Approach to Pulmonary Hypertension: From CT to Clinical Diagnosis[1]

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Abbreviations: CTEPH = chronic thromboembolic PH, PAH = pulmonary arterial hypertension, PCH = pulmonary capillary hemangiomatosis, PH = pulmonary hypertension, PVOD = pulmonary veno-occlusive disease

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the different types of PH and the pathophysiology of each group.
- List the essential structures in the parenchyma, bronchial arteries, pulmonary arteries, and heart that can guide one to an appropriate diagnosis in each subtype of PH.
- Recognize the common diseases in each subtype of PH that can be diagnosed with CT.

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Pulmonary hypertension (PH) is a condition characterized by increased pressure in the pulmonary circulation. It may be idiopathic or arise in the setting of other clinical conditions. Patients with PH tend to present with nonspecific cardiovascular or respiratory symptoms. The clinical classification of PH was recently revised at the World Health Organization symposium in Nice, France, in 2013. That consensus statement provided an updated classification based on the shared hemodynamic characteristics and management of the different categories of PH. Some features seen at computed tomography (CT) can suggest a subtype or probable cause of PH that may facilitate placing the patient in the correct category. These features include findings in the pulmonary arteries (peripheral calcification, peripheral dilatation, eccentric filling defects, intra-arterial soft tissue), lung parenchyma (centrilobular nodules, mosaic attenuation, interlobular septal thickening, bronchiectasis, subpleural peripheral opacities, ground-glass opacities, diffuse nodules), heart (congenital lesions, left heart disease, valvular disease), and mediastinum (hypertrophied bronchial arteries). An approach based on identification of these CT features in patients with PH will allow the radiologist to play an important role in diagnosis and help guide the clinician in management of PH.

Introduction

Pulmonary hypertension (PH) is a condition characterized by increased pressure in the pulmonary circulation (1). It may be idiopathic or seen with other conditions. PH is defined as mean pulmonary pressure of 25 mm Hg or more at rest (2,3). Pressures of 20 mm Hg or less at rest are considered normal, and pressures of 21–24 mm Hg are equivocal but often require further investigation (4).

Without treatment, PH has a poor prognosis and may progress to right ventricular failure and death. Patients with PH experience nonspecific cardiovascular and respiratory symptoms including dyspnea, fatigue, chest pain or angina, and syncope (1,5). Multiple noninvasive imaging techniques such as chest radiography, echocardiography, computed tomography (CT), and magnetic resonance (MR) imaging may be used for evaluation and investigation of PH.

Chest radiographs are abnormal in 90% of patients with idiopathic pulmonary arterial hypertension (PAH) at the time of diagnosis (4). Chest radiography may help assess the presence of PH, but the degree of PH does not correlate with the extent of imaging abnormalities, and chest radiography is rarely used as the sole imaging modality (4). At chest radiography, the central pulmonary arteries are classically enlarged with rapid tapering of peripheral pulmonary vasculature (pruning) (4). Chest radiography may also depict right-sided cardiac enlargement in idiopathic PAH.

TEACHING POINTS

- The CT approach to diagnosis of PH begins with identifying an enlarged pulmonary artery diameter greater than 29 mm, which is usually larger than that of the ascending aorta at the same level. This diameter must be measured in the axial plane at the bifurcation, orthogonal to the long axis of the pulmonary artery.
- Idiopathic PAH is diagnosed only in the absence of any other cause of PH and in the absence of any pulmonary or mediastinal finding that may be a cause of PH. The term *pulmonary arterial hypertension* should be reserved for those cases that fall into category 1.
- Developments in the understanding of the pathophysiology of PH have revealed that in all types there is an imbalance among vasodilators and vasoconstrictors, growth inhibitors, endothelial growth factors, mitogenic factors, and prothrombotic and antithrombotic factors that results in pulmonary endothelial dysfunction. These factors contribute to vascular smooth muscle cell proliferation, vasoconstriction, and thrombosis and eventual PH.
- Centrilobular ground-glass nodules are a well-known but poorly understood finding in patients with PH. They are considered a manifestation of severe PH and are rarely present in untreated idiopathic PAH. These ground-glass nodules may represent cholesterol granulomas due to degradation of excess of surfactant or to recurrent pulmonary hemorrhage or foci of plexogenic arterial lesions. In our experience, these nodules are more commonly encountered in patients with idiopathic PAH who have been receiving long-term (years) vasodilator therapy than in patients with a new diagnosis of idiopathic PAH.
- Some imaging findings in left heart disease overlap those found in veno-occlusive disease. The key to differentiation is the left atrial enlargement present in left-sided cardiac disease but not in PVOD.

Transthoracic two-dimensional Doppler echocardiography is the first-line modality for diagnosis of PH (6). It is widely available and is the most common imaging modality used to assess ejection fraction, left-sided heart disease, or intracardiac shunts (6,7). Occasionally, left-sided heart disease may be first diagnosed incidentally at CT (6,8). For detection of moderate PH, echocardiography has sensitivity of 79%–100% and specificity of 68%–98% (9). However, echocardiography has limited capability for evaluation of the pulmonary arteries beyond the main pulmonary artery and is quite limited in evaluation of right ventricular function (7). On the basis of echocardiographic findings, the probability of PH is classified as low, intermediate, or high. Further evaluation is reserved for patients with high or intermediate probability of PH (4).

Ventilation-perfusion (V/Q) scintigraphy is often used to identify or exclude chronic thromboembolic PH (CTEPH) in patients with suspected CTEPH (10). Although V/Q scintigraphy allows accurate assessment of parenchymal perfusion, it does not provide the anatomic information required to determine whether a patient with CTEPH is a good candidate for definitive treatment with thromboendarterectomy (10).

Cardiac MR imaging is one of the most accurate methods for assessing right ventricular size, morphology, and function (4,9,11). It can also be used to assess the anatomy of the pulmonary arteries and pulmonary blood flow (7). In our practice, cardiac MR imaging is often used to evaluate the effectiveness of treatment for PH (surgery or medication) (12). In other words, cardiac MR imaging is used to make sure that the right ventricle is not showing signs of failure (eg, dilatation or reduced ejection fraction) that would warrant additional intervention or medication.

Right heart catheterization allows direct measurement of pulmonary pressures, pulmonary resistance, and cardiac output (6). It remains the standard of reference for diagnosis of PH. Right heart catheterization may also be used to help predict the response to vasodilators (4,6). As it is invasive and provides little information about the lungs or mediastinum, right heart catheterization is usually performed in conjunction with other modalities (4,6).

CT is a routinely used imaging modality for evaluation of patients with suspected PH (7). Studies may be performed without intravenous contrast material using a high-resolution protocol when the lung parenchyma is the sole question. Intravenous contrast material may be used (often with a pulmonary angiography protocol) when CTEPH or other nonpulmonary causes of PH are suspected, such as fibrosing mediastinitis.

Our CT pulmonary angiography protocol is usually non–electrocardiographically gated and is performed craniocaudally using bolus tracking, with a region of interest placed over the main pulmonary artery set to a 100-HU threshold. An injection rate of 4–5 mL/sec is used with a total contrast material volume of 80–100 mL. Images are reconstructed with a 1-mm section thickness and 1-mm reconstruction interval.

In the initial workup of a patient with PH with no clear cause, a hybrid protocol consisting of nonenhanced exhalation images and a postcontrast inhalation pulmonary angiography protocol may be used. CT findings in the lung parenchyma, mediastinum (including the presence of bronchial arteries), pulmonary arteries, and heart can guide the radiologist to classify PH into one of the five categories of the 2013 Nice classification.

Dual-energy CT pulmonary angiography may be used in the setting of suspected CTEPH (13). Using different energies (usually 80 and 140 kV), this technique may allow creation of a snapshot of relative regional blood volume and detection of perfusion defects and help define the nature of the

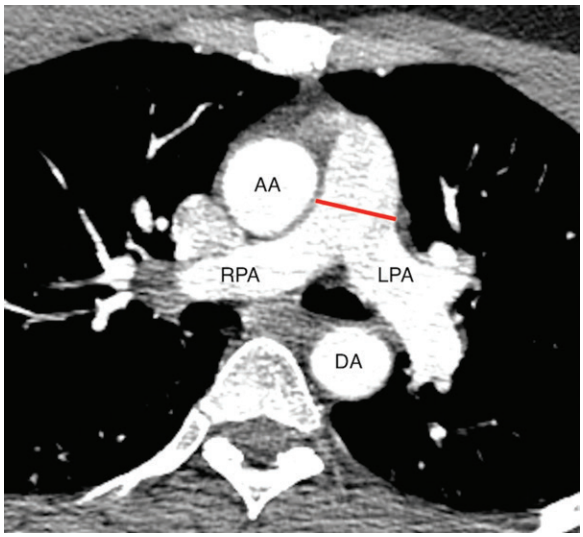


Figure 1. Measurement of pulmonary artery diameter. The measurement (red line) must be obtained in the axial plane at the bifurcation, orthogonal to the long axis of the pulmonary artery. In PH, the diameter of the main pulmonary artery tends to be greater than 29 mm and may be larger than that of the aorta on the same section. *AA* = ascending aorta, *DA* = descending aorta, *LPA* = left pulmonary artery, *RPA* = right pulmonary artery.

mosaic attenuation (14). We have not switched to routine use of dual-energy CT pulmonary angiography and continue to rely on V/Q scintigraphy in our practice.

The CT approach to diagnosis of PH begins with identifying an enlarged pulmonary artery diameter greater than 29 mm, which is usually larger than that of the ascending aorta at the same level (15). This diameter must be measured in the axial plane at the bifurcation, orthogonal to the long axis of the pulmonary artery (12) (Fig 1). Other findings such as increased segmental artery–to-bronchus ratio greater than 1:1 in three or more lobes increase the specificity for diagnosis of PH (15).

In this article, we review the different types of PH, their pathophysiology, and the key findings that allow a CT approach to diagnosis of PH. We also propose a simple checklist that aids proper categorization of the PH patient according to the 2013 Nice classification.

2013 Nice Classification of PH

Since 1998, a series of World Health Organization symposia have established a clinical categorization scheme that divides PH into five categories based on shared pathophysiology and treatment. The most recent such conference took place in Nice, France, in 2013. The 2013 Nice classification (Table 1) built on the previous meetings with minor modifications (16).

The 2013 Nice classification divides PH into five groups: group 1 = PAH (disorders of the pulmonary arteries themselves), group 2 = PH due to left heart disease, group 3 = PH due to lung diseases and/or hypoxia, group 4 = CTEPH, and group 5 = PH with unclear multifactorial mechanisms (16). Over the past 2 decades, the classification scheme has evolved as the understanding of PH has grown.

First, the terms *primary PH* and *secondary PH* have been abandoned. As spontaneous mutations may occur, "familial" has been replaced by "heritable." Schistosomiasis and the venulopathies (pulmonary veno-occlusive disease [PVOD] and pulmonary capillary hemangiomatosis [PCH]) have been included in group 1 disease. The 2013 classification also made strides to bring focus to segmental PH and persistent PH of the newborn (PPHN) (Table 1).

Idiopathic PAH is diagnosed only in the absence of any other cause of PH and in the absence of any pulmonary or mediastinal finding that may be a cause of PH. The term *pulmonary arterial hypertension* should be reserved for those cases that fall into category 1.

Understanding the Mechanisms of PH

Developments in the understanding of the pathophysiology of PH have revealed that in all types there is an imbalance among vasodilators and vasoconstrictors, growth inhibitors, endothelial growth factors, mitogenic factors, and prothrombotic and antithrombotic factors that results in pulmonary endothelial dysfunction (17–19). These factors contribute to vascular smooth muscle cell proliferation, vasoconstriction, and thrombosis and eventual PH (15,19). Each group has differences in the imbalances that lead to development of PH.

Group 1: PAH

Group 1 disease involves conditions with a significant arteriolar component of disease and the potential to respond to vasodilator therapy. One of the main diagnoses in this group is idiopathic PAH. Idiopathic PAH is characterized by angioproliferative lesions of endothelial cells and hyperplasia and hypertrophy of the layers of the vascular wall with increased muscle in precapillary arterioles (20,21).

Heritable PH is found in 6%–10% of patients with PH and is associated with many mutations of the bone morphogenic protein cascade (20,21). Known medications associated with PH include the anorexigens fenfluramine, dexfenfluramine, and benfluorex. Substances with a possible (but not definitive) link to the development of PH include cocaine, phenylpropanolamine, chemotherapeutic agents, and selective serotonin reuptake inhibitors (SSRIs) (21,22).

The prevalence of PH in patients with HIV infection is estimated to be 0.5% (23). The mechanism of PH in HIV infection closely resembles that of idiopathic PAH (24).

PVOD and PCH manifest with PH secondary to intimal fibrosis and occlusion of the pulmonary venules and to proliferation of capillaries within alveolar walls, respectively (25,26).

Persistent PH of the newborn is secondary to hypoxia with a subsequent inflammatory response that results in endothelial dysfunction and smooth muscle dysfunction (27).

Group 2: PH Due to Left Heart Disease

PH induced by left heart disease is the most prevalent form wordwide (28). It begins as increased back-pressure with congestion of the pulmonary capillary bed resulting in elevated left heart pressures (passive PH) (20,29,30). Group 2 PH is seen in patients with heart failure with preserved or reduced ejection fraction and in left-sided valvular diseases (28).

Group 3: PH Due to Lung Diseases and/or Hypoxia

Multiple factors may contribute to the development of group 3 PH (18,31). Almost 66% of patients with chronic obstructive pulmonary disease (COPD) have some degree of PH, usually mild (20,32–34). The prevalence of PH in interstitial lung disease varies from 32% to 84% (34). PH is seen in 20%–30% of patients with obstructive sleep apnea. Ten percent to 15% of patients with sleep apnea have concomitant COPD, which increases the likelihood of PH (34). In group 3, PH is believed to be a result of hypoxic pulmonary vasoconstriction and remodeling of the pulmonary vessels (20,31,35,36). Hypoxic vasoconstriction is initially reversible, but over time it may become irreversible (18,36).

Group 4: CTEPH

The pathophysiology of CTEPH remains unclear and may follow even just one episode of pulmonary embolism (37,38). Elevation of proinflammatory cytokines promotes scar formation with resultant remodeling of the pulmonary vasculature and formation of plexiform lesions in the pulmonary microvasculature (39,40). The prevalence of CTEPH is estimated to be about 3.8% of patients who survive an episode of acute pulmonary embolism (4,37).

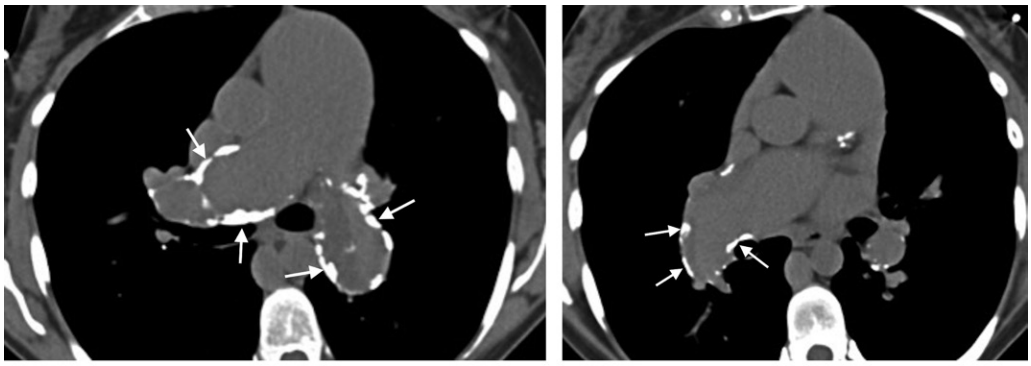
Group 5: PH with Unclear Multifactorial Mechanisms

The pathophysiology of PH in group 5 varies according to the underlying cause. Increased vascular resistance secondary to hypoxia and vascular remodeling secondary to inflammation are present, as in the other groups of PH (41). Vascular extrinsic compression (lymphadenopathy or

Table 1: Classification of PH (from Fifth World Symposium on PH, Nice, France, 2013)

1. PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 *BMPR2*
1.2.2 *ALK1*, *ENG*, *SMAD9*, *CAV1*, *KCNK3*
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1' PVOD and/or PCH
1" PPHN
2. PH due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. PH due to lung diseases and/or hypoxia
3.1 COPD
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung disease
4. CTEPH
5. PH with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen-storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Source.—Adapted, with permission, from reference 16.
Note.—COPD = chronic obstructive pulmonary disease, HIV = human immunodeficiency virus, PCH = pulmonary capillary hemangiomatosis, PPHN = persistent PH of the newborn, PVOD = pulmonary veno-occlusive disease.



a. b.

Figure 2. Group 1 PH in a 27-year-old woman with Eisenmenger syndrome secondary to a ventricular septal defect. Axial CT images (mediastinal window) at the level of the main pulmonary artery show enlargement of the pulmonary arteries and peripheral wall calcification (arrows).

mediastinal fibrosis) is partly responsible for the development of PH in these patients (42).

Chronic myeloproliferative disorder, splenectomy, chronic hemolytic anemia, and sickle cell disease involve a thrombophilic state that combines vascular remodeling and leads to PH development. Endocrine disorders (such as thyroid disease) may lead to PH owing to increased circulating antibodies, catecholamines, and vasodilators that result in left ventricular dysfunction (41).

CT Findings in PH

A structured approach to the CT findings in a patient with PH allows the radiologist to play an important role in appropriate categorization according to the Nice classification. These specific findings can be grouped into pulmonary artery, pulmonary parenchymal, cardiac, and mediastinal findings.

Pulmonary Artery Findings

Peripheral Calcification.—Peripheral calcification of the pulmonary arteries is a characteristic feature of long-standing PH and is usually seen in severe and late stages of PH (43–45). In our experience, this finding is most commonly encountered in patients with long-standing cardiac shunts (usually atrial septal defects) and Eisenmenger syndrome (Fig 2). The cause of these calcifications may be related to atheromatous calcification of the pulmonary artery or to thrombus eccentrically located in the wall of the pulmonary arteries that may calcify (46,47). Thrombus organized in the wall of the pulmonary artery has a peripheral crescent shape and tends to have obtuse angles with the vessel wall (13).

Mitral valve disorders may manifest with pulmonary artery calcifications, but these tend to be seen with left atrial calcifications as well. Rarely, chronic thromboembolic disease will have pulmonary artery calcifications, but other features of CTEPH including mosaic attenuation and enlarged bronchial arteries tend to be present (44). Therefore, eccentric calcified filling defects should prompt consideration of a long-standing right-to-left shunt and are not sufficient to make the diagnosis of CTEPH when present in isolation.

Peripheral Dilatation.—Most patients with PAH have pruning with lack of visualization of the peripheral arteries. Rarely, however, dilated peripheral arteries may be seen in PH and may allow diagnosis of portal hypertension or rarely hereditary hemorrhagic telangiectasia (HHT) or microscopic tumor emboli. Patients with liver cirrhosis may develop PH in 2%–10% of cases (48) and hepatopulmonary syndrome in 15%–20% (45). Dilated peripheral pulmonary arteries are a characteristic feature of hepatopulmonary syndrome that is rarely seen in patients with portopulmonary hypertension.

