XI PULMONARY HYPERTENSION, COR PULMONALE, AND PRIMARY PULMONARY VASCULAR DISEASES

Gerald W. Staton, jr., m.d.
Roland H. Ingram, jr., m.d.

A new classification has been proposed [*see Table 1*] that divides pulmonary hypertension into five broad categories: (1) pulmonary hypertension associated with disorders of the respiratory system, hypoxemia, or both (e.g., chronic obstructive pulmonary disease [COPD] and interstitial lung disease) [*see 14:III Chronic Obstructive Diseases of the Lung and 14:V Chronic Diffuse Infiltrative Lung Disease*]; (2) pulmonary venous hypertension (e.g., left ventricular heart disease, mitral valve disease, and pulmonary veno-occlusive disease) [*see 1:XI Valvular Heart Disease, 1:XIV Cardiomyopathies, and 1:XVIII Venous Thromboembolism*]; (3) pulmonary hypertension caused by chronic thrombotic disease, embolic disease, or both [*see 1:XVIII Venous Thromboembolism*]; (4) pulmonary arterial hypertension (e.g., primary pulmonary hypertension, pulmonary hypertension resulting from vasculopathy associated with collagen vascular diseases, or congenital heart disease) [*see 1:XV Adult Congenital Heart Disease and 15:V Scleroderma and Related Diseases*]; and (5) pulmonary hypertension resulting from disorders directly affecting the pulmonary vasculature (e.g., pulmonary capillary hemangiomatosis).[1,2]

Pulmonary Vascular Hypertension

Pulmonary hypertension is defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest or 30 mm Hg with exercise or as a pulmonary arterial systolic pressure of 36 to 50 mm Hg (tricuspid regurgitation velocity of 2.8 to 3.4 m/sec), as estimated by echocardiography. The prevalence of pulmonary hypertension is difficult to measure precisely, but it is very common; most patients with heart failure have some degree of pulmonary hypertension.

Physiology

The pulmonary vasculature delivers a thin film of blood to approximately 125 m^2 of alveolocapillary surface area, effecting efficient gas exchange.

The entire cardiac output is accommodated at perfusion pressures that are one fifth of those in the systemic circulation, even when cardiac output increases severalfold during exercise. The perfusional reserve of the pulmonary circulation resides in capillary recruitment that in turn minimizes pressure increases and maximizes alveolocapillary gas exchange surface. In contrast to systemic arterioles that are richly endowed with smooth muscle, the pulmonary arterioles have relatively sparse musculature; hence, they have far more modest vasoconstrictor capability, resulting in a much more passive circulatory system.

There are two additional, unique characteristics of the pulmonary vasculature. First, there is a differential effect of gravity on gas-containing parenchyma and blood that results in a much greater influence of gravity on blood flow than on ventilation. The effects of gravity create diminishing zones of perfusion from base to apex in the upright posture. Back pressures from the left side of the heart also increase pulmonary arterial pressures, both distending and recruiting vasculature. Second, there are two portions of the vasculature that are influenced in opposite directions by changes in lung gas volume. Alveolar vessels are lengthened and narrowed monotonically with increases in lung volume; this in turn produces an increase in their resistance to blood flow. In series with the alveolar vessels are the extra-alveolar vessels that are tethered by the lung parenchyma; their size increases with increases in lung gas volume. The result of this interplay is a rise in pulmonary vascular resistance both when lung volume decreases below usual levels and when it increases above usual levels [*see Figure 1*].

Therefore, the major responses of the normal pulmonary circulation to forward and backward vascular pressures and to changes in lung volume are passive responses. Hypoxic vasoconstriction and neural and humoral vasomotor responses are normally modest, in keeping with small quantities of vascular smooth muscle.

Table 1 Classification of Pulmonary Hypertension as Proposed at the World Symposium on Primary Pulmonary Hypertension, Evian, France, 1998[1]

Pulmonary hypertension associated with disorders of the respiratory system, hypoxemia, or both
Parenchymal lung disease (COPD, IPF, cystic fibrosis)
Chronic alveolar hypoxemia (long-term exposure to low oxygen tension, such as occurs at high altitudes)
Pulmonary venous hypertension
Mitral valve disease
Chronic left ventricular dysfunction
Pulmonary veno-occlusive disease
Pulmonary hypertension associated with chronic thrombotic or embolic disease, or both
Thromboembolic obstruction of proximal pulmonary arteries
Obstruction of distal pulmonary arteries
Pulmonary arterial hypertension
Primary pulmonary hypertension (sporadic, familial)
Pulmonary arterial hypertension related to collagen vascular disease (scleroderma, lupus erythematosus, rheumatoid arthritis), congenital systemic-to-pulmonary shunts (Eisenmenger syndrome), portoprimary hypertension, HIV infection, and drugs and toxins
Pulmonary hypertension caused by disorders directly affecting the pulmonary vasculature
Inflammatory
Pulmonary capillary hemangiomatosis

COPD—chronic obstructive pulmonary disease IPF—idiopathic pulmonary fibrosis

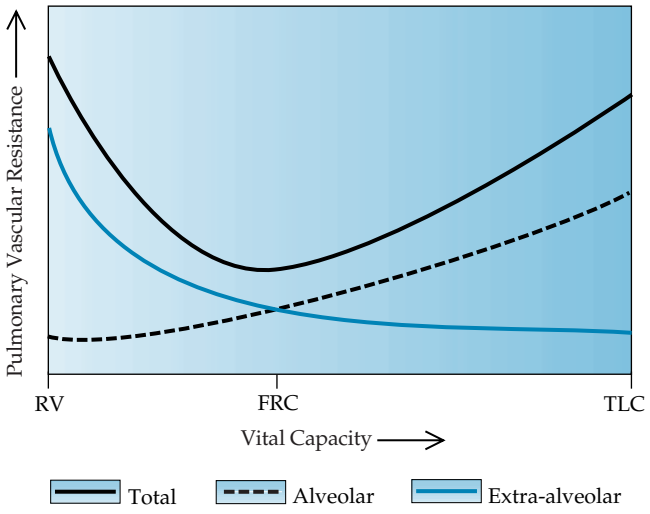


Figure 1 **Effects of lung volume on vascular resistance in alveolar, extra-alveolar, and total pulmonary circulation. The total vascular resistance is lowest at functional residual capacity (FRC) and is higher at low lung volume (residual volume [RV]) and high lung volume (total lung capacity [TLC]).**

PATHOGENESIS

Pulmonary hypertension can be caused by narrowing of the precapillary vessels (arteries and arterioles), loss of pulmonary capillary bed, or passive back pressure from the postcapillary vessels [*see Table 2*].

Precapillary pulmonary hypertension can be produced by several mechanisms. Embolic material, such as venous thrombi, can lodge in the pulmonary artery, producing acute obstruction or, if unresolved and organized into the vessel wall, chronic obstruction. In situ thrombosis can also occur. Chronically increased blood flow, as seen in large left-to-right shunts, is associated with remodeling of the pulmonary arterial walls to vessels that resemble systemic arteries and arterioles; this results in an increase in pulmonary vascular resistance and, ultimately, reversal of the shunt. Remodeling of the pulmonary arterial and arteriolar walls as a result of inflammation or endothelial dysfunction can also occur.

Loss of the pulmonary capillary bed as a result of destructive processes such as emphysema, interstitial fibrotic disease, or surgical resection will further increase resistance and produce pulmonary hypertension.

On rare occasions, the pulmonary veins can be obstructed by a primary process of the veins (pulmonary veno-occlusive disease) or during passage of the pulmonary veins through the mediastinum (neoplasm or mediastinal fibrosis). Any process that increases left atrial pressure (mitral stenosis or regurgitation) or increases left ventricular end-diastolic pressure (LVEDP) will also passively increase pulmonary arterial pressure without increasing pulmonary vascular resistance.

