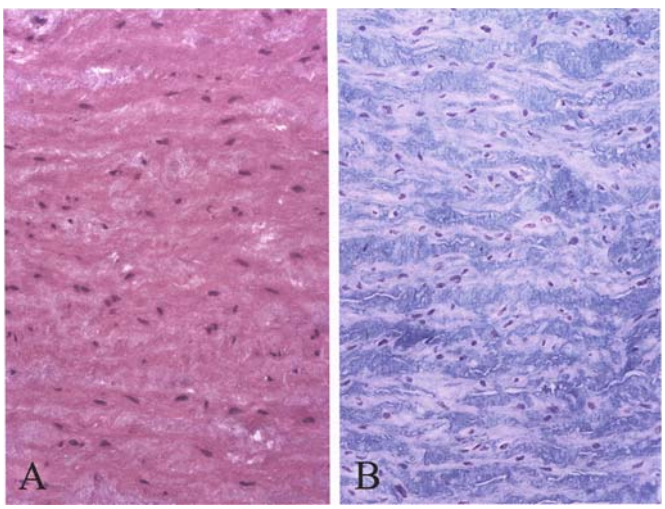


FIGURE 28.9. Medial myxoid change in pulmonary trunk of young woman with primary pulmonary hypertension. **A.** Basophilic mucosubstance with fine vacuolization separates elastic fibers. (H&E.) **B.** Alcian blue stain demonstrates abundant mucopolysaccharides.

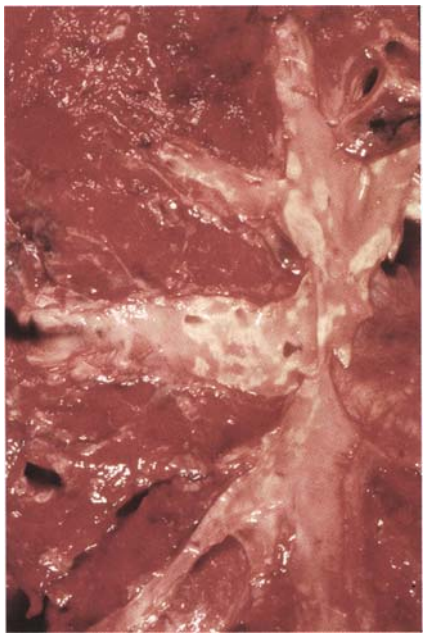


FIGURE 28.10. Pulmonary artery atherosclerosis in a patient with sickle cell disease and pulmonary hypertension. Atheromas are concentrated in segmental arteries.

pulmonary hypertension (Fig. 28.10).[118,119] Although a mild degree of pulmonary artery atherosclerosis may be seen in older individuals, atheromas usually are not conspicuous in the absence of pulmonary hypertension, especially in younger persons.[114] Atheromas also tend to be most obvious in the secondary and tertiary branches of the main pulmonary arteries.[118] Central pulmonary artery bands and webs are indicative of prior organized thromboemboli (Fig. 28.11) (see Pulmonary Thromboembolism, below).[120]

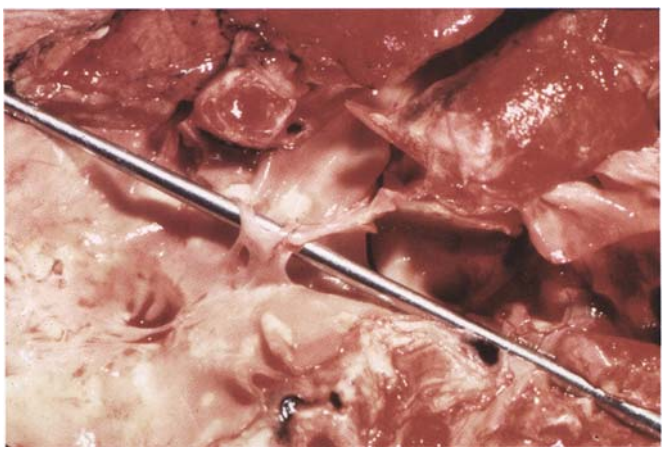


FIGURE 28.11. Pulmonary artery fibrous bands indicative of remote pulmonary embolus. Note also intimal atheromas.

Intraparenchymal Arteries

Macroscopically, when severe pulmonary hypertension is present, parenchymal pulmonary arteries are rigid and stand above the surrounding parenchyma. While many cases of pulmonary arterial hypertension are diagnosed clinically without lung biopsy, histopathologic evaluation can play a critical role in the diagnosis of patients with atypical clinical presentations. A common change in pulmonary arterial hypertension is medial hypertrophy of arterial walls (Fig. 28.12). In children, muscularization of arterioles may be the only histologic finding in pulmonary hypertension. While this appears to be rarely the case in adults, it has been described in chronic hypoxia.[121] Normal medial thickness in adults is 3% to 7% of the external vascular diameter. Mild hypertrophy ranges from 7% to 9%, moderate hypertrophy has a thickness of 10% to 14%, and severe disease typically has a thickness in excess of 15%.[122] There is often good correlation with the thickness of the medial smooth muscle and the measured pulmonary artery pressure. In contrast, intimal hyperplasia, while a common finding in pulmonary hypertension, has poor correlation with the severity of disease. Intimal hyperplasia is seen in two distinctive forms. Cellular intimal hyperplasia, a relatively nonspecific finding, is loose and lacking in collagen deposition (Fig. 28.13). Concentric laminar intimal hyperplasia, on the other hand, has dense deposition of collagen and elastin, and is a finding rarely seen except in primary pulmonary hypertension or other conditions, as described above, in which plexiform lesions develop (Fig. 28.14). Concentric

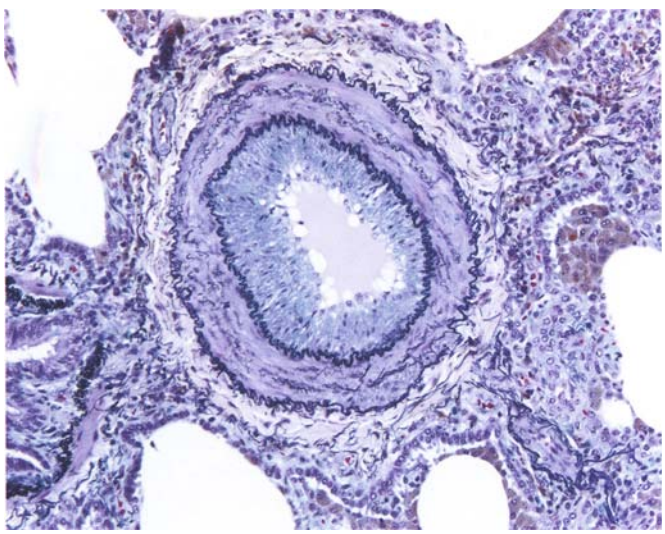


FIGURE 28.12. Medial hypertrophy. The Movat pentachrome stain highlights the double elastic laminae of this small pulmonary artery with medial thickening. Cellular intimal hyperplasia is also noted in this vessel.

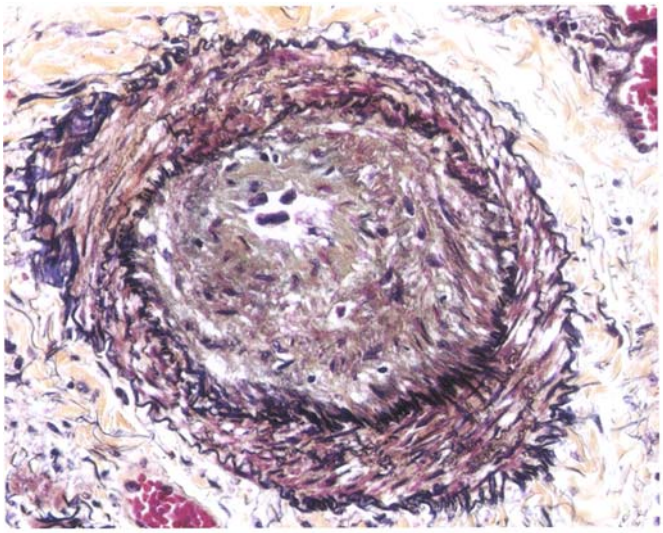


FIGURE 28.13. Cellular intimal hyperplasia. The Movat stain demonstrates the markedly increased intima of this small muscular pulmonary artery. The lumen is narrowed and nearly obliterated in this example of cellular intimal proliferation. Note also medial hypertrophy.

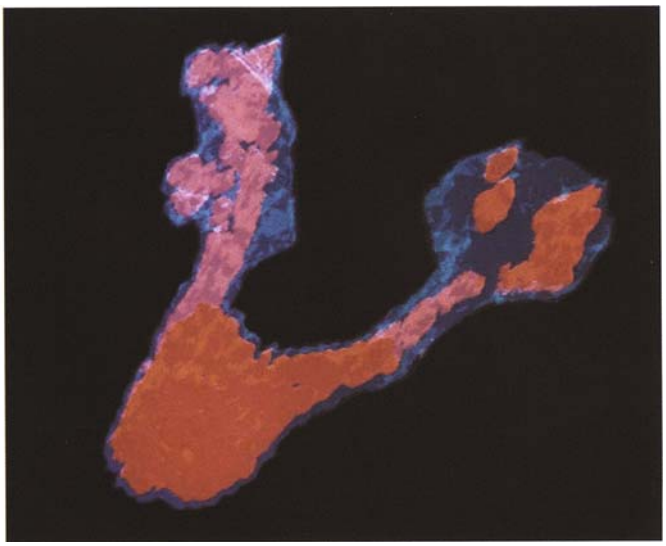


FIGURE 28.15. Three-dimensional reconstruction of a pulmonary artery and its branches in a case of primary pulmonary hypertension (PPH). This computerized three-dimensional reconstruction of the endothelial cell layers (blue) in a medium-sized pulmonary artery of a patient with PPH demonstrates that the plexiform lesions occur in the branching vessels, distal to the parent artery. Points of constriction, corresponding to concentric intimal lesions, are present just proximal to the plexiform lesions. The red highlights the luminal spaces of the vessels.

intimal fibrosis is often present upstream to a plexiform lesion, as shown by three-dimensional vascular reconstruction (Fig. 28.15).[123] Occasionally, dilation creates vessels with large lumina and very thin walls that are reminiscent of pulmonary veins, so-called dilatation lesions (Fig. 28.16).

Plexiform lesions are the hallmark angioproliferative lesion of severe primary pulmonary hypertension, and are characterized by an abnormal proliferation of endothelial cells forming multiple irregular lumina in a glomeruloid plexus (Fig. 28.17). Unlike the rigid round lumina of a recanalized thrombus, the plexiform lesion

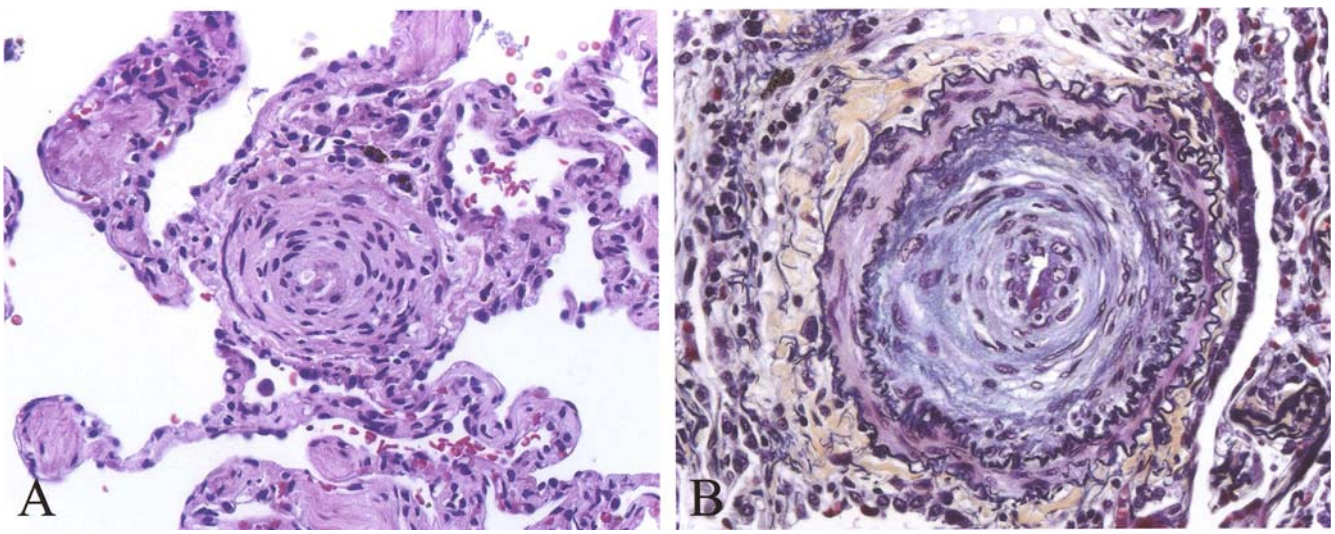


FIGURE 28.14. Concentric laminar intimal hyperplasia. **A.** This example of intimal hyperplasia demonstrates a concentric laminar, onion-skin appearance. There is associated marked narrowing of the lumen. **B.** The Movat stain highlights the predominantly intimal nature of this lesion. The smooth muscle layer between the two elastic laminae is only mildly hypertrophied.

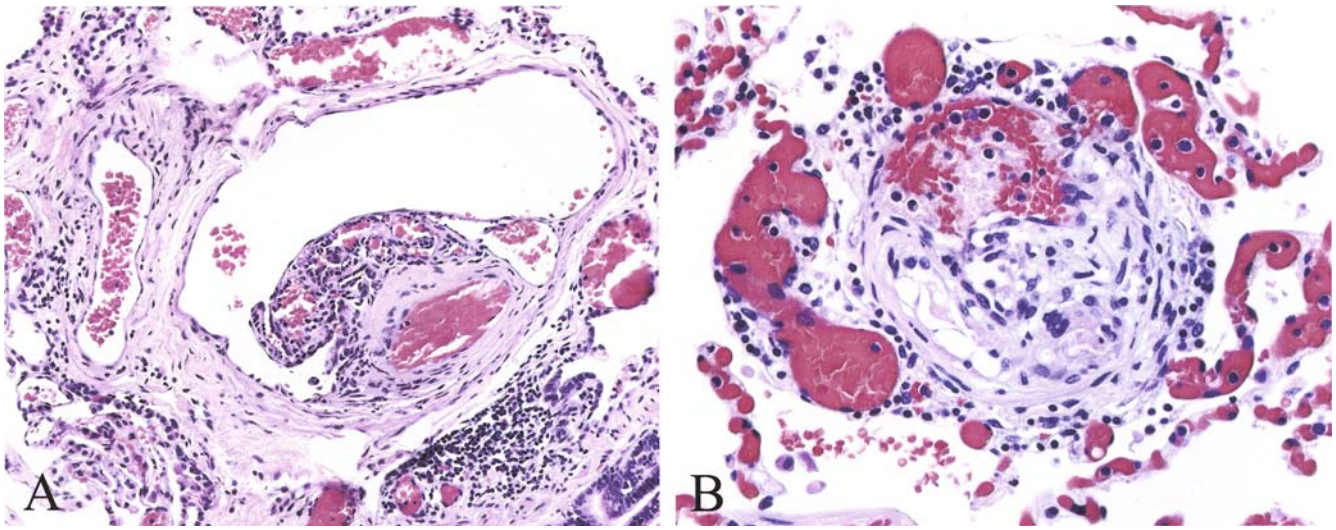


FIGURE 28.16. Dilatation lesions. **A.** The plexiform lesion at the lower right center is associated with a distal dilatation lesion characterized by thin-walled vascular structures. **B.** Multiple thin-walled vascular structures partially surround the plexiform lesion at the center. Three-dimensional reconstruction of these structures has shown that the dilatation lesions occur distal to the plexiform lesion.

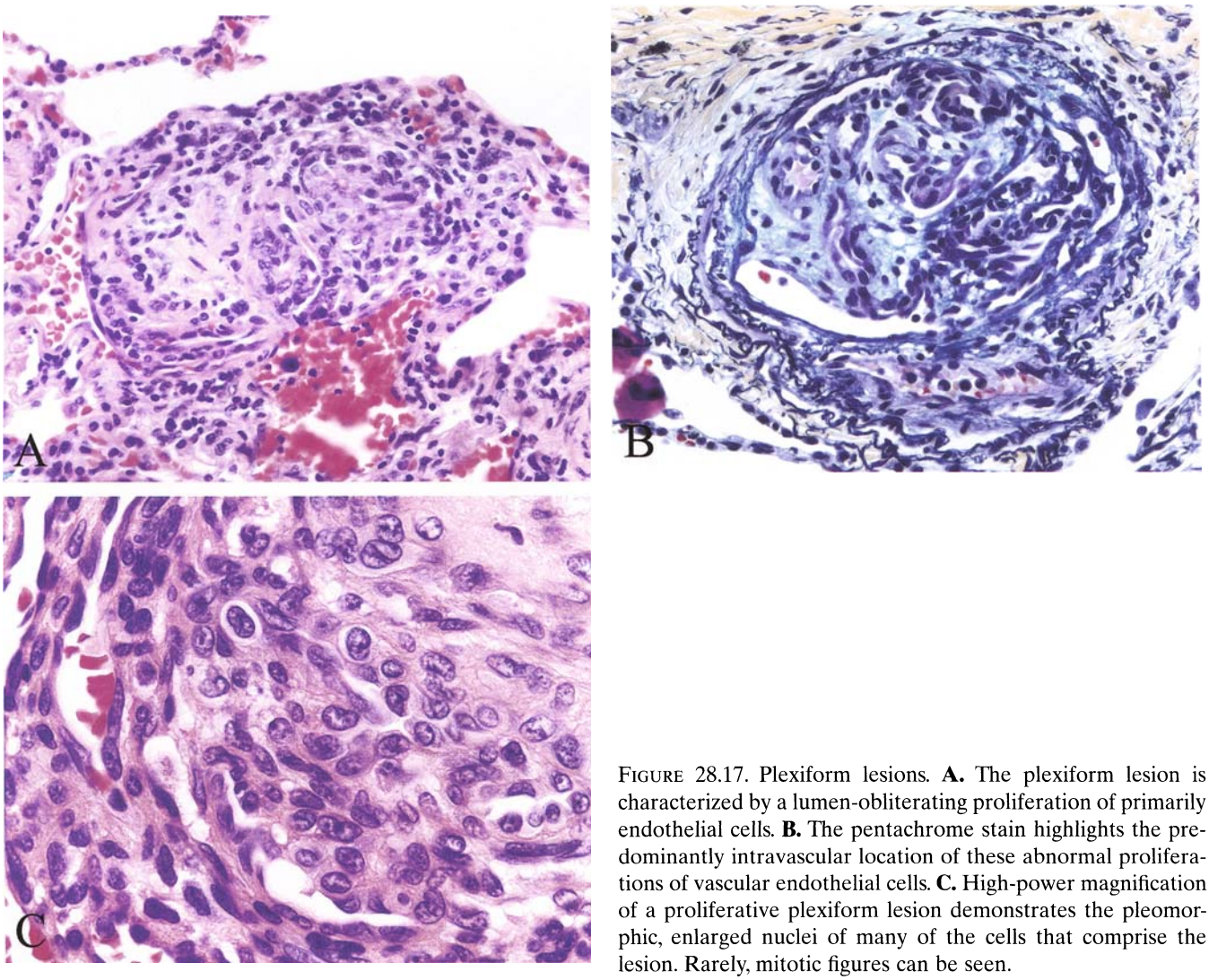


FIGURE 28.17. Plexiform lesions. **A.** The plexiform lesion is characterized by a lumen-obliterating proliferation of primarily endothelial cells. **B.** The pentachrome stain highlights the predominantly intravascular location of these abnormal proliferations of vascular endothelial cells. **C.** High-power magnification of a proliferative plexiform lesion demonstrates the pleomorphic, enlarged nuclei of many of the cells that comprise the lesion. Rarely, mitotic figures can be seen.

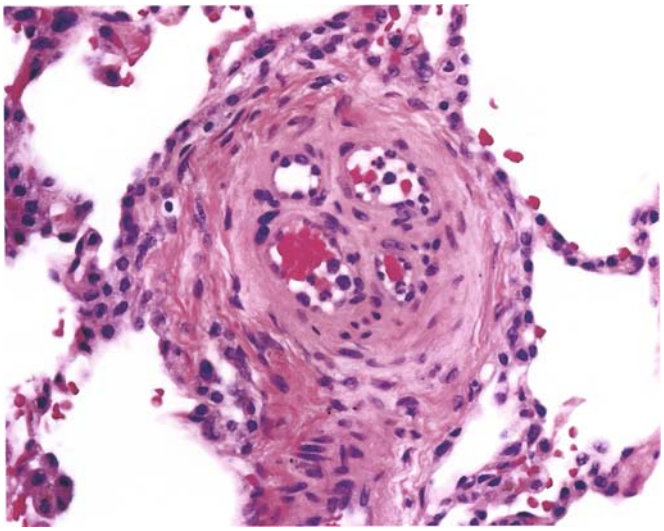


FIGURE 28.18. Recanalized vessel in contrast to plexiform lesions. The recanalized vessel shows sharply demarcated, "punched-out" intraluminal spaces. The wall of each of the spaces is often muscularized. Contrast with plexiform lesions in Figure 28.17 in which vascular spaces are slit-like, with a much more disordered appearance.

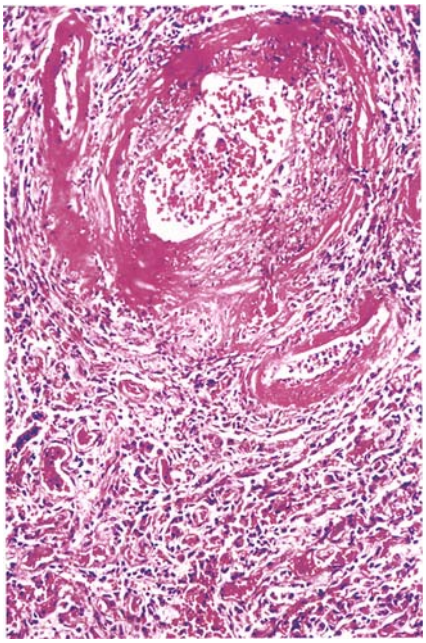


FIGURE 28.19. Fibrinoid arteritis. There is extensive fibrinoid necrosis and perivascular inflammation in this muscular artery from a patient with ventricular septal defect and pulmonary hypertension.

tends to form asymmetrical and slit-like channels within the vessel (Fig. 28.18). Plexiform lesions may be very sparse in a case, requiring examination of multiple sections, or may be widespread. While plexiform lesions are characteristic of the idiopathic and familial forms of pulmonary hypertension, they are not pathognomonic and may be seen in any case of severe pulmonary arterial hypertension.

Although rarely seen in treated patients, fibrinoid necrosis has been described in small vessels less than 100 μm in diameter, showing fibrin and necrosis within the medial smooth muscle. Fibrinoid arteritis has also been described as a feature of larger arteries, with acute inflammation throughout the vessel wall and adventitia (Fig. 28.19). Both fibrinoid necrosis and arteritis are features of severe pulmonary arterial hypertension, and usually suggest a more aggressive clinical course. Thromboembolic lesions are now rarely seen in patients with severe idiopathic pulmonary arterial hypertension because these patients are usually effectively treated with anticoagulants.

In cases of pulmonary arterial hypertension associated with collagen vascular disease, the vascular adventitia may be markedly thickened with collagen (Fig. 28.20). In addition, these cases may show other features of collagen vascular disease, such as constrictive bronchiolitis and lymphoid aggregates with germinal centers.

Prognosis and Treatment

Since the symptoms of early primary pulmonary arterial hypertension are subtle and nonspecific, the disease is typically diagnosed late in its course. The natural history is one of relentless progression to right-sided heart failure,

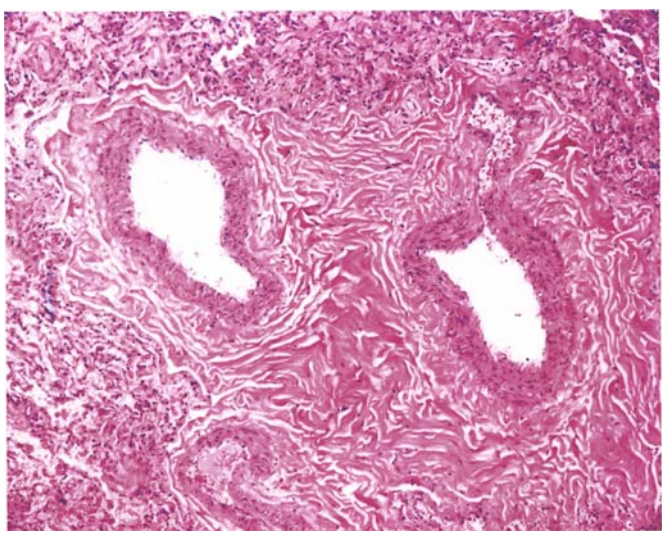


FIGURE 28.20. Adventitial fibrosis. Often the clue to a collagen vascular disease etiology for pulmonary vascular disease can be found in the markedly thickened, collagenized adventitia.

with a median survival of 2.8 years between diagnosis and death, in untreated patients.[124] Current treatment regimens have improved the survival considerably. Oxygen is used to treat patients with dyspnea and prevent further vasoconstriction from hypoxia. Patients have also been shown to derive benefit from long-term anticoagulation with warfarin.[125] While oral vasodilators, such as calcium channel blockers, can provide long-term benefit, only 20% of patients with primary pulmonary hypertension respond to calcium channel blockers.[126] Perhaps the most important advance in the treatment of IPAH has been the use of the prostacyclins, such as epoprostenol. Prostacyclins are potent, short-acting vasodilators and inhibitors of platelet aggregation that have improved exercise tolerance, quality of life, and long-term survival in patients with severe pulmonary arterial hypertension.[127] Unfortunately, the 6-minute half-life of the drug necessitates a complex delivery system capable of continuous intravenous administration. Cessation of the drug, even for a short time, can result in fatal rebound pulmonary hypertension. Despite the advancement in the medical management of primary pulmonary hypertension, many patients ultimately require lung transplantation. Lung transplant recipients with primary pulmonary hypertension have a reported 1-year survival of 73%, and a 5-year survival of 45%.[128] To our knowledge, there have been no reports of recurrent primary pulmonary hypertension following lung transplantation.

Associated forms of pulmonary arterial hypertension have typically utilized very similar treatment modalities, while also attempting to treat the underlying condition. Collagen vascular disease-associated pulmonary arterial hypertension has often been treated with immunosuppression in addition to the modalities used in primary pulmonary hypertension. While there have been reports of improvement following immunosuppression, there are no controlled studies that have demonstrated a benefit in long-term survival.[129] Similarly, antiretroviral therapy in HIV has had mixed results, with reports of regression of pulmonary hypertension, as well as other reports of accelerated disease during treatment.[130,131]

Pulmonary Artery Aneurysm

Pulmonary artery aneurysm (PAA) is an exceedingly rare lesion. A comprehensive autopsy study by Deterling and Clagett[132] documented only eight cases out of 109,571 (<0.01%) autopsies. The classification and etiologies of pulmonary artery aneurysm are summarized in Table 28.5.[133] A basic division of PAA lies between aneurysms with and those without arteriovenous communication.[133]

TABLE 28.5. Classification of pulmonary artery aneurysm (PAA)

Causes of PAA without arteriovenous communication
Infection (mycotic aneurysms)
Tuberculosis (Rasmussen aneurysms)
Syphilitic
Other (bacterial and fungal)
Structural cardiac abnormalities
Congential heart disease
Acquired cardiac abnormalities
Structural vascular abnormalities
Congenital
Cystic medionecrosis/atherosclerosis
Acquired
Marfan syndrome
Vasculitis
Behçet syndrome
Other
Pulmonary hypertension
Syndromes
Hughes-Stovin syndrome
Behçet syndrome
Trauma
Idiopathic
Causes of PAA with arteriovenous communication (PAVA)
Congenital
Isolated
Associated with hereditary hemorrhagic telangiectasia
Acquired
Infection
Trauma

Source: Bartter et al.,[133] with permission.

Etiology

Infection (mycotic aneurysm) is an important cause of proximal PAA and some cases of arteriovenous aneurysms.[133–135] Historically syphilis and tuberculosis were the most frequent infectious causes, but the pathogenesis differs greatly between the two entities. Syphilitic aneurysms are the result of chronic inflammation of the vasa vasora of proximal pulmonary arteries, while tuberculous (Rasmussen) aneurysms are the effect of inflammation and necrosis of more distal arteries traversing, or adjacent to, cavitary lesions in chronic progressive tuberculosis. A variety of other bacteria or fungi, notably *Staphylococcus aureus* and streptococci, may give rise to mycotic aneurysms.[133,134] Infectious agents also interact with congenital or acquired risk factors to contribute to the development of aneurysms.[134–137] Intravenous drug users who develop right-sided valvular endocarditis are a selective population at risk for mycotic PAA.[138]

Other predisposing factors contributing to nonarteriovenous PAA include congenital heart disease, pulmonary hypertension, and vasculitis.[139,140] Congenital cardiac anomalies accounted for 56% of central PAA in two

autopsy series.[132,141] The two most frequent anomalies are patent ductus arteriosus and atrial septal defect.[133,142,143] The mechanism of aneurysm formation may act through myxoid degeneration of the elastic arterial wall.[133,144,145] This degenerative condition has been well described in aortic aneurysm and is frequently seen in elastic pulmonary arteries in patients with pulmonary hypertension (Fig. 28.9) (see above). Marfan syndrome, a systemic congenital disorder of connective tissue, is associated with medial myxoid degeneration, not only of the aorta, but also of pulmonary arteries, and occasionally is associated with PAA.[133,146]

Among the vasculitides, Behçet disease is the most important cause of PAA, although rare cases due to giant cell arteritis or other forms of vasculitis have been described.[147] In Behçet disease aneurysms are usually multiple and peripheral.[148,149] In some cases of PAA, the cause of aneurysm formation is undetermined. A subset of (predominantly young male) patients with idiopathic PAA have recurrent superficial and deep venous thrombosis (Hughes-Stovin syndrome).[150,151] The presence of fever and hemoptysis in these patients has suggested an infectious etiology, which has never been proven.[133] It has also been theorized that Hughes-Stovin syndrome is a variant of Behçet disease.[152,153]

Trauma is another important cause of acquired PAA. Traumatic injury may be extrinsic due to blunt impact or penetrating lacerations, or intrinsic due to endovascular injury.[153] The latter is usually an iatrogenic complication of pulmonary artery catheters or embolotherapy using devices such as metal coils or balloons to control hemoptysis.[133,154] Intravascular coils have the potential to migrate through the vessel wall causing structural weakening and predisposing to aneurysm development (see Fig. 40.24 in Chapter 40).

Arteriovenous communicating aneurysms are mostly congenital in nature and may be isolated (60% of cases) or associated with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease) in 40% of cases.[133] Arteriovenous aneurysms are usually peripheral and present as one or more nodular densities on chest imaging studies.

Clinical Features

Pulmonary artery aneurysms are notoriously difficult to diagnose clinically due to the nonspecificity of signs and symptoms. Typical manifestations are cough, dyspnea, chest pain, and hemoptysis, the latter being a frequent initial manifestation.[133] Central aneurysms cause a prominence of the pulmonary artery on chest x-ray, which can be confused with other causes of radiographic hilar or mediastinal enhancement. Sudden death due to rupture is an important complication of PAA. In some cases an intimal tear with or without mural dissection may precede rupture.[136,137,144] Central aneurysms may be replaced surgically with a prosthetic graft. The standard treatment of peripheral arteriovenous aneurysms is embolotherapy.[154]

Pathology

The histopathology of PAA depends on the underlying cause and the location of the vessel (central vs. peripheral). In the series of cases studied by Butto and colleagues[136] in five patients with pulmonary hypertension, pulmonary arterial dilatation and saccular aneurysms were associated with intimal tears, fibrotic neointimal lesions, or laminar thrombi (three patients each); mural dissection (two patients); and ulcerated atheromas or calcification (one patient each) (Fig. 28.21).

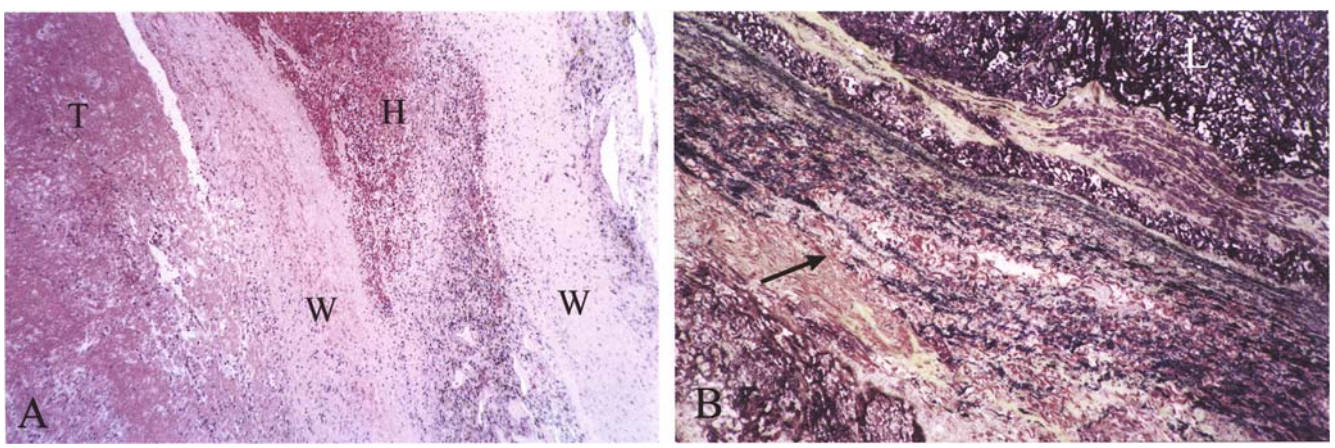


FIGURE 28.21. Dissecting aneurysm of pulmonary artery. **A.** Portions of pulmonary arterial wall (W) are separated and surrounded by organizing thrombus (T) and hematoma (H). **B.** Marked degeneration of mural elastica (arrow) adjacent to and infiltrated by organizing hematoma. L = lumen thrombus. (Movat stain.)

Medial myxoid degeneration was described as prominent in four of five patients. For peripheral arteriovenous aneurysms, a network of dilated vessels with a variable amount of smooth muscle, elastic fibers, and collagen is seen histologically (see Fig. 40.22 in Chapter 40).

Pulmonary Thromboembolism

Epidemiology

Pulmonary thromboembolism (PTE) is a frequent clinical event, a major cause of respiratory symptoms, and an important cause of death, including sudden unexpected death (see Chapter 31).[155–157] Precise statistics on the incidence of PTE are difficult to determine, and vary with the mode of study (i.e., clinical versus autopsy evaluation). It has been estimated that 600,000 persons each year in the United States experience PTE, resulting in approximately 300,000 hospital admissions and 50,000 deaths (10%). This likely represents a conservative estimate since the clinical diagnosis of PTE is notoriously difficult due to the nonspecificity of associated cardiorespiratory symptoms or the absence of symptoms in many cases. Furthermore, the lack of autopsy confirmation in the majority of fatal cases is a major impediment in determining the true incidence of fatal PTE.[158]

Even autopsy studies, however, do not provide a clear picture of the incidence of PTE, which is highly dependent on the thoroughness with which emboli are sought postmortem, and ranges widely from 6% to 69%.[155,159–161] A reasonable incidence of PTE documented at autopsy is 40% to 50%.[162] Pulmonary thromboembolism is estimated to be the solitary or major contributory cause of death in 3.5% to 18.1% of adults in acute general hospitals.[155,159–161,163]

Risk Factors

Although primary thrombosis of the pulmonary artery may occur (see below), the majority (90%) of pulmonary emboli originate as thrombi in the deep leg veins.[156,164] Therefore, patients most at risk for PTE are those also at risk for the development of deep venous thrombosis, notably patients with underlying heart disease, malignancy, or shock. Other important predisposing factors include hypercoagulable states, obesity, oral contraceptives, pregnancy, and postoperative status, especially following orthopedic surgery.[157] Most thrombi which give rise to PTE reside in the iliofemoral veins, as opposed to the superficial leg veins.[156,164] Outside of the deep leg veins, other venous beds such as the periuterine or periprostatic plexus may give rise to emboli. Indwelling central catheters, including Swan-Ganz catheters, are a cause of thrombi in the superior vena cava, and a potential source of PTE.[165] Atrial fibrillation may occasionally dislodge thrombi in the right atrial appendage. Disorders that predispose to clotting such as antithrombin III deficiency, factor V Leiden, deficiency of protein C, or the presence of lupus anticoagulant (antiphospholipid syndrome; see Chapter 20) may also predispose to venous thrombosis and PTE in approximately 10% to 15% of patients (see Chapter 31 for discussion of inherited thrombophilia).[156]

Clinical Features

There are no typical or specific presenting signs and symptoms of PTE. Dyspnea, tachypnea, and chest pain are seen in the majority of patients.[159,166] Nonproductive cough occurs in about 50%, while hemoptysis, wheezing, fever, or pleural friction rub are variable signs or symptoms in less than 50% of patients. The chest x-ray is equally nonspecific and may be normal in up to 20% to 30% of patients, including those with massive pulmonary emboli.[155,156] Transient radiographic infiltrates are common, but persistent opacities due to infarction occur only in about 10% of patients. Other radiographic features include elevation of the hemidiaphragm, linear atelectasis, or pulmonary oligemia (Westermark's sign).[155,159] Electrocardiogram changes are abnormal, but often transient and nonspecific, in the majority of patients. Hypoxemia (<80 mm Hg) occurs in about 85% of patients, and many also exhibit hypocarbia secondary to tachypnea and hyperventilation. Small unilateral, transient pleural effusions are seen in about one third of patients, but there are no diagnostic laboratory studies of pleural fluid that indicate a pulmonary embolus has occurred. Other tests used widely in the clinical evaluation of patients with suspected PTE are ventilation/perfusion lung scan, spiral computed tomography (CT) scan, Doppler imaging of leg veins, and serum analysis for D-dimer.[164,167,168] Pulmonary angiogram is still considered to be the clinical gold standard for diagnosing PTE, but this modality is being replaced by CT imaging, and is performed infrequently.[157]

Pathology of Acute Pulmonary Embolus

Morphologically, an acute fatal pulmonary embolus often presents as one or more deep red, firm, coiled clots situated in the pulmonary trunk and extending into the main pulmonary arteries (saddle embolus) (Fig. 28.22A).[169] When uncoiled, the embolus often is seen as a cast of the deep leg veins in which it was formed (Fig. 28.22B). Less frequently smaller emboli in multiple lobar or segmental arteries may cause death. Typically, pulmonary emboli fill and distend the pulmonary artery, which may be surrounded by acute adventitial hemorrhage. On cross section, alternating dark red and lighter striations (lines of Zahn) represent sequential layering of erythrocytes

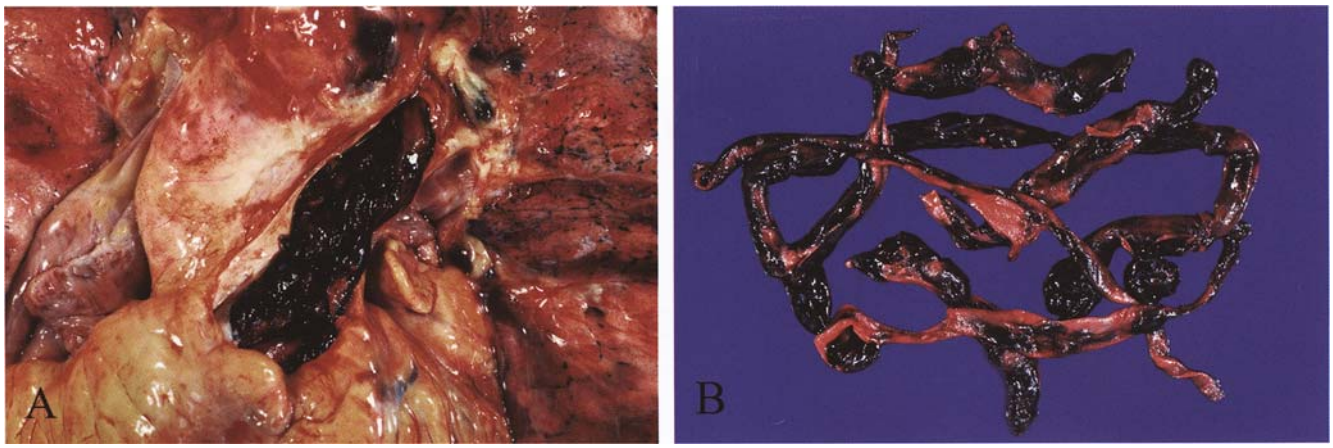


FIGURE 28.22. Fatal pulmonary embolus ("saddle embolus"). **A.** Pulmonary outflow tract is occluded by a deep red, coiled thromboembolus. **B.** Uncoiled embolus (from same specimen) forms a cast of deep leg vein.

and fibrin/platelets within the thromboembolus (see Fig. 31.13 in Chapter 31). Upon close inspection, the imprint of the venous valves may sometimes indent the surface of the embolus.[169,170] Acute microscopic changes in the pulmonary artery following impaction of an embolus include dilatation and congestion of adventitial vessels, perivascular hemorrhage, and acute inflammation of the pulmonary arterial wall (Fig. 28.23).[171] In patients with acute fatal pulmonary embolism, additional smaller organized thromboemboli are often indicative of antecedent minor embolic events (see below).[158] Emboli are more commonly seen in the lower lobes because of the greater blood flow to this region.

From the pathologist's perspective, it is important to distinguish antemortem emboli from postmortem clots (Table 28.6). Compared to the macroscopic features of emboli reviewed above, postmortem clots tend to be soft, gelatinous, and biphasic (red/yellow) in appearance due to the passive settling of erythrocytes and aggregation of leukocytes ("chicken fat" clot). Postmortem clots form a loose, nondistensive cast of the branches of the pulmonary artery in which they arise (see also Chapter 31).[170]

Histologically an acute fatal embolus is marked by layering of erythrocytes and condensed fibrin (Fig. 28.24A). A variable number of neutrophils may be entrapped within the clot. When sheets of neutrophils are present, a septic embolus should be considered (see below). One of

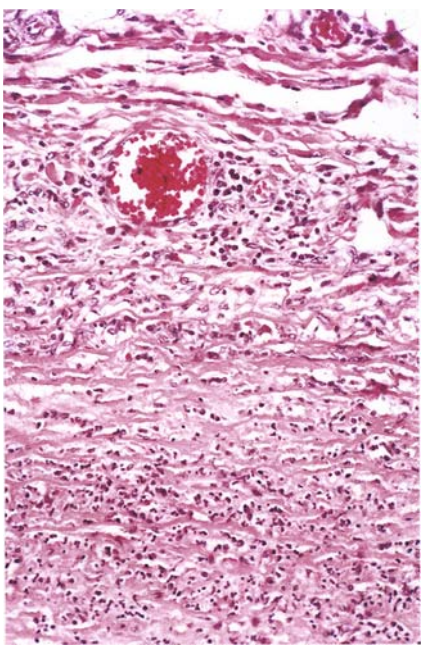


FIGURE 28.23. Acute inflammation of media of elastic pulmonary artery adjacent to impacted embolus. Adventitia (upper part) shows early spindle cell reaction, vascular congestion and chronic inflammation.

TABLE 28.6. Acute pulmonary embolus (PE) vs. postmortem clot (PMC): morphologic features

	PE	PMC
Color	Deep red	Biphasic (red/yellow)
Consistency	Firm	Soft, gelatinous
Shape	Coiled Cast of leg veins	Branching Cast of pulmonary artery
Linear striations	Present	Absent
Vascular distention	Present	Absent (loose within vessel)
Adhesion to vessel wall	Present in subacute emboli	Absent
Perivascular hemorrhage	Present	Absent

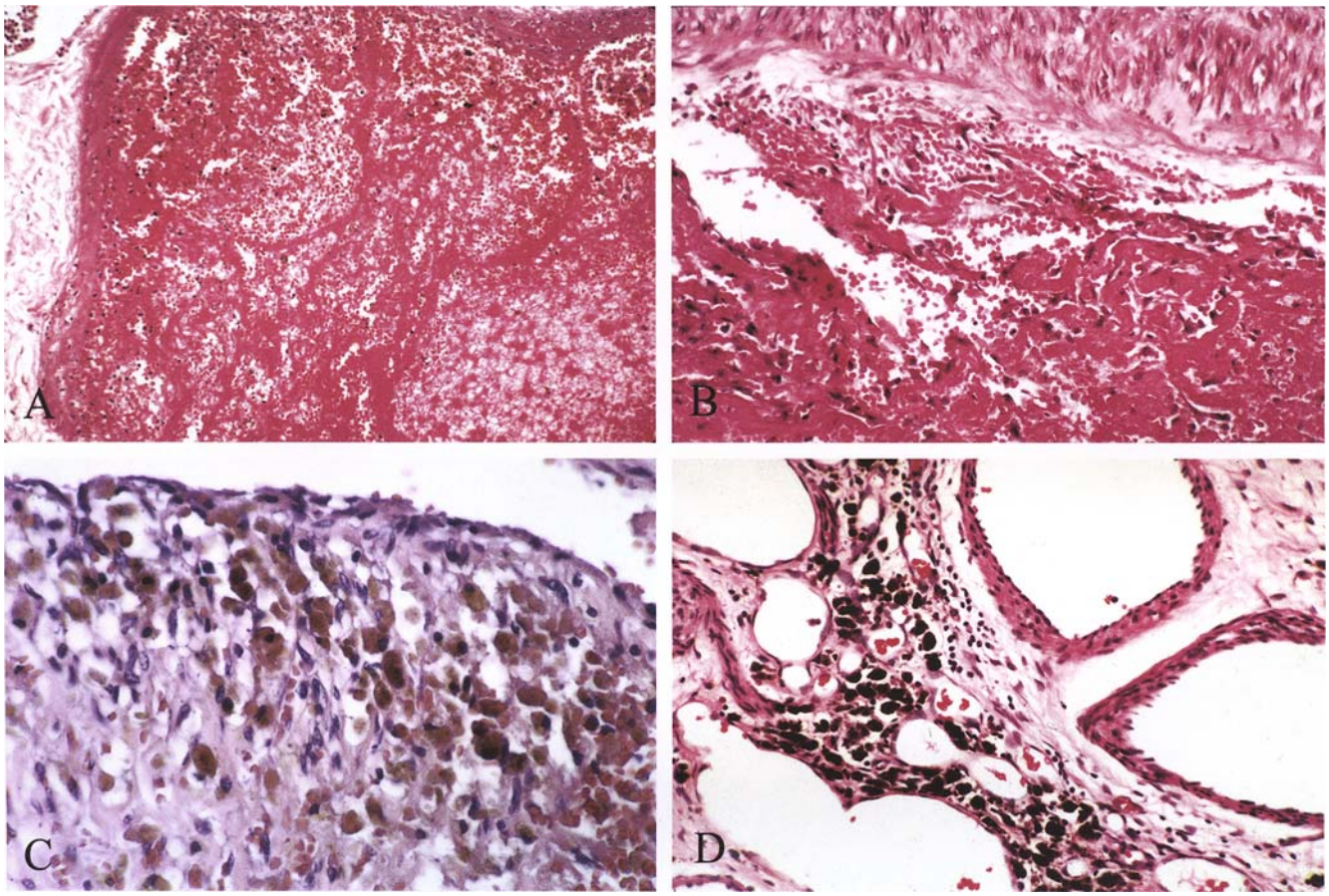


FIGURE 28.24. Organization of thromboembolus (see Table 28.7). **A.** Phase I. Laminar appearance of layered fibrin and erythrocytes. **B.** Phase II/III. Adherence of embolus with early fibroblast ingrowth and endothelial sprouts. **C.** Phase IV. Numerous hemosiderophages, abundant capillaries, and early collagenization. An endothelial layer (upper part) completely covers the organizing thromboembolus. Lumen is at top. **D.** Phase V/VI. Internal structure of completely organized, recanalized pulmonary embolus. Neo-vessels within the thromboembolus have muscularized walls. Hemosiderin is present in a dense fibrous stroma.

the earliest histologic transformations in an acute thromboembolus, occurring soon after it is formed, is pyknosis and karyorrhexis of leukocytes, with dispersed nuclear debris. Elongation of monocyte nuclei and amalgamation of erythrocytes (hyalinization) are also early events that provide a clue to the antemortem nature of the clot (Table 28.7).

Organization of Emboli

In those situations that are not immediately fatal, acute emboli may be dissolved by thrombolytic action, allowing restoration of blood flow. If thrombolysis is incomplete, the process of organization begins within about 1 to 3 days.[172] The early phases of organization involve migration of fibroblasts, myofibroblasts, and primitive mesenchymal cells from the blood vessel subintimal layer into the clot (Fig. 28.24B). Concomitantly endothelial cells migrate into and over the surface of the clot. In larger pulmonary arteries, hemosiderin-laden macrophages and primitive capillaries are part of an exuberant granulation tissue reaction that extends into the embolus (Fig. 28.24C) and gradually converts it into a fibrous lesion that may be eccentric, or bridge the lumen as an intravascular web (see Fig. 28.36B, below).[173] Fine luminal fibrous bands encountered in the lobar and proximal segmental arteries are the organized residua of prior thromboemboli (see Fig. 28.11; also see Fig. 31.15B in Chapter 31).[120,173] Within large recanalized emboli, internal neovessels may incorporate smooth muscle and elastic tissue in their walls[174] (Table 28.7) (Fig. 28.24D). The sources of blood flow through these recanalized vessels may be through the pulmonary artery or via the bronchial arteries (bronchopulmonary anastomoses).[170] Other histologic features of organized thromboemboli include myxoid change and dystrophic calcification (Figs. 28.25 and 28.26).

TABLE 28.7. Organization of thromboemboli: temporal phases

Phase	Duration*	Histologic Features
I	1–3 days	No reaction between thrombus and endothelium
II	3–8 days	Central hyalinization of erythrocytes Pyknosis of leukocytes Elongation of mononuclear cells Endothelial sprouts Surface endothelial proliferation
III	4–20 days	Capillaries, fibroblasts Hemosiderophages Further hyalinization Mononuclear swelling Karyorrhexis of leukocyte nuclei
IV	8 days–2 months	Reticulin and collagen fibers Numerous capillaries Marginal endothelial-lined sinuses Hyalinization persists
V	2–8 months	Reticulin, collagen, and elastic fibers Elastic fibers around internal vessels Cholesterol clefts Sparse remnants of thrombus Blood in internal vascular lumina
VI	6–12 months	Thrombus more homogeneous Recanalization by large vessels complete Dense connective tissue

*Approximate, based on Irniger,[174] for thrombi in systemic arteries. Time sequence may be more rapid for pulmonary arteries.

The organization of intravascular thrombi or emboli has been divided into six overlapping histologic phases by Irniger[172,174] (Table 28.7; Fig. 28.24). The timetable governing these phases of organization likely varies with the type and size of the involved vessel. In attempting to date the onset of a pulmonary thromboembolus, one must be cognizant that some degree of organization may have occurred at the systemic site of origin (see Chapter 31).

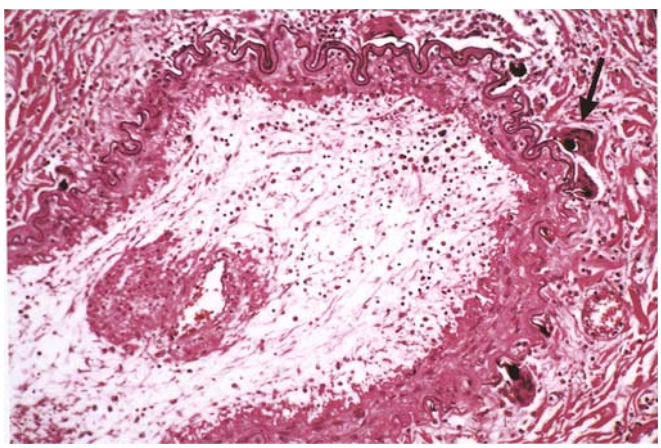


FIGURE 28.25. Organized pulmonary thromboembolus, myxoid change. A foreign-body giant cell reaction to the calcified elastica externa (arrow) is an unusual feature.

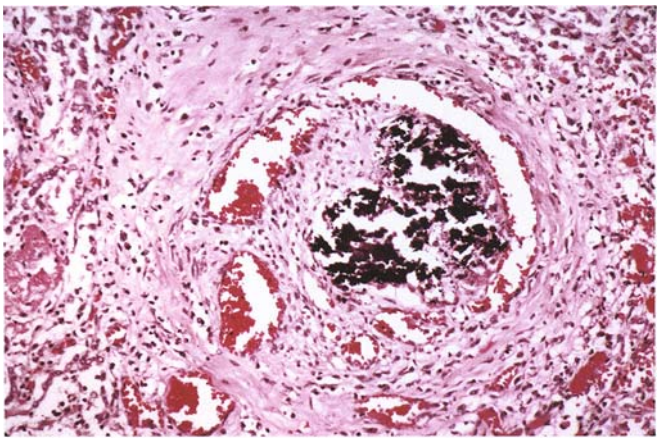


FIGURE 28.26. Organized, recanalized thromboembolus with dystrophic calcification.

Subsequent propagation of more recent thrombus may also occur within the pulmonary artery. In general, dating is considered to be approximate at best, and often unreliable.[172]

Pulmonary Infarction

By definition, pulmonary infarction implies ischemic necrosis of lung tissue. As demonstrated in the 1940s by Castleman,[175] and confirmed in subsequent studies, pulmonary infarction is a relatively infrequent event following pulmonary embolism. In a large autopsy series, Havig[161] found lung infarcts in 20% of cases as opposed to pulmonary emboli in 69%. The rich collateral blood supply to the lung through bronchial arteries, the pulmonary capillary bed, and possibly via retrograde flow in the pulmonary veins sustains the viability of lung tissue distal to pulmonary arterial occlusion.[176] Infarction tends to occur with peripherally situated emboli, and in patients with underlying heart failure, lung cancer, or emboli to more than one lobe.[177,178]

The earliest stage in the development of lung infarction, sometimes called the stage of preinfarction or incipient infarction, is histologically represented by capillary congestion and acute alveolar hemorrhage and edema, without lung necrosis.[178,179] The source of alveolar hemorrhage is probably derived from bronchial arteries via precapillary anastomoses.[176] If adequate collateral circulation commences, edema and hemorrhage may clear, and lung viability and architecture are preserved, thus accounting for the transient nature of alveolar infiltrates seen radiographically. As necrosis develops, alveolar septal nuclei disappear and a variable degree of acute inflammation occurs. The gross appearance of a recent lung infarct is that of a pleural-based hemorrhagic zone of parenchymal induration, the proximal portion of which forms a convex

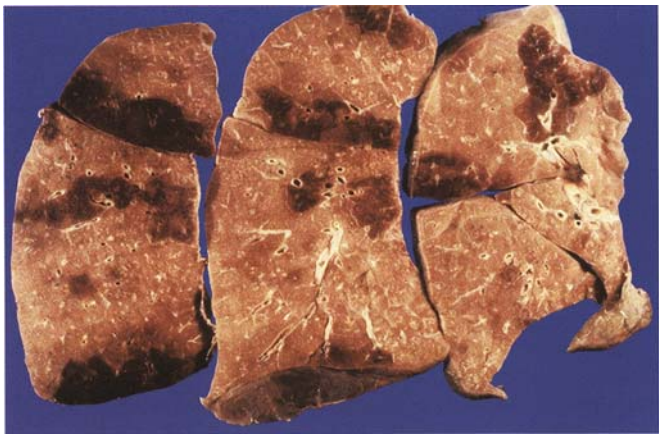


FIGURE 28.27. Multiple recent lung infarcts affecting upper and lower lobes of right lung.

hump directed toward the hilum (Fig. 28.27).[179] An occluded vessel is often seen proximal, but not necessarily adjacent, to the infarct (Fig. 28.28A).

Organization of an infarct proceeds centripetally from the periphery as granulation tissue and hemosiderin-laden macrophages extend from adjacent viable parenchyma to replace necrotic lung (Fig. 28.28B). Squamous metaplasia and endarteritis obliterans are frequent histologic findings in the region of an organizing infarct. Elastic stains are helpful in discerning the remnant elastic framework of lung parenchyma in the necrotic center of the infarct. Macroscopically organizing infarcts are yellow-tan and firm (Fig. 28.28A). Cavitation of infarcts is unusual and typically associated with superimposed pneumonia or abscess formation (infected infarct), or a result of septic emboli (Fig. 28.29).[180] Septic emboli typically arise

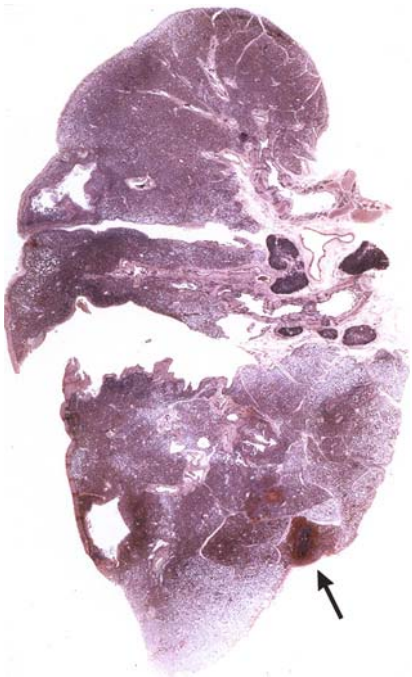


FIGURE 28.29. Septic emboli with peripheral cavitated infarcts in a child with hydrocephalus and infected ventriculoatrial shunt. An infected lobular infarct (arrow) has not yet cavitated. (Right lung whole mount, H&E.)

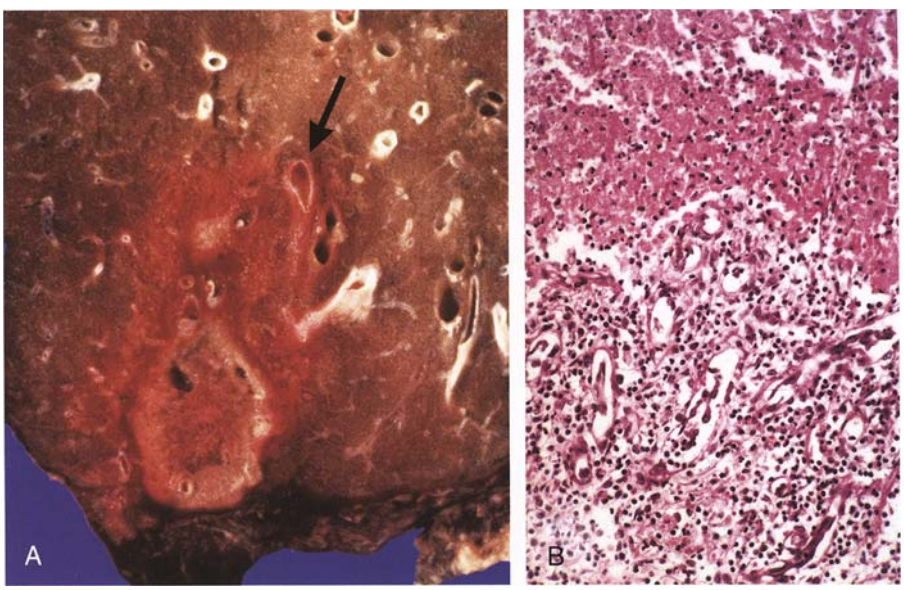


FIGURE 28.28. Organizing lung infarct. **A.** Note tan center of necrotic lung and peripheral hemorrhagic rim of granulation tissue. Thromboembolus (arrow) is seen proximally. **B.** Microscopic features of necrotic lung (top) and cellular granulation tissue (bottom).

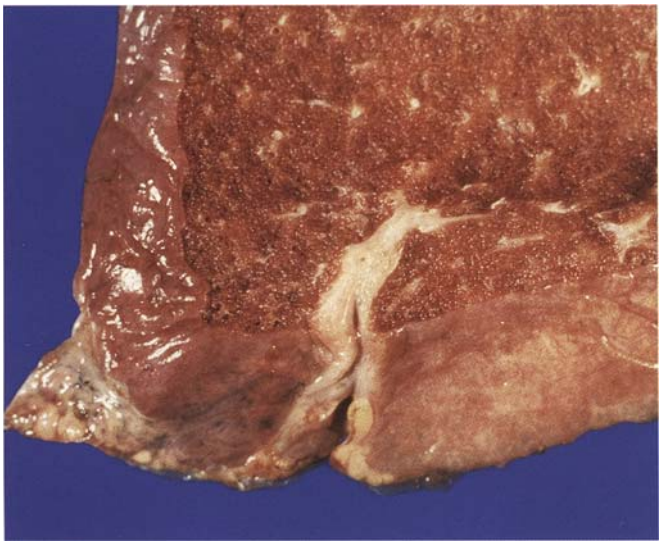


FIGURE 28.30. Completely organized lung infarct has formed a vertical scar. There is deep retraction of visceral pleura (pseudo-fissure).

from infective thrombophlebitis, indwelling vascular catheters, or right-sided valvular endocarditis. On chest x-ray or CT scan, septic emboli appear as multiple peripheral lung nodules that progress to cavitation.[181,182] Rare instances of cavitation of noninfected infarcts have also been reported.[180,183] Infarcts resulting from peripheral emboli may have a more rounded or lobular contour and radiographically simulate a neoplasm, sometimes prompting surgical resection.[184] Organizing fibrinous pleuritis is usually seen in the visceral pleura overlying an infarct.

Completely organized infarcts take the form of peripheral subpleural scars often associated with overlying pleural fibrosis and adhesions. At times the scar may be slit-like, with a deep pleural retraction producing a pseudo-fissure (Fig. 28.30). Elastic stains of organized lung infarcts show collapsed, entangled elastic fibers within a collagenous stroma (Fig. 28.31).[175]

Chronic Thromboembolic Pulmonary Hypertension

Organized thromboemboli in the major or peripheral pulmonary arteries may be an occult cause of pulmonary hypertension and respiratory failure.[185–189] Symptomatic chronic thromboembolic pulmonary hypertension affects approximately 3.8% of patients within 2 years following an episode of pulmonary embolism.[190] In some cases massive thrombotic occlusion and dilatation of the pulmonary artery suggests primary thrombosis as the underlying etiology, rather than organization of an embolus (Fig. 28.32).[191,192] However, unless an underlying defect of the artery exists, it is more likely that even massive clots were initiated by emboli.[170]

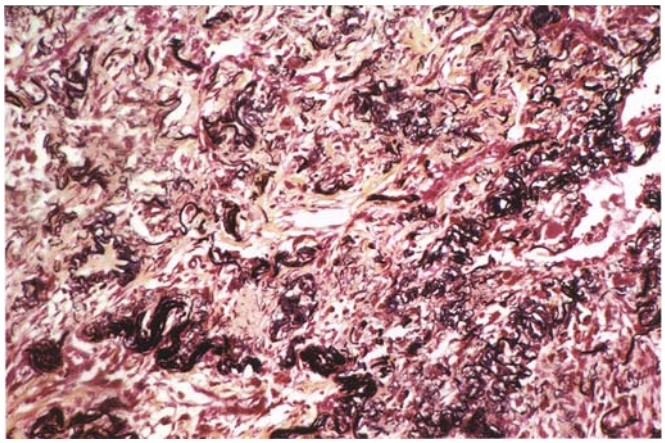


FIGURE 28.31. Histologic pattern of organized lung infarct includes entangled, thick elastic fibers in a collagenous background. (Elastic van Gieson.)

When significant central arterial occlusion occurs, the bronchial and intercostal collateral arteries greatly enlarge to supply the lung. Pulmonary artery endarterectomy may successfully remove fibrous tissue from within the central pulmonary artery, thereby restoring

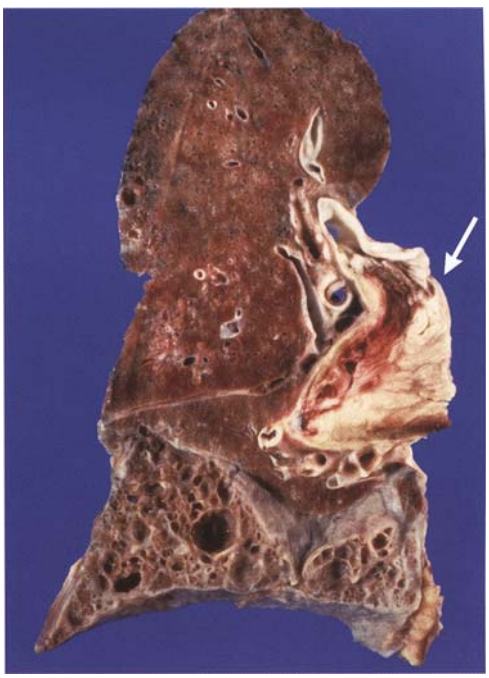


FIGURE 28.32. Massive thrombosis of central pulmonary artery (arrow) in patient with honeycomb lung. Pulmonary artery is greatly dilated. Layered thrombus resembles that seen in abdominal aortic aneurysms.

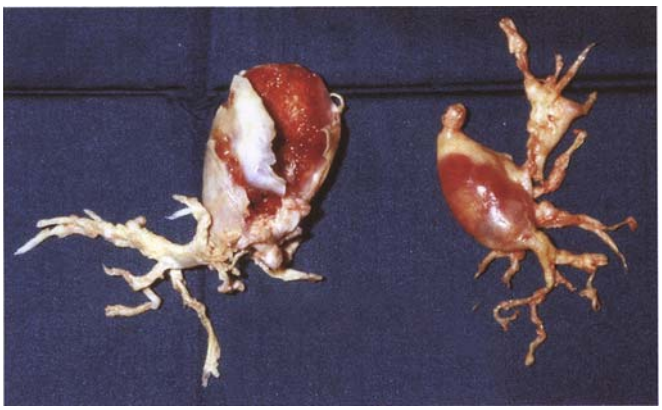


FIGURE 28.33. Pulmonary thromboendarterectomy specimen. Gray fibrotic organized thromboembolus is juxtaposed to more recent red thrombus, forming a cast of the pulmonary artery in a patient with chronic thromboembolic pulmonary hypertension. (Courtesy of E. Mayer, MD. From Mayer E, Klepetko W. Techniques and outcomes of pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc 2006;3:589–593, with permission.)

circulation and alleviating symptoms (Fig. 28.33).[186,193–195] Patients with massive unilateral thrombotic occlusion of the pulmonary artery tend to do more poorly after thromboendarterectomy than patients with bilateral occlusion.[196] The development of postobstructive small vessel occlusive vasculopathy in the ipsilateral lung has been proposed by Hirsch and colleagues[196] to account for this tendency.

Upon review of a large series of endarterectomy specimens, Blauwet et al.[197] noted that thromboendarterectomy was usually bilateral, with a larger amount of tissue removed from the right pulmonary artery. Most patients did not have identifiable coagulation disorders or autoimmune diseases. The histologic features of the extracted organized thromboemboli included collagen (100% of cases), elastin (67%), hemosiderin (56%), inflammation (53%), atherosclerosis (32%), and calcification (15%).[197] These authors encountered three cases in which primary pulmonary artery sarcomas presented clinically as chronic thromboembolic obstruction of the pulmonary arteries. Sclerosing mediastinitis with compression of central pulmonary arteries, and congenital unilateral absence of the pulmonary artery are two other important entities that may clinically simulate chronic thromboembolic occlusion of major pulmonary arteries.[16,198,199]

A study of the peripheral small pulmonary arteries of patients undergoing or following thromboendarterectomy for major vessel thromboembolic pulmonary hypertension disclosed a variety of lesions including concentric and eccentric intimal fibrosis, recanalized thrombi, and plexiform lesions.[200] Importantly, the presence of plexiform lesions was not pathognomonic for primary pulmonary hypertension nor did it exclude a diagnosis of chronic thromboembolic pulmonary hypertension.[200]

The organization of pulmonary emboli in small elastic and muscular pulmonary arteries recapitulates the pattern seen in the central arteries, that is, eccentric intimal fibrous lesions or recanalized "web lesions" (Fig. 28.34).[170] In microembolic pulmonary hypertension, showers of emboli occlude the peripheral vascular bed resulting in the insidious onset of dyspnea, pulmonary hypertension, and cor pulmonale.[187,201] As Wagenvoort[169,170] astutely points out, the presence of a central thromboembolus associated with numerous distal microemboli is suggestive of fragmentation and dispersal of an upstream pulmonary embolus.

The typical morphology of organized thromboemboli enables the recognition and distinction from plexiform

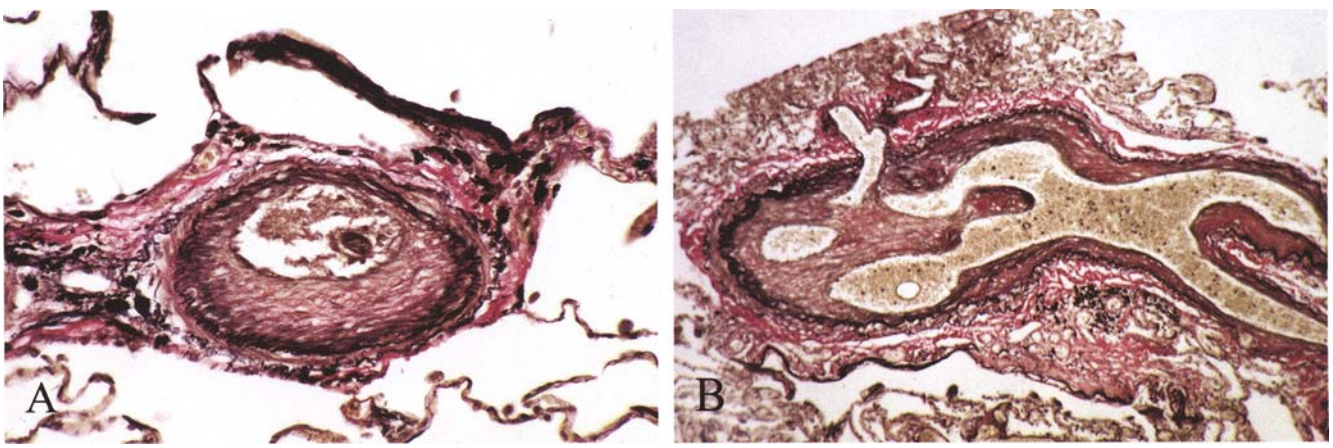


FIGURE 28.34. Organized lesions of microembolic pulmonary hypertension. **A.** Eccentric intimal fibrosis. **B.** Recanalized "web lesion." (Elastic van Gieson.)

lesions (see Figs. 28.17 and 28.18). Some cases of unexplained pulmonary hypertension may have a mixture of thromboembolic and plexogenic features. These cases likely derive from primary thrombosis rather than microembolization.

Treatment and Prognosis

The mainstay of prophylactic treatment for pulmonary embolism is anticoagulant therapy. In cases of failure of anticoagulant therapy or of multiple recurrent emboli, placement of an inferior vena caval filter device may be considered. Acute treatment of a recent embolus may include thrombolytic therapy or infrequently, embolectomy. Relatively few patients (approximately 2.5%) with clinically diagnosed and properly treated pulmonary emboli die acutely of pulmonary embolism.[202] Death within 1 year of a documented embolic event is usually due to another underlying disease like heart failure, cancer, or chronic lung diseases.[202] Paraskos et al.[203] also determined that the long-term survival of patients who survive acute embolism is dependent on the absence of prior heart disease.

In patients with symptomatic chronic thromboembolic occlusion of major pulmonary arteries, pulmonary thromboendarterectomy may be performed and ameliorate pulmonary hypertension.[186] Thrombi that originate distal to the proximal segmental arteries, however, are not amenable to endarterectomy.[186] Mortality rates for this procedure range from 5% to 24%. Reperfusion injury is a frequent complication (see Chapter 23). Patients with persistent pulmonary hypertension due to small vessel microembolization may be candidates for lung transplant.

Sickle Cell Disease

Pulmonary thromboembolism is important in the pathogenesis of lung injury in sickle cell disease (SCD). This autosomal recessive hereditary hemoglobinopathy is caused by a point mutation at the sixth position of the β-globin chain in which valine is substituted for glutamic acid.[204] Approximately 8% of African Americans are heterozygous for the sickle mutation, while 0.15% are homozygous.[205] Pulmonary complications of SCD are a major cause of morbidity and are responsible for an estimated 21% to 85% of deaths.[205] Historically, lung involvement in SCD has been differentiated into (1) acute chest syndrome, and (2) chronic lung disease.[205,206] Patients with SCD are also at increased risk for pneumonia, especially pneumococcal pneumonia, as a result of splenic infarction and autosplenectomy.[207–209] Patients who are heterozygous for the sickle cell mutation (i.e., sickle cell trait) may also be at increased risk for pulmonary complications, but at a much lower level.[210] Most reports of symptomatic lung involvement in sickle cell trait are anecdotal.[211]

Clinical Features

The diagnostic clinical features of the acute chest syndrome are those of a newly acquired radiographic pulmonary infiltrate associated with fever, cough, chest or bone pain, and hypoxemia.[204–206,212] The pathophysiology of acute chest syndrome is complex and incompletely understood. Contributing factors likely include microvascular stasis and thrombosis by rigid, deformed, polymerized erythrocytes, lung infarction, pneumonia, and thrombotic bone marrow or fat emboli.[204,206,213,214] In some cases the acute chest syndrome may progress to pulmonary edema resembling acute respiratory distress syndrome.[215]

Patients with chronic sickle cell lung disease complain of disabling dyspnea associated with severe hypoxemia, restrictive changes, and reduced carbon monoxide diffusing capacity (DL_{CO}) on lung function tests, and pulmonary hypertension with cor pulmonale.[216,217] Recurrent episodes of acute chest syndrome increase the risk for developing chronic lung disease.[216] Pulmonary hypertension occurs in up to 40% of patients with SCD and is an important risk factor for death, including sudden death.[218,219] The pathophysiology of chronic sickle cell lung disease and its relationship to acute lung injury is depicted in Figure 28.35.[206]

Pathology

The pathologic features of sickle cell lung disease are dominated by thrombotic angiopathy including organizing and recanalized thromboemboli, web lesions, and eccentric intimal fibrosis in elastic and muscular arteries (Fig. 28.36).[219–222] Thromboemboli in the central pulmonary arteries may be amenable to pulmonary thromboendarterectomy (see also Pulmonary Thromboembolism, above).[223] In some patients with pulmonary hypertension, vascular remodeling may also resemble that seen in primary pulmonary hypertension—concentric intimal fibrosis and plexiform lesions,[221,224,225] which have been reported in 60% of autopsied SCD patients.[224] As early as 1936, Yater and Hansmann[226] illustrated cellular intimal thickening of pulmonary arterioles in patients with SCD.

Sickled erythrocytes may focally distend alveolar capillaries, often in association with lobular foci of alveolar septal necrosis, edema, and hemorrhage (Fig. 28.36A).[222] Less frequently, more traditional pleural-based infarcts may be identified.[222] Other vascular lesions include fat emboli and bone marrow emboli, some of which may appear necrotic.[222,227,228] Fat embolism following bone

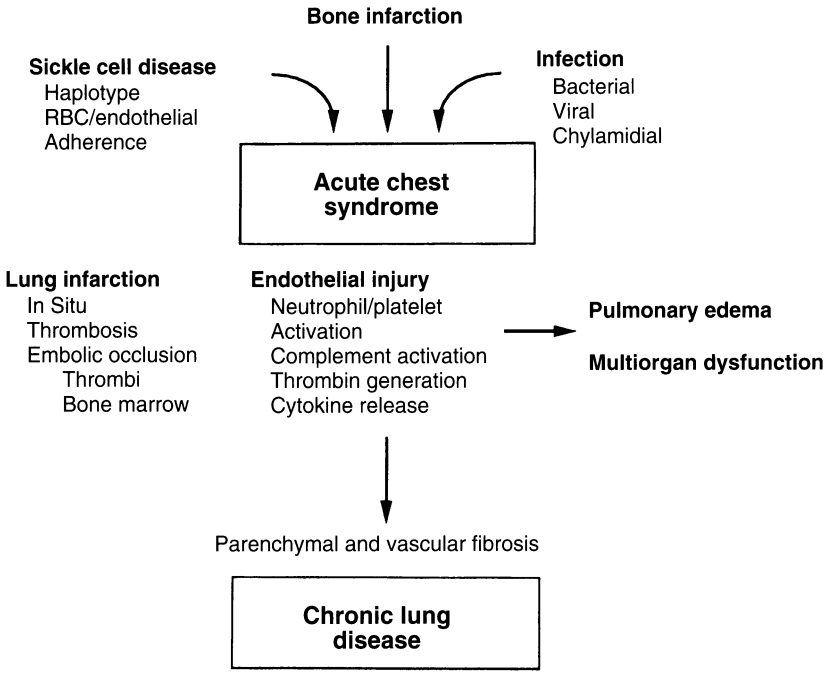


FIGURE 28.35. Pathogenesis and interrelationship of acute chest syndrome and chronic sickle cell lung disease. (From Weil et al.,[206] with permission. Official Journal of the American Thoracic Society. Copyright © 1993, American Lung Association.)

marrow infarction has been implicated as an important cause of acute chest syndrome and sudden death.[213,214,229] As in other forms of thrombotic pulmonary hypertension, bronchopulmonary anastomoses can be demonstrated between recanalized pulmonary arterial lumina and adjacent bronchial arteries.[230] In chronic sickle cell lung disease, the parenchyma is remodeled by patchy interstitial fibrosis (often in a perivascular distribution), healed infarcts, and hemosiderosis (Fig. 28.37).[221]

Vaso-occlusion in sickle cell disease is initiated by abnormal adherence of polymerized erythrocytes to endothelial cells (Fig. 28.36A), followed by propagation of the sickle cell thrombus.[231] Mediators that promote the expression of endothelial adhesion receptors include hypoxia, thrombin, tumor necrosis factor, platelet activating factor, and interleukin-1 (IL-1). Heightened production of endothelin-1, a potent vasoconstrictor, may also contribute to the acute chest syndrome.[232]

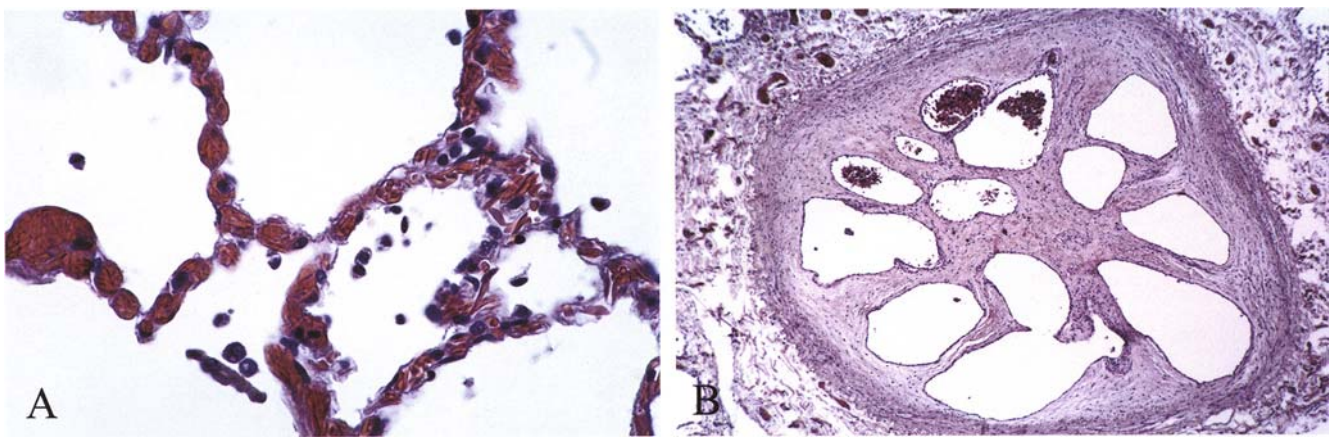


FIGURE 28.36. Sickle cell lung disease. **A.** Sickle cell thrombi in alveolar capillaries. **B.** Impressive web lesion, sometimes referred to as colander lesion, in large muscular pulmonary artery.

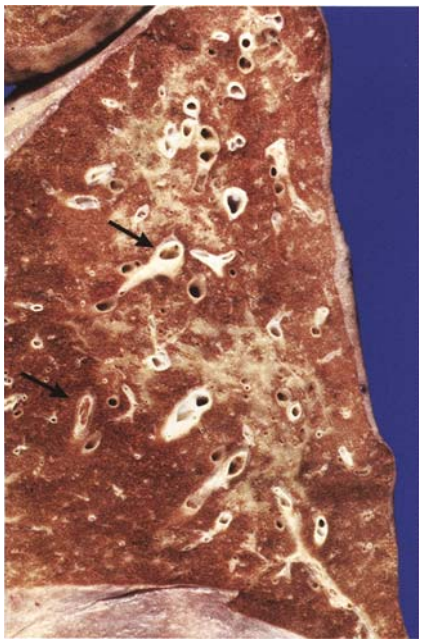


FIGURE 28.37. Chronic sickle cell lung disease. Lower lobe with interstitial fibrosis in a vaguely perivascular distribution. Prominent subsegmental arteries are sclerotic and contain organized thromboemboli (arrows).

Nonthrombotic Emboli

A variety of nonthrombotic emboli may be encountered in the pulmonary circuit.[233] Various tissues, often disrupted as a result of trauma, gain systemic venous access and embolize to the lung (see Chapter 31). Some, like bone marrow emboli, are essentially clinically innocuous incidental findings, whereas others (such as amniotic fluid emboli or fat emboli) may cause severe pathophysiologic disturbances.

Certain diseases, notably malignant neoplasms or some parasitic infections, are a source of nonthrombotic emboli. Inorganic substances accidentally or purposefully introduced into the systemic veins (e.g., air, pharmaceutical tablet filler materials, medical devices) can embolize to the lungs. Table 28.8 lists the major categories of nonthrombotic emboli and cites the chapters in which the various entities are primarily discussed.

Bone Marrow Emboli

Pulmonary bone marrow emboli are a frequent incidental histologic finding, reported in 16% of cases in one autopsy series.[234,235] Only rarely have pulmonary bone marrow emboli been implicated as a cause of respiratory impairment.[236,237] In some cases of sickle cell disease, following bone infarction, large emboli of necrotic bone marrow along with lipid droplets may embolize to the lung (see Sickle Cell Disease, above). Typically, incidental bone marrow emboli result from traumatic injury or iatrogenic manipulation or compression of bone as in closed-chest cardiac massage or the cutting of ribs at thoracotomy.[238] Following cardiac massage, bone marrow emboli may be documented even in the absence of rib fractures.[239] Other less common causes of bone marrow emboli include osseous metastases of neoplasms, epileptic seizures, or eclampsia.

Histologically adipose tissue and hematopoietic cells can be identified (see Fig. 31.20 in Chapter 31). Rarely, as in a case of multiple myeloma, abnormal hematologic cells may be discerned within the embolus.[237] Small particles of bone tissue may also be included. When there has been more extensive osseous trauma, fat emboli may also be documented with oil red O stain (see Fig. 31.17 in Chapter 31).[214] Bone marrow emboli are to be distinguished from bone particle emboli following bone marrow transplantation.[240]

Megakaryocytes

Megakaryocytes may occasionally be identified among the hematopoietic elements of bone marrow emboli (see above). However, as discussed in Chapter 44, there is a continuous circulation of megakaryocytes from the bone marrow through the lung, where megakaryocytes may frequently be seen in pulmonary capillaries, usually as an incidental histologic finding (Fig. 28.38).[241] In situations of acute lung injury or disseminated intravascular coagulation (DIC) intrapulmonary megakaryocytes may be greatly increased. In the exudative phase of diffuse alveolar damage, the number of megakaryocytes correlates

TABLE 28.8. Nonthrombotic pulmonary emboli

1. Tissue
   a. Bone, bone marrow (Chapter 31)
   b. Megakaryocytes (Chapter 44)
   c. Brain, adipose or other tissue (Chapter 31)
2. Tumor (Chapter 44)
3. Fat droplets (Chapter 31)
4. Amniotic fluid (Chapter 31)
   a. Decidua/trophoblast
5. Foreign body
   a. Tablet fillers (Chapter 26)
   b. Thrombogenic particles*
   c. Large foreign bodies
   d. Miscellaneous substances
6. Air (gas) (Chapter 31)
7. Parasites (Chapter 14)

Note: Chapters cited in parentheses are the source of the main discussion in the text. All other entities are primarily discussed in this chapter.
*Used for therapeutic embolization.

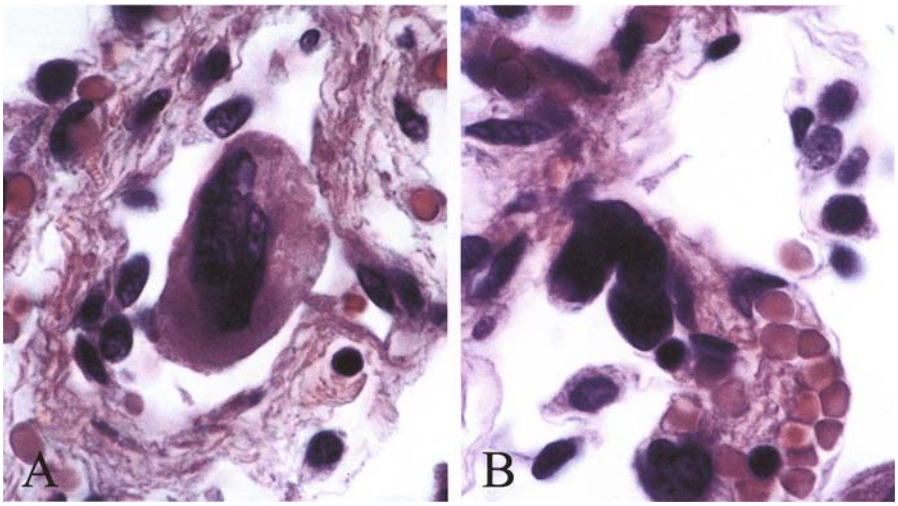


FIGURE 28.38. Pulmonary megakaryocytes. **A.** Intact megakaryocyte within a pulmonary arteriole. **B.** More typical appearance of lobulated megakaryocyte nucleus impacted and distorted in an alveolar capillary.

with the number of platelet fibrin thrombi.[242] Histologically megakaryocytes typically appear as deformed, large, lobulated, basophilic nuclei, with little apparent cytoplasm, tightly enclosed within a pulmonary capillary (Fig. 28.38B).

Other Tissue Emboli

A variety of other tissues such as brain, liver, adipose tissue, skeletal muscle, and even myocardium may embolize to the lung, usually as a result of extensive soft tissue trauma.[243–248] Adipose tissue emboli are to be distinguished from fat globule emboli, although both types of emboli may be seen in cases of extensive trauma. Brain tissue emboli (see Fig. 31.21 in Chapter 31) as a result of head trauma should not be confused with embolic or heterotopic brain tissue within the lungs in infants with neurologic malformations such as anencephaly or myelomeningocele, although the source of heterotopic brain tissue in those settings in fact may be embolization occurring in utero or at the time of delivery. Incidental skin emboli, including hair shafts, may result from skin lacerations, repeated venipunctures, or fractures.[249]

Tumor Emboli

Tumor embolization, as extensively reviewed in Chapter 44, is an important mode of spread of malignant neoplasms to and within the lungs.[250,251] Within the pulmonary vasculature neoplastic emboli incite and are intimately associated with organizing thrombosis and fibrocellular intimal proliferation.[252,253] In some cases thromboembolic and fibroproliferative pulmonary hypertensive changes greatly exceed identifiable tumor emboli, suggesting that tumor cells incite and are then destroyed by the thrombotic process.[254,255] More recently this phenomenon has been termed pulmonary tumor thrombotic microangiopathy.[253,256,257] Obliteration of the microvasculature can result in the insidious onset of dyspnea, pulmonary hypertension, and right ventricular failure (subacute cor pulmonale).[258,259]

The lung at autopsy may simply appear congested, providing little if any macroscopic evidence of massive tumor microembolization. In other cases, tumor emboli may be associated with prominent accentuation of interlobular septa reflecting the development of lymphangitis carcinomatosa.[258] Macroscopic tumor emboli within main or lobar pulmonary arteries are associated most frequently with choriocarcinoma or bulky tumors such as sarcomas, hepatocellular carcinomas, or renal cell carcinomas, which invade the inferior vena cava or its main tributaries.[260] Right-sided cardiac myxoma is an important benign tumor that has been reported to embolize to the lung.[261] The reader is referred to Chapter 44 for a detailed discussion and illustrations of pulmonary tumor emboli.

Fat Emboli

Release of fat globules into the systemic venous circuit and ultimately the lungs is an important complication of bone and soft tissue trauma or following bone infarction in sickle cell crisis (see above).[262–264] Intravascular fat globules are best recognized by oil red O or other lipid stains of frozen lung tissue (see Figs. 31.16 and 31.17 in Chapter 31). In routinely prepared hematoxylin and eosin (H&E) slides, lipid is dissolved by solvents and the pulmonary capillary bed appears greatly distended by

empty vacuoles. In precapillary vessels clear lipid vacuoles displace erythrocytes. Fat embolism is primarily discussed in Chapter 31.

Nonthrombotic Emboli Associated with Pregnancy and the Puerperium

Amniotic fluid embolism and the resultant release of thrombogenic material such as amniotic squames, lanugo hairs, and mucinous substance, is an important complication of pregnancy that can result in respiratory failure, DIC, shock, and death.[265,266] The autopsy diagnosis and histologic features of amniotic fluid embolism are covered in detail in Chapter 31.

Trophoblastic emboli to the lungs were first described by Schmorl in 1893 in eclamptic patients.[267] Attwood and Park[267] identified trophoblast emboli in 96 of 220 (44%) autopsies of pregnant or parturient women. The mechanism of trophoblast dispersal appears to be uterine contraction, especially in the setting of eclampsia. Trophoblast emboli usually represent incidental findings that do not evoke arterial thrombosis or pulmonary hypertension. They are most readily identified within the first few days of delivery, and dissipate over time.[267] Rare instances of massive trophoblastic pulmonary embolization have been reported to be a cause of death in patients with trophoblastic proliferations such as hydatidiform mole.[268] Fatal trophoblastic embolism not associated with trophoblastic disease is rare.[269–271] Histologically, cyto- and syncytiotrophoblast cells must be distinguished from those of metastatic choriocarcinoma and from pulmonary megakaryocytes. Compared to megakaryocytes with their large lobulated nuclei, syncytiotrophoblasts contain numerous round to oval nuclei with a coarsely granular chromatin pattern (Figs. 28.38 and 28.39). Immunohistochemical staining for human chorionic gonadotrophin or placental lactogen may also help to identify syncytiotrophoblasts.[271] In the case described by Delmis et al.,[271] numerous trophoblastic cells obliterated the pulmonary microvasculature and were associated with interstitial pneumonitis.

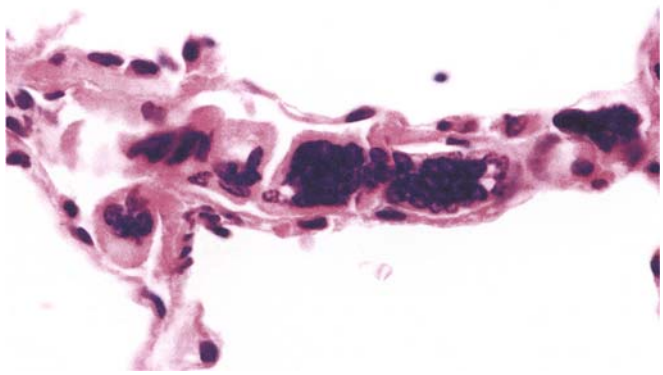


FIGURE 28.39. Multiple syncytiotrophoblasts in pulmonary arteriole. The patient died shortly after childbirth. (Courtesy of Joseph Felo, DO, Cuyahoga County Coroner's Office.)

There have been rare reports of decidua deposited within the lung. The presumed route being decidual embolization.[272] Release of decidua into the maternal circuit has been described in abruptio placentae.[273] However, decidual emboli have not been reported in conjunction with relatively more common trophoblastic emboli.[267] A case of ectopic pulmonary deciduosis has also been hypothesized to represent a variant of stromal endometriosis.[274]

Foreign-Body Emboli

Small foreign-body emboli, including birefringent fiber-like material and cotton fibers, are occasional incidental findings in the lungs of patients with intravascular or intracardiac prosthetic devices, repeated intravenous injections, or chronic indwelling intravenous catheters.[275,276] Clinically significant pulmonary foreign-body emboli, however, are most often seen in the context of illicit intravenous drug administration.[277] The most important source of foreign material in this setting derives from the practice of injecting aqueous suspensions of pharmaceutical tablets.[278] Inert tablet filler components that may be identified in the lungs of IV drug users include talc, cornstarch, microcrystalline cellulose, and crospovidone, among others.[279] See Chapter 26 for a complete discussion and description of embolized tablet filler materials, and Chapter 31 for the pulmonary complications of substance abuse.

There have been several reports of pulmonary birefringent microcrystalline emboli in patients receiving total parenteral nutrition (TPN).[280–282] Calcium phosphate has been implicated as the major component of TPN-associated crystalline emboli. In patients with suspected TPN-associated crystalline emboli, it is important to exclude intravenous injection of pharmaceutical tablet suspensions. Patients with indwelling venous access devices may be at risk for illicit use of psychoactive drugs. Tablet components, especially microcrystalline cellulose and talc, are also birefringent, but can be distinguished from calcium phosphate with appropriate histochemical stains and by elemental analysis.[279]

Xanthoma-like lipid deposits in the pulmonary capillaries and muscular pulmonary arteries have also been reported in a few pediatric patients on long-term intravenous hyperalimentation supplement (Fig. 28.40).[283] Histologically, finely vacuolated histiocytes expand the subintimal zone and constrict the vascular lumen. The lesion is reminiscent of vascular involvement in Gaucher

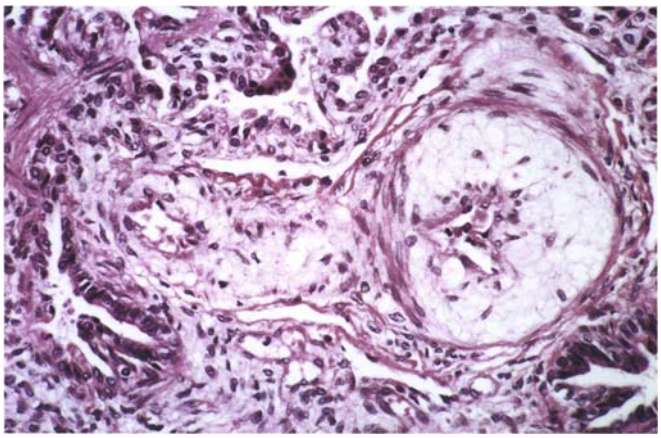


FIGURE 28.40. Intralipid vasculopathy. Subintimal accumulation of finely vacuolated histiocytes seen in a pediatric patient with bronchopulmonary dysplasia receiving intravenous lipid-rich hyperalimentation (Intralipid).

disease, but the two disorders are readily separable by the different clinical scenarios (see Chapter 16). Lipid-rich hyperalimentation fluid may also predispose to pulmonary vasculitis and deep-seated fungal infections due to *Malassezia* species (see Fig. 10.61 in Chapter 10).[284] Cholesterol emboli to the lung microvasculature are another rare form of nonthrombotic pulmonary embolization, reported in association with aortocaval fistulas.[285] In a well-documented case by Sabatine et al.,[285] cholesterol emboli were found in pulmonary and bronchial arteries where they produced marked intimal fibrosis and associated alveolar hemorrhage. Since an autopsy was not performed, the source of cholesterol crystals in that case was not identified.[285,286] Atheromatous lesions of the thoracic aorta may rarely be a source of cholesterol emboli to the bronchial arteries (Fig. 28.41). In this location, cholesterol emboli may be identified in transbronchial biopsy specimens.

Large foreign-body emboli including such items as bullets, hypodermic needles (see Fig. 31.53 in Chapter 31), intravascular catheters, or dislodged vena caval filters, are infrequent occurrences.[287] Numerous other materials such as Teflon, silicone, mercury, barium sulfate (following a barium enema), bile, or even fecal material have rarely gained intravenous access and embolized to the lungs.[233,288–297]

Thrombogenic materials such as Gelfoam or polyvinyl alcohol (Ivalon) used by interventional radiologists to inject bronchial or systemic collateral vessels to control intrapulmonary hemorrhage may sometimes find their way into the small pulmonary arteries (Fig. 28.42A).[154,298] The likely route of access of this material is via precapillary systemic-pulmonary arterial shunts. Within the bronchial or other systemic artery, polyvinyl alcohol induces thrombosis followed by lumen fibrous obliteration (Fig. 28.42B).[299] Arterial mural destruction and vascular remodeling may effectively extrude the foreign material into the perivascular space.[299] The complications of injected metal coils, also used to promote thrombosis, have been previously discussed (see Pulmonary Artery Aneurysm, above, and Chapter 41).

Air Embolism

Air can be introduced into the systemic circulation through traumatic laceration of the large veins of the head and neck, or in the course of a variety of procedures, including transthoracic fine-needle aspiration biopsy (see Chapter 1). Gas bubbles can also form in the vasculature during rapid decompression. In Caisson's disease, small nitrogen bubbles are transmitted into the systemic circulation. Rapid expansion of alveolar gas can also rupture lung capillaries causing injury and gas entry into systemic arteries through the pulmonary veins. The topic of air embolism and the approach to diagnosis at autopsy is discussed in Chapter 31.

Parasites

A variety of parasites may embolize to the lung as adult worms, ova, or larval forms. Among the nematodes, the larvae of ascaris travel as part of their life cycle via systemic veins to the pulmonary capillaries where they may

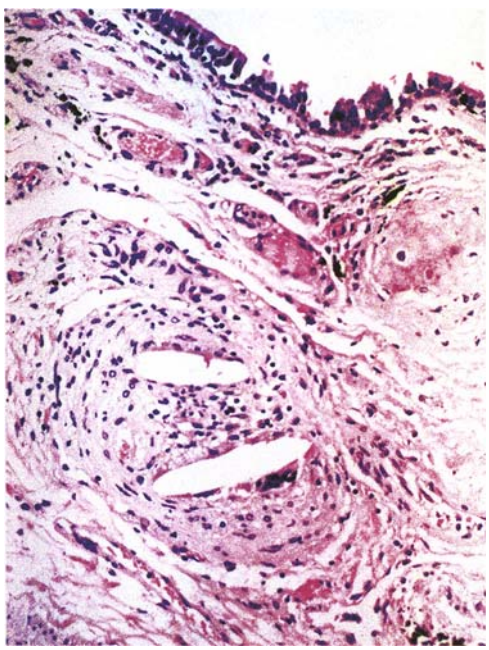


FIGURE 28.41. Cholesterol emboli in bronchial artery of 72-year-old man with thoracic aortic atheromatous lesions. (Courtesy of Dr. Victor Roggli, University of North Carolina.)

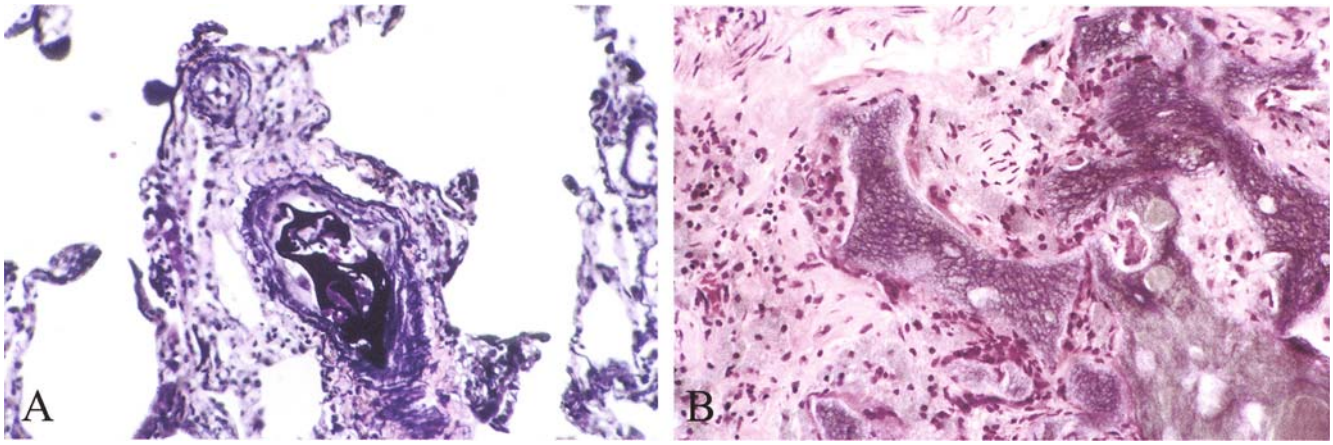


FIGURE 28.42. Interventional systemic/pulmonary artery arterial embolization. **A.** Darkly staining Gelfoam embolus in a small muscular pulmonary artery following injection of systemic pleural collateral arteries. Precapillary systemic-pulmonary arterial shunts allow passage of small particles into the pulmonary circuit. (Movat.) **B.** Ivalon (polyvinyl alcohol) laced with barium sulfate used for bronchial artery embolization to control hemorrhage in a patient with cystic fibrosis. Note foreign body reaction and background endoluminal fibrosis of bronchial artery.

produce Loeffler's syndrome. The dog heartworm *Dirofilaria immitis* is perhaps the most widely recognized nematode larva that can embolize to the lung causing necrotizing granulomatous lesions resembling pulmonary infarcts.[300,301]

Among the trematodes, schistosoma ova may embolize to the lungs, producing a foreign-body granulomatous reaction.[302] In patients with pipestem hepatic fibrosis, pulmonary hypertension may result from massive embolization of ova in conjunction with plexiform lesions. Adult flukes rarely embolize to the pulmonary artery. (For a full account of these and other parasites that embolize to the lung, see Chapter 14 on parasitic lung disease.)

Pulmonary Venous Hypertension

Pulmonary venous hypertension (PVH), also known as postcapillary pulmonary hypertension, is defined by a venous pressure in excess of 12 mm Hg and is the result of obstruction of venous outflow from the lung. Obstruction may be physiologic, the result of decreased cardiac output and increased diastolic pressure due to left ventricular cardiac failure, or have a mechanical basis. The site of obstruction ranges from intrapulmonary, as in pulmonary veno-occlusive disease, to the mitral or aortic valves. A list of causes of PVH is presented in Table 28.9.

Acute PVH frequently presents as high-pressure pulmonary edema. Chronic PVH not only causes pulmonary edema, but also induces venous, arterial, and parenchymal remodeling, which differs morphologically from that caused by precapillary (arterial) hypertension. The morphologic features of chronic PVH are relatively independent of the site of venous obstruction.

TABLE 28.9. Causes of pulmonary venous hypertension with or without pulmonary edema

Acute hydrostatic pulmonary edema
Left ventricular cardiac failure
Fluid overload
Chronic pulmonary venous hypertension (congestive vasculopathy)
Intrapulmonary
Pulmonary veno-occlusive disease
Obstruction of central pulmonary veins
Fibrosing mediastinitis
Left atrial
Cor triatriatum
Atrial myxoma
Mitral valve
Acquired mitral stenosis/insufficiency
Congenital mitral stenosis/atresia
Post–mitral valve
Chronic left ventricular failure
Aortic stenosis/insufficiency

Pulmonary Edema

Pulmonary edema, which is defined as the abnormal accumulation of extravascular water in the lung, can have many causes, the most important of which are (1) increased intracapillary hydrostatic pressure (i.e., high pressure or cardiogenic pulmonary edema), and (2) loss of integrity of the alveolocapillary membrane (i.e., permeability pulmonary edema)[303] (Tables 28.9 and 28.10). High-pressure pulmonary edema is an acute

TABLE 28.10. Causes of pulmonary edema other than pulmonary venous hypertension

Decreased plasma oncotic pressure
Hypoalbuminemia
Fluid overload
Decreased interstitial pressure
Lung reexpansion
Laryngospasm
Hanging
Lymphatic obstruction
Neoplastic
Fibrosing mediastinitis
Permeability pulmonary edema
Acute lung injury (Chapter 4)
Poorly understood mechanisms
Neurogenic pulmonary edema (Chapter 4)
High-altitude pulmonary edema (Chapter 4)
Drug-induced (Chapter 22)
Narcotics abuse (Chapter 31)
Cardiopulmonary bypass
Pulmonary embolism
Lung reperfusion (Chapter 23)

Note: Chapters cited in parentheses are the source of the main discussion in the text. All other entries are primarily discussed in this chapter.

complication of PVH that is most often the result of left ventricular cardiac failure (see below). The prototype of permeability pulmonary edema is the acute respiratory distress syndrome, which is discussed in Chapter 4. Other causes of pulmonary edema for which the pathogenesis is unknown or poorly understood, such as neurogenic pulmonary edema or high altitude pulmonary edema, are also considered in Chapter 4 and listed in Table 28.10.

Pathophysiology

In the normal adult, approximately 10 to 20 mL of extravascular fluid per hour are removed from the lung via lymphatic drainage.[304] Fluid flux within the lung is governed by intravascular and perivascular hydrostatic and oncotic pressures, according to the Starling equation[304] (Table 28.11). A low intracapillary hydrostatic pressure and a high oncotic pressure relative to the perivascular space (i.e., interstitial space) favor retention of fluid within the capillary bed. The opposite conditions promote extravascular leakage of fluid. Fluid from the intravascular compartment exits through relatively leaky interendothelial junctions.[304] Pinocytosis across the endothelial cell plays only a minimal role in fluid transit. Within the alveolar interstitium, fluid tracks to lymphatics that originate in the vicinity of the terminal bronchioles. The capacity of the interstitium is about 500 mL of fluid versus a volume of about 3000 mL in the air-space compartment.[305,306] The lymphatics transport fluid out of the lung to the ductus lymphaticus and then to the systemic veins. Fluid accumulation that exceeds lymphatic removal initially expands the interstitium in which it is retained by the relatively impermeable tight junctions of alveolar epithelial cells. Upon saturation of the interstitial compartment, alveolar flooding commences.[306] Lymphatic obstruction or reduced plasma oncotic pressure may contribute to pulmonary edema but is rarely its sole cause (Table 28.10).

Clinical Features

The most common cause of pulmonary edema (and PVH) is left-sided ventricular failure, irrespective of its underlying etiology (ischemia, myocarditis, cardiomyopathy, hypertension, etc.). Patients with pulmonary edema are typically anxious and exhibit the symptoms of dyspnea, tachypnea, and orthopnea. On lung auscultation, rales may be heard in the lower lung zones. Wheezing occurs secondary to submucosal edema and narrowing of the airways. Arterial blood gases reveal hypoxemia secondary to shunting of blood through flooded alveolar units and, initially, hypocarbia resulting from hyperventilation. Pulmonary capillary wedge pressure and central venous pressure are elevated. The chest x-ray in the early phase may show Kerley B lines, that is, parallel linear strands extending into the lung from the pleura reflecting edematous interlobular septa (Fig. 28.43A). Pulmonary arteries are prominent and accentuated in the upper lung zones (cephalization). Alveolar edema is seen radiographically as lower zone or perihilar ground glass infiltrates.

Pathologic Features

The early phase of interstitial edema is most obviously noted as dilated lymphatics, perivascular clear zones, and widened interlobular septa (Fig. 28.43B,C). In the stage of alveolar flooding, the lungs are of increased weight, deep red, and congested. Frothy fluid exudes from the cut lung surface and bubbles out of the airway lumina. Histologically, capillaries are engorged and distended with erythrocytes. Alveolar spaces are filled to a variable extent by eosinophilic hyalinized or slightly vacuolated proteinaceous fluid (Fig. 28.44). Occasional intraalveolar

TABLE 28.11. Starling equation

$Qf = K\ (Pmv - Ppmv) - K\ \sigma\ (\pi mv - \pi pmv)$
Qf, net filtration of fluid across endothelial membrane
K, filtration coefficient (conductance of fluid across the membrane)
Pmv, intracapillary hydrostatic pressure
$Ppmv$, perivascular hydrostatic pressure
σ, reflection coefficient (permeability of membrane to protein)
πmv, capillary plasma oncotic pressure
πpmv, perivascular fluid oncotic pressure

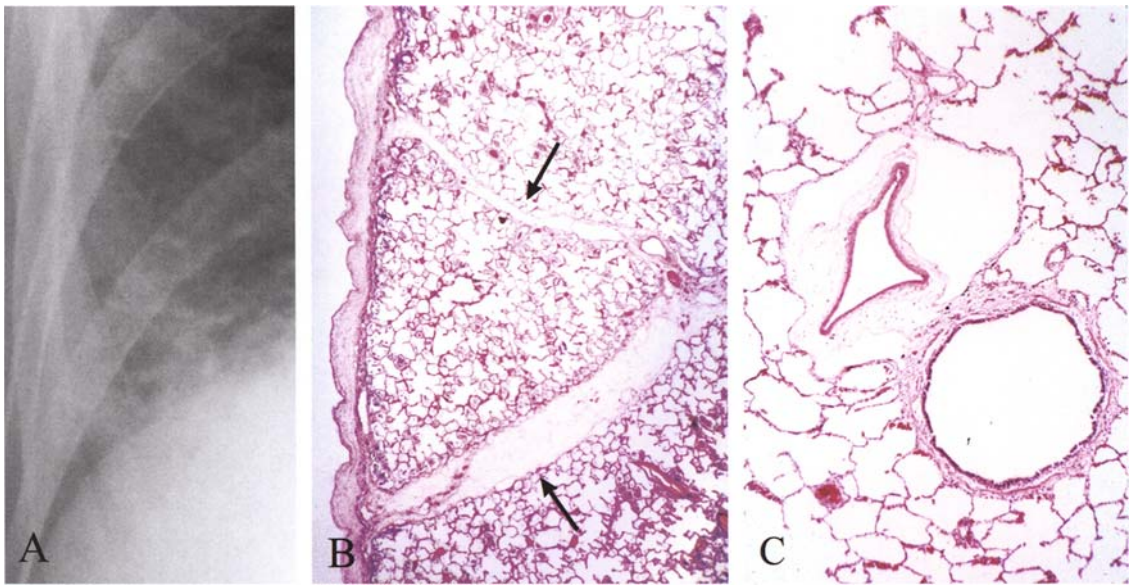


FIGURE 28.43. Pulmonary edema. **A.** Chest x-ray showing Kerley B lines as ill-defined parallel lines extending from the inferolateral pleura. **B.** Edematous expansion of visceral pleura and interlobular septa (arrows) corresponding to Kerley B lines. **C.** Early pulmonary interstitial edema. Perivascular clear zone with dilated lymphatics.

erythrocytes are present, but fibrin tends to be minimal, and hyaline membranes are not present unless acute alveolar injury has also occurred. Often the pulmonary changes are accompanied by transudative serous pleural effusions.

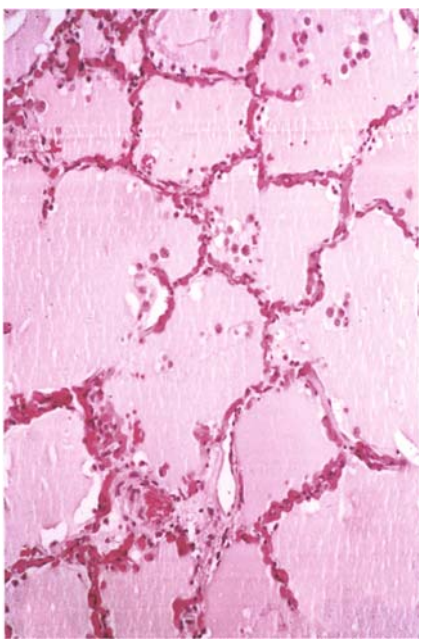


FIGURE 28.44. High-pressure pulmonary edema in patient with left ventricular cardiac failure. The alveolar capillary bed is congested and alveoli are flooded by homogeneous eosinophilic edema.

Chronic Pulmonary Venous Hypertension

With long-standing pulmonary venous hypertension, as is most often seen in chronic left ventricular cardiac failure or valvular heart disease, significant lung parenchymal and vascular remodeling may occur (congestive vasculopathy).[307–309] Virtually any cause of PVH, including extracardiac pulmonary vein obstruction as in fibrosing mediastinitis, may produce similar patterns of lung vascular remodeling.[198,199,310–314] Mitral stenosis is an important cause, and serves as a prototype of chronic PVH.[315,316] Approximately 8.2% of patients with mitral stenosis have extreme (≥80 mm Hg) pulmonary hypertension.[317] A list of causes of chronic PVH is presented in Table 28.9.

Clinical Features

The clinical features of congestive vasculopathy vary according to the underlying cause of PVH. In mitral stenosis the clinical profile includes dyspnea, orthopnea, wheezing, and hemoptysis. Rales and rhonchi may be prominent, but frequently there are no audible findings in the lungs. Chest x-ray findings may include cardiomegaly, pulmonary venous engorgement, and pulmonary edema. Typically pulmonary function tests indicate restriction, with reduced lung volumes and reduced DL_{CO}. Arterial blood gas values often show borderline or low pCO_2 and mild resting hypoxemia.[318,319]

Pathology

The lung parenchyma in congestive vasculopathy appears deep red-brown and is firm to palpation (brown

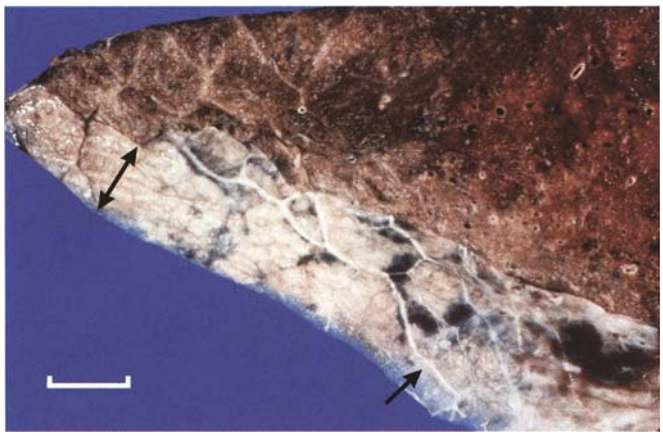


FIGURE 28.45. Chronic pulmonary venous hypertension ("brown induration"). Lung parenchymal surface is deep mahogany brown. Tan subpleural area of fibrosis and fibrotic interlobular septa (left upper corner) are apparent. Fibrotic lymphatic channels (arrow) appear as white linear cords on visceral pleural surface. Double-headed arrow indicates edges of visceral pleura (scale = 2 cm).

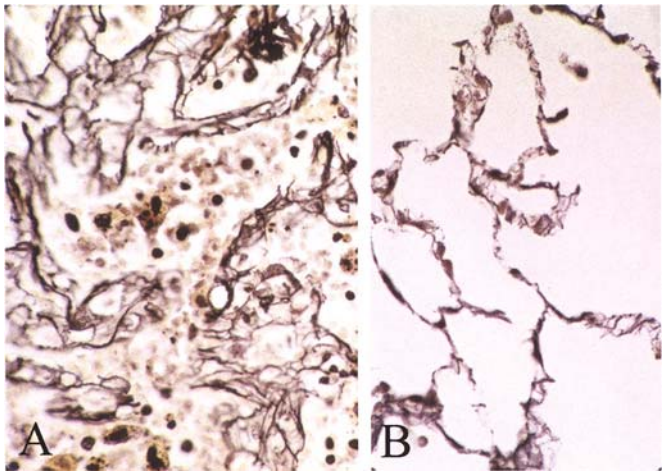


FIGURE 28.46. Chronic pulmonary venous hypertension. **A.** Alveolar changes include increased capillary profiles and reticulin fibers in alveolar septa. Hemosiderophages reside in alveolar spaces. **B.** Normal alveolar parenchyma for comparison. (Reticulin stain, both panels same magnification.)

induration) (Fig. 28.45). Histologically, alveolar and interlobular septa are fibrotic with increased collagen and reticulin fibers (Fig. 28.46).[320] Alveolar capillaries are dilated and congested with accentuated capillary profiles that may be so numerous as to simulate capillary hemangiomatosis (see below).[321,322] Numerous hemosiderin-laden macrophages (heart failure cells) are typically present in alveolar and interstitial compartments (Fig. 28.47).[323–325] On H&E stain, interstitial and perivascular elastic fibers (especially perivenous elastic fibers) may appear gray, refractile, and fragmented as a result of iron and calcium encrustation.[326,327] Parenchymal nodules of ectopic bone are also commonplace (see Figs. 21.26 and 21.27 in Chapter 21).

Pulmonary vein remodeling consists of intimal fibrosis and the development of a well-defined medial smooth muscle coat bounded by an internal and external elastic lamina ("arterialization") (Fig. 28.48).[307,324,328,329] At this

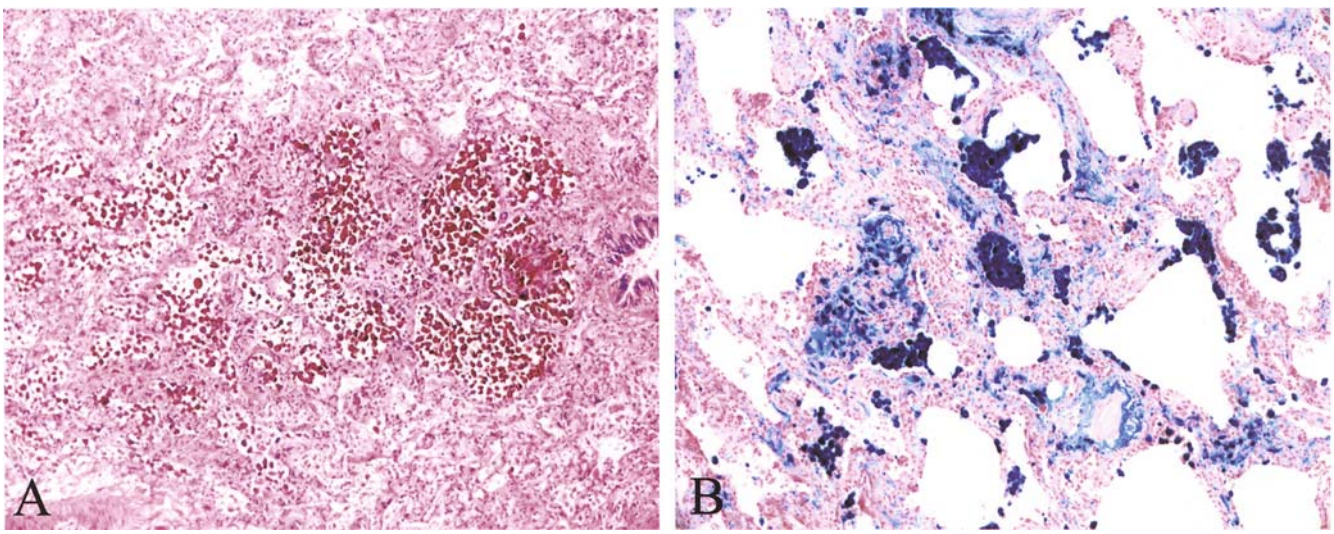


FIGURE 28.47. Chronic pulmonary venous hypertension. **A.** Prominent hemosiderin-laden macrophages are associated with mild septal thickening. **B.** Iron stain highlights prominent hemosiderin within both air-space macrophages and the interstitium.

stage it may be difficult to distinguish arteries from veins other than by location (i.e., veins in the interlobular septa, arteries adjacent to airways). As in acute pulmonary edema, lymphatic channels are dilated, and lymphatic vessels have thick walls.[308,330]

Venous hypertension is transmitted through the capillary bed to the pulmonary arteries, which may also undergo extensive remodeling.[324] Medial hypertrophy with extension of muscle into arterioles (<100 µm diameter) may be prominent. Paradoxically, the degree of medial hypertrophy may be disproportionately severe for the level of pulmonary hypertension and exceed the venous changes, a phenomenon that is not well explained.[307,324] Varying degrees of intimal fibrosis, mainly eccentric fibrosis, but sometimes concentric fibrosis, may involve long stretches of the pulmonary artery (Fig. 28.49). Arterial intimal fibrosis is more common in the upper lobe, whereas medial hypertrophy is generally more severe in the lower lobe. Concentric intimal fibrosis lacks the laminar appearance seen in idiopathic pulmonary hypertension. Adventitial fibrosis also is typically present, but plexiform and dilatation lesions and arterial necrosis are rare or absent.

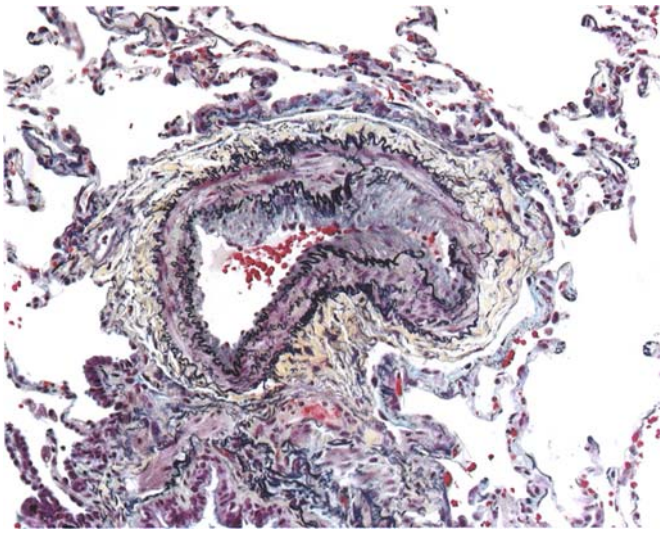


FIGURE 28.49. Pulmonary venous hypertension. In contrast to the concentric intimal hyperplasia associated with primary pulmonary hypertension, the intimal hyperplasia in pulmonary venous hypertension is often eccentric, with proliferation of the intima occurring over only a portion of the vessel wall. Note also medial hypertrophy and adventitial fibrosis in this muscular pulmonary artery. (Movat stain.)

Prognosis and Treatment

Patients with PVH are treated by addressing the underlying etiology. In the most common scenario of left ventricular failure, this is achieved by optimizing the medical management of the underlying congestive heart failure. In cases where surgical intervention is possible, such as valvular disease, there is a rapid fall in pulmonary pressures, despite persistence of the arterial medial hypertrophy and intimal fibrosis. The rapid improvement appears to be the result of elimination of edema from the vessel walls and interstitium. Pulmonary vascular findings may persist even after clinical resolution of the venous hypertension. Rarely, complete regression of the histologic lesions has been observed.

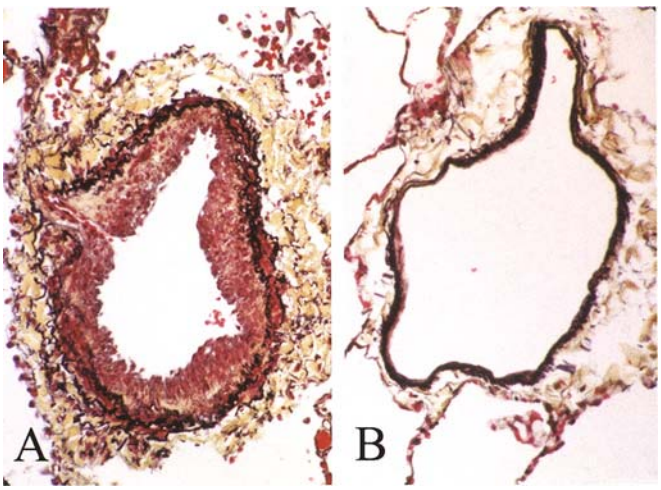


FIGURE 28.48. Chronic pulmonary venous hypertension. **A.** Arterialization. Pulmonary vein from patient with mitral stenosis has a well-defined muscular media and intimal fibrosis. **B.** Similarly sized vein from normal individual is seen for comparison. (Movat stain, both panels same magnification.)

Pulmonary Veno-Occlusive Disease

Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary hypertension, accounting for approximately 10% of all cases classified clinically as primary pulmonary hypertension, with an estimated annual incidence of 0.1 to 0.2 cases per million persons.[331–333]

The disease may present at any age, but typically is seen in children and young adults. Adult cases show a male predominance (male-to-female ratio of 2:1), while childhood cases show no sex predilection. The disease may present with an acute flu-like pneumonia, or slowly progressive exertional dyspnea and fatigue.[334] As the disease progresses, there are increasing symptoms of right-sided heart failure, including exertional syncope, chest pain, cyanosis, and hepatosplenic congestion. Since these symptoms are also typical of primary pulmonary hypertension, there can be significant diagnostic confusion in these cases. Pleural effusions are commonly seen in patients with PVOD, while they are rare among patients

with primary pulmonary hypertension. Similarly, hemoptysis, an unusual symptom in primary pulmonary hypertension, may occur in patients with PVOD, but is rarely massive.[335]

Radiologically PVOD may be suspected with a combination of a normal-sized left atrium, normal left-sided heart valves, a normal ejection fraction, normal-sized major pulmonary veins, yet enlarged pulmonary arteries. Kerley B lines and changes suggesting edema without shunting to the upper lobes may be seen. The wedge pressure is usually normal or low in patients with PVOD and is not elevated as is the case in congestive heart failure. Following injection of saline, the pressure curve shows immediate elevation that tapers to normal or low pressures as the collateral flow drains away the increased pressure. Extrapulmonary vein obstruction would lead to a persistently elevated pressure, as all vessels are equally involved.[336]

There have been isolated reports of PVOD as a cause of sudden death in both adults and infants.[337,338] It appears that PVOD is a common pattern of injury from a wide variety of etiologies. Chemical and pharmaceutical exposures have been associated with the development of PVOD in a number of cases. Drugs with the highest association with PVOD include bleomycin, mitomycin, and carmustine.[339] Additionally, some have suggested a greater risk in the setting of bone marrow transplantation, as opposed to cytoreductive chemotherapy.[340] Other causes of PVOD include viral infection, toxins, radiation, autoimmune disease, and pregnancy.[333,341] A few familial cases have also been described.[342]

Pathogenesis

Relatively little is known about the mechanism for development of PVOD. It is hypothesized that the disease process is initiated by endothelial damage, either through direct toxicity as in the case of drug exposure, or immune-mediated injury, perhaps secondary to infection. Since thrombotic occlusion of pulmonary veins is often seen, thrombotic diathesis has also been invoked as a part of the mechanism of PVOD. However, many cases of PVOD do not show evidence of pulmonary venous thrombosis or recanalization. Therefore, thrombosis may be a secondary phenomenon, rather than an initiating event in the development of this disease.

Pathology

Pulmonary veno-occlusive disease is a challenging diagnosis, particularly in adult patients. Pediatric populations do not have the complicating findings of age-related changes and chronic heart failure.

Pulmonary veno-occlusive disease is a disease process of small veins and venules, with occasional involvement of the larger veins of the hilum. Most cases of PVOD have widespread bilateral parenchymal lesions that consist of areas of venous congestion, or venous infarction (Figs. 28.50 and 28.51). Venous infarcts are characterized by ischemic necrosis of tissue at the periphery of the pulmonary lobule with preservation of the central portion of the lobule, where the best oxygenated blood is able to sustain the tissue (Fig. 28.51). These infarcts are distinct from the wedge-shaped arterial infarcts seen in cases of embolic disease. Veins can best be appreciated as they approach and drain into the interlobular septum. The process is characterized by intimal fibrosis within pulmonary veins traversing the interlobular septa (Fig. 28.52A,B). The fibrosis is variably dense, and can appear very loose and edematous. The venous lumen is narrowed or occluded, and may show localized thrombosis, or evidence of recanalization. The occlusion of veins may be partial or complete, and have variable cellularity ranging from cellular and spindle-like to overtly hyalinized, as seen in cases of old organized thrombus (Fig. 28.53). Over time, veins may become arterialized with additional elastic fibers and abundant smooth muscle creating distinct internal and external laminae, and may be confused with pulmonary arteries if the anatomic location is not properly identified (Fig. 28.52C).

Arteries and arterioles may show mild medial hypertrophy.[343] Similar to the venous lesions, half of cases show some degree of intimal fibrosis in arteries. While the mechanism of arterial intimal fibrosis may be similar to the venous lesions, the arteries usually appear less affected. Occasionally arterial occlusive lesions are

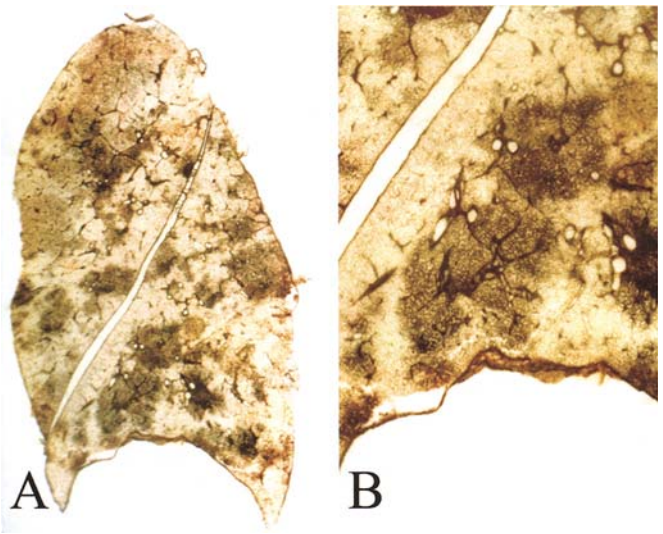


FIGURE 28.50. Pulmonary veno-occlusive disease. Gough-Wentworth whole-mount sections show multifocal parenchymal infiltrates and areas of congestion. **A.** Full mount, low power. **B.** Higher power showing infiltrates and congestion.

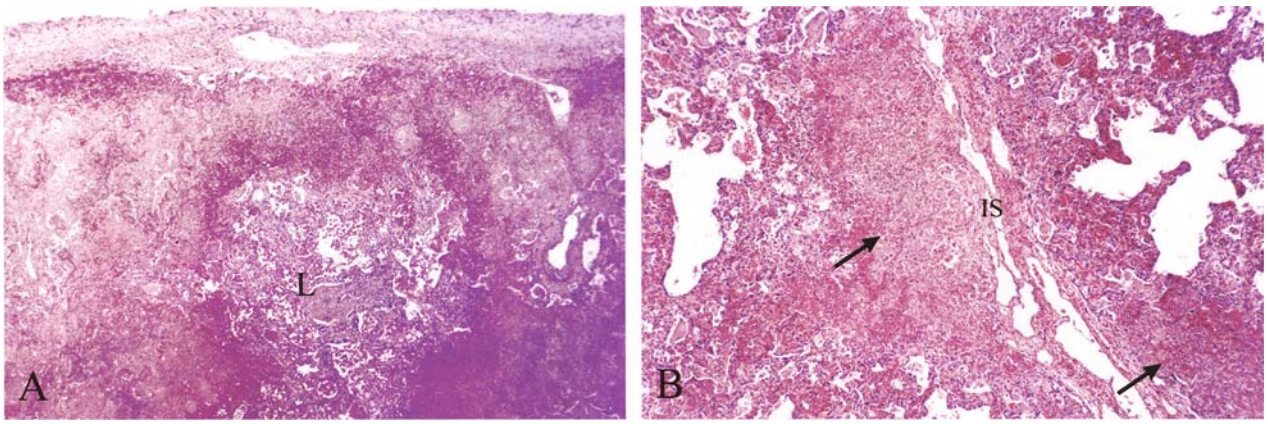
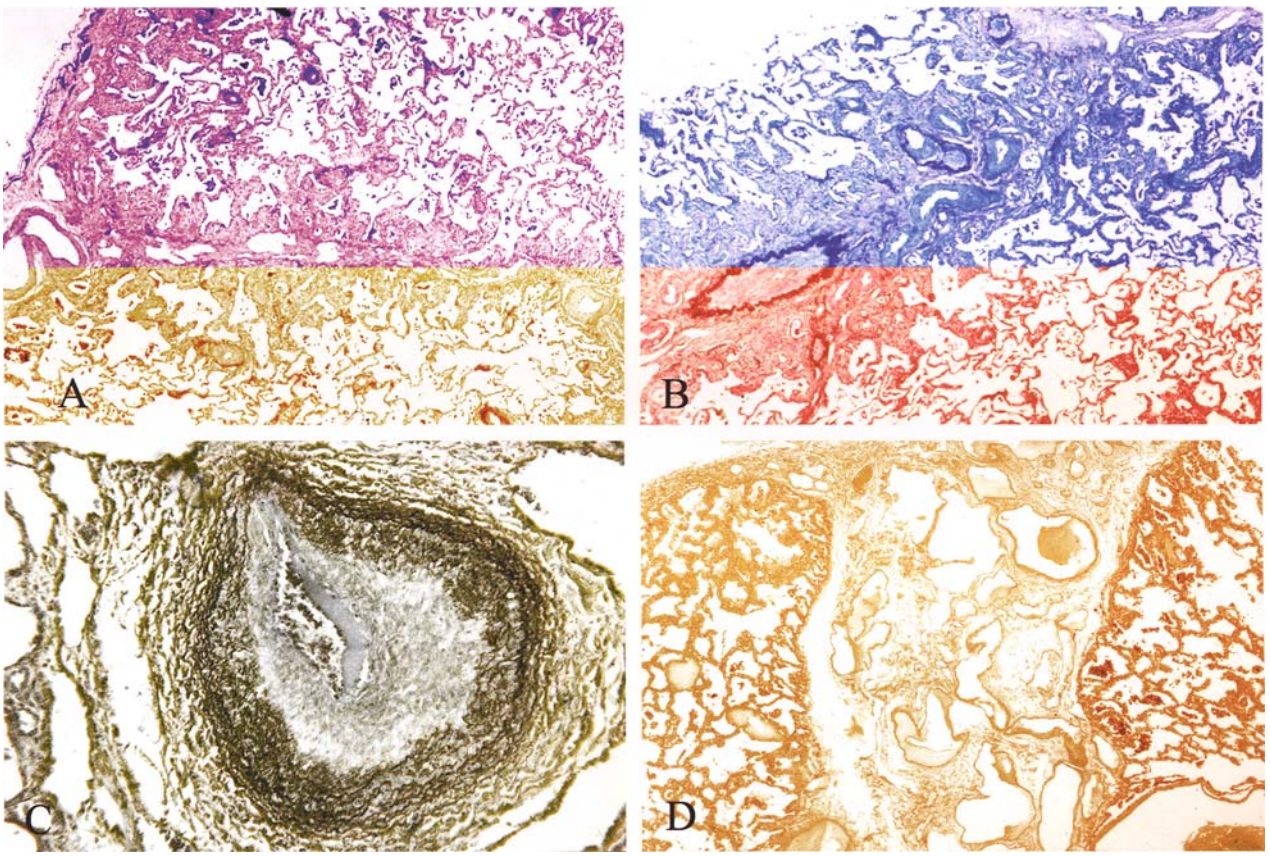


FIGURE 28.51. Pulmonary veno-occlusive disease. **A.** Ischemic necrosis of lung tissue occurs in the periphery of the secondary lobule. The centrilobular parenchyma (L) is still viable. **B.** Venous infarct (arrows) along interlobular septum (IS).



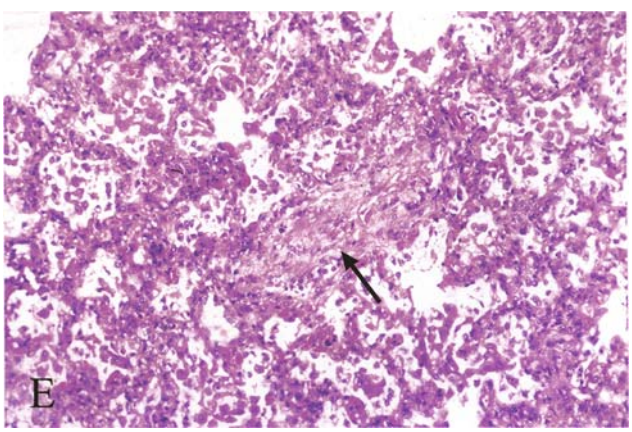


FIGURE 28.52. Pulmonary veno-occlusive disease. **A.** Thickened pleural vessels and interlobular septum. Fibrotic reaction centers on interlobular septum and few small sclerotic veins nearby. (Verhof van Gieson.) **B.** Veins in interlobular septum are sclerotic and one is almost occluded. (Verhof van Gieson.) **C.** Larger septal vein nearly occluded by intimal fibrosis. Note arterialization and dilated peripheral lymphatics. (Elastic van Gieson.) **D.** Lymphatic spaces can become very dilated in veno-occlusive disease, giving appearance of lymphangiomatosis. **E.** Endothelial cell hyperplasia sometimes gives almost neoplastic appearance or, as seen here, simulates nonspecific interstitial pneumonia. Note sclerotic vein in center of reaction.

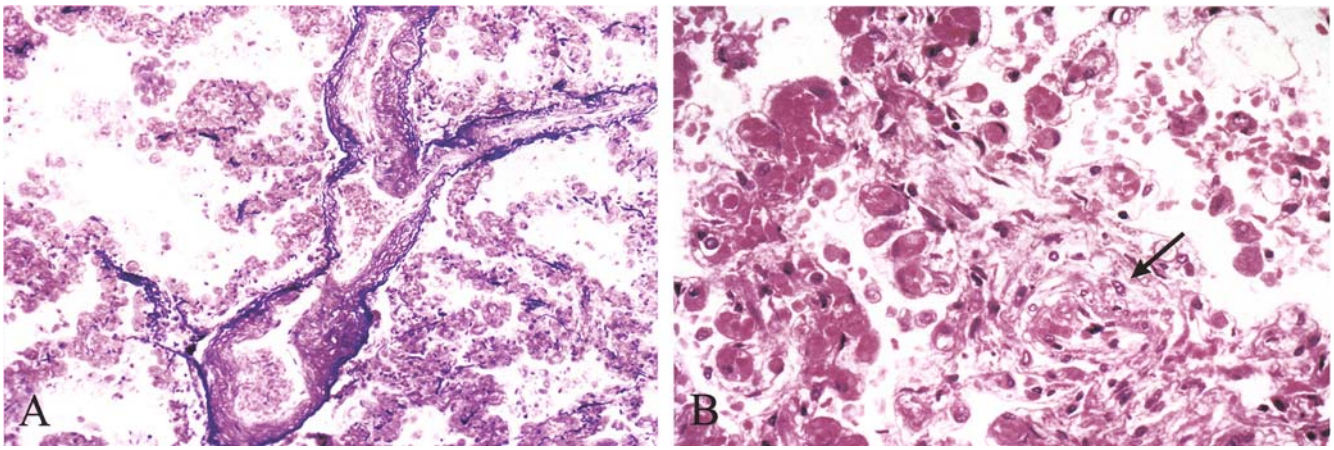


FIGURE 28.53. Pulmonary veno-occlusive disease. **A.** Central vein shows irregular intimal and mural fibrosis with some duplication of elastica caused by increased pressure or obstruction. There is surrounding capillary engorgement. (Verhof van Gieson.) **B.** Fibrotic, partially obstructed vein (arrow) associated with marked capillary proliferation and dilatation.

severe.[343] Arterial thrombosis and recanalization is common, but no plexiform, necrotizing, or dilated arterial lesions are present. The presence of arterial thrombosis is a feature of veno-occlusive disease that is not shared with other forms of pulmonary venous hypertension. Lymphatics are often markedly dilated and can give the appearance of lymphangiomatosis (Fig. 28.52D).

The surrounding lung parenchyma has prominent edema, and may show evidence of chronic hemorrhage, such as hemosiderin-laden macrophages, interstitial hemosiderosis, or interstitial fibrosis. Iron encrustation (otherwise known as endogenous pneumoconiosis) may be seen in cases of PVOD as the result of long-standing chronic hemorrhage into the interstitium. Foreign-body giant cells may be present, and the overall process may be confused with asbestosis or other pneumoconioses, or chronic aspiration (see Chapter 21). The presence of interstitial thickening centered on the interlobular septum can be a very useful pattern in diagnosing PVOD.[336] There can be dilation of capillaries within the fibrosis, or if collapsed, the endothelial cells can appear similar to lymphocytes and mimic a cellular interstitial pneumonia (Fig. 28.52E). There may be striking patches of pulmonary capillary congestion and distention, often with a nearby thickened vein (Fig. 28.53). These areas of congestion are the result of adjacent venous occlusion, although the discrete area of occlusion may not be present within the section, and may require step-sections for identification. In addition to the congestion of capillaries, there may be proliferation of capillaries within areas of fibrosis in an attempt at collateralization. Furthermore, these vessels can extend around arteries and veins, into their walls or in the thickened intima.

Often cases with extensive capillary proliferation, especially into the vascular adventitia, raise the diagnostic dilemma of primary PVOD versus pulmonary capillary hemangiomatosis (PCH) (see below). Many believe that PCH may in fact represent one of the patterns of primary PVOD rather than a distinct diagnostic entity. The two entities share the same age demographics, poor prognosis, and many of the same histologic findings, suggesting that the two diseases have more similarities than differences.

Pulmonary veno-occlusive disease remains a difficult diagnosis, and is likely underdiagnosed. The mixed histologic presentation of PVOD can easily be confused with entities such as hemangiomatosis, cellular interstitial pneumonia, vascular neoplasms of the lung, hemosiderosis due to heart failure, Goodpasture's disease, chronic passive congestion, lymphangiomatosis, or pulmonary hypertension. The prevalence of congestive heart failure and associated hemosiderosis makes the diagnosis especially challenging in the adult population. Pediatric cases often present with a more straightforward histologic appearance and therefore many pediatric pathologists are more aware of the condition and are more comfortable making the diagnosis.

Prognosis and Treatment

Treatment with vasodilators, anticoagulants, and immunosuppressive agents has met with limited success. While vasodilators have improved survival considerably in pulmonary arterial hypertension, there are conflicting data on their application in PVOD, including reports of massive pulmonary edema and death.[344] Like other patients with pulmonary hypertension, PVOD patients are usually treated with anticoagulation unless there is a history of significant hemoptysis. However, there have not been studies to document benefit in patients specifically with

a diagnosis of PVOD. Steroids and other immunosuppressants have had only scattered anecdotal reports of success.[345] Overall, prognosis remains poor, with most patients dying within 2 years of diagnosis, unless lung transplantation is undertaken.[346] There are no reports of recurrence after lung transplantations.

Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis (PCH) is a locally aggressive vascular proliferation of capillary-like vessels that is a rare cause of pulmonary hypertension. The entity was first described in a 71-year-old woman and has since been encountered in patients ranging in age from 6 to 71 years, but most occurring in the 20- to 40-year age group.[347–349] It is recognized to occur in congenital, familial, and sporadic forms. Congenital PCH often occurs in association with other developmental abnormalities, and has been known to cause significant proximal occlusion of the airways.[350] The familial form has an autosomal recessive inheritance pattern, and appears to be very rare with only a single documented affected family.[351] The more common spontaneous form of the disease typically presents in young patients with the onset of symptoms stereotypic for pulmonary hypertension. Often these cases are initially diagnosed as primary pulmonary hypertension or pulmonary veno-occlusive disease. The presence of hemoptysis or pleural effusion should raise suspicion for the possibility of PCH. When clinically suspected, the lesion is typically diagnosed via pulmonary angiography. Biopsy is rarely undertaken, and can result in massive hemorrhage. Therefore, the histologic findings are often only seen at autopsy

Pathogenesis

While PCH has been considered by some to represent a low-grade vascular neoplasm, most consider the lesion to be a benign vascular proliferation in response to either an infectious agent, such as *Mycoplasma pneumoniae*, or inflammation due to an underlying collagen vascular disease.[347,352,353] The typical symptoms of hemoptysis and hemorrhagic pleural effusion are secondary to vascular invasion within bronchioles, air spaces, and the pleura. The mechanism of the associated pulmonary hypertension, however, has remained elusive. Current theories include vascular obliteration by capillary growth, in situ thrombosis, and hypoxic pulmonary vasoconstriction.[354] There has been a report of a case of PCH without pulmonary hypertension.[355] In this patient, there was significant alveolar and bronchiolar capillary proliferation, but no proliferation within vessel walls. Therefore, it seems likely that vascular compression by adjacent capillary proliferation may be the dominant mechanism of pulmonary hypertension in PCH.

Pathology

Pulmonary capillary hemangiomatosis is characterized by interstitial proliferation of small, engorged capillary-sized vascular channels, often in a vaguely lobular and patchy distribution (Fig. 28.54). Vascular proliferation occurs around the bronchovascular bundle, as well as throughout the alveolar septa and pleura. Sometimes the

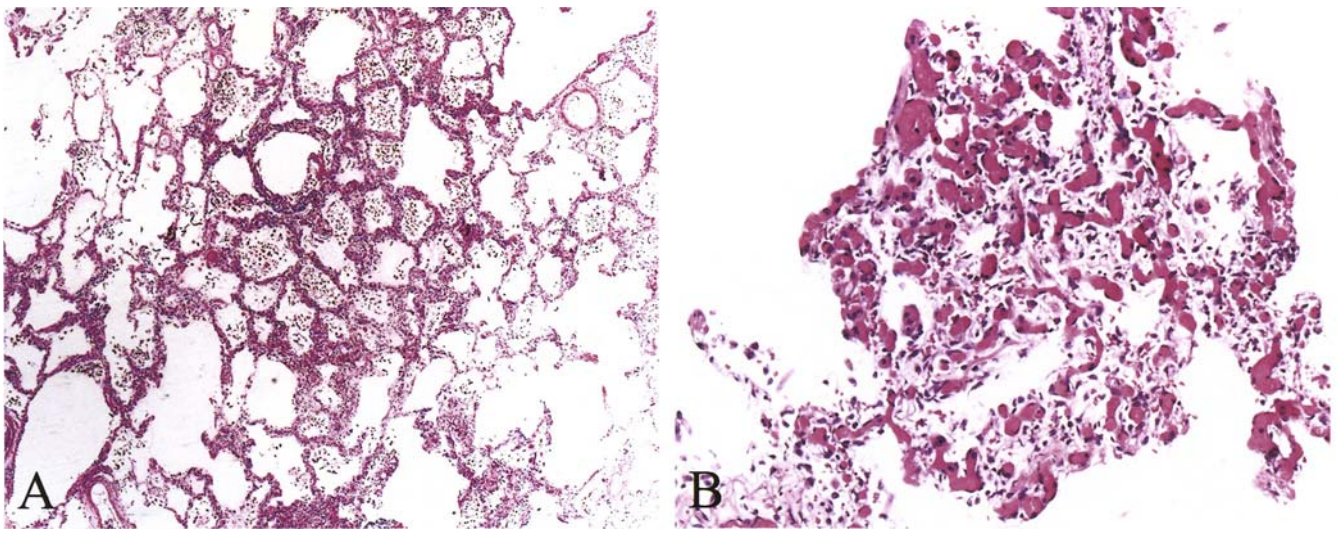


FIGURE 28.54. Pulmonary capillary hemangiomatosis (PCH). **A.** Low-power view of PCH demonstrates the patchy septal thickening by a proliferation of capillary-sized structures. A clue to this disease is the low-power appearance of patchy "congestion." **B.** Higher magnification shows the proliferation of capillary structures within the septa (many more than the typical single-capillary thickness seen in normal septa).

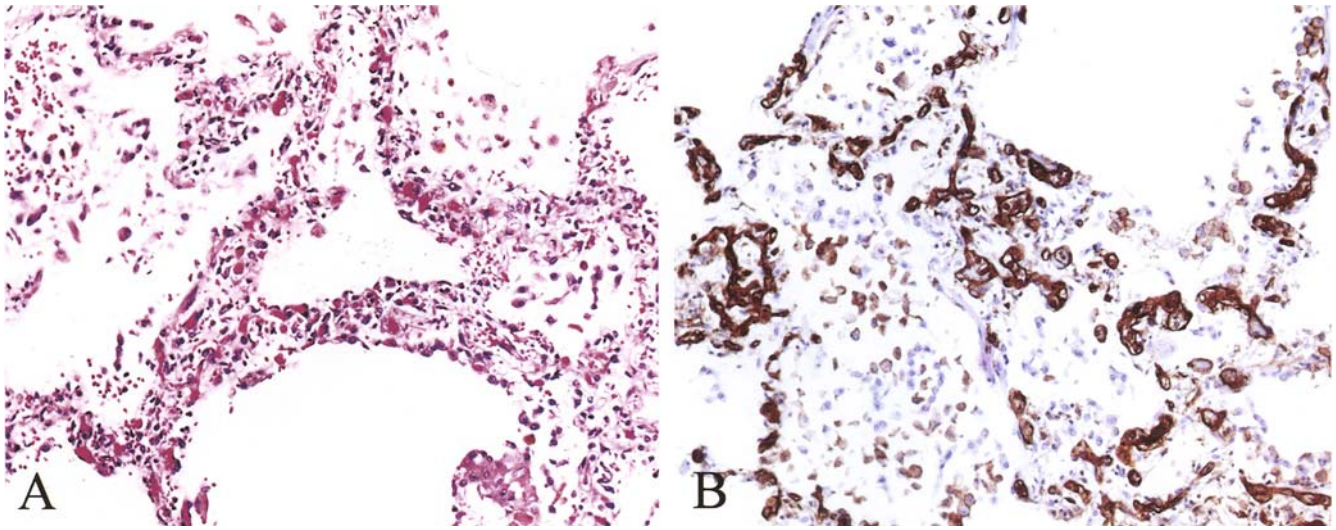


FIGURE 28.55. Pulmonary capillary hemangiomatosis. **A.** Septal thickening due to capillary-like proliferation and endothelial hyperplasia, mimicking interstitial pneumonia. **B.** CD31 immunohistochemical staining highlights the numerous endothelial-lined, thin-walled capillary-sized spaces within the alveolar septa.

engorgement is associated with thick-walled central or eccentric vessels. Endothelial cells are cytologically bland. Venous infiltration by capillary-sized channels is associated with intimal fibrosis and secondary veno-occlusive disease. The alveolar septa are typically expanded creating possible confusion with interstitial pneumonia (Fig. 28.55A). Therefore, it is critical to recognize the vascular nature of the disease. The vascular channels stain with the usual endothelial markers such as CD31, CD34, and factor VIII–related antigen (Fig. 28.55B). Frequently, there are increased numbers of hemosiderin-laden macrophages in air spaces, presumably from microvascular hemorrhages. True interstitial fibrosis with collagen deposition may be seen in cases with significant hemosiderosis.

A secondary pulmonary hypertensive change is reported that involves thickening of the walls, both medial hypertrophy and fibrointimal proliferation, but not the more severe degrees of pulmonary hypertension, specifically necrotizing, plexiform, or dilatation lesions. Vascular tumors or proliferations have not been described outside the lung in these patients.

There is considerable overlap in the histologic manifestations, clinical presentation, and prognosis of pulmonary veno-occlusive disease and of pulmonary capillary hemangiomatosis. This has led many to question whether PCH is a true diagnostic entity, versus a manifestation of primary PVOD.[336]

Prognosis and Treatment

Overall, the prognosis of the disease is poor, with a median survival of 3 years from time of diagnosis. To date, there have been a few reported cases of successful treatment or stabilization of disease using interferon-α-2a, again suggestive of a possible role of inflammation.[354] Epoprostenol, a common therapy in PPH, is contraindicated for PCH because it may lead to the development of pulmonary edema. Otherwise, lung transplantation remains the only alternative. While there are no reported cases of PCH recurring in a single transplanted lung, there is a report of PCH rapidly developing de novo following a double lung transplant.[356]

Hypoxic Pulmonary Hypertension

Hypoxia is a potent vasoconstrictor of pulmonary arteries.[357] The constrictive nature of hypoxia within the lung exerts both a positive and a deleterious effect. Hypoxic vasoconstriction shunts blood to better ventilated lung zones, thereby improving ventilation-to-perfusion matching and maintaining blood oxygen tension. On the other hand, chronic hypoxia causes vascular remodeling and sustained pulmonary hypertension, leading to cor pulmonale.[121] Hypoxic vasoconstriction may occur in situations of alveolar hypoxia or hypoxemia of mixed venous blood.[357,358] Acidosis potentiates the constrictive effect of hypoxia.[357]

The clinical situations in which hypoxic vasoconstriction develops can be broadly categorized as follows: (1) reduced ambient levels of inspired oxygen, as experienced at high altitude; (2) conditions of hypoventilation including chest wall or diaphragmatic muscle weakness, obesity, and central hypoventilation; (3) deformities of

the thoracic cage, as in severe kyphoscoliosis; (4) mechanical airway obstruction, as with tumor, an aspirated foreign body or obstructive sleep apnea; (5) chronic obstructive airways disease (e.g., emphysema and chronic bronchitis); and (6) other lung disorders associated with hypoxemia. The hypoxia of high altitude, kyphoscoliosis, and obstructive sleep apnea are considered in detail below. The histopathologic features of hypoxic pulmonary hypertension, however, are similar regardless of the cause of hypoxia.[121,359]

High Altitude

Terrestrial hypoxia not only causes pulmonary hypertension in individuals who live at higher altitudes, but also is important to the thousands of individuals who transiently ascend to higher altitudes for recreational purposes of traveling, trekking, and mountain climbing.[360] Dwellers at high altitude, such as in the Peruvian Andes or the Tibetan plateau, develop elevated pulmonary artery pressure, and experience an increased incidence of congenital heart defects as well as hyperplasia and tumors of the carotid body.[360] Individuals who rapidly ascend to high altitude from the lowlands may experience high-altitude pulmonary edema, as discussed in Chapter 4. Some long-term dwellers at high altitude may suffer a fulminant form of pulmonary hypertension and cor pulmonale referred to as chronic mountain sickness or Monge disease.[360,361]

Residents of altitudes higher than 3000 m have, on average, a resting pulmonary artery pressure greater than that of residents at sea level.[121] This difference is accentuated upon exercise. The effect of high altitude is variable among individuals, but there is evidence that vascular remodeling affects a greater proportion of individuals as altitude increases.[121] It is also probable that populations that have lived at high altitude for generations have genetically adapted to their environment.[121,362]

The condition of chronic mountain sickness was first described in 1928 by Monge[363] and beautifully summarized by Saldana and Arias-Stella[360] as a condition of extreme cyanosis, erythrocytosis, central nervous system (CNS) symptoms, hypoxemia (<70% O_2 saturation), excessively elevated pulmonary artery pressure, and right heart failure. The most important treatment for patients with Monge disease is descent to a lower altitude.

Sleep Apnea Syndrome

Sleep apnea syndrome is a relatively common condition of repeated apneic events occurring during sleep, resulting in episodic severe hypoxia and hypoxemia.[364–367] Sleep apnea has been divided into central sleep apnea caused by defective neurologic control of breathing, in which there is absence of both respiratory efforts and airflow, and obstructive sleep apnea due to excessive pharyngeal adipose and other soft tissues, in which there is increased respiratory efforts despite partial or complete occlusion of the upper airway.[364–367] Obstructive sleep apnea is frequently associated with obesity.[368–372] The constellation of obesity, sleep apnea, hypersomnolence, and hypercarbia was designated by Burwell et al.[373] as the Pickwickian syndrome, after Dickens' novel, *The Pickwick Papers*, which has the minor character of Joe the fat boy, who exhibits many of the features of obstructive sleep apnea.[374]

Patients with obstructive sleep apnea frequently manifest nocturnal restlessness and snoring, are often hypertensive, may develop severe cor pulmonale due to sustained pulmonary hypertension, and have an increased risk of stroke, coronary artery disease, and sudden death.[368,374–376] The cause of pulmonary hypertension in obstructive sleep apnea is complex, and probably multifactorial.[377] Generally mild pulmonary hypertension has been shown to occur in the absence of underlying lung disease.[376,377] Left ventricular dysfunction with pulmonary venous hypertension or obesity appears to be an important contributing factor in many patients.[377–379] Using echocardiography, Guidry and colleagues[380] showed that patients with sleep-disordered breathing (SDB) had a small but significant increase in right ventricular wall thickness compared to a control population without SDB.

Kyphoscoliosis

Pulmonary hypertension and cor pulmonale have long been associated with severe spinal deformities that distort the dimensions of the thoracic cage and constrict the lungs.[381] Pulmonary function tests in patients with kyphoscoliosis are characterized by reduced lung volumes, ventilatory flow rates, and diffusing capacity. Arterial blood gases show hypercapnia and hypoxemia due to the small volume of lung that is ventilated.[382] The onset of pulmonary hypertension and cor pulmonale is a poor prognostic sign that frequently heralds death. Pulmonary hypertension tends to occur in those patients who develop hypoxemia.[381,383]

Pathophysiology and Pathologic Features of Hypoxic Pulmonary Hypertension

Hypoxia exerts its effects mainly on the small muscular pulmonary arteries and precapillary nonmuscular arterioles, but the mechanism of hypoxic vasoconstriction and vascular remodeling is complex and not completely understood.[384] Hypoxia profoundly affects the vascular endothelium to release vasoconstrictive and proliferative mediators. Chronic hypoxia promotes muscle and fibroblast proliferation as well as extension of smooth muscle

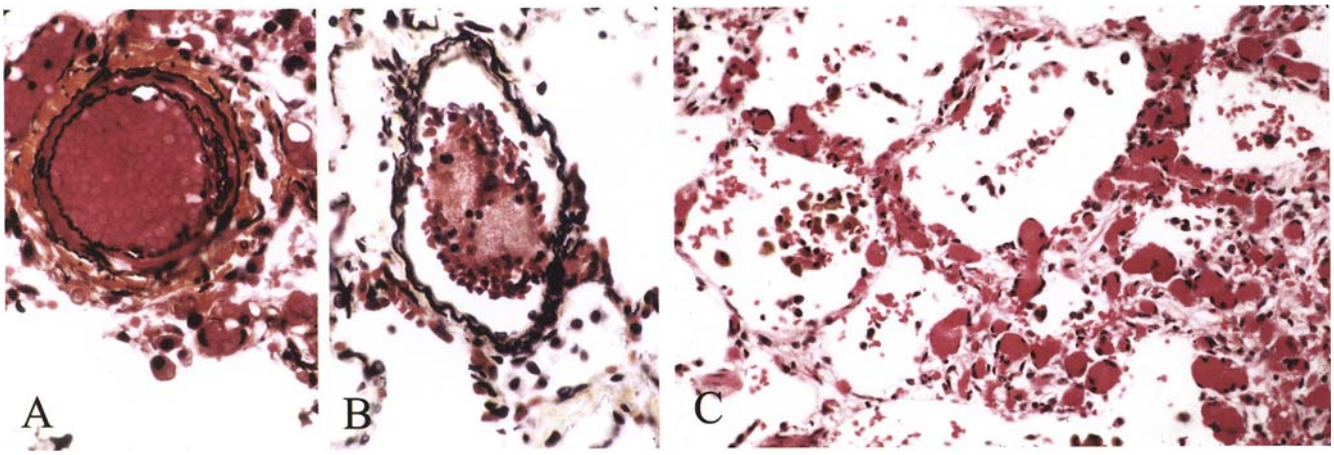


FIGURE 28.56. Hypoxic vasculopathy. **A.** Muscularization due to chronic hypoxia in a patient with obstructive sleep apnea. The normally nonmuscularized arteriole has a well-developed muscular wall. **B.** Normal arteriole for comparison. (Movat, same magnification as **A.**) **C.** Capillary proliferation in a patient with severe obstructive sleep apnea and congestive heart failure.

into nonmuscularized vessels, probably by acting on pericytes and intermediate cells in the vascular wall.[385] A loss of vessels has also been identified in experimental animals, although recent reports suggest that increased vascularity occurs through hypoxia-induced angiogenesis.[386–388] Other mechanisms of vascular remodeling in hypoxia may include release of mitogenic stimuli from smooth muscle cells, endothelial apoptosis, elevated levels of angiotensin-converting enzyme (ACE), inflammatory mediators (IL-8, IL-6), and reactive oxygen species.[384] Modulators such as endothelin-1, vascular endothelial growth factor, angiotension II, and nitric oxide have also been implicated in hypoxic vascular remodeling.[389,390] The increase in mitogenic factors has been proposed to occur through the regulation/induction of various transcription factors such as hypoxia-inducible factor-1 (HIF-1).[384] Additionally, hypoxia contributes to pulmonary hypertension indirectly by promoting vasoconstriction and increased shear stress.[384]

The pathologic features of hypoxia-induced pulmonary hypertension are similar among the various predisposing conditions.[121,359] The effects of hypoxia on the pulmonary trunk and main pulmonary arteries are well seen in dwellers of high altitude. The studies of Saldana and Arias-Stella[360,391,392] indicate a greater medial thickness and persistence of the aortic configuration of thick, continuous elastic fibers in the central pulmonary arteries in individuals born and raised at high altitude. In general, the main histologic manifestation of chronic hypoxia in parenchymal vessels is muscularization of arterioles, with development of distinct internal and external elastic laminae, and a medial muscle coat that sometimes extends into vessels as small as 30 to 40 μm (Fig. 28.56A,B).[393–395] Medial hypertrophy of larger muscular arteries may also be seen, but frequently muscularization of arterioles is associated with normal or minimally altered muscular arteries.[121,359,395,396] Autopsy data in patients with Monge disease are limited; however, one study showed hypermuscularization of small pulmonary arteries above that normally seen in dwellers at similar altitude.[360] Another general feature of hypoxic vasculopathy is longitudinally oriented smooth muscle bundles within the intima of muscular pulmonary arteries, although intimal fibrosis tends to be mild (Fig. 28.57).[121,359,396] Pulmonary veins may also show excessive smooth muscle of a lesser degree than that seen in arteries.[397]

Although the capillary network is usually described as normal, in some patients with severe sleep apnea syndrome and right ventricular hypertrophy extreme capillary proliferation and hemosiderosis may be seen

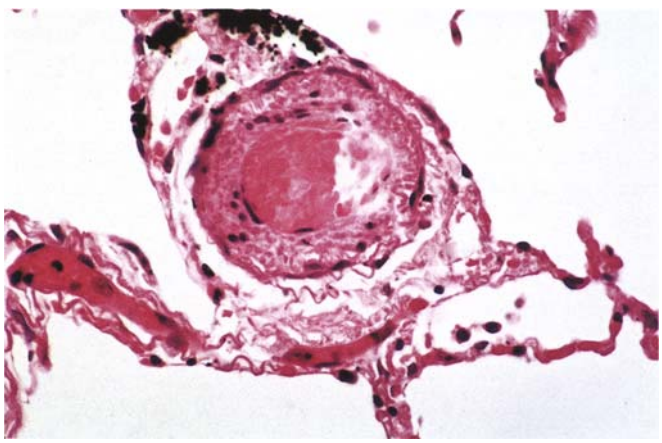


FIGURE 28.57. Hypoxic arterial remodeling in a patient with severe kyphoscoliosis. Note concentric intimal thickening with longitudinally oriented muscle bundles.

(Fig. 28.56C).[394] The degree of capillary proliferation may simulate that seen in pulmonary capillary hemangiomatosis (see above), the key distinction being the absence of capillary infiltration of vessels and veno-occlusive–like changes. The cause of this proliferation is not completely determined, but it likely relates to concomitant left ventricular cardiac failure or possibly a direct angiogenic effect of hypoxia on the capillary bed.

Pathologic features of patients with kyphoscoliosis include small, distorted lungs.[383,398] In a quantitative study, Davies and Reid[398] documented fewer numbers of alveoli that were irregularly emphysematous or atrophic. In patients with cor pulmonale, medial hypertrophy of muscular pulmonary arteries with extension of muscle into arterioles has been reported.[383,398]

The carotid body, an oxygen-sensing chemoreceptor organ, undergoes hyperplasia in the setting of chronic hypoxia both in humans and animals living at high altitude, and in various hypoxic pulmonary conditions such as cystic fibrosis, cyanotic congenital heart disease, sleep apnea syndrome, and emphysema.[399,400] Occasionally chronic hypoxic overstimulation of the carotid body may lead to the development of a paraganglioma as was reported by Saldana et al.[401] in 30 patients living at high altitude in the Andes. In Saldana et al.'s series there was an unexplained increased incidence in females.

Pulmonary Vascular Changes in Lung Disease

Interstitial Pulmonary Fibrosis

Patients with interstitial fibrosis, such as idiopathic pulmonary fibrosis, frequently develop cor pulmonale as a result of pulmonary hypertension (see Chapter 19).[402] In areas of interstitial fibrosis, muscular pulmonary arteries exhibit changes of medial hypertrophy and concentric or eccentric intimal fibrosis (Fig. 28.58). Longitudinally oriented intimal smooth muscle with extension of muscle into peripheral arterioles has also been reported.[403] The arterial changes are similar, regardless of the cause of interstitial fibrosis.[403] Pulmonary veins also develop hyalinized fibrosis. The pulmonary capillary bed is greatly reduced and the distance between capillary and epithelial basement membrane is increased, limiting the diffusion of oxygen and carbon dioxide. Bronchial arteries are often hypertrophied with increased bronchopulmonary anastomotic shunts.[403] The mechanisms responsible for vascular changes in interstitial fibrosis include injury and remodeling secondary to the surrounding chronic inflammation and fibrosis with obliteration and restriction of the vascular bed.[404] Hypoxia may also contribute to vasoconstriction.[402] Since the vasculature in the nonfibrotic areas may be normal, the presence or absence of pulmonary hypertension is dependent on the overall extent of fibrosis.

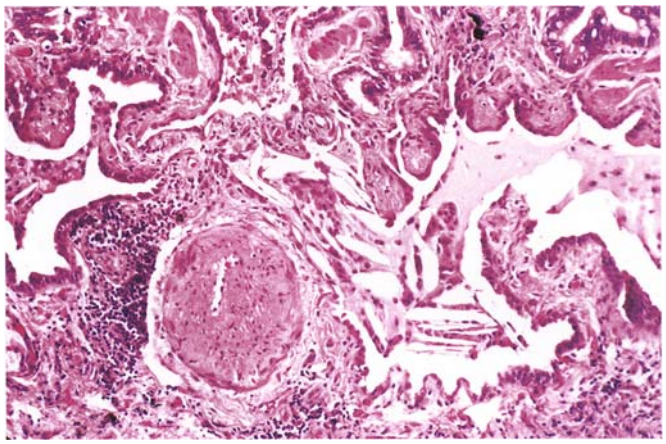


FIGURE 28.58. Idiopathic pulmonary fibrosis. Severe concentric intimal fibrosis of a muscular pulmonary artery in region of advanced honeycombing.

Diffuse Alveolar Damage

The pulmonary vascular lesions in diffuse alveolar damage are progressive, vary with the stage and duration of the parenchymal disease, and reflect the evolution of vascular remodeling in this rapidly unfolding form of alveolar injury and fibrosis (see Chapter 4).[405] In the exudative phase macroscopic or microscopic thrombi are seen along with hypoxic vasoconstriction.[406] The capillary bed, as assessed by vascular injection studies, is extensively obliterated.[407] Thromboemboli, most likely representing in situ thrombosis, have been identified in 95% of lungs studied by vascular injection at autopsy.[406,408] Both macrothrombi, in elastic and large muscular pulmonary arteries, and microthrombi in small arteries and arterioles may be identified.[406] In the proliferative phase, medial hypertrophy and eccentric or concentric intimal fibrosis are characteristic. Arterial and venous lumina are narrowed by layered fibrin, proliferating myointimal cells, hyperplastic endothelial cells, and fibromyxoid connective tissue (Fig. 28.59). Morphometric studies demonstrate hypermuscular arteries in the intermediate and late stages of diffuse alveolar damage.[406,409] The variability in medial thickness of muscular arteries also increases with the duration of the acute respiratory distress syndrome (ARDS).[406] In the late fibrotic phase, arteries, veins, and capillaries become dilated and distorted in a background of fibrous parenchymal remodeling (see Figs. 4.8 and 4.18 in Chapter 4).

Chronic Obstructive Pulmonary Disease

Pulmonary hypertension is the major cardiovascular complication of chronic obstructive pulmonary disease

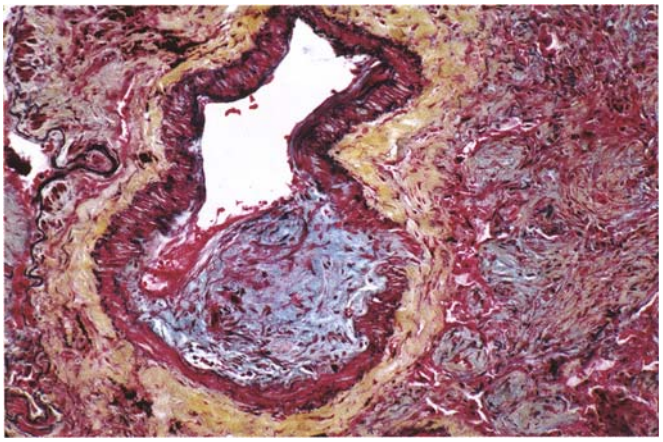


FIGURE 28.59. Diffuse alveolar damage. Fibromyxoid intimal proliferation of muscular pulmonary artery in proliferative phase diffuse alveolar damage (DAD). Note also medial hypertrophy and adventitial fibrosis. The adjacent lung parenchyma is totally effaced by confluent air-space fibrosis. (Movat.)

(COPD).[410] The vascular changes in emphysematous lungs are thought to be the result of chronic hypoxia.[410] In patients with stable COPD, severe pulmonary hypertension (>40 mm Hg) occurs in fewer than 5% of patients.[411] A significant proportion of patients with severe pulmonary hypertension have additional causes such as cardiac disease, obstructive sleep apnea, or appetite suppressant history. Chaouat and colleagues,[411] in a large cohort of patients with COPD, found severe pulmonary hypertension without causes other than COPD in only 1.1% of patients overall and in 41% of patients with COPD and severe pulmonary hypertension. Patients with COPD as the only detectable cause of severe pulmonary hypertension typically had hypercapnia, very low DL_{CO}, severe exertional dyspnea, and a short life expectancy.[411]

Early morphologic studies noted a well-developed muscular coat in small pulmonary arteries, indicative of peripheral extension of muscle, in patients with right ventricular hypertrophy.[410,412] Longitudinal intimal muscle fibers and mild intimal fibrosis were also noted; however, the medial thickness of larger muscular arteries was found to be normal.[410,412] On the other hand, Naeye and Greenberg[413] found increased medial thickness in end-stage panacinar emphysema due to α_1-antitrypsin deficiency. Magee et al.[414] correlated vascular changes with morphologic severity of emphysema and found increased intimal thickness (compared to nonsmoker control lungs) in all emphysema groups, and medial hypertrophy associated with severe emphysema. Hale and colleagues[415] emphasized the importance of cigarette smoke as a possible independent contributor to medial and intimal thickening. The destruction of the pulmonary capillary bed, which may be extensive in emphysema, is not considered to be a main factor in the production of pulmonary hypertension.[121,416,417] Dunnill's[416] suggestion of compression of pulmonary arteries by emphysematous air spaces has not been given serious consideration in more recent studies.

Liebow,[418] using the vinylite cast technique, described expansion of the bronchial arterial circulation as well as marked enlargement of the bronchopulmonary venous system in advanced emphysema. Collaterals between bronchopulmonary and pulmonary veins theoretically represent a source of right to left shunt.

Acknowledgments. The authors acknowledge the contribution of Dr. C.A. Wagenvoort, who wrote the chapters on pulmonary vascular disease in the first two editions of this text. His lucid morphologic descriptions of pulmonary vascular remodeling have influenced and benefited pathologists for over 40 years, and have been integrated into this edition.

The authors also thank Diane Gillihan for expert secretarial help, Vince Messina for photographic support, and the staff of the Brittingham Memorial Library for bibliographic assistance.

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