There are two types of vessels in hepatopulmonary syndrome that explain this feature. Type 1 is distal vascular dilatation with multiple vessels extending toward the pleura and subpleural space (subpleural telangiectases). Type 2 is arteriovenous malformations and nodular dilatations of the peripheral vessels (49). Type 1 is seen in nearly 86% of patients with hepatopulmonary syndrome (Fig 3) (49). Clearly, the presence of a nodular shrunken liver will also help in categorizing the PH as portal hypertension related.

Patients with HHT may also rarely present with PH, as there is overlap of the mutations in the bone morphogenic cascade between these two conditions. The dilated peripheral vessels can often be connected to adjacent veins. These malformations tend to be larger than those seen in hepatopulmonary syndrome, and cirrhosis is typically absent.

When the peripheral arteries are dilated and begin to simulate a tree-in-bud appearance,

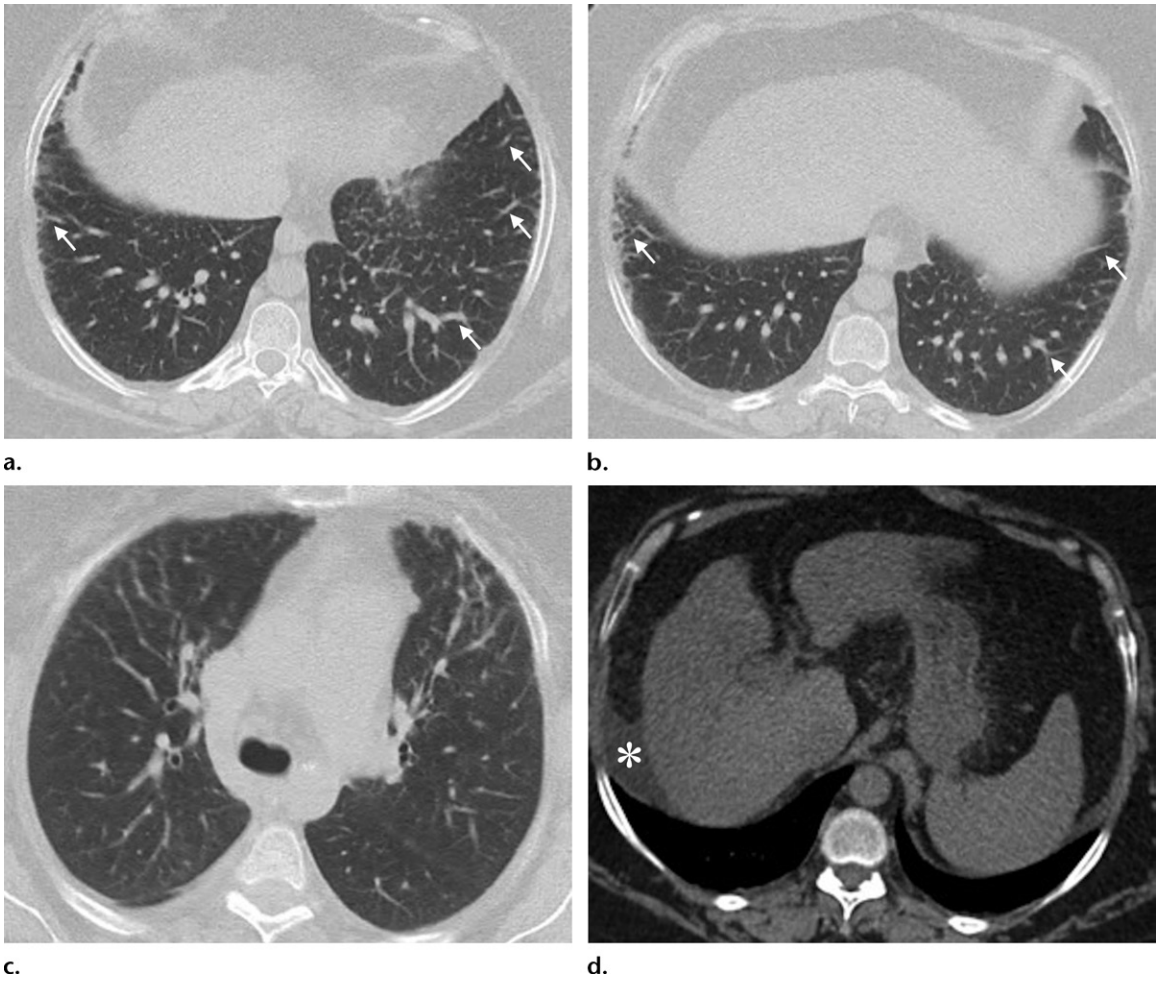


Figure 3. PH with portal hypertension (group 1) in a 46-year-old woman with rapidly progressive respiratory symptoms and PH. **(a, b)** Axial thin-section CT images at the level of the lower lobes show distal vascular dilatation with multiple vessels (arrows) extending toward the pleura and subpleural space. **(c)** Axial thin-section CT image shows enlargement of the main pulmonary artery. **(d)** Axial CT image at the superior abdomen shows signs of cirrhosis and portal hypertension with perihepatic free fluid (*). The findings are characteristic of type 1 hepatopulmonary syndrome.

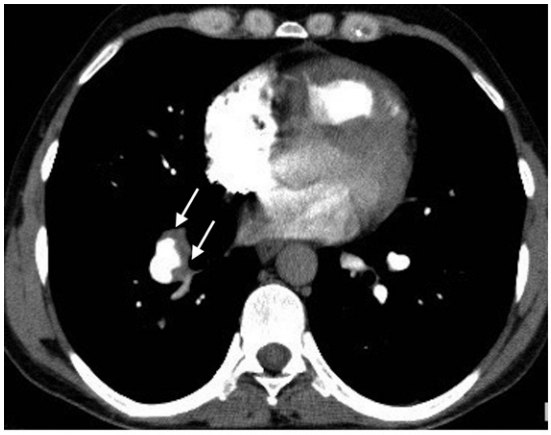
microscopic tumor emboli should be considered. This rare entity is discussed later.

Eccentric Filling Defects.—The presence of mural thrombus or eccentric emboli in the pulmonary arteries is a key finding in CTEPH (Fig 4). These filling defects tend to form obtuse angles with the arterial wall (44). These defects may cause narrowing of the vessel and irregular contours of the intima. Other findings of CTEPH include poststenotic dilatation and rarely webs, beaded vessels, and obstructed thread-like arteries (44). The diagnosis of CTEPH rests on these pulmonary artery findings but requires the presence of nonarterial findings, including mosaic attenuation and enlarged bronchial arteries.

In situ thrombus is formed secondary to chronic high pressure and is seen in almost any case of group 1 PH, most notably portopulmonary hypertension and Eisenmenger syndrome. In these cases, mosaic attenuation will be absent. Enlarged bronchial arteries may be seen in Eisenmenger syndrome but should be absent in portopulmonary hypertension.

Intra-arterial Soft Tissue.—Pulmonary intravascular tumor emboli are a rare complication in patients with known malignancy and even more rarely may represent an initial manifestation of neoplasm (6). Between 2% and 26% of patients with malignancies will have microscopic subsegmental artery involvement (5,44). Primary tumors most often reported include those of the breast, stomach, liver, kidney, lung, and prostate and choriocarcinoma (6). Tree-in-bud appearance related to distal or subsegmental involvement and dilatation of the peripheral pulmonary arteries may be seen (15,44,50).

In the case of pulmonary artery sarcoma and macroscopic tumor emboli, these filling defects can mimic bland emboli but may be differentiated by enhancement at CT or MR imaging and



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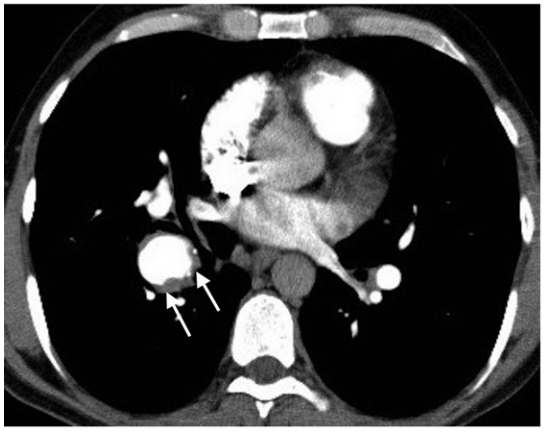

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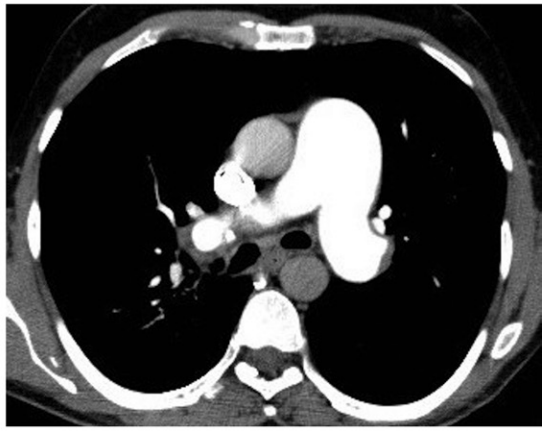


c.

Figure 4. CTEPH (group 4) in a patient with PH. **(a)** Axial CT image (mediastinal window) at the level of the lower lobes shows peripheral wall thrombus (in situ thrombus) (arrows) in the right pulmonary artery. **(b)** Axial CT image (mediastinal window) obtained superior to **a** shows similar right lower lobe pulmonary artery dilatation with peripheral (in situ) thrombus (arrows). **(c)** Axial CT image (mediastinal window) shows enlargement of the main pulmonary artery.

fluorodeoxyglucose uptake at positron emission tomography (6,9). Right ventricular enlargement will be present with possible hypertrophy or even signs of right ventricular failure (Fig 5) (15).

Undifferentiated sarcoma or leiomyosarcoma of the pulmonary arteries results in PH secondary to occlusion of the arterial lumen by the tumoral volume or to subsequent bland arterial thrombosis (45). Primary sarcomas develop in the central pulmonary artery adjacent to the pulmonary valve and tend to occupy and expand the vessel lumen with an acute angle, simulating acute pulmonary embolism (Fig 6). Extension to the contralateral pulmonary artery or the right ventricle is not uncommon.

Pulmonary Parenchymal Findings

Centrilobular Nodules.—Centrilobular ground-glass nodules are a well-known but poorly understood finding in patients with PH (11). They are considered a manifestation of severe PH and are rarely present in untreated idiopathic PAH (51). These ground-glass nodules may represent cholesterol granulomas due to degradation of excess of surfactant or to recurrent pulmonary hemorrhage or foci of plexogenic arterial lesions (11,43,52). In our experience, these nodules are more commonly encountered in patients with idiopathic PAH who have been receiving long-term (years) vasodilator therapy than in patients with a new diagnosis of idiopathic PAH.

Diffuse centrilobular ground-glass nodules in an untreated patient with PH should cause consideration of PCH or PVOD (Fig 7). Both are rare conditions included in group 1. The nodules in PCH represent proliferation of capillary channels within the alveolar wall, while PVOD represents intimal fibrosis with narrowing and occlusion of pulmonary veins (25).

These two entities overlap but may be distinguished, as PVOD is more likely to manifest with thickened septal lines, pleural or pericardial effusion, and lymphadenopathy (9,11,25,53,54). The findings may overlap those of pulmonary edema but can be clinically considered when left heart evaluation with echocardiography shows normal function in the setting of PH. Diagnosis of PVOD and PCH is important, as vasodilators may result in flash edema and death. Any administration of vasodilators must be performed in a controlled environment.

Mosaic Attenuation.—Mosaic attenuation in PH is almost always due to regional differences in

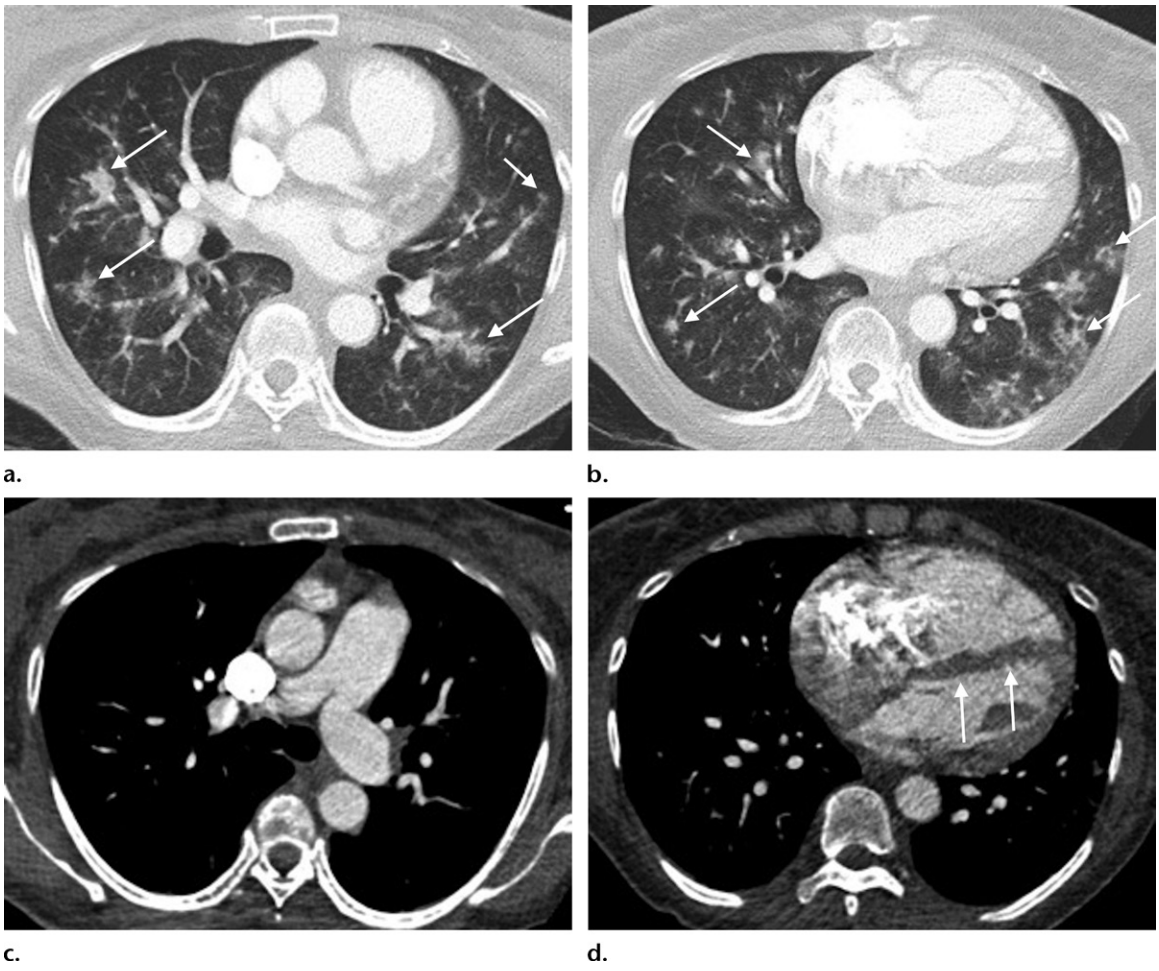


Figure 5. PH with multifactorial causes (group 5) in a 46-year-old woman with metastatic choriocarcinoma. **(a, b)** Axial thin-section CT images at the level of the lower lobes show peribronchovascular solid and ground-glass nodules (arrows) consistent with hematogenous metastases of choriocarcinoma. The ground-glass halo around the nodules is compatible with hemorrhage. **(c, d)** Axial CT images (mediastinal window) at the level of the main pulmonary artery **(c)** and right ventricle **(d)** show main pulmonary artery enlargement, right ventricular dilatation, and leftward bowing of the interventricular septum (arrows in **d**). These findings of increased pulmonary arterial pressure are suggestive of arterial tumor emboli.

lung perfusion (54), resulting in areas of oligemia (lower attenuation) and hyperemia (higher attenuation) (9). Decreased blood flow to the areas of lower attenuation is associated with segmental or subsegmental areas of vascular attenuation or obliteration, with enlarged vasculature in the normal parenchyma (54).

CTEPH is the most common cause of mosaic attenuation in patients with PH (Fig 8) (11,54). This finding has also been described in group 2 and group 3 PH, but much less frequently (46,54). In group 2 conditions, the lighter areas tend to represent foci of pulmonary edema. In group 3 conditions, the lighter areas tend to represent foci of inflammation or fibrosis.

In CTEPH, 77%–100% of patients will have mosaic attenuation (45,55), as compared with 74% in cardiac causes of PH (group 2) and less than 8% in lung diseases (group 3) (45,46). In CTEPH, mosaic attenuation tends to have a segmental and subsegmental distribution (45).

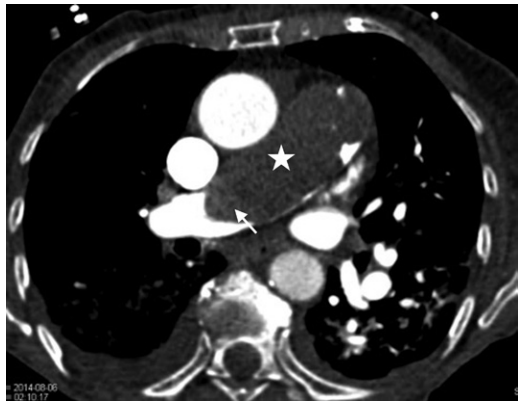
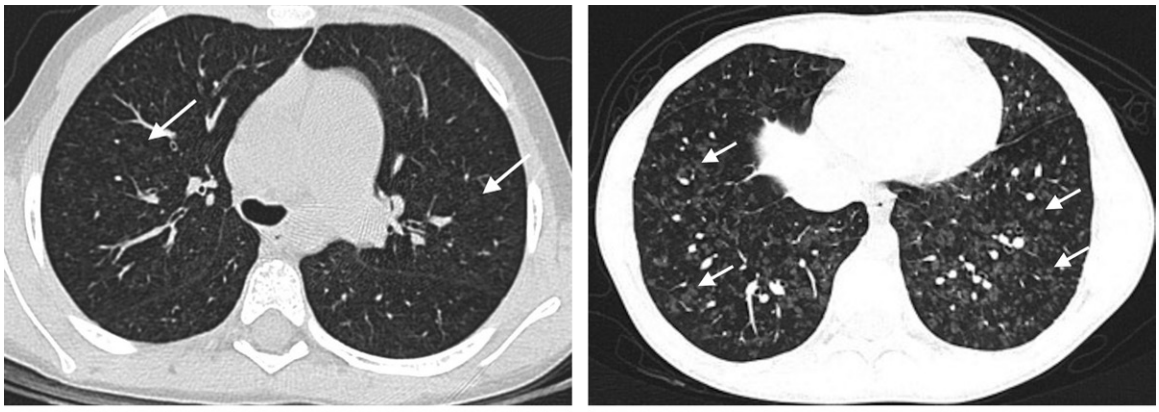
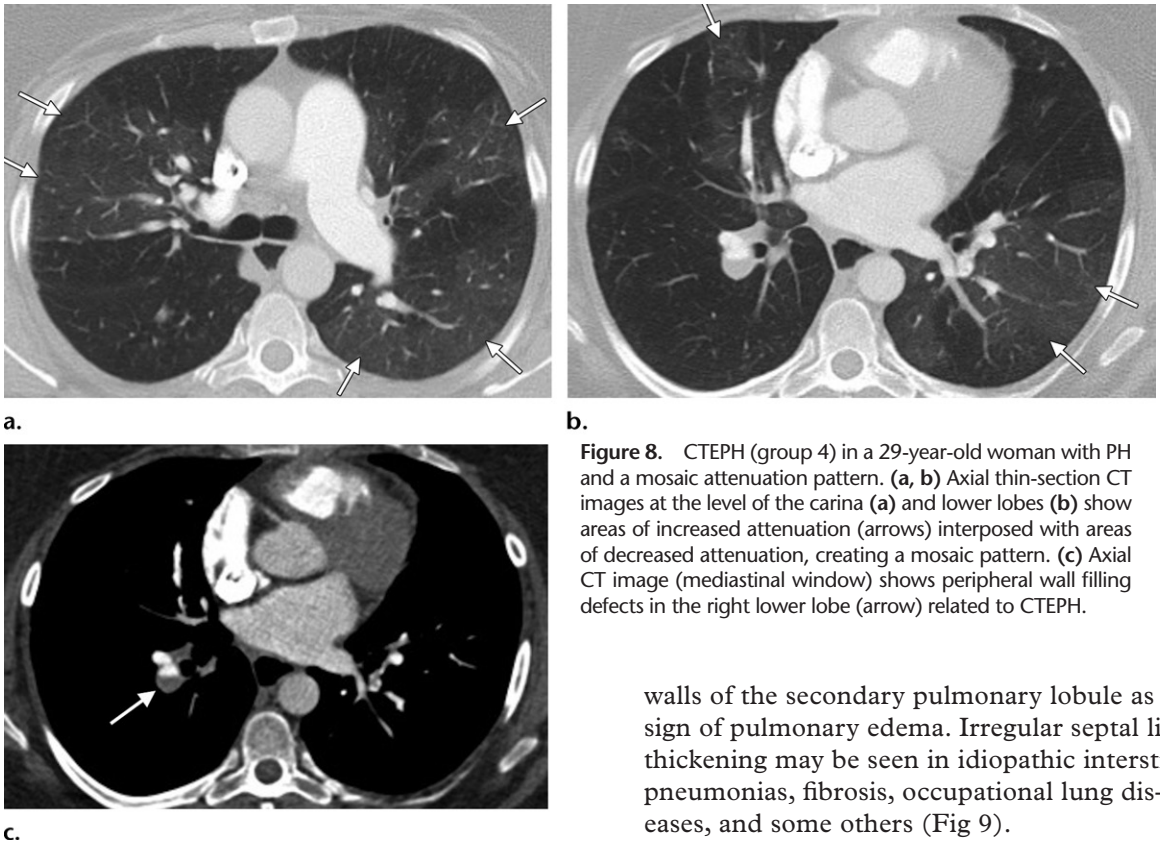


Figure 6. PH with multifactorial causes (group 5) in a 90-year-old woman with primary pulmonary artery sarcoma with increasing size of the pulmonary artery. Axial CT image (mediastinal window) shows enlargement of the main pulmonary artery with a large and lobular filling defect (☆), with expansion of the lumen of the artery and extension to the right pulmonary artery. There are some subtle areas of enhancement inside the tumor (arrow).



a. b.

Figure 7. PCH (group 1) in patients with PH and centrilobular nodules. **(a)** Axial thin-section CT image at the level of the pulmonary artery in a 10-year-old boy shows multiple small centrilobular nodules (arrows) and ground-glass opacities. **(b)** Axial thin-section CT image at the level of the lower lobes in a 14-year-old boy shows multiple small centrilobular nodules (arrows) and ground-glass opacities.



a. b. c.

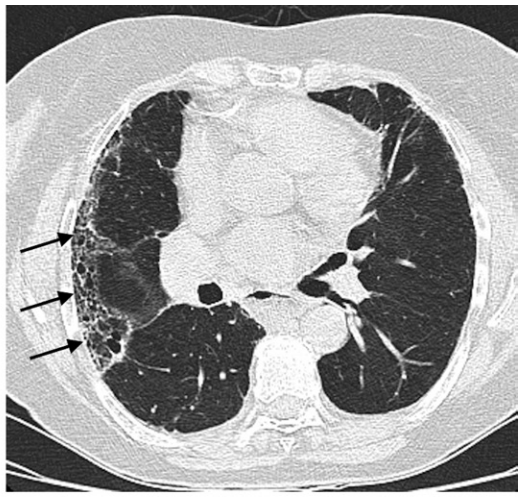
Figure 8. CTEPH (group 4) in a 29-year-old woman with PH and a mosaic attenuation pattern. **(a, b)** Axial thin-section CT images at the level of the carina **(a)** and lower lobes **(b)** show areas of increased attenuation (arrows) interposed with areas of decreased attenuation, creating a mosaic pattern. **(c)** Axial CT image (mediastinal window) shows peripheral wall filling defects in the right lower lobe (arrow) related to CTEPH.

The darker regions will also demonstrate reduced vessel size and lack of air trapping.

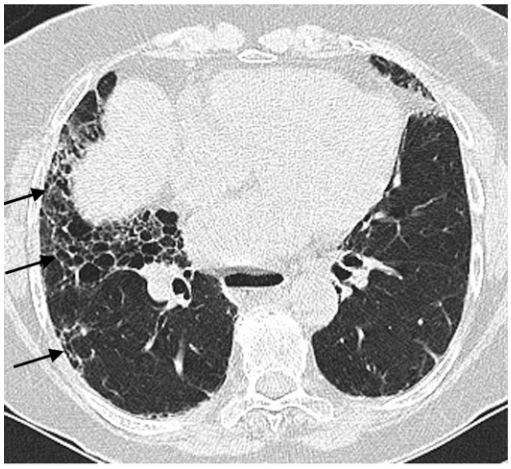
Interlobular Septal Thickening.—Interlobular septal thickening in PH is most commonly seen in patients with left heart disease (group 2). The thickening may be smooth (left heart disease), irregular (fibrosis [group 3]), or nodular (sarcoidosis or lymphangitic carcinomatosis [group 5]) (4,46). Smooth thickening occurs secondary to dilatation of lymphatics or venules in the walls of the secondary pulmonary lobule as a sign of pulmonary edema. Irregular septal line thickening may be seen in idiopathic interstitial pneumonias, fibrosis, occupational lung diseases, and some others (Fig 9).

One key group to remember that manifests with smooth septal line thickening is the subgroup of PVOD and PCH (group 1), which may manifest with findings similar to those of congestive heart failure. Unlike in patients with left heart disease, echocardiography will not show signs of left heart disease. Smooth septal lines, geographic or nodular ground-glass opacities, and pleural effusion should raise suspicion for PVOD or PCH over other causes of PH (25).

Some other less common causes of PH and interlobular septal thickening are mediastinal fibrosis, metastasis, and sarcoidosis, all group 5



a.



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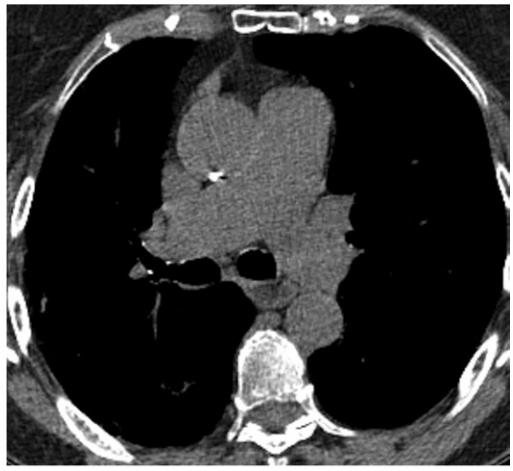


c.

Figure 9. Pulmonary fibrosis (group 3) in a 68-year-old woman. **(a, b)** Axial thin-section CT images at the level of the intermediate bronchus **(a)** and lower lobes **(b)** show interlobular septal thickening and honeycombing (arrows). **(c)** Axial CT image (mediastinal window) shows enlargement of the main pulmonary artery.

conditions. In mediastinal fibrosis, septal thickening results from venous obstruction (9). Nodular interlobular septal thickening may be seen in sarcoidosis or lymphangitic spread of tumor. In sarcoidosis, 40%–60% of patients may have PH without evidence of pulmonary fibrosis (42).

Bronchiectasis.—PH is an expected finding in patients with long-standing bronchiectasis secondary to hypoxic pulmonary vasoconstriction and destruction of the vascular bed (Fig 10) (54,56). The presence of PH is an independent predictor of mortality in patients with bronchiectasis due to any cause, secondary to hypoxia (56).

Bronchiectasis may also be seen in group 3 PH in association with parenchymal fibrosis (traction bronchiectasis) and occasionally in group 5 PH in the setting of sarcoidosis (9,57).

In CTEPH (group 4), bronchiectasis occurs in almost 64% of cases, predominantly in the lung bases at the level of the segmental and subsegmental bronchi. The bronchiectasis tends to be present in areas of occluded or narrowed pulmonary arteries (58). The cause of the bronchiectasis in CTEPH remains somewhat obscure. As with mosaic attenuation and enlarged bronchial arteries, the presence of bronchiectasis may be used to confirm CTEPH when eccentric filling defects are encountered in the pulmonary arteries. Bronchiectasis is not a feature of Eisenmenger syndrome.

Subpleural Peripheral Opacities.—Subpleural opacities are present in 72%–87% of patients with CTEPH, and in this setting are often manifestations of pulmonary infarction or subpleural scarring from healed infarction (Fig 11) (45,59,60).

Patients with chronic hemolytic anemia or schistosomiasis (group 5 and group 1, respectively) may present with this finding secondary to pulmonary infarction as well (9).

Reticular peripheral subpleural opacities are characteristic findings in interstitial lung disease (usually nonspecific interstitial pneumonia or usual interstitial pneumonia) as part of group 3 PH.

Ground-Glass Opacities.—Ground-glass opacities are defined as increased lung parenchyma attenuation without obscuration of the underlying vascula-

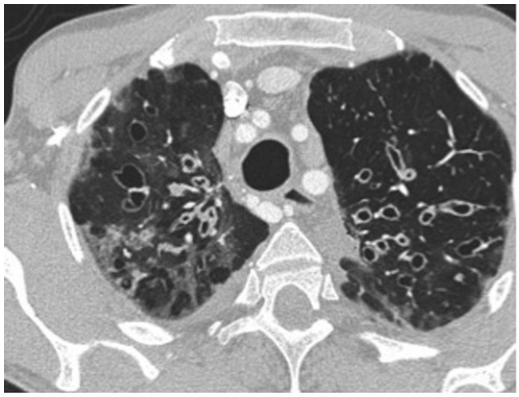
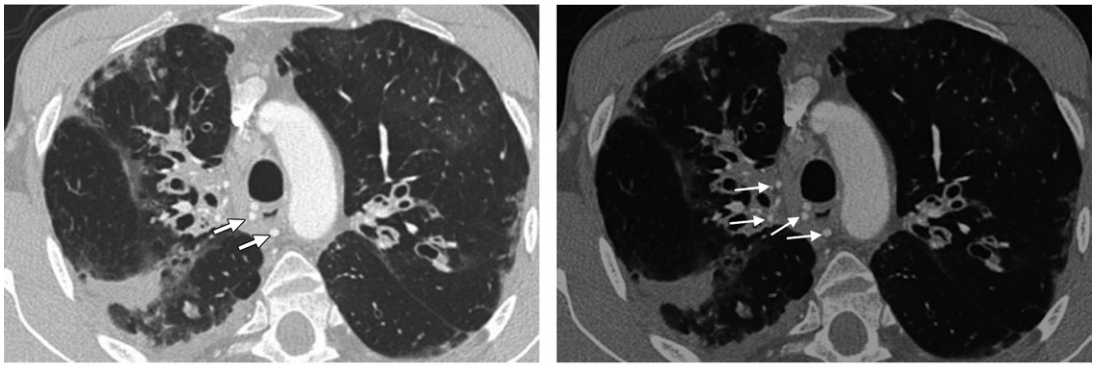
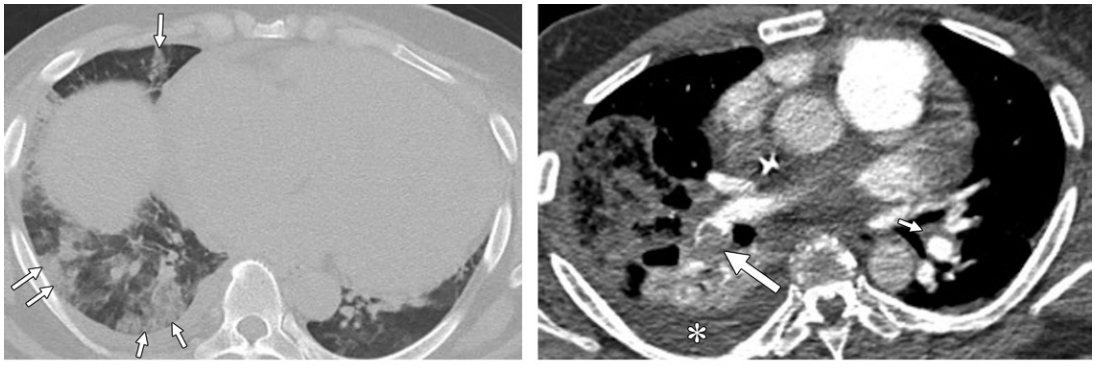


Figure 10. Cystic fibrosis (group 3). **(a, b)** Axial thin-section CT images at the level of the great vessels **(a)** and aortic arch **(b)** show dilatation of multiple bronchi, especially in the upper lobes, with enlarged bronchial arteries (arrows in **b**). **(c)** Axial CT image (mediastinal window) at the same level as **b** shows enlarged bronchial arteries (arrows).

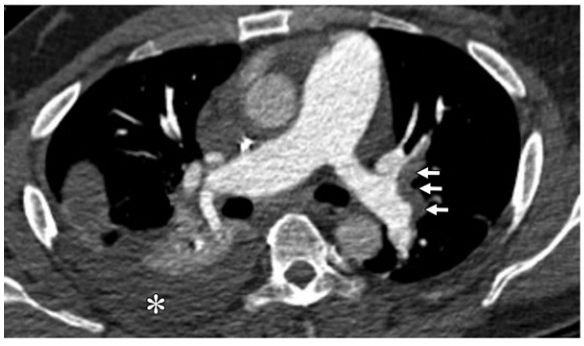
a.



b. **c.**



a. **b.**



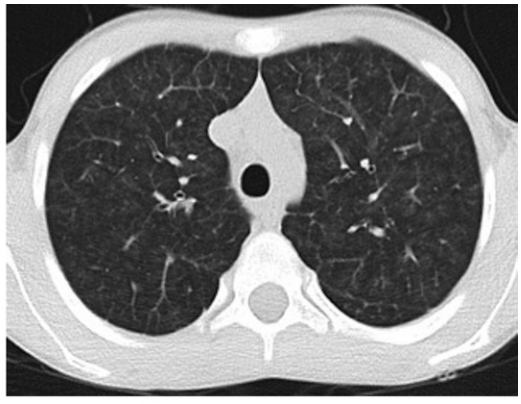
c.

Figure 11. CTEPH (group 4) in a patient with PH and pulmonary embolism. **(a)** Axial thin-section CT image through the lower lobes shows basal subpleural wedge-shaped opacities in the right lower lobe (arrows), which may represent pulmonary infarcts. **(b, c)** CT images show enlargement of the main pulmonary artery, with a central clot in the right pulmonary artery (large arrow in **b**) related to acute pulmonary embolism and an eccentric clot in the left pulmonary artery (small arrows). There is right pleural effusion (*).

ture or airways (54,61). Ground-glass opacities are often secondary to lung diseases unrelated to PH.

When encountered with PH, ground-glass opacities may be seen with pulmonary edema (group 2), some interstitial lung diseases (group 3), connective tissue disorders (group 1), and secondary drug or toxic reactions (group 1) and less frequently with chronic hemolytic anemia (group 5) or schistosomiasis (group 1).

When the ground-glass opacities manifest as centrilobular nodules, they may be secondary to



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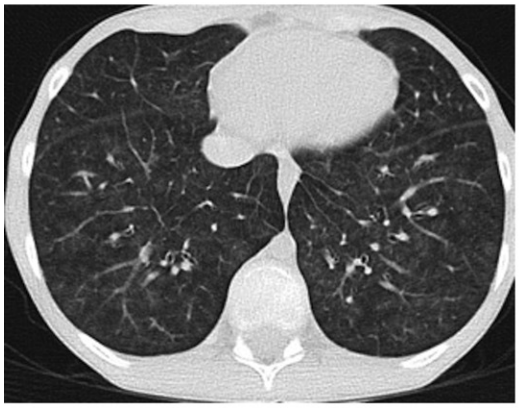

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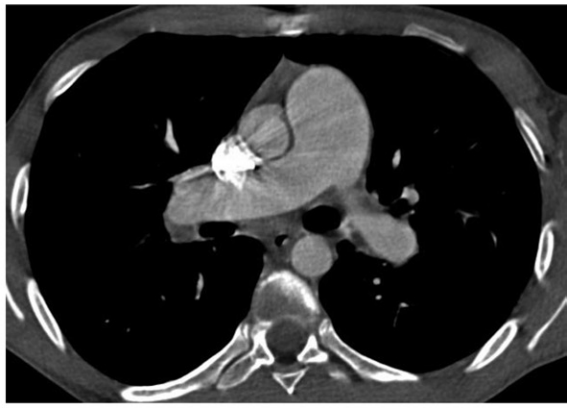
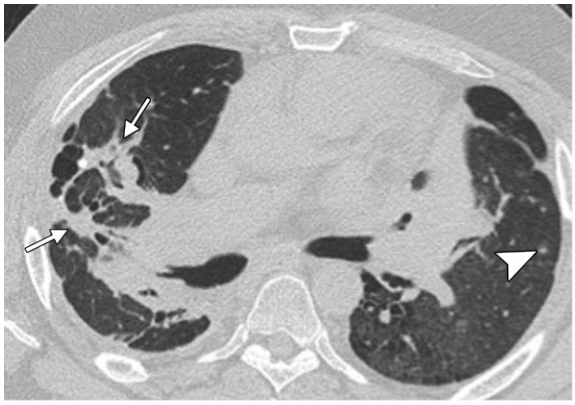
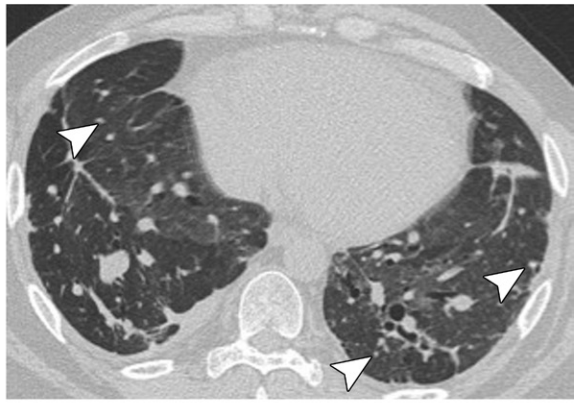


c.

Figure 12. PVOD (group 1) in a 13-year-old boy with PH. **(a, b)** Axial thin-section CT images at the level of the aortic arch **(a)** and lower lobes **(b)** show diffuse bilateral centrilobular ground-glass opacities and interlobular septal thickening. **(c)** Axial CT image (mediastinal window) shows an enlarged main pulmonary artery.



a.



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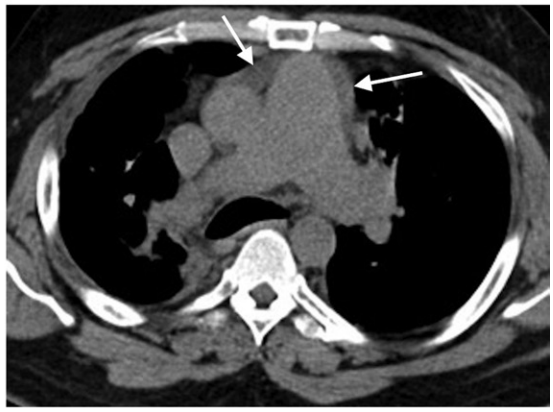
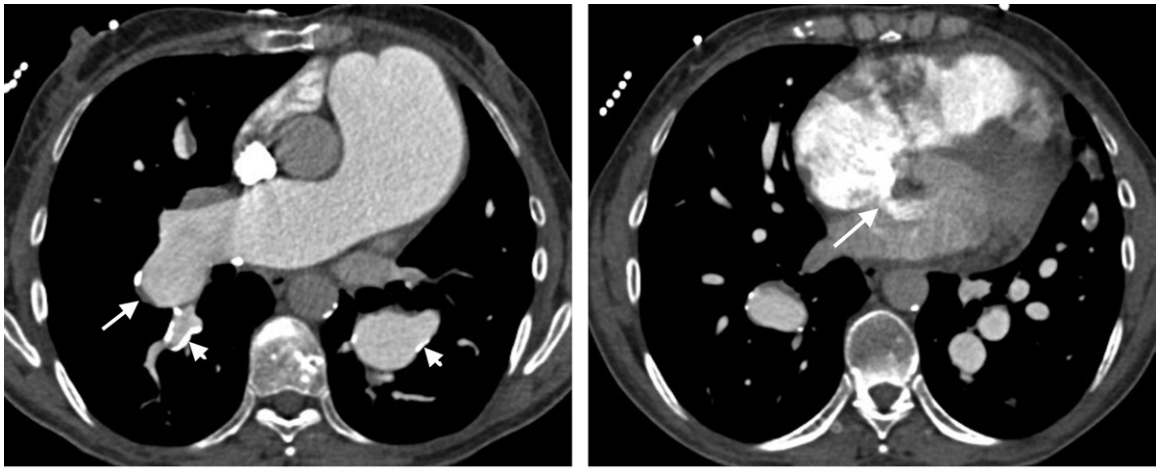


c.

Figure 13. Diffuse solid nodules in a 43-year-old woman with a history of sarcoidosis (group 5). **(a, b)** Axial thin-section CT images at the infracarinal level **(a)** and lower lobes **(b)** show bilateral upper lobe areas of consolidation (arrows in **a**) and small nodules (arrowheads). There is also traction bronchiectasis, most evident in the right upper lobe. **(c)** Axial CT image (mediastinal window) shows enlargement of the main pulmonary artery with a small pericardial effusion (arrows).

PVOD or PCH (group 1), as described earlier (Fig 12).

Diffuse Solid Nodules.—The most common entity with diffuse nodules and associated PH is sarcoidosis (Fig 13). PH occurs in 5%–74% of patients with sarcoidosis, whereas diffuse



a. b.

Figure 14. PH with congenital heart disease (group 1) in a patient with Eisenmenger syndrome secondary to an atrial septal defect. **(a)** Axial CT image (mediastinal window) at the level of the main pulmonary artery shows marked enlargement of the pulmonary artery with a small mural thrombus (large arrow) and calcifications (small arrows). **(b)** Axial CT image (mediastinal window) through the lower lobes shows marked enlargement of the segmental and subsegmental pulmonary arteries and shunt reversal from the right atrium to the left atrium (arrow).

nodules are seen in 15%–25% of patients with sarcoidosis (42,62). These nodules may be ill-defined with diameters that usually do not exceed 4 mm. The nodules tend to be bilateral with a peripheral or perilymphatic axial distribution and an upper and middle lung vertical distribution (62,63). Smaller nodules may be seen around a bigger coalescence, creating the galaxy sign (64), or may organize around the intrapulmonary lymphatics, creating the "sarcoid cluster" sign (65).

Other findings associated with sarcoidosis include hilar lymphadenopathy and upper lung fibrotic changes (62). Extensive fibrosis in the setting of sarcoidosis may result in PH and secondary right heart failure (62).

Uncommon causes of diffuse solid nodules in the setting of PH include metastases and metastatic pulmonary calcification (group 5). Pulmonary tumor thrombotic microangiopathy (PTTM) is an unusual complication of cancer reported in 1.4% of patients who died of their cancer (66). In this condition, micrometastases in the arteries initiate a cascade of thrombus and remodeling that results in increased pulmonary vascular resistance and pulmonary pressures. It manifests with diffuse nodular opacities, beaded pulmonary arteries, and occasionally lymphangitic carcinomatosis. PTTM is extremely rare but has been reported to have an association with adenocarcinomas, most notably gastric cancer (66).

Metastatic pulmonary calcification may develop in patients with chronic renal failure. It is characterized by multiple pulmonary nodules that demonstrate calcification, best seen with a mediastinal window (67). These patients may rarely present with PH, which is usually reversible after renal transplantation (68).

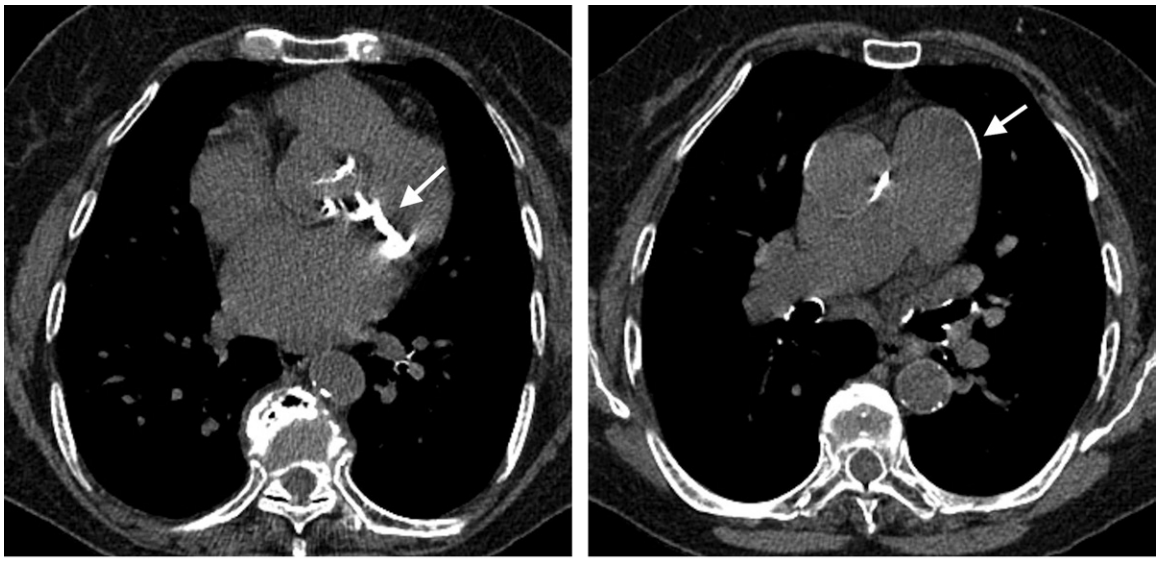
Cardiac Findings

Congenital Lesions.—Patients with untreated left-to-right shunts (atrial septal defects, partial anomalous pulmonary venous return, ventricular septal defects, and patent ductus arteriosus) can present with PH (Fig 14) (45). Ventricular septal defects have a higher risk of producing Eisenmenger syndrome than other cardiac congenital syndromes. Almost 50% of patients with ventricular septal defects and almost 10% with atrial septal defects will develop PH (4,45).

There is also a higher incidence of PH in patients who have been treated for a shunt lesion. Patients with treated cyanotic congenital heart disease (most notably transposition of the great arteries) may also present with PH (15).

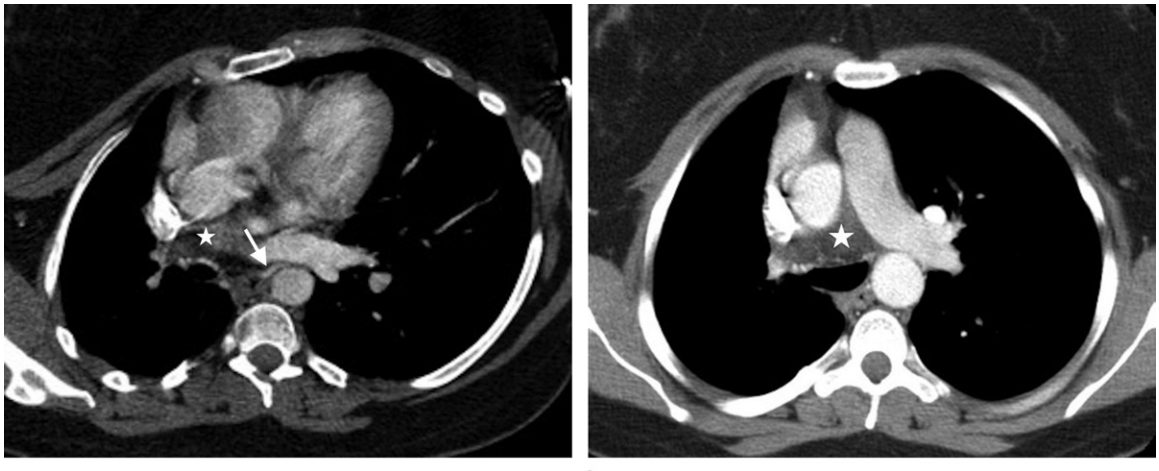
Left Ventricular Disease and Valve Anomalies.—Left heart disease is one of the most common causes of PH (46). Restrictive myocardial disease, left ventricular systolic or diastolic dysfunction, and valvular disorders are the principal causes of PH secondary to left heart disease (6,9). The prevalence of PH has been reported as up to 100% in patients with severe left-sided valvular disease (9). Less commonly, left atrial tumors or masses (such as myxoma, sarcoma, metastasis, or thrombus) that compromise the pulmonary venous return may result in PH (9).

Some imaging findings in left heart disease overlap those found in veno-occlusive disease.

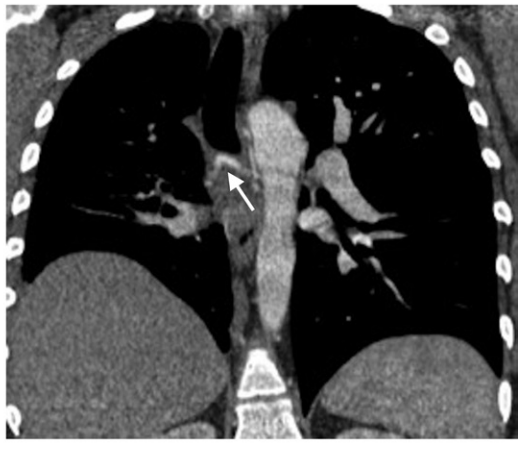


a. b.

Figure 15. PH due to left heart disease (group 2) in a patient with mitral valve disease. Axial CT images (mediastinal window) at the level of the mitral valve **(a)** and main pulmonary artery **(b)** show marked calcification of the mitral valve and annulus (arrow in **a**) with severe PH and calcification of the pulmonary arteries (arrow in **b**).



a. b.



c.

Figure 16. PH with congenital heart disease (group 1) in a patient with an interrupted right pulmonary artery. Axial **(a, b)** and coronal **(c)** CT images (mediastinal window) show absence of the right pulmonary artery (☆ in **a** and **b**) with hypertrophied bronchial arteries (arrow in **a** and **c**).

The key to differentiation is the left atrial enlargement present in left-sided cardiac disease but not in PVOD (15,45).

Leaflet thickening, valvular calcifications, and left atrial chamber dilatation are radiologic findings of mitral valve disease that may result in PH (Fig 15) (15). Aortic valve calcification and left ventricular myocardial thickening are related to aortic stenosis, which is another common cause of PH (15).

Mediastinal Findings

Hypertrophied Bronchial Arteries.—The bronchial arteries provide the blood supply for the walls of the bronchial tree and the proximal pulmonary arteries (11). They usually arise from the descending aorta near the carina and anasto-

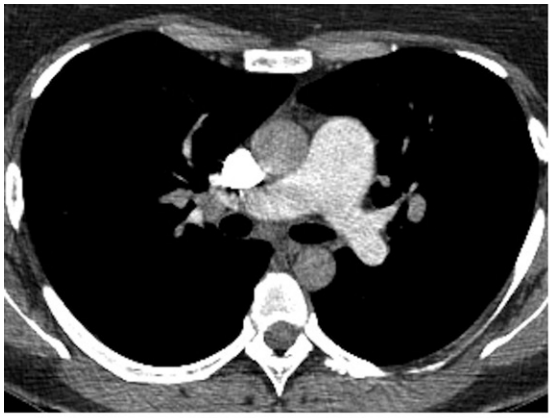
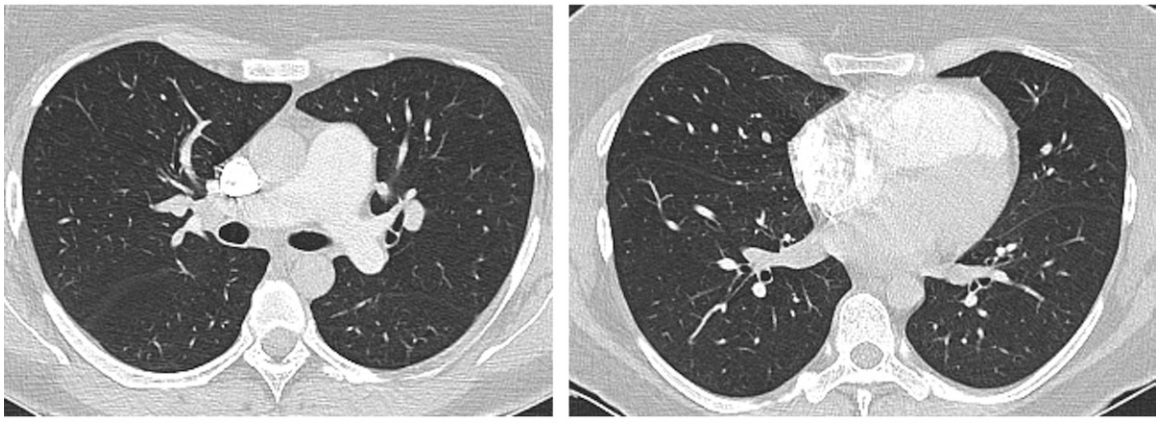


Figure 17. Idiopathic PAH (group 1) without mediastinal or pulmonary abnormality. **(a)** Axial CT image (mediastinal window) shows enlargement of the main pulmonary artery without any other associated findings. **(b, c)** Axial thin-section CT images (lung window) at the level of the main pulmonary artery **(b)** and lower lobes **(c)** show no pulmonary abnormalities.

a.



b. **c.**

mose with the pulmonary arteries at the level of the lower lobe segmental arteries. Hypertrophy occurs secondary to increased bronchial artery blood flow from obstruction in the proximal pulmonary arteries.

Dilatation of the bronchial arteries, and nonbronchial systemic arteries, is a frequent finding of CTEPH, seen in 47%–77% of cases (45,58,59). The bronchial arteries are considered hypertrophied when their diameter exceeds 1.5 mm (45,58). In patients with CTEPH, bronchial blood flow may be as much as 30% of the systemic blood flow (44). Nonbronchial systemic collaterals—commonly the intercostal, inferior phrenic, and internal mammary arteries—may be seen in almost 45% of patients with CTEPH (58).

Enlarged bronchial arteries are frequently encountered in Eisenmenger syndrome and after repair of cyanotic heart disease. In this context, they are sometimes referred to as aortopulmonary collateral arteries (Fig 16). Other conditions associated with enlarged bronchial arteries include Takayasu arteritis and fibrosing mediastinitis.

Absence of Mediastinal Abnormalities: Idiopathic PAH.—If no associated pulmonary or mediastinal findings are found that suggest a diagnosis of a specific subtype of PH or a specific disease, one should consider idiopathic PAH. Radiologically, idiopathic PAH is a diagnosis of exclusion (9). The principal features of idiopathic PAH include central pulmonary artery dilatation, abrupt decrease in the caliber of segmental and subsegmental arteries, and absence of signs of intraluminal thrombus (45) (Fig 17).

A mosaic attenuation pattern may be seen but is less common than in other causes of PH, most notably CTEPH (45). Bronchial artery hypertrophy is another distinguishing feature between idiopathic PAH and CTEPH (58). Bronchial artery enlargement is typically absent in idiopathic PAH.

Conclusion

We suggest this approach to PH—based on findings in the pulmonary arteries, pulmonary parenchyma, heart, and bronchial arteries—to guide one to the proper subtype of PH (Table 2).

The radiologist should play an important role in diagnosis and management of patients with PH. CT assessment of the lung parenchyma, pulmonary arteries, bronchial arteries, and heart may provide valuable information as to the subtype of PH according to the 2013 Nice classification and help facilitate appropriate categorization (Table 2). This approach will allow the radiologist

to be an important part of the multidisciplinary team and ensure that the patient with PH is managed appropriately.

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Table 2: PH from CT to Clinical Diagnosis

Findings of PH	Subtypes of PH
Pulmonary artery findings	
Peripheral calcification	Group 4: CTEPH Group 2 Group 1
Peripheral dilatation	Group 1 Group 5
Eccentric filling defects	Group 4 Group 1
Intra-arterial tumor	Almost always group 5
Pulmonary parenchymal findings	
Centrilobular nodules	Group 1: PCH Group 1: PVOD
Mosaic attenuation	Group 4: CTEPH Group 1, group 2, and less frequently group 3
Interlobular septal thickening	Group 3: irregular thickening Group 2: smooth thickening Group 1: PVOD, connective tissue disorders
Bronchiectasis	Group 3 Group 4: CTEPH Less frequently group 5
Subpleural peripheral opacities	Group 4: CTEPH Less frequently group 3
Ground-glass opacities	Group 1 Group 3 Group 2
Diffuse solid nodules	Almost always group 5
Cardiac findings	
Congenital lesions	Group 2: Eisenmenger syndrome and congenital heart disease Group 1
Left ventricular disease and signs of left ventricular failure	Group 2 Group 1
Valve anomalies	Group 2 Group 1
Mediastinal findings	
Hypertrophied bronchial arteries	Group 4: CTEPH Group 2: Eisenmenger syndrome and congenital heart disease
No associated pulmonary or mediastinal findings	Group 1: idiopathic PH

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