Regardless of the cause of pulmonary hypertension, when pulmonary hypertension occurs, the vasculature responds by undergoing changes that further increase its resistance [*see Figure 2*].[3-5] Secondary erythrocytosis (by increased blood viscosity), hypoxemia or hypoxia, and acidosis (by vasoconstriction) will also worsen pulmonary hypertension.

The patterns of histopathologic change seen in pulmonary hypertension are medial hypertrophy, intimal thickening, plexogenic pulmonary arteriopathy, thrombotic pulmonary arteriopathy, and veno-occlusive disease.[6] Historically, these patterns were felt to be specific for the different causes of pulmonary hypertension. However, studies indicate that these changes likely represent a final common pathway of response to pulmonary vascular injury and persistent pulmonary hypertension.[7]

DIAGNOSIS

The diagnostic evaluation of pulmonary hypertension [*see Figure 3*] begins with a careful history and physical examination.

The clinical features of pulmonary hypertension remain the same regardless of the underlying cause.[8] Early in the process, the symptoms of pulmonary hypertension can be minimal and nonspecific. Dyspnea, weakness, and fatigue are common; these symptoms are sometimes associated with chest pain that can mimic angina pectoris. Syncope, which is often exertional, can occur late in pulmonary hypertension; it is a sign of poor prognosis. Hoarseness caused by compression of the recurrent laryngeal nerve (Ortner syndrome) and hemoptysis related to increased bronchial collateral circulation can occur. Symptoms of right ventricular failure occur late in the disease and also indicate a poor prognosis.

Physical Examination

During physical examination, the jugular veins may be distended, and there may be prominent A waves, signifying decreased right ventricular (RV) compliance. Also, increased V waves may indicate tricuspid regurgitation. In patients with COPD, palpation of the chest may detect an RV heave in the parasternal area or in the subxiphoid area. On auscultation of the heart, there may be an increased P_2, an RV S_4, an RV S_3, a pulmonic ejection click, the murmur of tricuspid regurgitation (at the lower right sternal border and increased with inspiration), and, occasionally, pulmonic regurgitation (Graham Steell mur-

Table 2 Relation between Site, Pathogenesis, and Disorders of the Pulmonary Circulation

Site	*Pathogenesis*	*Disorders*
Precapillary	Intravascular obstruction, increased blood flow, vascular remodeling or inflammation, vasospasm, increased blood viscosity	Pulmonary emboli or in situ thrombosis, left-to-right shunt, alveolar hypoxia, vasculopathy caused by collagen vascular disorder or primary pulmonary hypertension, polycythemia
Capillary	Destruction of capillary bed	Emphysema, interstitial lung disease, surgical removal
Postcapillary	Passive back pressure from pulmonary venous obstruction, high left atrial pressure, high LVEDP	Pulmonary veno-occlusive disease, pulmonary venous obstruction in the mediastinum, mitral regurgitation or stenosis, left ventricular failure

LVEDP—left ventricular end-diastolic pressure

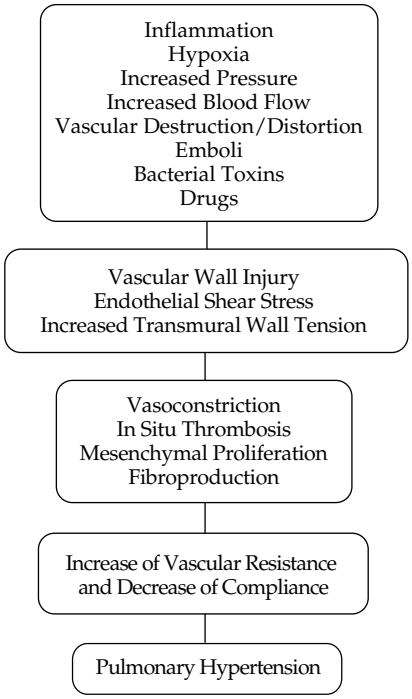


Figure 2 **Mechanisms of pulmonary hypertension. Irrespective of the initiating event or events, pulmonary hypertension worsens over time because of vascular wall injury, endothelial shear stress, and an increase in transmural wall tension. These processes result in vasoconstriction, vascular wall remodeling, and in situ thrombosis.**

mur). Hepatomegaly, ascites, and lower extremity edema are each extrathoracic indicators of right ventricular failure.

Initial Imaging and Physiologic Testing

Chest radiography The chest radiograph can also provide clues to the diagnosis of pulmonary hypertension. Symmetrical enlargement of the pulmonary arteries, with rapid tapering of the distal vessels (pruning) and enlargement of the right ventricle, can be found but usually is not seen until later in the process. Asymmetrical enlargement of the central pulmonary arteries may be seen in patients with chronic thromboembolic pulmonary hypertension. Clues to the underlying cause of pulmonary hypertension include pulmonary venous congestion (e.g., LV failure), hyperinflation (COPD), or interstitial lung disease (e.g., interstitial pulmonary fibrosis).

Electrocardiography In mild cases of pulmonary hypertension, the electrocardiogram may be normal. In more severe cases, the ECG will show changes of right ventricular hypertrophy and right atrial enlargement. These changes are to be contrasted with the typical ECG findings seen in COPD, which largely reflect the hyperinflation of the lungs and low diaphragms.

Transthoracic echocardiography Transthoracic echocardiography with Doppler estimation of pulmonary arterial pressure is the noninvasive method of choice in screening populations of patients with a high incidence of pulmonary hypertension; such patients include those with with systemic sclerosis or the CREST syndrome (calcinosis, Raynaud phenomenon,

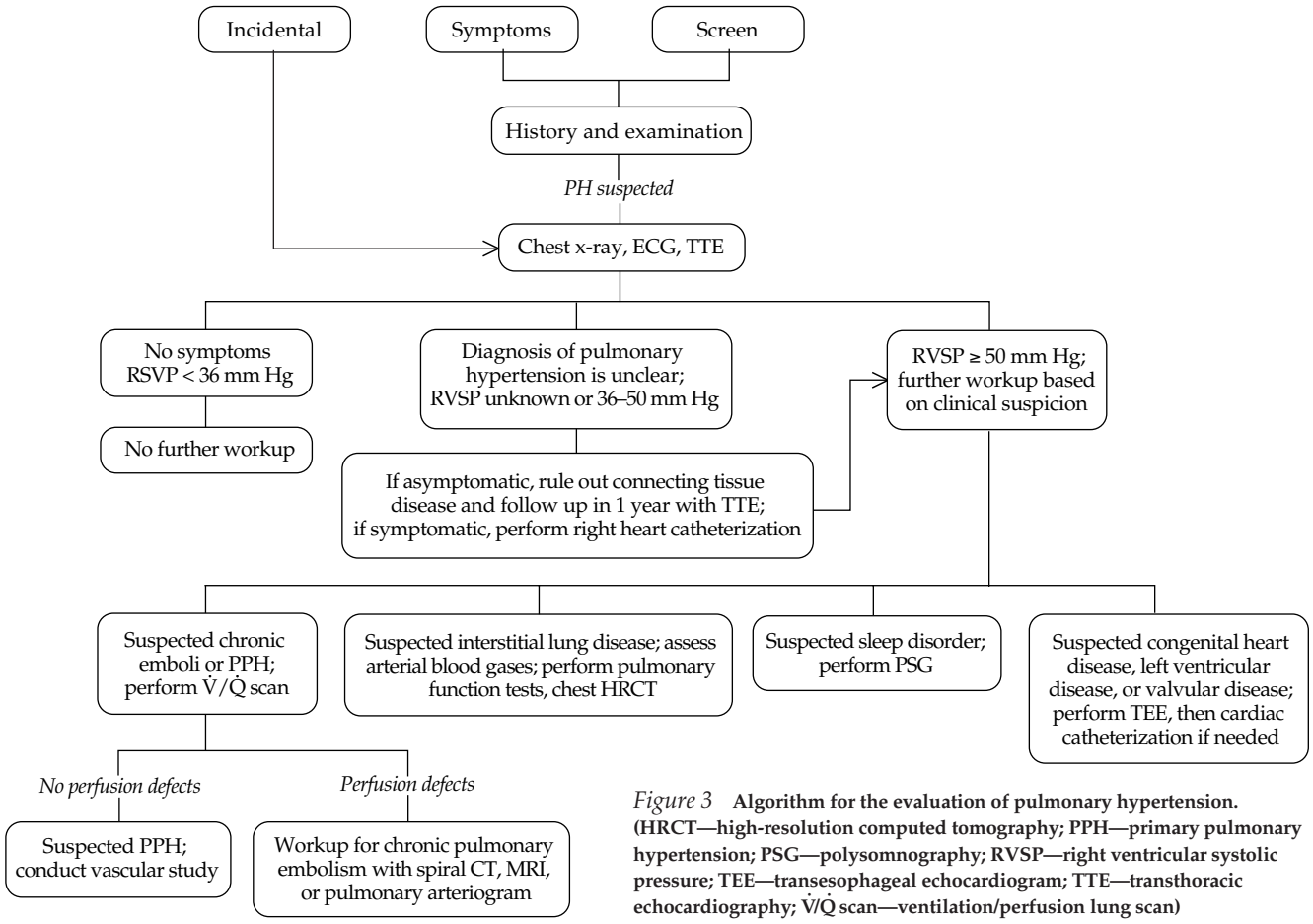


Figure 3 **Algorithm for the evaluation of pulmonary hypertension. (HRCT—high-resolution computed tomography; PPH—primary pulmonary hypertension; PSG—polysomnography; RVSP—right ventricular systolic pressure; TEE—transesophageal echocardiogram; TTE—transthoracic echocardiography; V̇/Q̇ scan—ventilation/perfusion lung scan)**

esophageal dysmotility, sclerodactyly, and telangiectasias), those who have a family history of pulmonary hypertension, and patients with cirrhosis who are being evaluated for liver transplantation. Transthoracic echocardiography is also useful in evaluating patients with symptoms suggestive of pulmonary hypertension. Findings indicative of pulmonary hypertension include hypertrophy, enlargement of the right ventricle and atrium, and abnormal motion of the septum [*see Figure 4*]. On Doppler echocardiography, a tricuspid regurgitant flow of 2.8 to 3.4 m/sec corresponds to a peak pulmonary arterial systolic pressure of 36 to 50 mm Hg and defines mild pulmonary hypertension. Because the test is noninvasive, it can be repeated as often as necessary in the serial care of patients with pulmonary hypertension. In some patients, transesophageal echocardiography may be necessary to detect congenital defects. If hypoxemia suggestive of a right-to-left intracardiac shunt is present, injection of agitated saline filled with air bubbles during the echocardiogram will allow detection of the shunt.[9]

Tests to Diagnose Underlying Cause of Pulmonary Hypertension

Pulmonary function testing Measurements of pulmonary function can be useful in evaluating patients with pulmonary hypertension. Detection of significant airflow obstruction or a severe restrictive defect may indicate that all or a portion of the pulmonary hypertension is caused by intrinsic lung disease. By contrast, isolated reduction of the diffusion capacity or minimal reduction in the lung volumes can be seen in any of the primary pulmonary vasculopathies. Arterial blood gases at rest and pulse oximetry with exercise detect complicating resting or exercise hypoxemia that should be remedied therapeutically. The finding of hypercapnia is most compatible with severe chronic airflow obstruction, sleep apnea, or chest wall disease.

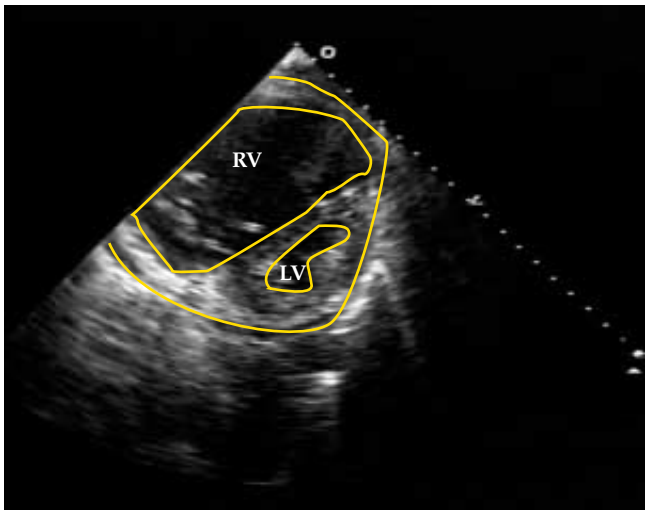
Polysomnography Patients suspected of having a sleep disorder of breathing that may be causing or contributing to pulmonary hypertension should undergo nocturnal polysomnography.

Ventilation-perfusion lung scanning Ventilation-perfusion lung scanning can be very useful in evaluating patients with pulmonary hypertension, especially when chronic thromboembolic pulmonary hypertension is suspected. Patients with chronic thromboembolic pulmonary hypertension will have multiple perfusion defects of different sizes (usually interpreted as indicating a high probability of pulmonary embolism), whereas patients with other causes of pulmonary hypertension will have either homogeneous or mildly mottled perfusion [*see Figure 5*]. The presence of radioactivity in the head or kidney suggests a right-to-left shunt.

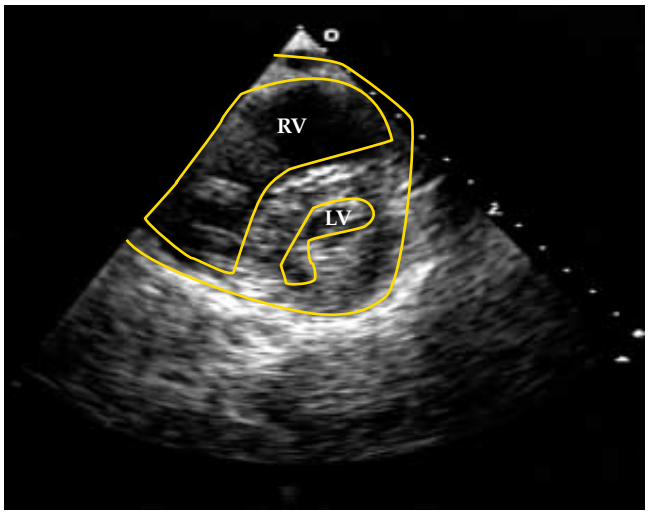
Computed tomography Computed tomography of the chest using spiral or helical or electron-beam techniques can visualize central pulmonary thromboemboli more safely and, in some cases, more accurately than angiography. High-resolution CT of the chest can detect emphysema or interstitial lung disease not seen on routine chest radiography.

Cardiac catheterization and pulmonary arteriography If severe pulmonary hypertension remains unexplained, complete cardiac catheterization with pulmonary arteriography should be performed to exclude congenital heart disease, proximal or peripheral pulmonary arterial stenosis, and valvular

a



b



c

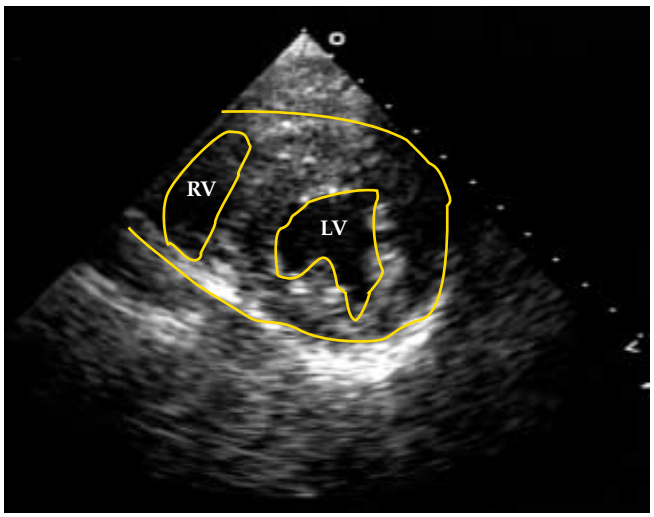
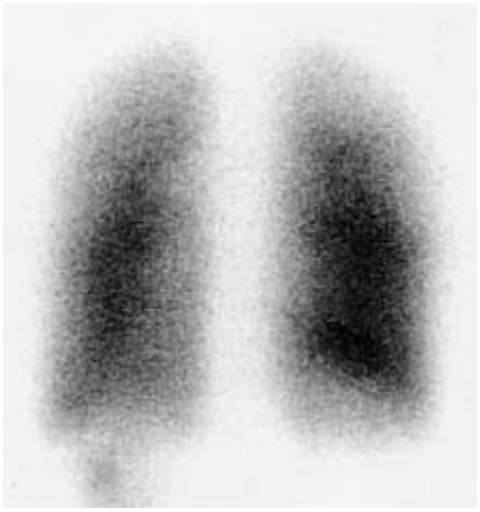


Figure 4 **(*a*) Echocardiogram of a patient with chronic pulmonary hypertension. (*b*) Echocardiogram of a patient with acute pulmonary hypertension. (*c*) Echocardiogram of the patient shown in Figure B after clot lysis. (LV—left ventricle; RV—right ventricle)**

a



b

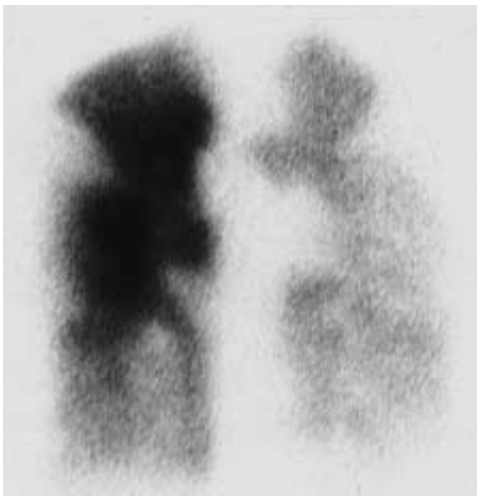


Figure 5 **Perfusion lung scans of a patient with primary pulmonary hypertension showing homogeneous perfusion (*a*) and of a patient with chronic thromboembolic pulmonary hypertension, showing large bilateral perfusion defects (*b*).**

heart disease. Because of the increased risk of complications, pulmonary arteriography in this situation should be performed by experienced angiographers using selective injections and minimal nonionic contrast. In those patients who are thought to have primary pulmonary hypertension, vasodilator testing with such agents as nitric oxide, prostacyclin, and adenosine, with monitoring of gas exchange and pulmonary hemodynamics, should be performed.[8]

Lung biopsy It is very uncommon that a lung biopsy is required to establish the cause of pulmonary hypertension. The only exception would be in patients in whom one of the interstitial lung diseases is suspected as a cause of pulmonary hypertension. Bronchoscopic lung biopsy is contraindicated in patients with severe pulmonary hypertension; in such cases, open or video-assisted biopsy is the technique of choice. Such a biopsy poses a greater risk for patients with pulmonary hypertension than for patients without pulmonary hypertension.

TREATMENT

Pulmonary hypertension is a general finding; treatment depends on the underlying cause. Disorders that affect the pulmonary circulation acutely (e.g., pulmonary embolism, pulmonary edema, and the acute respiratory distress syndrome) are covered elsewhere [*see 1:XVIII Venous Thromboembolism and 14:X Pulmonary Edema*], as are congenital heart defects that can cause pulmonary hypertension [*see 1:XV Adult Congenital Heart Disease*] and diseases that affect the lung airways and parenchyma, such as COPD and the interstitial lung diseases [*see 14:III Chronic Obstructive Diseases of the Lung and 14:V Chronic Diffuse Infiltrative Lung Disease*]. In this subsection, we cover the processes that chronically affect the pulmonary vasculature directly (i.e., those pertinent to categories 3 through 5; see above), as well as the common features of acute and chronic cor pulmonale, irrespective of cause.

Cor Pulmonale

DEFINITION

Cor pulmonale is the term used for right heart dilatation, hypertrophy, and heart failure caused by pulmonary hypertension resulting from disorders of the pulmonary parenchyma, the pulmonary vasculature, the thoracic cage, or the neuromuscular system, excluding congenital heart disease and disorders of the left side of the heart. Cor pulmonale can occur acutely in settings of rapid-onset right ventricular overload or chronically with the slow onset of pulmonary hypertension.

ACUTE COR PULMONALE

Pathogenesis

The right ventricle normally pumps at low pressures, even when cardiac output is dramatically increased by exercise. In response to an acute increase in pulmonary vascular resistance, the right ventricle distends, producing an increase in right ventricular systolic and diastolic volume, but is unable to generate high pressures (the pressure generated is usually less than a mean pressure of 40 mm Hg). If the right ventricle cannot adequately compensate, increases in right ventricular end-diastolic pressure (RVEDP) and right atrial pressure occur, producing acute right heart failure. Additionally, the reduced cardiac output from the right ventricle to the left ventricle and the shift of the interventricular septum toward the left ventricle cause a reduction in left ventricular filling and systemic shock.[10] Decreased coronary perfusion caused by low systemic diastolic pressure further reduces the ability of the right ventricle to overcome the added resistance, producing a rapid decline to death.

The disorders that cause acute cor pulmonale are diseases that produce sudden obstruction of the pulmonary vasculature, such as massive pulmonary thromboembolism[11]; acute embolism caused by other materials, such as air, bone marrow, fat, amniotic fluid, or tumor; or obstruction of the microvasculature caused by high airway pressure or destruction, as is seen in acute respiratory distress syndrome.[12]

Diagnosis

In the setting of acute respiratory failure or shock with evidence of acute right heart failure, immediate bedside echocardiography can demonstrate acute cor pulmonale. Features that are seen include pulmonary hypertension (usually mild), right

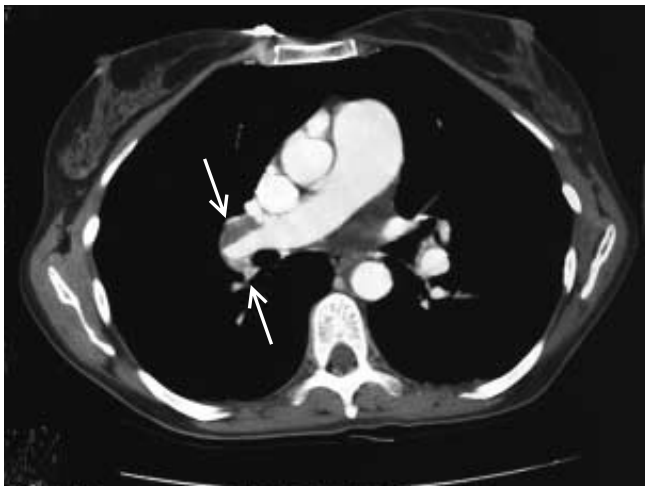


Figure 6 **Spiral CT scan of the chest of a patient with chronic thromboembolic pulmonary hypertension showing large defects in the right main pulmonary artery (arrows).**

ventricular dilatation without hypertrophy, tricuspid regurgitation, septal flattening with paradoxical septal motion, and left ventricular diastolic dysfunction [*see Figure 5*].[13] Relief of the obstruction, as occurs through lytic therapy in patients with pulmonary embolism, results in resolution of the echocardiographic findings [*see Figure 6*].

Treatment

Rapid recognition of acute cor pulmonale and relief of the pulmonary vascular obstruction, if possible, are the key to survival for patients with acute cor pulmonale. For example, thrombolytic therapy for patients with acute massive pulmonary embolism will result in complete resolution of the acute cor pulmonale.[14]

CHRONIC COR PULMONALE

Pathogenesis

In response to a chronic increase in pulmonary vascular resistance, the right ventricle will distend and undergo hypertrophy. When the ability of the right ventricle to compensate is overwhelmed, increases in RVEDP and right atrial pressure occur, producing the syndrome of right heart failure.

The pulmonary hypertension that results in chronic cor pulmonale is produced by increased pulmonary vascular resistance caused by varying combinations of pulmonary vascular destruction or obstruction, hypoxia or acidosis leading to hypoxic vasoconstriction, and remodeling of the pulmonary vasculature. Some of these changes (e.g., hypoxic vasoconstriction and some remodeling) are reversible with therapy, whereas others (vascular bed destruction) are not.

The disorders that cause chronic cor pulmonale include all primary and secondary causes of pulmonary hypertension, with the exception of disorders of the left heart and congenital heart disease.

Diagnosis

Chronic cor pulmonale may be difficult to detect early because the manifestations of the underlying lung disease dominate the clinical picture. The clinical features and evaluation are the same as those described for chronic pulmonary hypertension (see above). Echocardiography has become the most useful means of detecting right heart changes caused by pulmonary hypertension.

Treatment

The nature and severity of the underlying lung disease determine the outcome of patients with chronic cor pulmonale. For example, cor pulmonale secondary to sleep apnea may be entirely reversible with appropriate treatment, whereas cor pulmonale caused by idiopathic pulmonary fibrosis is usually irreversible.

The most important treatment of chronic cor pulmonale is the treatment of the underlying lung disease [*see 14:III Chronic Obstructive Diseases of the Lung, 14:V Chronic Diffuse Infiltrative Lung Disease, 14:VI Ventilatory Control during Wakefulness and Sleep, and 14:VII Disorders of the Chest Wall*]. In patients with hypoxemia, controlled-flow supplemental O_2 should be given at rest to maintain O_2 saturation above 90%, during exercise, and during sleep. Patients should be monitored for acute increases in arterial carbon dioxide pressure (P_aCO_2).[15]

Although digitalis has the same effect on the failing right heart as on the left, its use in such cases has not been associated with benefit (except in patients with concomitant left ventricular dysfunction) and may be associated with greater toxicity. Diuretics are useful in reducing the edema, ascites, and liver congestion but must be used carefully to avoid reducing right ventricular filling pressures, which may lead to decreasing cardiac output. Theophylline and beta agonists have beneficial effects beyond their bronchodilator effects because of positive inotropic and pulmonary vasodilator actions. Phlebotomy in patients with secondary polycythemia[16] and noninvasive mechanical ventilation of patients with chronic respiratory failure[17] may also improve hemodynamics.

Although agents such as hydralazine and calcium channel blockers cause pulmonary vasodilatation, in patients with chronic cor pulmonale, gas exchange is usually impaired, negating any potential positive effect of these drugs. Epoprostenol (prostacyclin) and three of its analogues have been studied in several types of chronic pulmonary hypertension and seem to be beneficial.[18]

Primary Pulmonary Vascular Diseases

PRIMARY PULMONARY HYPERTENSION

Idiopathic or primary pulmonary hypertension (PPH) is a condition in which the pulmonary vasculature is the primary site of the disease.[1,19] By definition, other causes of pulmonary hypertension are excluded.

Epidemiology

PPH is rare, having an estimated clinical incidence of 1 to 2 per million people a year and a prevalence of 1,300 per million population. Although the disease can occur at any age, the mean age at diagnosis is 36 years.[19] The disease is more frequent in females than in males (ratio, 1.7:1 to 3.5:1) and is equally represented in all races. Approximately 6% to 12% of cases are familial.[20]

In the United States, the mortality from PPH rose substantially from 1979 to 1996, possibly because of the introduction of anorexigens.[21]

Etiology and Pathogenesis

The cause of PPH is unknown, although there are several clinical conditions associated with the development of PPH. In ad-

dition, the ingestion of certain drugs or other materials has been associated with PPH.[22] In the 1960s and again in the 1990s, ingestion of appetite suppressants such as aminorex, fenfluramine, and dexfenfluramine were associated with an epidemic of pulmonary hypertension.[23] Additionally, ingestion of contaminated rapeseed oil, L-tryptophan, amphetamines, cocaine, and monocrotaline extracts are associated with PPH.[22] Other conditions associated with PPH are splenectomy/asplenia, portal hypertension, HIV infection,[24] and autoimmune thyroid disorders.[22]

As is true of many diseases, it is thought that PPH results from an inciting factor in a genetically susceptible individual. Studies of inheritance have suggested an autosomal dominant pattern with markedly reduced penetrance in familial PPH, with the involved gene on chromosome 2. The gene for familial pulmonary hypertension, *PPH1,* has now been identified as heterogeneous germline mutations of the gene coding for the bone morphogenic protein receptor 2.[20] The exact mechanism accounting for how abnormalities of this receptor produce primary pulmonary hypertension are being investigated.[25]

Studies of the pulmonary vasculature in PPH suggest endothelial injury and dysfunction early in the process.[26] In PPH, expression of endothelial nitric oxide synthetase is reduced (nitric oxide is a pulmonary vasodilator) and expression of endothelin 1, a potent pulmonary vasoconstrictor and a mitogen, is increased. There is an excess of thromboxane (a vasoconstrictor and potent stimulus for platelet aggregation) relative to prostacyclin, a pulmonary vasodilator. Other vasoactive mediators, such as serotonin, another pulmonary vasoconstrictor, may also play a role, especially in pulmonary hypertension associated with appetite suppressants, which inhibit serotonin reuptake. Abnormal α_1-adrenoceptor affinity and responsiveness may produce downstream signaling events that cause defects in ion channel activity and control of intracellular calcium and could contribute to vasoconstriction and to smooth muscle proliferation and growth.[27] As a consequence of the endothelial dysfunction and resultant pulmonary vasoconstriction, intimal proliferation, smooth muscle hyperplasia and hypertrophy, and other remodeling phenomena occur, further increasing pulmonary vascular resistance.[28] In situ thrombosis may also play a role in endothelial injury and vascular obstruction.[29]

Diagnosis

The diagnosis of primary pulmonary hypertension can be made when clinical findings [*see* Pulmonary Vascular Hypertension, Diagnosis, *above, and Figure 3*] are present and other causes of pulmonary hypertension have been excluded.

Treatment

Medical therapy No cures for PPH have been developed, although treatment has improved outcome significantly. Physical activity should be encouraged but is limited by symptoms. Pregnancy is poorly tolerated and should be prevented (oral contraceptives should not be used, because they may increase the risk of thrombosis). Invasive medical procedures should be avoided as much as possible. Medications that worsen pulmonary hypertension (e.g., decongestants, beta blockers, and appetite-suppressant drugs) should be avoided. Patients with PPH should receive long-term warfarin anticoagulation therapy to achieve an INR (international normalized ratio) of 1.5 to 2.5, and they should avoid medications that interfere with warfarin metabolism. Oxygen should be used for resting or exercise-induced hypoxemia or if the patient will be exposed to high altitudes, such as on an airplane flight. Diuretics are useful to help control edema and ascites. Use of digoxin is controversial.[30]

Vasodilators have changed the outlook for patients with pulmonary hypertension. For patients who have an acute vasodilator response to the agents mentioned, a trial of a calcium channel blocker, such as nifedipine or diltiazem, should be initiated. The patient should be monitored closely during this time because some patients will deteriorate with this therapy. If the patient responds, the therapy can be continued and titrated to maximum benefit. High doses are often required. Patients should be warned that abrupt withdrawal of therapy can lead to rebound pulmonary hypertension that can be fatal.[30]

If the patient did not show a vasodilator response during right heart catheterization or fails to respond to calcium channel blockers, the patient should be started on epoprostenol.[31] Epoprostenol must be given intravenously and, because of a 3- to 5-minute half-life, by continuous infusion. Serious side effects include abrupt discontinuance of therapy because of drug-delivery system malfunction or I.V. access infections. Minor side effects include headache, jaw pain, rash, diarrhea, and joint pain. The dose must be gradually increased over time to maintain maximum benefit. Epoprostenol appears to have effects that go beyond vasodilation and may include the decreased production of endogenous vasoconstrictor substances and antiplatelet and antiproliferative properties that seem to ameliorate what previously appeared to be irreversible vascular changes.

Analogues of prostacyclin that can be given by other routes (i.e., subcutaneous [UT-15], oral [beraprost], or inhaled [iloprost]), agents that increase endogenous prostacyclin, other vasodilators such as inhaled nitric oxide, phosphodiesterase-5 inhibitors,[32] and antagonists of endothelin (i.e., bosentan[33] and sitaxsentan[34]), and combinations of these medications are being studied to replace continuous-infusion epoprostenol.[31] Oral supplementation with L-arginine, the precursor of nitric oxide, is associated with modest reductions in pulmonary arterial pressure and pulmonary vascular resistance, suggesting increased nitric oxide production.[35]

Creation of a small atrial septal defect by percutaneous balloon atrial septostomy may result in unloading of the right ventricle and improvement in symptoms related to right heart failure.[36] Indications include recurrent syncope and right heart failure despite maximum medical therapy, deterioration despite maximum medical therapy while the patient is awaiting transplantation, and exhaustion of all other options. Because right-to-left shunting at the atrial level occurs, hypoxemia worsens but is usually well tolerated in patients without severe preprocedure hypoxemia.

Lung transplantation Lung transplantation is indicated for patients in whom PPH has progressed despite optimal medical therapy. In most centers, heart-lung transplantation is no longer performed because it was found that the right ventricle recovered both form and function when pressure fell after even a single-lung transplantation. Indications for referral for transplant evaluation include New York Heart Association (NYHA) functional class III or IV despite medical therapy; failure of epoprostenol therapy and the occurrence of severe side effects from epoprostenol are additional indications for referral for transplant evaluation. These guidelines take into consideration the course of the disease and the waiting time for transplantation.

The surgical mortality for patients with PPH is 20%; this mortality is higher than that for patients receiving lung transplanta-

tion for other forms of pulmonary hypertension,[37] partly because of the greater complexity of the transplant surgery. The 1-year survival for patients receiving lung transplantation for primary pulmonary hypertension is 65%; the 3-year survival is 55%; and the 5-year survival is 44%. These values are lower than those seen with other diagnoses.[37] No randomized study of medical versus surgical therapy has been performed. Comparison of survival data from different studies suggests that survival may be higher with medical therapy than with transplantation, although it is likely that only the more severely ill patients received lung transplantation.[38]

Prognosis

A National Institutes of Health (NIH) registry of patients with PPH in the 1980s defined the natural history of the disease.[39] The mean life expectancy from diagnosis was 2.8 years, and the 5-year survival was 22% to 38%. Patients younger than 14 years and older than 65 years had lower survival, as did patients with more severe symptoms. Patients with acute responses to vasodilators had a better prognosis. This study also developed a formula, utilizing data from right heart catheterization (right atrial pressure, cardiac index, and mean pulmonary arterial pressure), that predicted survival of patients before the availability of prostacyclin and lung transplantation. With these new therapies, the natural history of the disease has changed; the 5-year survival is 54% with medical therapy and 44% after lung transplantation.[39]

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Epidemiology

The epidemiology of chronic thromboembolic pulmonary hypertension is unknown. An estimated 0.1% to 0.5% of patients with acute pulmonary embolism will experience chronic pulmonary hypertension, suggesting that about 500 to 2,500 cases occur each year in the United States. There are conflicting data on the male-to-female ratio. The disease has been seen in adults of all ages, but more than 50% of patients are younger than 45 years. The reason for the development and lack of resolution of pulmonary emboli in these patients is unknown. A minority of the patients are found to have hypercoagulability states, such as deficiencies of protein C or S or of antithrombin III. About 10% will have circulating lupus anticoagulant.[40] The incidence of factor V Leiden and other hypercoagulable syndromes has not been adequately studied. Abnormalities of the fibrinolytic system have been sought, but no consistent patterns have been detected.[40] Embolization of so-called aged clot, lack of therapy for the initial episode of embolism, and recurrent emboli have all been hypothesized.

Pathogenesis

Chronic thromboembolic pulmonary hypertension results from the organization (rather than lysis) of the clots from a single massive episode of pulmonary embolism or multiple episodes of pulmonary embolism. As a consequence of obstruction and distortion of the proximal pulmonary vasculature, the pulmonary vascular resistance is increased, and over time, pulmonary hypertension develops and worsens.[41]

Diagnosis

Clinical manifestations Patients with chronic thromboembolic pulmonary hypertension usually present months or years after the initial embolic event with symptoms of pulmonary hypertension.[40] The initial event may have been diagnosed as an episode of embolism (in only 50% of cases) or may have been undiagnosed or misdiagnosed as pneumonia or another clinical entity. The reason for the delay in onset of symptoms is unknown, although it is suspected that organization of the clot and the increased pulmonary arterial pressure result in progressive remodeling of the obstructed and unobstructed pulmonary vasculature, gradually worsening the pulmonary hypertension and finally resulting in right ventricular failure.

Physical examination A pulmonary arterial flow murmur is the only finding on physical examination that is characteristic of chronic thromboembolic pulmonary hypertension. It is best heard over the lung fields while the patient holds his or her breath.

Imaging and physiologic testing The chest radiograph may be normal or may show abnormalities suggestive of pulmonary hypertension. Findings that suggest chronic thromboembolic pulmonary hypertension include asymmetrical enlargement of the pulmonary arteries, regions of hyperperfusion and hypoperfusion, and focal fibrotic areas of old infarction that may be associated with local pleural thickening or cavitation. Pleural effusions can sometimes be seen.

The electrocardiogram may be normal or have changes of right ventricular hypertrophy or strain, right atrial enlargement, and right bundle branch block.

Pulmonary function tests will most commonly show no abnormality of lung volumes or of spirometry measurements, although about 20% of patients will have restriction, probably related to previous infarction.[41] Frequently, carbon monoxide diffusion in the lung is mildly reduced; this reduction is thought not to be proportional to the degree of obstruction. Hypoxemia is common and is often worsened by exercise. The hypoxemia is the result of a combination of ventilation-perfusion inequality, low cardiac output, and, sometimes, a patent foramen ovale with a right-to-left shunt.[41]

The ventilation-perfusion lung scan is the best method of screening patients with pulmonary hypertension to identify those in whom the disorder may be caused by chronic thromboemboli.[40] Patients with chronic thromboemboli will have at least one segmental or larger perfusion defect [*see Figure 5*]. This pattern can also be seen with tumor or fibrosing mediastinitis. Patients with primary pulmonary hypertension will have either a homogeneous pattern or a patchy, nonsegmental pattern. In chronic thromboemboli, the degree of obstruction is underestimated by the defects seen on the perfusion scan.[40]

When large perfusion defects are seen on the ventilation-perfusion scan, additional testing is needed to confirm that the defects are caused by chronic thromboembolism. Spiral CT is a noninvasive imaging technique that avoids the risks of angiography; it can allow identification of proximal chronic clots and detect other causes of pulmonary vascular obstruction [*see Figure 6*].[41] Otherwise, right heart catheterization and pulmonary angiography are needed to accurately measure the right-sided hemodynamics, exclude intracardiac shunts, measure wedge pressure to assess left heart function, and accurately assess the full extent of pulmonary vascular obstruction angiographically.

The use of pulmonary angiography in patients with pulmonary hypertension has been thought to be associated with a significant risk of death or adverse outcome. Use of oxygen, small

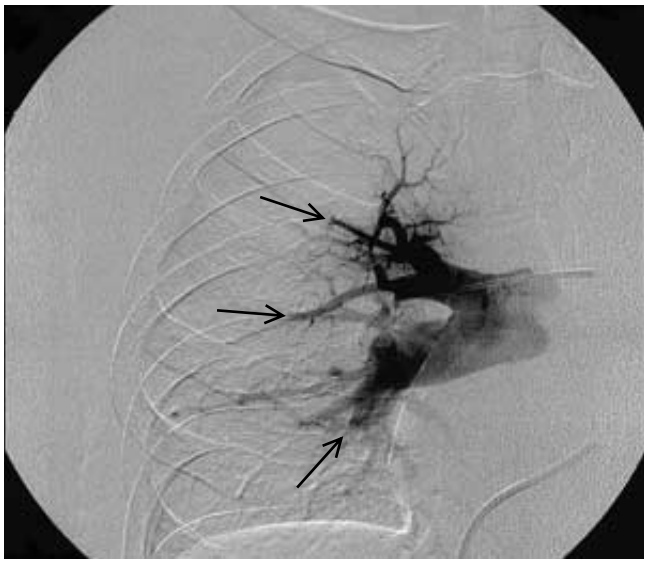


Figure 7 **Pulmonary arteriogram of a patient with chronic thromboembolic pulmonary hypertension showing multiple abrupt terminations (arrows) of the pulmonary arterial branches, with no distal flow characteristic of chronic pulmonary embolism.**

amounts of nonionic contrast dye, and a limited number of injections has reduced the risk dramatically.[41] Results of pulmonary angiography must be interpreted with the understanding that the patterns of pulmonary hypertension are different from those of acute embolism [*see Figure 7*].[41] In some cases, direct visualization of the pulmonary vasculature by pulmonary angioscopy is needed to confirm the presence and extent of obstruction.[41]

Treatment

There is no effective medical therapy for chronic thromboembolic pulmonary hypertension. Vasodilators, angioplasty of the obstructed areas, and thrombolytic therapy have not been effective. Preoperative anticoagulation is needed to prevent further emboli and in situ thrombosis. Placement of an inferior vena cava filter is recommended.[41]

Surgery for chronic thromboembolic pulmonary hypertension is associated with significant risk and therefore should not be done unless the patient meets criteria for surgery. The criteria used in one of the large centers were an elevated pulmonary vascular resistance (> 300 dynes/sec/cm^{-5}), severe disability (at least NYHA class III), and surgically accessible disease.[40] Contraindications or factors that increase risk include significant comorbid disease, especially renal disease, coronary artery disease, other lung disease, and massive obesity.

Pulmonary thromboendarterectomy is performed through a median sternotomy, with cardiopulmonary bypass, deep hypothermia, and periods of complete arrest (because of the brisk backbleeding from the increased bronchial collateral circulation), allowing better visualization in a bloodless field.[40] Dissection of the pulmonary artery starts in the proximal vessels and extends into the subsegmental branches, including the intima and some media. If an atrial septal defect or a patent foramen ovale is found, it is corrected.

Besides experiencing the usual complications associated with cardiac surgery, these patients have some specific problems, including reperfusion pulmonary edema in the previously obstructed areas, resulting in hypoxemia caused by shunting of blood from the previously unobstructed but remodeled pulmonary arterial bed into these newly opened areas.[41] Altered mental status is very common and seems to relate to the total circulatory arrest time.

Prognosis

Without surgery, the survival rate for patients with chronic thromboembolic pulmonary hypertension is low. In patients whose mean pulmonary arterial pressure is 40 to 50 mm Hg, 5-year survival is 30%; in those whose pulmonary arterial pressure is greater than 50 mm Hg, 5-year survival is 10%.[40]

Mortality associated with pulmonary thromboendarterectomy ranges from 5% to 24% and is lowest in the institutions with the greatest experience. The patients who survive have improvement of functional status from NYHA class III or IV to NYHA class I or II.[40] The right heart recovers quickly, and the pulmonary arterial pressure may continue to fall for up to 1 year after surgery. Most patients are able to return to work.

OTHER CAUSES OF PULMONARY HYPERTENSION

Collagen Vascular Diseases

Pulmonary hypertension with little or no parenchymal lung disease is a life-threatening manifestation of the collagen vascular diseases.[42] The clinical course and pathologic changes are similar to those of primary pulmonary hypertension. The pathophysiology is unknown, although autoantibodies, immunoglobulin, and complement have been found in the vessel walls, suggesting involvement of immune complexes.[43] Patients with scleroderma, particularly those with the CREST syndrome, have a high incidence of pulmonary hypertension; the incidence ranges from 2% to 35% in patients with scleroderma to 50% in those with CREST. The incidence in patients with other disorders varies from 23% to 53% in those with mixed connective tissue disease to 0.5% to 14% in those with systemic lupus erythematosus; it is rare in those with rheumatoid arthritis, Sjögren syndrome, and dermatopolymyositis.

The role of immunosuppressive therapy in patients with pulmonary hypertension secondary to collagen vascular diseases is unclear. Sanchez and coworkers[42] reviewed the literature and found improvement in pulmonary hemodynamics with various immunosuppressive regimens in seven of 11 published cases.[42] There have been no randomized, controlled trials.

Other than immunosuppressive therapy, treatment of pulmonary hypertension in patients with collagen vascular diseases should be patterned after the protocol for primary pulmonary hypertension detailed above.[44,45]

Although patients with pulmonary hypertension secondary to collagen vascular disorders are sometimes excluded from consideration of lung transplantation, transplants have been performed in such patients, with prolonged survival.[46]

Although several disorders are associated with vasculitis involving the pulmonary vasculature, pulmonary hypertension is rare. The exceptions to this rule are Takayasu disease [*see 15:VIII Systemic Vasculitis Syndromes*], in which pulmonary arteritis and hypertension probably occur in the majority of cases,[47] and rheumatoid arthritis[48] and systemic lupus erythematosus, in which pulmonary hypertension occurs much less commonly.[49]

Pulmonary Veno-occlusive Disease

Pulmonary veno-occlusive disease is a rare but distinct form of pulmonary hypertension characterized by obstruction of the small

intrapulmonary veins.[50] About one third of patients are children, and there are some cases that seem to be related to HIV infection, use of chemotherapy drugs, or bone marrow transplantation.

Patients with this disorder experience increasing dyspnea, sometimes with hemoptysis. Findings on chest radiography suggest left ventricular failure; such findings include enlarged pulmonary arteries, Kerley B lines, pulmonary edema, and pleural effusions. The diagnosis should be considered when these radiographic findings are associated with no echocardiographic evidence of left ventricular dysfunction, mitral valvular disease, or obstruction to flow in the left atrium. CT scan of the chest can provide support for the diagnosis[51] and can help exclude obstruction of the pulmonary veins in the mediastinum (fibrosing mediastinitis or tumor). The diagnosis can be confirmed by open lung biopsy, which will show the combination of chronic congestion, pulmonary hypertensive changes in the pulmonary arteries, and narrowing or occlusion of the pulmonary veins by eccentric or concentric intimal fibrosis.

Vasodilator therapy, as is used in primary pulmonary hypertension, is sometimes partially successful but has been associated with the development of pulmonary edema. Lung transplantation is the only effective therapy.[52]

Hematologic Disorders

Sickle cell disease, by way of recurrent episodes of obstruction by sickled cells, emboli, and in situ thrombosis, can be associated with the development of precapillary pulmonary hypertension [*see 5:IV Hemoglobinopathies and Hemolytic Anemias*].[53]

Patients with chronic myeloproliferative disorders,[54] amyloidosis,[55] and the POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome[56] have been noted to have complicating pulmonary hypertension.

Other Causes of Pulmonary Hypertension

Permanent residence at high altitude may be associated with the development of pulmonary hypertension.[57] This response is maladaptive and occurs in only a small portion of the population living at high altitude.[58] In these patients, pulmonary arterial systolic pressure can be reduced through the use of calcium channel blockers[59] or by moving the patient to a lower altitude.

Patients with obstructive sleep apnea without other forms of lung disease often have complicating pulmonary hypertension.[60] Development of pulmonary hypertension is associated with greater body mass index and degree of daytime hypoxemia, small airway closure during tidal breathing, and heightened pulmonary pressor responses to hypoxia and increased pulmonary blood flow.[60,61] Treatment of sleep apnea is associated with improvement in pulmonary hemodynamics[62] [*see 14:VI Ventilatory Control during Wakefulness and Sleep*]. Because these patients are often sedentary and obese, complicating and recurrent pulmonary thromboembolic disease should always be looked for.

Compression or stenosis of the pulmonary arteries or veins in the mediastinum by tumor or fibrosing mediastinitis [*see 14:IX Disorders of the Pleura, Hila, and Mediastinum*] or stenosis of multiple peripheral segments of the pulmonary artery can produce precapillary or postcapillary pulmonary hypertension. These disorders can usually be diagnosed by spiral CT or pulmonary angiography.

A rare cause of pulmonary hypertension is pulmonary capillary hemangiomatosis, a disorder that clinically mimics pulmonary veno-occlusive disease.[63] The lung biopsy specimens of these patients have patchy regions of severe congestion that contain capillary-sized blood vessels that appear to invade the walls of the pulmonary veins and, to a lesser degree, the pulmonary arteries. A CT scan can assist in differentiating this disorder from primary pulmonary hypertension.[64] The only effective treatment is lung transplantation.

PULMONARY ARTERIOVENOUS MALFORMATIONS

Abnormal, direct communications between branches of the pulmonary arteries and veins, producing a right-to-left shunt, are called pulmonary arteriovenous malformations (AVMs). Such lesions may be acquired (e.g., as a result of trauma or as a complication of cirrhosis) [*see 4:IX Cirrhosis of the Liver*] or congenital.[65]

Congenital pulmonary AVMs can be either single or multiple. They may be isolated to the lung or, much more commonly, can occur as part of an autosomal dominant syndrome of widespread AVMs in skin, mucous membranes, lungs, and other internal organs. The autosomal dominant syndrome is known as Osler-Weber-Rendu disease or hereditary hemorrhagic telangiectasia (HHT)[66] [*see 5:XIII Hemorrhagic Disorders*].

Diagnosis

Clinical manifestations Pulmonary AVMs may produce severe symptoms or complications, but most patients are asymptomatic. The diagnosis is suggested by solitary or multiple pulmonary nodules found on routine chest radiography. Dyspnea is the most common symptom, occurring at first with exercise and later at rest. Dyspnea that worsens in the upright position and improves on reclining (platypnea) has been seen in these patients. It may be caused by worsening of the right-to-left shunt in the lung bases with the patient in the upright position, producing hypoxemia (orthodeoxia). Hemoptysis, usually mild and related to bronchial mucosal telangiectasia, is the second most common symptom. Neurologic complaints are also seen.[66,67] Headache, tinnitus, seizures, symptoms that mimic transient ischemic attack, and completed stroke may relate to complicating polycythemia, paradoxical embolus, or brain abscess. Patients with HHT may have bleeding from AVMs outside the lungs, which is often sufficient to produce anemia.

Physical findings include mucous membrane telangiectasia in the patients with HHT, cyanosis, plethora, digital clubbing, and extracardiac murmurs that increase with inspiration heard over AVMs in the lungs.

Imaging and physiologic testing Patients with pulmonary AVMs have hypoxemia, with the degree of hypoxemia being proportional to the magnitude of the shunt. As a consequence, chronic respiratory alkalosis and polycythemia may occur. Pulmonary function tests are normal except for a mildly decreased diffusing capacity.

The diagnosis is most often suggested by the finding on chest radiograph of a well-defined solitary pulmonary nodule or multiple nodules with a feeding artery, draining vein, or both.

Echocardiography with contrast can also suggest the diagnosis.[68] Spiral CT with I.V. contrast will confirm the vascular nature of lesions and may detect others that were not obvious from standard radiography. The definitive diagnostic procedure, however, is pulmonary angiography, which allows demonstration of all significant lesions; this is important in planning therapy.

Treatment

The natural history of pulmonary AVMs is poorly understood. In asymptomatic patients, the treatment decisions must be

made with the recognition of the risk of hemoptysis, paradoxical embolization, and brain abscess.

The treatment options include thoracotomy with selective resection or percutaneous embolization. In patients with solitary or unilateral lesions, resection can be performed with minimal morbidity and mortality.[66] The only consideration is the possibility of the development of pulmonary hypertension after the low-resistance AVMs are removed in patients whose pulmonary vasculature has become remodeled in response to the high flow through the AVMs. In such patients, percutaneous balloon obstruction of the AVMs allows preoperative measurement of pulmonary hemodynamics.

The techniques and safety of percutaneous embolization have been improved. With the use of detachable balloons and metal coils, single or multiple AVMs can be treated.[66,69] The main risk is systemic embolization of the obstructing material. This technique is rapidly replacing surgery as the treatment of choice.

PULMONARY ARTERIAL ANEURYSMS

Aneurysms of the pulmonary arteries are very rare.[70] They are seen as congenital anomalies, often along with abnormalities of the other great vessels and heart; as part of connective tissue disorders (e.g., Marfan syndrome); as a consequence of trauma (pseudoaneurysms caused by Swan-Ganz catheters may be confused for pulmonary aneurysms**),** infection (syphilis, tuberculosis, pyogenic bacteria, or fungi), or immunologic disorders (Behçet disease[71] or Hughes-Stovin syndrome); and in association with pulmonary diseases such as pulmonary hypertension or bronchiectasis.

In many cases, pulmonary arterial aneurysms are asymptomatic. However, cough, dyspnea, and particularly hemoptysis can be seen. Rupture of the aneurysm into an airway can be associated with sudden, massive, and usually fatal hemoptysis. Dissection of the pulmonary artery can also occur. The diagnosis can be made from a contrast-enhanced CT scan or by pulmonary angiography.

Aneurysms of the main and proximal right and left pulmonary arteries can be surgically repaired.[72] Aneurysms in smaller pulmonary arteries can be removed by surgical resection of the involved area of lung.

Roland H. Ingram, Jr., M.D., has no commercial relationships with manufacturers of products or providers of services discussed in this subsection.

Gerald W. Staton, Jr., M.D., participates in the speakers' bureaus for GlaxoSmithKline, Merck & Co., Inc., and InterMune, Inc.

References

1. Gaine S: Pulmonary hypertension. JAMA 284:3160, 2000

2. Fishman AP: Clinical classification of pulmonary hypertension. Clin Chest Med 22:385, 2001

3. Hampl V, