Pulmonary Hypertension and Pulmonary Vascular Disease

**Important Topics**

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### Abbreviations Used in This Chapter

- ACS: acute chest syndrome
- ANCA: antineutrophilic cytoplasmic antibody
- BD: Behçet disease
- BMPR2: bone morphogenetic protein receptor type 2
- CPTE: chronic pulmonary thromboembolism
- CSS: Churg-Strauss syndrome
- DAH: diffuse alveolar hemorrhage
- FES: fat embolism syndrome
- GPA: granulomatosis with polyangiitis
- HIV: human immunodeficiency virus
- HPAH: heritable pulmonary arterial hypertension
- HPS: hepatopulmonary syndrome
- ILD: interstitial lung disease
- IPAH: idiopathic pulmonary arterial hypertension
- IPH: idiopathic pulmonary hemosiderosis
- MPA: microscopic polyangiitis
- PA: pulmonary artery
- PAH: pulmonary arterial hypertension
- PAN: polyarteritis nodosa
- PAP: pulmonary artery pressure
- PCH: pulmonary capillary hemangiomatosis
- PH: pulmonary hypertension
- PVD: pulmonary vascular disease
- PVOD: pulmonary veno-occlusive disease
- PVRi: pulmonary vascular resistance index

Pulmonary hypertension (PH) and pulmonary vascular disease (PVD) are often associated with nonspecific symptoms of respiratory dysfunction and nonspecific pulmonary function test findings. PH may result from cardiac or pulmonary abnormalities, or vascular diseases primarily affecting the small arteries or veins. In most cases, PVD and PH are assessed using techniques and imaging modalities other than high-resolution computed tomography (HRCT). However, in some patients, HRCT may be performed to determine whether lung disease is present as a cause of the patient’s disability or to evaluate specific small vessel diseases. If vascular disease is suspected, assessment of the lung using multidetector-row spiral HRCT with contrast infusion is an ideal technique. Furthermore, in patients who have known PH, HRCT may be performed when the etiology of the vascular disease is unclear. Only those vascular diseases commonly assessed using HRCT are described in this chapter.

### High-Resolution Computed Tomography Findings of Pulmonary Vascular Disease

PH and PVD may be associated with a number of findings on HRCT (1–3). These include alterations in the size of large or small pulmonary arteries; mosaic perfusion, commonly seen in patients who have pulmonary vascular obstruction of various causes; findings of pulmonary edema and hemorrhage, including ground-glass opacity, consolidation, or interlobular septal thickening; centrilobular nodular opacities; and cardiac abnormalities.

**Pulmonary Artery Abnormalities**

Of primary importance in making the diagnosis of PVD is the recognition of increased or decreased pulmonary artery (PA) diameter. In most cases, the diameters of main,
right and left, and intrapulmonary artery branches can be determined on HRCT obtained without contrast infusion, because these arteries are usually outlined by mediastinal fat or air-containing lung.

**Increased Artery Diameter**

Dilatation of the main PA usually indicates the presence of PH and can be an important finding in recognizing the presence of PVD on HRCT (Fig. 22-1). Even when HRCT scans are obtained at 2-cm intervals, at least one image traverses the main PA, allowing its measurement on soft-tissue window scans.

The main PA measures up to 30 mm in diameter in normal subjects. This measurement is best made at a right angle to the long axis of the PA, lateral to the ascending aorta, and near the level of its bifurcation. In a CT study of normal subjects by Guthaner et al. (4), the main PA diameter (PAD) was found to average 28 ± 3 mm. Kuriyama et al. (5) measured PADs in both normal subjects and patients who have PH. In normal subjects, the main PA averaged 24.2 ± 2.2 mm in diameter at a level near its bifurcation (5). Based on these data, the authors concluded that 28.6 mm (mean plus 2 standard deviations) should be considered the upper limit of normal for main PAD; this value was found to accurately distinguish patients who have PH from normal subjects. Also, Kuriyama et al. (5) found that the main PAD correlated well with pulmonary artery pressure (PAP).

In a study of patients who had chronic lung disease or PVD (6) who were awaiting lung or heart-lung transplantation, considerably more overlap in PAD was seen between patients who had normal or elevated PAPs. Main PAD measured 28 ± 7 mm in patients having normal PAP (≤18 mm Hg) and 33 ± 11 mm in those who have PH (pressure > 18 mm Hg).

The diameter of the main PA may also be compared with that of the aorta; this is quickly and easily done on HRCT. In normals, the PA is usually smaller than the adjacent aorta. In a study by Ng et al. (7), the ratio of the diameter of the main PA to the aortic diameter (A) was measured using HRCT in 50 patients who had a variety of pulmonary and cardiovascular diseases, and also had PAPs measured at right heart catheterization. Measurement of vessel diameters was made at the level at which the right PA traverses the mediastinum. Both the diameters of the PA and the PA/A ratio were significantly related to PAP (r = 0.74, p < 0.0005) (7). For patients younger than 50 years, PAP correlated more closely with PA/A (r = 0.77, p < 0.00005) than with PAD (r = 0.59, p < 0.005); for patients older than 50 years, the opposite was true. More important, a PAD to aortic diameter ratio of more than 1 strongly suggests PH (Fig. 22-1A). In this study (7), the specificity and positive predictive value of this finding were 92% and 96%, respectively. The sensitivity and negative predictive value were lower, measuring

![PH in a patient with Eisenmenger syndrome associated with congenital heart disease. HRCT was performed to exclude lung disease. A: Marked dilatation of the main pulmonary artery and right pulmonary artery is visible (white arrows). The main pulmonary artery is significantly larger than the aorta. Calcification of the artery wall (black arrows) reflects atherosclerosis. B: Enlargement of central pulmonary artery branches is also visible (arrow). C: Despite marked enlargement of central arteries, peripheral pulmonary vessels appear normal or reduced in diameter.](image-url)
70% and 52%, respectively. Thus, a PA/A of less than 1 does not necessarily mean PAP is normal.

Devaraj et al. (8) assessed the accuracy of CT and echocardiographic measurements in predicting the presence of PH in 77 patients. The ratios of the diameter of the main pulmonary artery to the diameter of the ascending aorta and of the cross-sectional area of the pulmonary artery to the diameter of the ascending aorta ($r^2 = 0.45$, $p < 0.001$) correlated equally with mean pulmonary artery pressure (mPAP). The ratio of the diameter of the main pulmonary artery to the diameter of the thoracic vertebra, the segmental arterial diameter, and the segmental artery-to-bronchus ratio were related to mPAP, but did not strengthen correlations compared with the ratio of the diameter of the main pulmonary artery to the diameter of the ascending aorta alone.

Dilatation of main pulmonary arteries may also be seen in the presence of PH. The right and left pulmonary arteries should be of approximately equal size, although the left PA appears slightly larger in most subjects. In the study by Kuriyama et al. (5), the proximal right PA measured 18.7 ± 2.8 mm in diameter in normals, and the left PA averaged 21.0 ± 3.5 mm. In the study by Ackman Haimovici et al. (6) of transplantation patients, the left PA averaged 21 ± 5 mm in those who have normal PAP.

Pulmonary artery aneurysms are rare. They may be posttraumatic, mycotic, or related to some vasculitis syndromes. Pulmonary artery aneurysms may be seen in Behçet disease (BD); Hughes-Stovin syndrome, which is likely a variant of BD and rarely in giant cell arteritis (9–11).

Within the lung, the diameter of a small PA and its neighboring bronchus should be approximately equal, although vessels usually appear slightly larger than their accompanying bronchus, particularly in dependent lung regions. In patients who have PH or increased blood volume or blood flow (12), significant dilatation of these small vessels relative to adjacent bronchi may be seen (Fig. 22-1B) (13).

Focal dilatation of peripheral pulmonary arteries may be seen in patients with acute or chronic pulmonary embolism, owing to impaction of clot within the vessel. A similar phenomenon may be seen in patients with tumor embolism or other causes of nonthrombotic pulmonary embolism (11,14,15). Arteries in the lung periphery appear irregularly dilated and may have a beaded or varicose appearance in patients with tumor embolization (11). This may mimic the appearance of tree-in-bud (16,17). Dilatation of small vessels in the lung periphery may also be seen in hepatoportal syndrome (HPS) (13), pregnancy (11,18), in patients with multiple small pulmonary arteriovenous fistulas (11), and in some cardiac malformations.

### Decreased Artery Diameter

Decreased diameter of some intrapulmonary arteries is common in patients who have PH or regional decrease in pulmonary blood flow associated with large or small artery disease (Fig. 22-2). This abnormality is usually recognized in association with inhomogeneous lung attenuation (i.e., mosaic perfusion) (Fig. 22-2C,D) (2,19–21). An abrupt decrease in size of a PA along its course, visible on lung window scans, is suggestive of chronic pulmonary thromboembolism (CPTE) as the cause of PH or PVD. Asymmetry in the size of pulmonary arteries in the right and left lungs visible on lung window scans may also be seen in patients who have CPTE.

Narrowing of central pulmonary arteries with thickening of their walls, localized regions of stenosis, and poststenotic dilatation may be seen in patients with Takayasu arteritis or giant cell arteritis (9,11).

#### Pulmonary Artery Obstruction

Obstruction of large or small PA branches by thrombus or nonthrombotic emboli occurs in several abnormalities, most commonly acute or CPTE (22–24), but also including pulmonary artery sarcoma (25) and tumor emboli (14,15). Current multidetector spiral CT scanners allow contrast-enhanced volumetric HRCT (11) for the detailed assessment of both pulmonary arteries and the lung parenchyma.

#### Mosaic Perfusion and Mosaic Lung Attenuation

**Mosaic perfusion** refers to inhomogeneous lung attenuation resulting from inhomogeneous blood flow (2,11,19–21). It may result from vascular disease (e.g., CPTE, vasculitis) or airways disease (see Chapter 7). Mosaic perfusion is commonly associated with decreased size of pulmonary vessels within relatively lucent lung regions (Figs. 22-2 and 22-3). If the combination of decreased vessel size and decreased lung attenuation is visible, a diagnosis of mosaic perfusion is easily made.

In a study of pulmonary parenchymal abnormalities in 75 patients with CPTE, 58 (77.3%) patients showed typical findings of mosaic perfusion with normal or dilated arteries in areas of increased attenuation (26). In this study, areas of relatively increased attenuation averaged −727 HU, whereas areas of decreased attenuation averaged −868 HU. In another study of patients with PH due to CPTE, PH of other causes, and a variety of other pulmonary diseases, HRCT was believed to show mosaic perfusion in all patients with CPTE (27). Considerably more variation in vessel size in different lung regions was also visible in the patients with CPTE. Overall, HRCT had a sensitivity of 94% to 100% and a specificity of 96% to 98% in making the diagnosis of CPTE (27). Mosaic perfusion is less frequent in patients with acute pulmonary embolism, but may be seen (28–30). Patients with large vessel vasculitis resulting in pulmonary artery stenosis may also show this finding. Such diseases include Takayasu arteritis and giant cell arteritis (9). Some patients who have PVD may show perfusion abnormalities without a clear-cut decrease in vessel size or may show patchy ground-glass opacity that mimics the appearance of mosaic perfusion. If it is unclear whether inhomogeneous lung attenuation represents mosaic...
perfusion, the terms *mosaic lung attenuation* or *mosaic pattern* may be used (19,21,31).

In patients who have PH, mosaic lung attenuation is seen significantly more often in patients who have PH due to vascular disease than in patients who have PH due to cardiac or lung disease, and CPTE is the most common disease responsible for this finding. The frequency with which mosaic lung attenuation is seen on CT in patients who have various causes of PH has been studied by Sherrick et al. (19). In this study, 23 patients had PH due to vascular disease, 17 patients had PH due to cardiac disease, and 21 patients had PH due to lung disease. Of the 23 patients with PH due to vascular disease, 17 (74%) had mosaic lung attenuation. Twelve of the 17 patients with mosaic lung attenuation due to vascular disease had CPTE, 2 had idiopathic or primary PH, 2 had pulmonary veno-occlusive disease (PVOD), and 1 had fibrosing mediastinitis associated with vascular obstruction. Among the 17 patients with PH due to cardiac disease, only 2 (12%) patients had a mosaic pattern of lung attenuation (19). Of the 21 patients with PH due to lung disease, 1 (5%) patient had mosaic lung attenuation.

Abnormalities of pulmonary perfusion in patients with PH do not always result in mosaic perfusion recognizable on HRCT. In a study of five patients with scleroderma, normal lung parenchyma, and PH, HRCT showed a reduction in the anterior to posterior lung attenuation gradient, when compared to patients without PH (2,32). This is perhaps related to reduced compliance of the pulmonary vasculature in the patients with PH.

### High-Resolution Computed Tomography Differentiation of Causes of Mosaic Attenuation

On HRCT, it is often possible to distinguish among ground-glass opacity, mosaic perfusion caused by airways disease, and mosaic perfusion caused by vascular disease. In two studies (20,33), an accurate distinction was possible in more than 80% of cases based on HRCT findings. However, findings may be nonspecific or misleading in some cases.

In patients with mosaic perfusion resulting from airways disease, the presence of airway abnormalities in lucent lung regions may allow the correct diagnosis. Abnormal dilated or thick-walled airways (i.e., bronchiectasis) are visible in approximately 70% of patients with mosaic perfusion related to airways disease (34–38). It is important to note, however, that dilatation of segmental and subsegmental bronchi has also been reported in some patients with CPTE (39). In a study by
section iii    High-Resolution CT Diagnosis of Diffuse Lung Disease

Remy-Jardin et al. (39), cylindrical bronchial dilatation was found in 21 of 33 (64%) patients with CPTE, and bronchial wall thickening was identified in 4 (12%).

Lobular areas of lucency (i.e., mosaic attenuation with a lobular pattern) are more common in patients with airways disease than in vascular disease. In a study by Im et al. (40) of 48 consecutive patients with lobular areas of low attenuation seen on HRCT, 46 (95%) had symptoms related to respiratory disease, and only 2 patients had vascular disease.

In patients with pulmonary vascular obstruction (e.g., CPTE) as a cause of mosaic perfusion, dilatation of central pulmonary arteries may be present as a result of PH, and areas of low attenuation are usually larger than pulmonary lobules (e.g., segments or lobes).

Ground-glass opacity may be accurately diagnosed as the cause of inhomogeneous lung opacity if it is associated with other findings of infiltrative disease such as consolidation, reticular opacities, honeycombing, or nodules. Ground-glass opacity may also result in very ill-defined and poorly marginated areas of increased opacity, lacking the sharply marginated and geographic appearance sometimes seen in patients with mosaic perfusion. Ground-glass opacity can often be diagnosed simply because lung looks too dense, although this is quite subjective and depends on using consistent window settings and being familiar with the appearance of normal lung parenchyma.

Expiratory HRCT scans may be useful in the diagnosis of mosaic attenuation and often allow the differentiation of mosaic perfusion resulting from airways obstruction from other abnormalities when inspiratory scans are inconclusive. In patients with ground-glass opacity, expiratory HRCT typically shows a proportional increase in attenuation in areas of both increased and decreased opacity. In patients with mosaic perfusion resulting from airways disease, attenuation differences are accentuated on expiration; relatively dense areas increase in attenuation, whereas lower attenuation regions remain lucent (i.e., air trapping is present) (see Chapter 3) (34,41–43).

In a study by Arakawa et al. (20) of patients showing mosaic attenuation as their predominant HRCT abnormality, the accuracy of HRCT in correctly diagnosing the type of disease present increased from 81% to 89% in patients with ground-glass opacity and from 84% to 100% in diagnosing airways disease when expiratory scans were included in the analysis (20). Some patients who appear to show ground-glass opacity on inspiratory scans and...
show air trapping on expiratory scans may thus be correctly diagnosed as having obstructive disease.

In patients with mosaic perfusion resulting from vascular disease, air trapping is not usually seen, and expiratory HRCT findings often mimic those seen in patients with ground-glass opacity. However, in a study of patients with inhomogeneous lung attenuation of various causes (33), air trapping was believed to be present on expiratory scans in some patients with vascular disease when scans were viewed blindly. Furthermore, air trapping has been reported in patients with acute pulmonary embolism, likely due to hypoxic bronchoconstriction (29). In 15 patients with pulmonary embolism studied by Arakawa et al. (29), mosaic perfusion was identified in 7 (46.7%) patients and air trapping in 9 (60%) patients. Of 32 areas of mosaic perfusion identified, 23 (71.9%) showed air trapping on expiratory scans.

**Findings of Pulmonary Edema and Hemorrhage**

Pulmonary edema may be associated with various PVDs, including some causes of PH and pulmonary vasculitis (2,44–46). It may be manifested by centrilobular, patchy, or diffuse ground-glass opacity, consolidation, interlobular septal thickening, peribronchovascular interstitial thickening, or a combination of these.

Pulmonary hemorrhage may also result in diffuse pulmonary abnormalities, and is common in pulmonary vasculitis syndromes. It may appear as centrilobular or diffuse ground-glass opacity, consolidation, or sometimes associated with interlobular septal thickening (46). Pulmonary edema and pulmonary hemorrhage are discussed in Chapter 18.

Pulmonary infarction resulting from vascular disease typically shows focal areas of consolidation, often wedge shaped and peripheral, and may be associated with a feeding vessel, surrounding ground-glass opacity (i.e., the "halo sign"), central lucencies, and absent air bronchograms (47,48). In a recent study (49), CT findings occurring with a higher frequency with pulmonary infarction than with other causes of consolidation included a feeding vessel (32% vs. 11%, respectively; \( p = 0.029 \)) and central lucencies (46% vs. 2% respectively; \( p < 0.001 \)). Air bronchograms, in contrast, were seen in a lower percentage of patients with pulmonary infarction (8% vs. 40%, respectively; \( p = 0.003 \)). Localized nodular or masslike opacities, with or without cavitaton, may also be seen in vasculitis syndromes, particularly granulomatosis with polyangiitis (GPA) (Wegener granulomatosis) and Churg-Strauss granulomatosis (50,51).

**Centrilobular Opacities and Nodules**

In patients with PH, ill-defined centrilobular opacities may be seen in patients who have plexogenic angioipathy (52), capillary pulmonary hemangiomatosis associated with proliferation of small vessels (53,54), PVOD with pulmonary edema, lobular mosaic perfusion, pulmonary hemorrhage, or cholesterol granulomas likely related to repeated episodes of hemorrhage (2,55).

Processes resulting in a vascular and perivascular inflammation, including vasculitis (56) and reaction to injected substances, such as talc (57–59), can produce ill-defined centrilobular opacities visible on HRCT. Connolly et al. (56) reported hazy or fluffy centrilobular, perivascula r opacities in eight children with vasculitis, including five with GPA (Wegener granulomatosis), one with systemic lupus erythematosus, one with scleroderma-polymyositis overlap syndrome, and one with Churg-Strauss syndrome (CSS). In these eight children, centrilobular opacities were associated with the onset of active disease or an exacerbation of pre-existing disease. In four of five patients, this abnormality disappeared on treatment.

**Cardiovascular Abnormalities Associated with Pulmonary Hypertension**

In addition to enlargement of the pulmonary arteries, a number of cardiovascular abnormalities visible using CT have been associated with PH, and many of these are related to right ventricular dysfunction and failure. These findings are largely beyond the scope of this book and are principally used in the assessment of patients with acute pulmonary embolism. Nonetheless, some useful findings are reviewed briefly.

Enlargement of the right ventricle and right atrium is common in patients who have PH, being seen in all patients who had PH studied by Bergin et al. (27). Findings of right atrial or right ventricular enlargement with flattening of the ventricular septum, or septal bowing to the left, are valuable in the diagnosis of PH, but require contrast infusion. Additional findings of PH include dilatation of the inferior vena cava (23,27), contrast reflux into the inferior vena cava (60), measurement of right ventricular (RV) and left ventricular (LV) short axes, RV/LV short-axis ratio, and superior vena cava and ayzygos vein diameters (61,62). Pericardial thickening or effusion may also be present. ECG-gated MDCT can be useful in the identification of cardiac abnormalities associated with PH (63).

**PULMONARY HYPERTENSION**

PH is defined as an abnormal elevation of pressure in pulmonary circulation, with a mean pulmonary arterial pressure higher than 25 mm Hg, regardless of the underlying mechanism. The clinical classification system for PH was updated at the Fourth World Symposium on Pulmonary Hypertension in Dana Point, California, in 2008 (63,64).

PH may have a variety of causes, and its treatment may vary considerably depending on its etiology (65,66). The treatment of PH in different diseases may require pharmacologic intervention with the use of anticoagulants or vasodilators, embolectomy, or lung transplantation (66).

The assessment of patients who have PH usually involves techniques other than HRCT (63–66). However,
HRCT may be performed (a) to assess patients who have PH related to lung disease (i.e., emphysema or pulmonary fibrosis), (b) in patients having PH of unknown cause, (c) in patients believed to have vasculitis or small vessel disease, or (d) in patients being evaluated for lung transplantation. Also, patients who have PH occurring because of CPTE often have CT for diagnosis.

The term primary pulmonary hypertension has been used to refer to PH of obscure cause or, more specifically, to idiopathic PH associated with plexogenic arteriopathy (66). PH associated with a specific disease has been referred to as secondary pulmonary hypertension. Secondary PH is most commonly associated with lung disease (e.g., emphysema, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis) and cardiac disease (e.g., chronic left-to-right shunts, left heart failure, mitral valve lesions), but other diseases (e.g., drug use, embolism of foreign material, obesity, sleep apnea, human immunodeficiency virus [HIV] infection, pericardial disease) may also result in PH (2,11,19,66).

In 2003, the clinical classification of PH was revised by the Third World Symposium on Pulmonary Arterial Hypertension held in Venice (67). In this classification, the terms “primary PH” and “secondary PH” were discarded in favor of a more precise description based on etiology, histologic findings, and associated diseases (67). Subsequently, at the Fourth World Symposium on PH held in 2008 in Dana Point, California, the consensus of an international group of experts was to maintain the general philosophy and organization of the Venice classifications. However, in response to a questionnaire regarding the previous classification, a majority of experts (63%) felt that modification of the Venice classification was required to accurately reflect information published over the past 5 years, as well as to clarify some areas that were unclear (68,69).

In the Dana Point classification (Table 22-1), a large category termed “pulmonary arterial hypertension (PAH)” is divided into (a) idiopathic pulmonary arterial hypertension (IPAH), (b) heritable pulmonary arterial hypertension (HPAH), (c) PAH associated with drugs or toxins, (d) PAH associated with collagen-vascular disease, HIV, portal hypertension, congenital heart disease, schistosomiasis, or chronic hemolytic anemia, and (e) PAH associated with venous or capillary abnormalities, specifically PVOD and pulmonary capillary hemangiomatosis (PCH), presenting in a similar fashion and with similar histologic abnormalities of small pulmonary arteries, including intimal fibrosis, medial hypertrophy, and plexiform arteriopathy. This classification also recognizes separate categories for PH with left heart disease, PH associated with lung disease and/or hypoxemia, PH due to chronic thrombotic and/or embolic disease, and PH with unclear multifactorial mechanisms (Table 22-1).

**Pulmonary Arterial Hypertension**

The diseases described using this term are characterized, at least in part, by plexogenic arteriopathy, a histologic abnormality consisting of a disorganized proliferation of small muscular arteries, endothelial cells, smooth muscle cells, and myofibroblasts (i.e., a plexiform lesion) (Fig. 22-4) (66). This abnormality has also been referred to as pulmonary hypertensive arteriopathy (70,71). As indicated previously, PAH may be idiopathic, familial, associated with various conditions, or associated with

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<th>TABLE 22-1 Clinical Classification of Pulmonary Hypertension (DANA POINT, 2008)</th>
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<td>1. Pulmonary arterial hypertension</td>
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<tr>
<td>1.1. Idiopathic PAH</td>
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<td>1.2. Heritable</td>
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<td>1.2.1. BMPR2</td>
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<td>1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)</td>
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<td>1.2.3. Unknown</td>
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<td>1.3. Drug- and toxin-induced</td>
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<td>1.4. Associated with</td>
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<tr>
<td>1.4.1. Connective tissue diseases</td>
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<td>1.4.2. HIV infection</td>
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<td>1.4.3. Portal hypertension</td>
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<td>1.4.4. Congenital heart diseases</td>
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<td>1.4.5. Schistosomiasis</td>
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<td>1.4.6. Chronic hemolytic anemia</td>
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<td>1.5 Persistent pulmonary hypertension of the newborn</td>
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<td>1’. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis</td>
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<td>2. Pulmonary hypertension owing to left heart disease</td>
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<tr>
<td>2.1. Systolic dysfunction</td>
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<td>2.2. Diastolic dysfunction</td>
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<td>2.3. Valvular disease</td>
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<td>3. Pulmonary hypertension owing to lung diseases and/or hypoxia</td>
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<td>3.1. Chronic obstructive pulmonary disease</td>
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<td>3.2. Interstitial lung disease</td>
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<td>3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
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<td>3.4. Sleep-disordered breathing</td>
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<td>3.5. Alveolar hypoventilation disorders</td>
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<td>3.6. Chronic exposure to high altitude</td>
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<td>3.7. Developmental abnormalities</td>
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<td>4. Chronic thromboembolic pulmonary hypertension</td>
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<tr>
<td>5. Pulmonary hypertension with unclear multifactorial mechanisms</td>
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<tr>
<td>5.1. Hematologic disorders: myeloproliferative disorders, splenectomy</td>
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<tr>
<td>5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis</td>
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<td>5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders</td>
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<tr>
<td>5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis</td>
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significant venous or capillary abnormalities (PVOD and PCH). Many of the causes of PAH result in similar HRCT findings, although PVOC and PCH show additional findings on HRCT that generally result in a distinct appearance.

**Idiopathic Pulmonary Arterial Hypertension**

IPAH is most common in patients 30 to 40 years of age, and women are affected more often than men. Symptoms include the insidious onset of dyspnea on exertion. Progressive symptoms, cor pulmonale, and death within a few years are typical. Pathologic abnormalities principally involve muscular pulmonary arteries (less than 1 mm in diameter) (67).

Enlargement of the central pulmonary arteries is common in patients with IPAH (Table 22-2) (11). In an HRCT study of 15 patients with IPAH (73), the main pulmonary artery was larger than the aorta in 93%. Mosaic attenuation may be seen, but is not a conspicuous feature of this disease, as it is in patients with CPTE (2,19). In one study, HRCT in five patients with IPAH showed enlargement of central pulmonary arteries, normal lung parenchyma (n = 3), and mosaic lung attenuation (n = 2) (Figs. 22-5 and 22-6). Interlobular septal thickening is visible in about 10% of patients (73). Cardiomegaly was visible in all 15 patients with IPAH in one study (67). Pericardial and pleural effusions were seen in 60% and 13%, respectively (73).

**Heritable Pulmonary Arterial Hypertension**

The primary genetic defect associated with HPAH, identifiable in more than 70% of cases, is a mutation in the gene encoding bone morphogenetic protein receptor type 2 (BMPR2), a member of the transforming growth factor beta superfamily; other mutations are more rarely associated. BMPR2 mutations also occur in 10% to 40% of apparently isolated cases of IPAH (68,74,75). IPAH and HPAH have similar clinical, functional, and survival characteristics (75).

**Drug and Toxin-Induced PAH**

PAH has a clear association with the use of various drugs and toxins use (52,67,68), including fenfluramine and dexfenfluramine taken for weight loss (Fig. 22-7). Clinical, functional, and hemodynamic features are similar to IPAH.

**PAH Associated with Other Diseases**

PAH occurring in the absence of lung disease may be seen in patients who have collagen-vascular disorders such as scleroderma, mixed connective tissue disease, rheumatoid disease, and systemic lupus erythematosus (76,77). The association is most clearly documented for patients with scleroderma. Generally, the histologic, CT, and HRCT findings are similar to those of IPAH. However, in patients with scleroderma and PAH, the prognosis is markedly worse than in patients with IPAH (68).

PAH is also associated infection with HIV (78–80), liver disease with portal hypertension (portopulmonary hypertension) (81,82), congenital heart disease, schistosomiasis, and chronic hemolytic anemia (68).

**Pulmonary Veno-Occlusive Disease and/or Pulmonary Capillary Hemangiomatosis**

PVOD and PCH are uncommon, but increasingly recognized as causes of PH (68). PVOD and PCH are quite similar in terms of lung abnormalities, pathologic features, clinical presentation, and associations.
Figure 22-5  A–C: Idiopathic PH with plexogenic arteriopathy.  
A: Enlargement of the main pulmonary artery and right pulmonary arteries is visible at tissue windows (arrows). A small pericardial effusion is present.  
B: At a lung window, central pulmonary artery branches (arrows) are increased in diameter and appear much larger than their adjacent bronchi.  
C: Pulmonary arteries appear relatively small in the lung periphery (arrows). Lung parenchyma shows a slightly inhomogeneous attenuation, likely due to mosaic perfusion.

Figure 22-6  A–C: Idiopathic PH with plexogenic arteriopathy.  
A: Enlargement of the main and left pulmonary artery is visible at tissue windows (arrows).  
B and C: Lung window scans through the upper lobes show inhomogeneous lung attenuation with a lobular or centrilobular distribution.  
Relatively large vessel size in areas of increased attenuation (arrows) suggests mosaic perfusion as the cause of inhomogeneous opacity. A similar appearance was visible in the lower lobes. Histologic examination of the lungs after removal for lung transplantation showed plexogenic arteriopathy.
Pulmonary Veno-Occlusive Disease

PVOD is a rare disorder in which gradual obliteration of the pulmonary veins by intimal thickening and fibrosis leads to PAH (83–86). Interlobular or small postcapillary veins may be involved (Fig. 22-8), and the process may involve the lung in a diffuse or patchy fashion (85). Venous obstruction leads to edema of the interlobular septa, septal lymphatic dilatation, and venous infarcts. Patchy dilatation and proliferation of alveolar capillaries are associated with interstitial fibrosis and hemorrhage, and lead to secondary hyperplasia of muscular pulmonary arteries (85).

PVOD is typically idiopathic, but has multiple associations, including viral infections, inhaled toxins, deposition of immune complexes in patients with collagen-vascular diseases, Langerhans histiocytosis, a genetic predisposition, AIDS, and use of contraceptive or cytotoxic chemotherapeutic agents. In addition, radiation injury has been proposed as a possible cause. It may affect any age, but it is most common in children and young adults. Symptoms are nonspecific and consistent with PH. Characteristic of PVOD and PCH is elevated PAP but normal or low pulmonary capillary wedge pressure (85). The disease is generally fatal within a few years (85).

HRCT findings have been described in a number of patients (2,11,53,73,83,85,87,88). The most common findings include (a) smooth interlobular septal thickening (Fig. 22-9); (b) diffuse or multifocal regions of ground-glass opacity, which may be geographic and patchy, perihilar or peripheral, or centrilobular (Fig. 22-10); (c) pericardial or pleural effusions; (d) enlarged central pulmonary arteries; and (e) pulmonary veins of normal caliber; this combination of findings is highly suggestive of PVOD (Table 22-3) (87). In the one study (87), 7 of 8 patients had interlobular...
septal thickening, and all 8 patients had regions of ground-glass opacity. In a study of 15 patients with pathologically proven PVOD, 93% showed interlobular septal thickening, and 87% showed ground-glass opacity. Centrilobular ground-glass opacities were visible in 67% of the 15 patients, whereas 33% showed panlobular opacities (73). In comparing the HRCT findings in patients with PVOD to those of IPAH, ground-glass opacities \( (p = 0.003) \), centrilobular ground-glass opacities \( (p = 0.03) \), interlobular septal thickening \( (p < 0.0001) \), and mediastinal lymph node enlargement \( (p < 0.0001) \) were significantly more frequent in the patients with PVOD (Table 22-4) (73). Histologic correlation with CT findings (87) has shown that thickened interlobular septa corresponded to the presence of septal fibrosis and venous sclerosis. Ground-glass opacity may be related to alveolar wall thickening or pulmonary edema.

Central pulmonary arteries were considered to be enlarged in 7 of 8 in one study (87). In another study, the main pulmonary artery was larger than the aorta in all 15 (73). Mosaic perfusion may be seen, but is not a prominent feature of this disease (87). Pericardial or pleural effusion (73,87) and mediastinal lymph node enlargement may be seen (73). Cardiomegaly is common, and although right-sided chambers are enlarged, the left atrium and ventricle are normal in size (85).

**Pulmonary Capillary Hemangiomatosis**

PCH is a very rare cause of PAH, most often occurring in young adults and associated with dyspnea and hemoptysis (89). Although slow progression is typical, mean survival is only 3 years. As with PVOD, PCH is idiopathic,
but many associations have been reported, including systemic lupus erythematosus, scleroderma, Takayasu arteritis, Kartagener syndrome, hypertrophic cardiomyopathy, and genetic factors (54,85,89). It has been suggested that PCH may occur secondary to PVOD, because both entities share a number of clinical and pathologic characteristics (86).

Pathologically, PCH represents a patchy interstitial proliferation of thin-walled capillary-size blood vessels within alveolar walls. The sheets of vessels surround, compress, and appear to invade the walls of pulmonary veins and are associated with intimal fibrosis, venous occlusion, interstitial edema, and hemorrhage (86,90). Chest radiographs may be normal, except for findings of PAH, or may show small nodular opacities.

HRCT findings have been reported in a few patients who have this disease (85,91). Ill-defined centrilobular nodules of ground-glass opacity, diffuse in distribution, are most typically described, and patchy or lobular areas of ground-glass opacity may also be seen (Figs. 22-11 and 22-12, Table 22-5). HRCT in two patients who had PCH showed mediastinal and hilar lymph node enlargement, enlargement of pulmonary arteries, and pleural effusions (53). In both patients (53) and in one other reported patient (54), HRCT showed smooth thickening of interlobular septa, small ill-defined centrilobular nodules, and focal regions of lobular or centrilobular ground-glass opacity. In comparison to patients with PVOD, thickened interlobular septa were sparse and few in number (85). Pathologic correlation in these cases showed that the centrilobular opacities correlated with proliferations of small

### TABLE 22-3 HRCT Findings in Pulmonary Veno-Occlusive Disease

<table>
<thead>
<tr>
<th>HRCT finding</th>
<th>PVOD</th>
<th>IPAH</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric dilatation of the central pulmonary arteries</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Interlobular septal thickening</td>
<td>67%</td>
<td>27%</td>
<td>0.03</td>
</tr>
<tr>
<td>Ground-glass opacities</td>
<td>67%</td>
<td>27%</td>
<td>0.03</td>
</tr>
<tr>
<td>Normal size pulmonary veins</td>
<td>67%</td>
<td>27%</td>
<td>0.03</td>
</tr>
<tr>
<td>Combination of the previous four findings</td>
<td>67%</td>
<td>27%</td>
<td>0.03</td>
</tr>
<tr>
<td>Ill-defined centrilobular ground-glass opacities or nodules</td>
<td>67%</td>
<td>27%</td>
<td>0.03</td>
</tr>
<tr>
<td>Mediastinal lymph node enlargement</td>
<td>67%</td>
<td>27%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Most common findings.*
*Finding(s) most helpful in differential diagnosis.*

### TABLE 22-4 Comparison of Frequency of HRCT Findings in Patients with Pulmonary Veno-Occlusive Disease and Idiopathic Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>HRCT finding</th>
<th>PVOD</th>
<th>IPAH</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground-glass opacity</td>
<td>87%</td>
<td>33%</td>
<td>0.003</td>
</tr>
<tr>
<td>Centrilobular ground-glass opacity</td>
<td>67%</td>
<td>27%</td>
<td>0.03</td>
</tr>
<tr>
<td>Septal lines</td>
<td>93%</td>
<td>13%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>27%</td>
<td>13%</td>
<td>NS</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>60%</td>
<td>60%</td>
<td>NS</td>
</tr>
<tr>
<td>Mediastinal node enlargement</td>
<td>80%</td>
<td>0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>73%</td>
<td>100%</td>
<td>NS</td>
</tr>
<tr>
<td>Enlarged pulmonary artery</td>
<td>100%</td>
<td>93%</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant.


### FIGURE 22-11 A-C: Pulmonary capillary hemangiomatosis. HRCT at three levels shows patchy areas of ground-glass opacity, a common finding in this disease. This appearance is nonspecific. The diagnosis was made at open lung biopsy.
capillary-size vessels and intra-alveolar hemosiderin-laden macrophages.

**Use of High-Resolution Computed Tomography in Determining Treatment in Pulmonary Arterial Hypertension**

Therapy commonly used for treatment of patients with PAH can be harmful or even fatal in patients with PVOD or PCH (73,85,88,92). Vasodilators such as prostan bolins and calcium channel blockers are used to treat PAH, and have been shown to increase exercise potential, hemodynamics, and long-term survival. However, these drugs may result in severe pulmonary edema or death in patients with postcapillary PH. In patients with PVOD and PCH, dilation of pulmonary small muscular arteries and arterioles occurring with vasodilator treatment likely results in increased transcapillary hydrostatic pressure and pulmonary edema because of the presence of fixed, elevated pulmonary venous resistance. Lung transplantation remains the most effective means of prolonging survival and improving quality of life for patients with PVOD or PCH (85,88).

It has been recommended that HRCT be performed prior to vasodilator treatment in patients with PAH. The presence of HRCT findings that suggest the diagnosis of PVOD or PCH, such as interlobular septal thickening or centrilobular ground-glass opacities, should lead to further evaluation before vasodilator treatment is instituted (73,92). In a study by Resten et al. (92), 73 consecutive patients with severe PH treated with epoprostenol (prostan bolin) were retrospectively separated into two groups. Group 1 included 12 patients with epoprostenol therapy failure, leading to death in an average of 1.9 months; 6 of these patients subsequently evaluated at autopsy had PVOD or PCH. The second group of 61 patients improved clinically with epoprostenol; this group was comprised of patients with IPAH, familial PAH, and PAH related to drugs, collagen-vascular disease, and HIV infection. Pretreatment HRCT findings of ground-glass opacity (p = 0.004), a centrilobular pattern of ground-glass opacities (p = 0.003), interlobular septal thickening (p = 0.04), pericardial effusion (p = 0.04), pleural effusion (p = 0.01), and mediastinal lymphadenopathy (p = 0.009) were all more common in group 1, and strongly correlated with a risk of clinical worsening with epoprostenol treatment (Table 22-6, Fig. 22-12) (92).

**TABLE 22-5** HRCT Findings in Pulmonary Capillary Hemangiomatosis

<table>
<thead>
<tr>
<th>Finding</th>
<th>Treatment failure</th>
<th>Treatment response</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilatation of the central pulmonary arteries</td>
<td>83%</td>
<td>38%</td>
<td>0.004</td>
</tr>
<tr>
<td>Ill-defined centrilobular ground-glass opacities</td>
<td>67%</td>
<td>21%</td>
<td>0.003</td>
</tr>
<tr>
<td>Lobular ground-glass opacities</td>
<td>67%</td>
<td>21%</td>
<td>0.003</td>
</tr>
<tr>
<td>Interlobular septal thickening inconspicuous</td>
<td>67%</td>
<td>21%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**TABLE 22-6** Frequency of HRCT Findings in Patients with Pulmonary Arterial Hypertension Who Had Epoprostenol Failure or Response

<table>
<thead>
<tr>
<th>HRCT finding</th>
<th>Treatment failure</th>
<th>Treatment response</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ground-glass opacity</td>
<td>83%</td>
<td>38%</td>
<td>0.004</td>
</tr>
<tr>
<td>Centrilobular ground-glass opacity</td>
<td>67%</td>
<td>21%</td>
<td>0.003</td>
</tr>
<tr>
<td>Septal lines</td>
<td>58%</td>
<td>26%</td>
<td>0.04</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>83%</td>
<td>43%</td>
<td>0.01</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>75%</td>
<td>43%</td>
<td>0.04</td>
</tr>
<tr>
<td>Mediastinal node enlargement</td>
<td>67%</td>
<td>16%</td>
<td>0.009</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>92%</td>
<td>95%</td>
<td>NS</td>
</tr>
<tr>
<td>Enlarged pulmonary artery</td>
<td>100%</td>
<td>98%</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, not significant.

Pulmonary Hypertension Associated with Lung Disease or Hypoxemia

In patients who have PH resulting from lung disease, a pulmonary abnormality should be easily visible on HRCT (Fig. 22-13). Common lung diseases resulting in PH include emphysema, pulmonary fibrosis related to idiopathic pulmonary fibrosis or other fibrotic lung diseases, and COPD (68,93). The absence of a recognizable lung abnormality on HRCT in a patient who has known PH should suggest other causes than lung disease. Elevation of PAP as a result of lung disease is usually modest (68).

Although HRCT can be valuable in detecting lung disease in patients with known PH, it has been shown that HRCT may be of limited value in predicting the presence of PH in patients with lung fibrosis or interstitial lung disease (ILD) (94–97). In a study of 65 patients with advanced idiopathic pulmonary fibrosis using right heart catheterization and HRCT, the HRCT determined severity of fibrosis, ground-glass opacity, honeycombing, the diameter of the main pulmonary artery, and the ratio of the pulmonary artery to aorta diameter did not differ between those with and without PH (95). Furthermore, there was no significant correlation between mPAP and any of the HRCT measurements (95). In a study by Alhamad et al. (96), CT measurements of the main PAD, the ratio of PAD to the ascending aorta diameter, right PAD, and left PAD were obtained in 100 patients with ILD and 34 without ILD. A PAD greater than 25 mm in patients with ILD was predictive of PH, with a sensitivity of 86.4% (32 of 37), but the specificity of this measurement was only 41.2% (26 of 63).

Another study also compared PAD to PAP in patients with lung fibrosis. The authors found that PA dilatation can occur in the absence of PH in patients with pulmonary fibrosis and is an unreliable sign of PH in these patients (97). In this study, in patients without pulmonary fibrosis, there were strong correlations between main PAD and both mPAP (r = 0.67, p < 0.0001) and pulmonary vascular resistance index (PVRi) (r = 0.78, p < 0.0001); in patients with pulmonary fibrosis, no significant correlations were found (r = 0.23, p = 0.22 for mPAP and r = 0.23, p = 0.28 for PVRi). On the other hand, measuring the PAD/ascending aorta diameter ratio significantly strengthened correlations in the patients with lung fibrosis (r = 0.54, p < 0.005 for mPAP and r = 0.48, p = 0.04 for PVRi) (8).

PH may also be associated with chronic hypoxemia, such as may occur with sleep apnea or other sleep-related hypoxemia syndromes, other causes of alveolar hypoventilation, or chronic exposure to high altitude (67). These may result in few CT abnormalities other than cardiomegaly and enlargement of the main pulmonary artery and its branches.

Chronic Thromboembolic Pulmonary Hypertension

Chronic Pulmonary Thromboembolism

The diagnosis of chronic thromboembolic pulmonary hypertension (98) is often difficult because symptoms and pulmonary function test results are usually nonspecific (99,100). Also, CPTE is a relatively rare cause of PH (27). Contrast-enhanced multidetector spiral HRCT is most appropriate in the assessment of patients who...
have suspected CPTE, allowing both the diagnosis of thromboembolic vascular obstruction and a delineation of lung abnormalities. Findings of right ventricular and right atrial enlargement are common, as are findings of pulmonary artery occlusions, eccentric filling defects within pulmonary artery branches, irregular or nodular thickening of pulmonary artery walls, narrowing of an artery lumen, recanalized arteries with a concentric thickened wall, intra-arterial webs, and bronchial artery enlargement (101).

Dedicated HRCT (without contrast infusion) may be obtained as the initial examination in some patients because of unexplained dyspnea or other nonspecific symptoms (102) (Figs. 22-2 and 22-3). HRCT findings in patients who have CPTE reflect variable obstruction of large and small arteries, and include (a) symmetric or asymmetric dilatation of the central pulmonary arteries, with a diameter often exceeding that of the ascending aorta; (b) reduced diameter of segmental arteries, which thus appear smaller than their accompanying bronchi; (c) abruptly truncated segmental arteries; (d) variation in the size of arteries; and (e) mosaic perfusion (Figs. 22-2 and 22-3, Table 22-7) (101). Calcification of the walls of central arteries or thrombus may be seen (Fig. 22-14).

Inhomogeneous lung attenuation representing mosaic perfusion is common in patients who have CPTE, and decreased vessel size in less opaque regions is commonly visible (Figs. 22-2 and 22-3). In the absence of airways abnormalities and air trapping, this combination of findings is strongly suggestive of CPTE. In a study of pulmonary parenchymal abnormalities in 75 patients who had CPTE, 58 (77.3%) patients showed mosaic perfusion with normal or dilated arteries in areas of relative increased attenuation (26). In a study of patients who had PH due to CPTE, PH of other causes, and a variety of other pulmonary diseases, HRCT was believed to show mosaic perfusion in all patients who had CPTE (27). Considerably more variation in the size of segmental vessels in different lung regions was also visible in the patients who had CPTE compared to patients who had other lung diseases, and this was the most accurate finding in making the correct diagnosis (27). Overall, HRCT had a sensitivity of 94% to 100% and a specificity of 96% to 98% in diagnosing CPTE based on these findings (27).

Peripheral wedge-shaped, pleural-based opacities suggest the presence of infarcts in patients who have pulmonary embolism (26), but are nonspecific and uncommon in patients who have chronic disease (27). In contrast, scars from prior pulmonary infarction are commonly seen on CT in patients who have CPTE, appearing as parenchymal bands or irregular linear opacities (23,27). These were identified in the majority of patients who had CPTE in one study, but they were also seen in 22% to 26% of patients who had PH of other cause (27).

Radionuclide imaging also has a high sensitivity and specificity in making the diagnosis of CPTE (27). In one study, it identified 94% of patients with this diagnosis. However, specificity in this study was only 75%, which was lower than that of HRCT.

<table>
<thead>
<tr>
<th>TABLE 22-7 HRCT Findings in Chronic Pulmonary Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric or asymmetric dilatation of the central pulmonary arteries</td>
</tr>
<tr>
<td>Abruptly truncated segmental arteries</td>
</tr>
<tr>
<td>Variation in the size of arteries$^b$</td>
</tr>
<tr>
<td>Mosaic perfusion$^a,b$</td>
</tr>
<tr>
<td>Intravascular filling defects on contrast-enhanced CT$^a,b$</td>
</tr>
<tr>
<td>Peripheral wedge-shaped opacities</td>
</tr>
</tbody>
</table>

$^a$Most common findings.
$^b$Finding(s) most helpful in differential diagnosis.


**Sickle Cell Anemia**

Pulmonary abnormalities associated with sickle cell anemia include pneumonia, acute chest syndrome (ACS), PH with cor pulmonale, and pulmonary fibrosis (103). PH occurs in 10% to 30% of patients, and is the cause of death in about 3% (67,104). It likely occurs because of in situ thrombosis of distal arteries, sometimes associated with the development of plexogenic lesions (67).

ACS is characterized by fever, cough, chest pain, hypoxia, prostration, and pulmonary opacities on chest radiographs. It is likely related to sickling of red blood cells with pulmonary microvascular occlusion and infarction, although pneumonia has also been implicated in the pathogenesis of this syndrome. Infarction and pneumonia are not easily differentiated using chest radiography or ventilation-perfusion scintigraphy.

HRCT findings in patients who have ACS (105) include patchy airspace consolidation, likely related to edema or infarction, ground-glass opacity, and vascular attenuation (Fig. 22-15). In one study of patients who had ACS, Bhalla et al. (105) assessed the ability of HRCT to diagnose small vessel abnormalities, thus helping distinguish vascular obstruction from pneumonia as a cause of symptoms. In 9 of 10 patients with moderate to severe ACS, HRCT was believed to show findings of microvascular occlusion and hypoperfusion (i.e., a paucity or absence of small vessels). These regions of hypoperfusion were associated with ground-glass opacity, probably related to hemorrhagic edema. In all patients, the degree of hypoxia was out of proportion to the extent of consolidation evident at chest radiography.

The end result of repeated episodes of pneumonia or ACS in patients who have sickle cell anemia is termed *sickle cell lung disease* (106). Its prevalence in patients who have sickle cell anemia is 4%. Postmortem examinations have shown pulmonary fibrosis and obliteration of pulmonary arterioles (106); fibrosis is likely related to small areas of infarction (11,107). With sufficient occlusion of the pulmonary vascular bed, PH and cor pulmonale may develop (Fig. 22-15) (11,107).

HRCT findings in 29 patients with a history of one or more episodes of ACS were reported by Aquino et al. (108) and are most consistent with fibrosis and infarction. Twelve of the 29 (41%) patients had significant multifocal ILD, including interlobular septal thickening, parenchymal bands, traction bronchiectasis, and architectural distortion. Mosaic perfusion with decreased vessel size, likely as a result of vascular obstruction, was seen in two patients, both with PH. A correlation was found between the extent of abnormalities and the number of episodes of ACS ($p = 0.02$) (108).

In a study by Sylvester et al. (109) of 33 patients with chronic sickle cell disease, HRCT findings of lobar volume loss (67% of cases), prominence of central (70%) or peripheral (52%) vessels, reticular pattern (82%), irregular linear opacities (42%), and ground-glass opacity (58%) were the most frequent. Lobar volume loss, irregular reticular opacities, and prominent central vessels were each correlated with pulmonary function test findings of restriction (109). These findings are believed to be related to fibrosis associated with chronic disease. In another study (110), HRCT revealed mild basilar focal fibrosis in patients with sickle cell disease, many of whom had PH. HRCT fibrosis severity tended to increase with increased pulmonary artery systolic pressures and also correlated with the results of pulmonary function testing (110).

**Nonthromboembolic Pulmonary Embolism**

In addition to pulmonary thromboembolism, embolism of a variety of materials may result in similar symptoms and radiographic findings (11,14,101). These include pulmonary tumor embolism, fat embolism, embolism of injected substances, and embolism of parasites.

**Pulmonary Artery Tumor Embolism.** The diagnosis of pulmonary arterial tumor emboli is difficult to establish clinically (14,101,111). Symptoms include progressive dyspnea due to PH and cor pulmonale, or a more acute presentation that mimics pulmonary thromboembolism. Most often, patients have a known history of neoplasm, but tumor emboli may occasionally be the first
manifestation of disease. HRCT with contrast infusion may show large enhancing intravascular tumor emboli. Peripheral arteries may be occluded or show focal areas of dilatation due to growing intravascular tumor deposits (Fig. 22-16) (11). Arteries may have a beaded appearance or may mimic the appearance of tree-in-bud (16,17). This may result from filling of small centrilobular arteries by tumor or thrombotic microangiopathy, wherein fibroc cellular intimal hyperplasia of small pulmonary arteries is initiated by tumor microemboli (101).

Four cases of intravascular pulmonary metastases were reported by Shepard et al. (15). All four patients had invasive tumors (atrial myxoma, renal cell carcinoma, osteosarcoma, chondrosarcoma). Three cases had histopathologic documentation of PA tumor emboli. At CT, all patients demonstrated multifocal dilatation and beading of peripheral pulmonary arteries, primarily in a subsegmental distribution and involving multiple lobes. In two cases, small, peripheral wedge-shaped opacities distal to some abnormal pulmonary arteries suggested pulmonary infarction. A CT appearance of multiple subpleural opacities, some wedge shaped, has also been reported by Kim et al. (112) in a woman who had carcinoma of the cervix and histologic confirmation of intravascular emboli and distal areas of lung infarction.

**Fat Embolism.** Fat embolism occurs in more than 90% of patients with traumatic bone injury, and rarely in other conditions, but most examples are asymptomatic (14,101). The term “fat embolism syndrome (FES)” is

![Figure 22-16](image)

**FIGURE 22-16** A: Intravascular tumor emboli. Magnified view of CT scan at the level of the lingula demonstrates beaded appearance of the peripheral pulmonary arteries. The findings were due to intravascular tumor emboli from breast carcinoma. (Courtesy of Drs. Lynn Broderick and Robert Tarver, Indiana University Medical Center, Indianapolis.) B: Intravascular tumor emboli in a young patient with a thigh sarcoma. A beaded vessel is clearly seen on HRCT (arrow). C: Intravascular tumor emboli in a patient with metastatic osteogenic sarcoma.
used to describe a clinical entity characterized by pulmonary, cerebral, and cutaneous abnormalities; it occurs in only 1% to 4% of patients with major fractures. Lung is most frequently affected, and patients develop acute respiratory failure that may lead to acute respiratory distress syndrome with dyspnea, hypoxemia, and sometimes hemoptysis. This characteristic occurs from 12 hours to 3 days following the injury, and resolves within 1 or 2 weeks (14). The clinical diagnosis of FES is made by the presence of at least one major and four minor criteria as defined by Gurd and Wilson (113). Major criteria include respiratory distress, cerebral involvement manifested by various symptoms, and petechial hemorrhage. Minor criteria include tachycardia, pyrexia, retinal changes, fat present in the urine, jaundice, a sudden drop in hematocrit or platelet levels, increasing erythrocyte sedimentation rate, and fat globules in the sputum.

Several factors likely contribute to the lung injury present in FES. Fat droplets gaining access to the systemic circulation at the site of bone injury cause direct mechanical obstruction of the pulmonary microvasculature; triglycerides transported to the lung are hydrolyzed to free fatty acids, which act locally to increase permeability of the capillary bed and damage lung alveolar cells; and platelet and white blood cell aggregation stimulated by fat globules cause release of vasoactive substances that may cause edema, hemorrhage, and vessel disruption (14,101,114,115).

CT and HRCT findings have been described in several studies (114–119). Findings include (a) patchy or geographic areas of ground-glass opacity, (b) smooth interlobular septal thickening in the regions showing ground-glass opacity (i.e., crazy paving), (c) patchy consolidation, and (d) centrilobular or subpleural nodules. Abnormalities involve both dependent and nondependent lung regions, as well as the upper lobes to the same degree as, or more frequently than, the lower lobes (114,115,119). Pleural effusions are commonly seen (115,119). Contrast-enhanced scans did not prove to be of value (105). In one study, the extent of CT abnormalities correlated negatively with PaO₂ (r = 0.8, p < 0.05) (119).

Ground-glass opacities or consolidation were seen in all 11 patients reviewed in two separate studies, although ground-glass opacities were more frequent (115,119). In a study of 9 patients with mild FES, 7 had ground-glass opacity, whereas none showed consolidation (114). In this latter study (114), ground-glass opacities showed a peripheral, subpleural, nondependent distribution in 3 patients, while the ground-glass opacities had a patchy distribution with sharp margination between areas of involved and noninvolved lung in 4 patients, resulting in geographic appearance. Associated interlobular septal thickening was seen in 5 of 7 patients with ground-glass opacity in one study (114).

Ill-defined or well-defined centrilobular and subpleural nodules from a few millimeters to 1 cm in diameter have been a consistent finding in several studies (115,117–119). These opacities may reflect perivascular edema, hemorrhage, or an inflammatory response resulting from ischemia and cytotoxic emboli (115,117,118). It has been suggested that in patients with an appropriate history of trauma, this finding may be used to suggest the diagnosis (115). Poorly marginated centrilobular or subpleural nodules were seen in four of five patients in one study (115); in three cases, the nodules were peripheral, with upper lobe predominance in two patients. These nodules may be associated with peripheral artery branches (119). Nodular opacities were seen in only two of nine patients with mild FES (114).

**Embolism of Foreign Material.** Injection of foreign substances such as talc, cellulose, crospovidone, starch, or mercury may be seen in drug abusers (101,120). This may result in small vessel obstruction and thrombosis, PH, pulmonary infarction, or the development of perivascular fibrosis and granulomas appearing as centrilobular nodules or branching opacities (11,14,120).

Talcosis secondary to intravenous (IV) injection of talc is seen almost exclusively in drug users who inject crushed oral medications, including talc (magnesium silicate) (121,122). The injected talc particles result in small vascular granulomas composed of multinucleated giant cells surrounded by a small amount of fibrous tissue (123,124). HRCT findings in patients who have talcosis resulting from IV injection include (a) nodules as small as 1 mm in diameter, which may be diffuse or centrilobular, (b) branching centrilobular opacities due to perivascular granulomas or fibrosis (Figs. 13-37 and 13-38), and (c) diffuse ground-glass opacities, (d) confluent perihilar masses resembling progressive massive fibrosis (Figs. 13-37 and 13-38), and (e) panlobular emphysema with a basal predominance (57,59,101,123,125). The confluent masses may appear high in attenuation because of contained talc. Emphysema is usually seen in patients injecting crushed methylphenidate (methylphenidate hydrochloride [Ritalin]) tablets (123,125). Injection of cellulose, crospovidone (an insoluble cellulose derivative used in tablets), and starch may result in centrilobular nodules and branching opacities similar to those seen in talcosis. Embolization of cement to pulmonary artery branches may occur in patients having percutaneous vertebroplasty. This complication has been reported in as many as 4.6% of cases and is most common when leakage of cement into paravertebral veins is observed (101,126–128). Cement embolization may be associated with dyspnea, and anticoagulation is used in treatment.

**Embolism of Parasites.** Pulmonary embolism of hydatid cysts, secondary to rupture of hepatic cysts into the hepatic vein or inferior vena cava, or rupture of mediastinal cysts into the heart or pulmonary artery, may rarely occur in a patient with echinococcus, resulting in vascular...
obstruction and acute or chronic PH (14,101). Segmental pulmonary artery branches may show focal dilatation.

PH has been reported in as many as 70% of patients with hepatosplenic schistosomiasis mansoni, portal hypertension, and esophageal varices, and in 20%, PH is moderate to severe (129).

HEPATOPULMONARY SYNDROME

A variety of thoracic CT findings may be seen in patients with cirrhosis (130). HPS is defined by the triad of hepatic dysfunction, intrapulmonary vascular dilatation, and abnormal arterial oxygenation (hypoxemia) (131–133). Clinically, HPS is typically manifested with progressive dyspnea and hypoxemia in a patient with cirrhosis. It may also be associated with platypnea and orthodeoxia, defined respectively as dyspnea and hypoxemia, occurring when upright and relieved when recumbent (131,132). PAP is normal or reduced.

Although the pathogenesis of vascular dilatation is unknown, some investigators have suggested that nitric oxide associated with portal hypertension might influence the autoregulation of peripheral pulmonary vasculature, resulting in vasodilatation (133). Although it would seem logical that the hypoxemia of HPS is due to a right-to-left shunt through dilated pulmonary vessels, this is not usually the case. Hypoxemia in patients who have HPS has multiple complex causes and is believed to occur primarily because of a limitation in oxygen diffusion occurring because of vascular dilatation (diffusion-perfusion impairment) (131). In patients who have diffusion-perfusion impairment, the use of 100% oxygen results in a decrease

**FIGURE 22-17** Perivascular fibrosis and granulomatosis in a body builder who injected powdered steroids for years. Lung biopsy showed perivascular interstitial and vascular granulomas containing two crystalline substances, cellulose and crospovidone, commonly used as binders in tablets. A: HRCT shows branching centrilobular opacities. B: At a higher level, a focal region of fibrosis is visible in the posterior right lung, similar to that seen in patients with talcosis.

**FIGURE 22-18** Perivascular fibrosis and granulomatosis in a young man who injected crushed tablets intravenously. Lung biopsy showed perivascular granulomas containing talc, cellulose, and crospovidone. A and B: HRCT at two levels shows small well-defined centrilobular nodules and branching centrilobular opacities.
in the size of the apparent shunt with significant improvement in oxygenation. In patients who have arteriovenous fistulas, this does not occur.

Based primarily on arteriographic findings, Krowka et al. (132,133) classified the lesions of HPS into two types. The type 1 (minimal) pattern is most common (85%); it is associated with a spidery appearance of peripheral vessels and, usually, a good response to treatment with 100% oxygen. Type 2 lesions (15%) represent small, discrete pulmonary arteriovenous fistulas; type 2 lesions are associated with a poor response to 100% oxygen.

The radiologic manifestations of HPS have been recently reviewed (11,13,134). Radiographic findings in patients who have HPS may include bibasilar nodular or reticular opacities on chest radiographs and peripheral arteriolar dilatation on pulmonary angiography (134). Mild enlargement of central pulmonary arteries may also be seen (134).

CT and HRCT findings in HPS include vascular dilatation in the peripheral lungs associated with an abnormally large number of visible terminal artery branches (Table 22-8, Figs. 22-19 and 22-20). The abnormality is almost always bilateral and predominant in the lower lobes. On HRCT, the peripheral vascular branches are several millimeters in diameter and may extend to the pleural surface (134), a finding not seen in normal subjects. In some cases, the peripheral vascular branches are sufficiently large that they may be seen to opacify after contrast infusion. HRCT is useful in excluding pulmonary fibrosis or emphysema as the cause of the plain film abnormalities. Also of importance in the CT diagnosis of HPS is the recognition of associated hepatic disease, with findings of cirrhosis, splenomegaly, varices, and ascites (134).

HRCT may be helpful in the diagnosis of HPS by demonstrating the dilated peripheral pulmonary vessels or increased pulmonary artery-to-bronchus ratios in patients with liver disease and hypoxemia (130,135). In one study (135), 10 patients with HPS, 12 patients with normoxic cirrhosis, and 12 healthy controls were studied using conventional CT and HRCT. The mean diameters of the main pulmonary trunk and right and left main pulmonary arteries did not differ between the three groups. Mean diameters of right lower lobe basal segmental pulmonary arteries and the basal segmental pulmonary artery-to-bronchus ratios were significantly higher in HPS than in normoxic cirrhosis ($p = 0.01$ and $p = 0.03$) and normal controls ($p = 0.002$ and $p < 0.001$).

<table>
<thead>
<tr>
<th>TABLE 22-8 HRCT Findings in Hepatopulmonary Syndrome</th>
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<tbody>
<tr>
<td>Dilatation of peripheral pulmonary vessels(^{a,b})</td>
</tr>
<tr>
<td>Arteriovenous fistulas(^b)</td>
</tr>
<tr>
<td>Lower lobe predominance(^a)</td>
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</table>

\(^a\)Most common findings.

\(^b\)Findings most helpful in differential diagnosis.

The extent of the vascular dilatation tends to correlate with the degree of hypoxemia (134). In one study (13), HRCT findings in eight patients with HPS were compared with those of eight healthy subjects and with four patients with normoxic cirrhosis. On HRCT, the ratio of segmental arterial diameter to adjacent bronchial diameter in the right lower lobe was significantly increased in HPS patients compared with control subjects and patients who had normoxic cirrhosis ($p = 0.002$). The diameter of peripheral pulmonary arteriovenous fistulas was also increased in HPS patients compared with control subjects and patients who had normoxic cirrhosis ($p = 0.002$).
arteries in the right lower lobe was $7.3 \pm 1.6$ mm, compared to $4 \pm 0.4$ mm in patients who had normoxic cirrhosis. The ratio of arterial diameter to adjacent bronchial diameter was $2.0 \pm 0.2$ mm in patients who had HPS compared to $1.2 \pm 0.2$ mm in patients who had normoxic cirrhosis ($p < 0.05$) (13).

**PULMONARY VASCULITIS**

The term “systemic vasculitis” refers to a variety of clinicopathologic disease entities, each of which is characterized pathologically by cellular inflammation and destruction of blood vessel walls; the lungs may be involved along with other organs (51,136–138). Systemic vasculitis syndromes have been classified in a number of ways, but none of the proposed systems is ideal or universally accepted (9,50,136,137).

The American College of Rheumatology published criteria for the classification of vasculitis in 1990, which were reviewed at an International Consensus Conference in Chapel Hill, North Carolina (137). The Chapel Hill classification system (137) divides the systemic vasculitis syndromes into three groups based on the size of vessels primarily involved (Table 22-9). These are (a) large vessel vasculitis, (b) medium-size vessel vasculitis, and (c) small vessel vasculitis. Antineutrophilic cytoplasmic antibody (ANCA)-associated small vessel vasculitis, specifically GPA (Wegener granulomatosis), Churg-Strauss granulomatosis, and microscopic polyangiitis (MPA) are the systemic vasculitis syndromes most often associated with pulmonary abnormalities (51,139).
Although the Chapel Hill classification has been widely adopted for the description of pulmonary vasculitis, it has been modified by some authors to include BD and pauci-immune vasculitis (136,140), and by others to include primary immune complex-mediated vasculitis and secondary vasculitis resulting in pulmonary capillaritis and diffuse alveolar hemorrhage (DAH) (138,141). Categories of CT abnormalities used in two diagnostic schemes include (a) localized nodular and patchy opacities, (b) diffuse airspace consolidation or ground-glass opacities due to pulmonary hemorrhage, (c) large pulmonary artery stenosis or aneurysms (9,50), and (d) findings of chronic PH (9). These systems include examples of vasculitis not usually considered in the Chapel Hill classification.

### Large Vessel Vasculitis

Large vessel vasculitides predominantly affect the aorta and its largest branches. These vasculitides are suspected when there are signs and symptoms of ischemia (140).

#### Giant Cell (Temporal) Vasculitis

Temporal arteritis is relatively common (140). Affected patients are generally older than 50 years. Arteries of the head and neck or aorta are typically involved, and the most common symptoms include headache and tenderness in the region of the temporal artery. Thoracic aortic aneurysm may occur. Large and medium-size pulmonary arteries are rarely involved in this disease (9). However, CT may show involvement of large pulmonary artery branches, with wall thickening, stenosis, and thrombosis (9). Generally speaking, giant cell arteritis resembles Takayasu arteritis in its manifestations.

#### Takayasu Arteritis

Takayasu arteritis affects large and medium arteries, most often the aorta and its branches. Women, usually younger than 40 years, are affected in 90% of cases. In early disease, pathology shows vessel inflammation and poorly defined necrotizing and nonnecrotizing granulomas; in later lesions, marked intimal proliferation and fibrosis of the media and adventitia, with destruction of elastic tissue, are present. These abnormalities lead to stenosis, occlusion, and, occasionally, vascular dilatation and aneurysm formation. The thoracic aorta is commonly involved. Pulmonary arteries are involved in 50% to 80% of cases; occasionally, pulmonary artery involvement occurs without aortic disease (9). PH may occur in late-stage disease, but is seldom severe.

On CT, stenosis or obstruction of main or segmental or smaller pulmonary arteries is often seen in late-stage cases (Fig. 22-21), and infarction may result. Poststenotic dilatation of the pulmonary artery may result in pulmonary artery aneurysm. The pulmonary artery wall may appear abnormally thickened with active inflammation, and enhancement can be seen with contrast infusion (9,11,50,140). Arterial obstruction may be associated
Pulmonary artery aneurysms appear as one or more, unilateral or bilateral, rounded hilar or perihilar opacities measuring from 1 to 7 cm in diameter (145). On CT, these may opacify with contrast, may partially contain thrombus, or may not opacify because of thrombosis (Fig. 22-22A,C). In one study of 46 aneurysms in 13 patients, 11 (24%) involved the main right or left pulmonary arteries, 25 (54%) were lobar, and 10 (22%) were segmental; 15 (33%) contained thrombus (145). Poor definition of an aneurysm may be associated with surrounding hemorrhage (Fig. 22-22D,E). Hemoptysis may occur due to leakage or rupture of an aneurysm and may be massive and life threatening. Pulmonary artery aneurysm is thus associated with a poor prognosis. However, aneurysms may decrease in size or resolve with treatment using prednisone of cyclophosphamide. This is typically preceded by thrombosis.

Pulmonary artery thrombosis or occlusion may be associated with infarction or focal hemorrhage or atelectasis (146). Diffuse, patchy, or centriflobular consolidation or ground-glass opacity may also be seen, likely related to multiple areas of pulmonary hemorrhage (Fig. 22-22E); this was present in 7 of 13 (54%) patients in one study (145). Decreased attenuation peripheral to aneurysms (i.e., mosaic perfusion) was seen in 8 of 13 (62%) patients (145). Narrowing and cut-offs, or an irregular appearance of peripheral pulmonary artery branches, have also been reported (147). Occasional cases of organizing pneumonia or eosinophilic pneumonia with consolidation and ill-defined nodular opacities have also been reported in BD (148). Pneumonia is common in patients who are immunosuppressed. Pleural effusion is common and is usually attributed to pulmonary infarction or infection (146).

Pulmonary vasculitis or thromboses with lung injury may eventually result in nonspecific findings of lung fibrosis, emphysema, or airways disease and a restrictive or obstructive pattern on pulmonary function (10,143,146). In a study of HRCT in 29 women with BD, 11 showed abnormalities, including findings of fibrosis, ground-glass opacity, and thickening of interlobular septa. However, no significant difference in pulmonary function test values was found between patients with normal or abnormal HRCT (149). In a study of 34 patients with BD using inspiratory and expiratory HRCT (143), 9 (26.5%) patients had abnormal findings on inspiratory scans, although these abnormalities were quite nonspecific. Findings included pleural thickening and irregularity (6 patients), major fissure thickening (2 patients), parenchymal bands and irregular reticular opacities (4 patients), emphysema (2 patients), bronchiectasis (1 patient), and stable parenchymal nodules (2 patients). On expiratory scans, air trapping was considered to be present in 24 (70.6%) patients with BD and 9 of 20 (45%) matched control subjects without BD. This difference was statistically significant (p < 0.01). The authors suggest that expiratory air trapping in BD may be related to decreased blood flow to bronchioles, which in turn results in spasm, inflammation, or fibrotic stricture. Despite the presence of air trapping, pulmonary function tests of both the study and the control groups were normal, and there was no significant difference between the two groups (143).
FIGURE 22-22  BD in a 25-year-old man with pulmonary artery aneurysms, pulmonary hemorrhage, and frank hemoptysis. A: Large left pulmonary artery aneurysm (arrow) is partially lined by thrombus and is densely opacified on a volumetric HRCT. B: Surface display reconstruction shows two left-sided pulmonary artery aneurysms (arrows). C: At a different level, an aneurysm is thrombosed (arrow). D: Lung window scan at the level of A shows poor definition of the aneurysm because of surrounding hemorrhage. Patchy and centrilobular hemorrhage is also visible in the right lower lobe. E: Lung window scan at the level of C shows right lower lobe hemorrhage. Vessels in the right lower lobe appear smaller than those in the anterior lung. This may be related to thrombosis shown in C. This patient subsequently died as a result of aneurysm rupture. Postmortem slice of the left lung (F) shows the left pulmonary artery aneurysm (arrow) and adjacent hemorrhage.
**TABLE 22-10 HRCT Findings in Behçet Disease**

<table>
<thead>
<tr>
<th>Pulmonary artery aneurysm$^a,b$</th>
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<tbody>
<tr>
<td>Ground-glass opacities or consolidation, patchy or centrilobular$^a,b$</td>
</tr>
<tr>
<td>Mosaic perfusion$^a$</td>
</tr>
<tr>
<td>Superior vena cava thrombosis$^a$</td>
</tr>
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$^a$Most common findings.
$^b$Findings most helpful in differential diagnosis.

Thrombosis of the superior vena cava and brachiocephalic veins may occur, resulting in superior vena cava syndrome, mediastinal edema, and widening of the mediastinum as seen on chest radiographs. Pleural fluid may be seen, representing effusion associated with pulmonary infarction, hemothorax due to rupture of a pulmonary artery aneurysm, or chylothorax due to great vein obstruction.

*Hughes-Stovin syndrome*, described in 1959 (150), is a large vessel vasculitis characterized by pulmonary artery aneurysms and thrombosis, superior vena cava thrombosis, and thrombophlebitis, but an absence of cutaneous and oral ulcers. It likely represents BD or a variant or forme frusta of BD (141,146).

**Medium-Size Vessel Vasculitis**

*Polyarteritis Nodosa*

Polyarteritis nodosa (PAN) typically affects small to medium-size systemic arteries, resulting in necrotizing vasculitis. Involvement of arterioles, venules, and capillaries is absent, as is glomerulonephritis (137). The presence of these abnormalities indicates the presence of MPA, which may otherwise resemble PAN. Pulmonary artery involvement is rare. Although rare cases of pulmonary hemorrhage have been reported with PAN (9), such cases may represent MPA.

**Small Vessel Vasculitis Associated with Antineutrophilic Cytoplasmic Antibody**

Small vessel vasculitis primary affects vessels smaller than arteries, such as arterioles, venules, and capillaries (151,152).

**Granulomatosis with Polyangiitis (Wegener Granulomatosis)**

GPA or Wegener granulomatosis is a rare, multisystem disease of unknown cause that may be associated with involvement of the upper and lower respiratory tracts, glomerulonephritis, and necrotizing vasculitis that affects small and medium-size vessels and a variety of organs and tissues (137). Criteria of value in diagnosis include (a) nasal or oral inflammation, (b) an abnormal chest radiograph, (c) an abnormal urinary sediment, and (d) granulomatous inflammation on biopsy or hemoptysis (153). In some patients, the disease may be limited to the respiratory tract.

GPA most commonly affects patients between the ages of 30 and 60 years. Most patients have sinusitis and cough, and hemoptysis is common. Renal disease associated with hematuria, proteinuria, and renal failure is ultimately present in 80% to 90% of patients, but as few as 40% have renal involvement at first presentation (138).

Lung disease associated with GPA is characterized by a neutrophilic capillaritis, granulomatous inflammation, necrotizing vasculitis affecting small and medium-sized vessels, and geographic parenchymal necrosis. The presence of serum antineutrophilic cytoplasmic antibody (C-ANCA) is characteristic and is seen in as many as 90% to 95% of patients with active disease; its specificity is about 90% (2,138). C-ANCA is present in only 63% of patients with inactive disease (136). C-ANCA is primarily associated with antibodies directed against proteinase 3 located in azurophilic granules of neutrophils and monocytes (141).

Radiographic manifestations include multiple pulmonary nodules or masses, often cavitary; solitary nodule or mass; and focal or diffuse consolidation (Table 22-11) (141,154–156). Abnormalities are identified on the initial chest radiograph in 45% of patients, and are seen at some time in the course of disease in 85%.

CT findings in GPA have been reported in a number of studies (9,50,56,156–161). The typical appearance is that of multiple nodules, usually limited in number, ranging in size from a few millimeters to 10 cm in diameter, without a zonal predominance, and having a random distribution (Fig. 22-23) (155–157). Masses may also appear peribronchial or peribronchovascular (Fig. 22-24) (162). In a study of 10 patients (157), CT scans revealed multiple pulmonary nodules in 7 patients and a single nodule in 1. The nodules ranged in diameter from 2 mm to 7 cm, and most had irregular margins.

Lee et al. (159) reported the HRCT findings in 30 patients with GPA. Abnormal findings were seen in 29 of 30 (97%) patients at presentation. The most common appearance is that of nodules or masses, seen in 27 of 30 (90%) patients; masses were multiple in 23 of 27 (85%) patients, bilateral in 18 (67%), subpleural in 24 (89%), and peribronchovascular in 11 (41%). Cavitation of nodules is common (Fig. 22-25), being present in all nodules larger than 2 cm in one study (157); the cavity walls are often thick and irregular or shaggy, although thin-walled cavities may also be seen, and thick-walled cavities tend to become thin walled with treatment (Fig. 22-25). In the

**TABLE 22-11 HRCT Findings in Granulomatosis with Polyangiitis (Wegener Granulomatosis)**

| Multiple nodules or masses with a random distribution$^a,b$ |
| Peribronchovascular nodules or masses |
| Cavitation of nodules or masses, with a thick or thin wall$^a,b$ |
| Consolidation or ground-glass opacity, diffuse or patchy$^a$ |
| Bronchial wall thickening$^a$ |
| Centrilobular nodules |

$^a$Most common findings.
$^b$Findings most helpful in differential diagnosis.
study by Lee et al. (159), cavitation was present in 33 of 216 (15%) nodules and in 13 of 27 (48%) patients. These findings are believed to be due to necrotizing vasculitis involving medium-size muscular arteries (2).

Consolidation or ground-glass opacity is also a common manifestation of GPA, usually related to pulmonary hemorrhage (Fig. 22-26). This may be the result of small vessel vasculitis or capillaritis (2). Lee et al. (159) reported that patchy areas of consolidation and ground-glass opacity were seen in 7 of 30 (23%) patients. Consolidation may occur as an isolated finding or in association with pulmonary nodules. The distribution of consolidation is variable, being lobular, patchy, or diffuse in different patients.
Additional CT findings include pleural thickening, pleural effusion (Fig. 22-25B), and hilar or mediastinal lymph node enlargement (159). Lee et al. (159) also reported thickening of segmental or subsegmental bronchial walls in 22 (73%) patients; large airways were abnormal in 30%. Bronchial abnormalities are now a recognized feature of this disease, and bronchial inflammation may be seen commonly on pathology (159).

Ill-defined centrilobular nodules or centrilobular branching opacities, likely reflecting the presence of small vessel vasculitis, have also been reported (56,159).

Pulmonary abnormalities may clear completely with treatment, or some scarring may result. In a study of 10 patients who had GPA (158,159), the reversibility of pulmonary lesions after treatment was assessed using serial CT, during a period ranging from 6 to 54 months (mean, 20 months). Follow-up CT showed a decrease in the extent of disease in all cases. Ground-glass opacity cleared without residual scarring, as did 69% of nodules and 40% of areas of pulmonary consolidation. Masses cleared in all cases, but some scarring resulted; scarring was less common with clearing of nodules or consolidation. Some nodules and areas of consolidation persisted.

HRCT may provide information not available on chest radiographs in patients who have GPA. In a study of 10 cases (157), CT scans contributed additional information in 7. CT may demonstrate nodules and cavitation not apparent in radiographs or may exclude the possibility of nodules in treated patients.

HRCT may be a useful adjunct to the clinical assessment of pulmonary disease activity. The utility of HRCT for monitoring pulmonary disease activity was assessed in 73 patients who had GPA (163). In this study, the status of pulmonary disease activity at the time of examination was scored according to clinical, bronchoscopic, bronchoalveolar lavage (BAL), and radiographic findings. Lung nodules and masses and areas of parenchymal opacification were significantly associated with active disease; these were seen in 60% of patients believed to have active disease and 20% of patients who had past lung disease. Parenchymal bands and septal thickening were observed in both groups with pulmonary involvement, but no significant difference was found between patients who had active or past disease in frequency of these findings; these findings were seen in 32% to 48% of patients who had active disease, and 13% to 22% of patients who had past disease.

**Churg-Strauss Syndrome**

CSS is associated with a necrotizing vasculitis of small to medium-size vessels with eosinophilic and granulomatous inflammation (137). It is associated with ANCA, usually P-ANCA (perinuclear pattern), in 50% to 75% of cases (51,136). The P-ANCA pattern is associated with antibodies directed against a wide variety of intracellular antigens, most frequently myeloperoxidase, also found in azurophilic granules of neutrophils and monocytes (138). CSS is characterized by a triad of (a) asthma, (b) hypereosinophilia, and (c) necrotizing vasculitis.

Although it is often associated with vasculitis, CSS is usually considered in the category of eosinophilic lung disease (51) or when patients with difficult-to-control asthma develop significant cardiac, gastrointestinal, or neurologic disease (138). It is typically manifested by radiographic findings of simple pulmonary eosinophilia (i.e., fleeting consolidation), chronic eosinophilic pneumonia (i.e., peripheral areas of consolidation), or pulmonary edema due to cardiac involvement with heart failure (141,164–167). Pulmonary nodules or masses may be seen, but in distinction to GPA, cavitation is rare (Fig. 22-27) (50). CSS is discussed in detail in Chapter 14.

**Microscopic Polyangiitis**

MPA results in systemic necrotizing small vessel vasculitis (136,137). Although the histology is similar to classic PAN, the involvement of arterioles, venules, and capillaries distinguishes it from PAN. Also, ANCA (usually P-ANCA) is present in 45% to 70% (51,136); ANCA is rare in PAN. Anti-myeloperoxidase is seen in 35% to 65% of patients, and a positive C-ANCA can be seen in 10% to 15% of patients (138).

MPA typically occurs in middle-age adults with a mean age at presentation of 50 years; men are most commonly involved. Glomerulonephritis develops in 90% of patients, and other organs may be involved. Pulmonary hemorrhage related to capillaritis occurs in 25% to 30%, associated with dyspnea and hemoptysis (9,50,136). CT findings
are typical of pulmonary hemorrhage (Fig. 22-28). Pleural effusion and pulmonary edema are seen in about 10%, likely related to renal disease. Progression to pulmonary fibrosis is rare. Treatment using cyclophosphamide and steroids often results in remission.

**Isolated Pauci-Immune Pulmonary Vasculitis**

This entity is associated with DAH and capillaritis, without evidence of a collagen-vascular disease, ANCA, antibasement membrane antibodies, or renal disease (51,136,168). The median age of onset is 30 years. Recurrences of hemorrhage may occur, but the prognosis appears favorable (141). Isolated pauci-immune pulmonary capillaritis and idiopathic pauci-immune rapidly progressive glomerulonephritis due to vasculitis can be considered to be organ-specific subsets of MPA (138).

**DIFFUSE ALVEOLAR HEMORRHAGE**

DAH can result from a variety of diseases and abnormalities, and making a specific diagnosis may be difficult (169–171). DAH can be associated with various causes of large, medium, or small pulmonary vessel vasculitis discussed earlier (GPA [Fig. 22-26], CSS, MPA [Fig. 22-28], BD [Fig. 22-20], isolated pauci-immune pulmonary vasculitis), associated with deposition of immune complexes in the walls of small vessels and capillaries.

DAH may also be seen in association with pulmonary capillaritis occurring without other manifestations of vasculitis (Table 22-9). Pulmonary capillaritis is characterized by inflammation and neutrophilic infiltration of the alveolar interstitium and pulmonary capillaries, fibrinoid necrosis, disruption of the epithelial-endothelial basement membrane, leakage of red blood cells and neutrophils into the alveolar spaces (i.e., DAH), and thrombi within the alveolar capillaries and venules (Fig. 22-29A,B) (172). With time, hemosiderin and hemosiderin-containing macrophages accumulate in the alveoli and interstitium (Fig. 22-29C).

Causes of capillaritis include primary antibody-mediated vasculitis, such as antiglomerular basement
DAH may also be seen in patients without capillaritis or other manifestations of vasculitis (Table 22-12). In patients with DAH unassociated with capillaritis, histologic findings are largely limited to alveolar hemorrhage and alveolar and interstitial hemosiderin-laden macrophages.

**HRCT Findings**

Chest radiographic findings are often nondiagnostic, and hemoptysis may be lacking even in patients who have sufficient hemorrhage to result in anemia (177). On HRCT, patients with DAH generally show similar abnormalities regardless of its cause (140,141). HRCT findings include ground-glass opacity or consolidation in the presence of acute hemorrhage; ill-defined centrilobular nodules may predominate in some patients (Table 22-13, Figs. 22-26, 22-28, and 22-30). Abnormalities may be diffuse or may predominate in the lower lobes. If possible, DAH should be distinguished from focal pulmonary hemorrhage occurring as a result of bronchiectasis, chronic bronchitis, active infection (e.g., tuberculosis), chronic infection, neoplasm, arteriovenous malformation, or pulmonary embolism (46,170).

Within days of an acute episode of hemorrhage, the presence of interlobular septal thickening may be seen in association with ground-glass opacity (i.e., crazy paving) as hemosiderin and hemosiderin-laden macrophages begin to accumulate in the interstitium (Fig. 22-31) (46,173). In later stages, only an interstitial abnormality may be visible; fibrosis may sometimes result.

**Goodpasture Syndrome**

Antiglomerular basement membrane disease (Goodpasture syndrome) most frequently occurs in young patients, 20 to 30 years of age; men are affected four times as commonly as women (169). Hemoptysis, usually mild, and anemia are present in about 90%. Other common

| TABLE 22-12 Diffuse Alveolar Hemorrhage Unassociated with Pulmonary Capillaritis |
|---------------------------------|------------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | IPH              | Goodpasture syndrome (some cases) | Diffuse alveolar damage | Elevated pulmonary venous pressure | Anticoagulation | Coagulation disorders | Thromocytopenia | Inhalation injury, toxic exposures | Barotrauma | Drug-associated disease (e.g., chemotherapy) | Illicit drug use (particularly cocaine smoking) | PVOD | PCH | Lymphangiomyomatosis |

membrane disease (Goodpasture syndrome), Henoch-Schönlein purpura, or secondary vasculitis occurs in collagen diseases such as systemic lupus erythematosus, essential cryoglobulinemia, inflammatory bowel disease, and others (Table 22-9) (46,140,141,173–176).
symptoms include cough, dyspnea, and weakness. Findings of renal disease are usually, but not always, present; these include hematuria, proteinuria, and renal failure. Antiglomerular basement membrane antibodies are almost always (95%) present in the serum (178). These antibodies are directed against the alpha-3 chain of type IV collagen and cross react with alveolar basement membranes (Fig. 22-32A). A pulmonary capillaritis is present in many cases. Renal biopsy shows glomerulonephritis with linear deposition of IgG in the glomeruli.

Although plain radiographs may be normal, they usually show diffuse airspace consolidation or ground-glass opacity, bilateral and symmetric, and often with a parahilar predominance (Fig. 22-32B). After an acute episode of hemorrhage, there is a tendency for the airspace opacities to resolve, being superseded by an interstitial abnormality or interlobular septal thickening (Kerley B lines). HRCT usually shows consolidation or ground-glass opacity and may be abnormal in the face of subtle plain film findings; interlobular septal thickening may be seen with resolution (46,141,170).

**Idiopathic Pulmonary Hemosiderosis**

Idiopathic pulmonary hemosiderosis (IPH) is a disease of unknown origin, characterized by recurrent episodes or diffuse pulmonary hemorrhage without associated glomerulonephritis or a serologic abnormality (46,173,179). Pathologic findings are largely limited to alveolar hemorrhage and alveolar and interstitial hemosiderin-laden macrophages; capillaritis is absent. Hemosiderosis and interstitial fibrosis may develop with recurrent episodes of hemorrhage in long-standing cases.

IPH most commonly occurs in young children (i.e., under the age of 10 years) or young adults (180). In adults, males are affected twice as often as women. IPH is sometimes associated with celiac disease, cow’s milk allergy, thyroid disease, or immunoglobulin A gammopathy, and has recently been reported in infants with exposure to toxic mold (Stachybotrys) (181–184). Symptoms include cough, hemoptysis, dyspnea, and anemia. The diagnosis is usually made by exclusion. About a quarter of patients die as a result of respiratory insufficiency or cor pulmonale.
Plain radiographic and CT findings are similar to those of Goodpasture syndrome. Cheah et al. (170) reported the HRCT findings in four patients who had IPH. Predominant findings in the acute phase of disease included diffuse nodules and diffuse ground-glass opacity (Fig. 22-33); nodules, ill-defined centrilobular nodules, and ground-glass opacity have also been reported by others in patients with IPH (173,185–187).

**Immune Complex Small Vessel Vasculitis**

Diseases associated with circulating immune complexes include collagen-vascular disease, Henoch-Schönlein purpura, essential cryoglobulinemia, antiphospholipid syndrome, IgA nephropathy, Behçet syndrome, and others (77,188). Deposition of immune complexes in the walls of small pulmonary vessels may occur in these diseases, resulting in capillaritis with DAH (137). The appearance of DAH is similar in each of these diseases. Behçet syndrome, which may result in other findings, is discussed in Chapter 18.

**Collagen-Vascular Diseases**

Diffuse pulmonary hemorrhage may occur with many collagen diseases (2,9,50,57,59,77,140,141,189–192). Among patients with collagen-vascular disease, DAH is most frequent as a complication of systemic lupus erythematosus. It occurs in a few percent of patients, and is uncommon as the initial manifestation of disease. It is usually associated with progressive disease and multiorgan involvement. It has a high mortality (46,193,194). Hemoptysis is frequent and may be massive.

Radiographic and HRCT findings are similar to those reported for other causes of diffuse pulmonary hemorrhage, most frequently including consolidation and ground-glass opacity (Figs. 22-34 and 22-35) (195); the appearance of crazy paving may be seen (196). HRCT can show ill-defined centrilobular, perivascular opacities, correlating with the presence of perivascular inflammation or hemorrhage (Fig. 22-36).
FIGURE 22-34  Pulmonary hemorrhage associated with systemic lupus erythematosus. Diffuse but geographic ground-glass opacity is visible.

FIGURE 22-35  Pulmonary hemorrhage associated with systemic lupus erythematosus. A and B: HRCT shows patchy areas of ground-glass opacity and consolidation, with a parahilar distribution, and sparing the lung periphery.

Henoch-Schönlein Purpura

Henoch-Schönlein purpura is characterized by abnormalities of small vessels (capillaries, venules, or arterioles) associated with IgA-predominant deposits (137,141). Symptoms include purpura, abdominal pain, gastrointestinal hemorrhage, arthralgia, and glomerulonephritis, although not all are typically present and glomerulonephritis occurs in only 20%. It may occur at any age, but is usually seen in young children, and often follows a respiratory tract infection. Relapses are common,
but the prognosis is good. Chronic renal failure develops in a small number of cases.

Pulmonary involvement occurs in as many as 6% of patients (188). Diffuse or patchy consolidation may result from capillaritis and pulmonary hemorrhage. Hemoptysis is often associated. Pleural effusion may be seen.

**Essential Cryoglobulinemia**

This disease is characterized by involvement of small vessels with purpura, arthralgia, glomerulonephritis, hepatosplenomegaly, and lymph node enlargement (137,141,197). Serum globulins that precipitate with cold are present. Many cases are related to hepatitis C infection; others are associated with other infections, lymphoma, lymphoproliferative disease, or collagen-vascular diseases. Pulmonary disease is uncommon and difficult to characterize. Findings of DAH or a reticular pattern may be seen.

**REFERENCES**

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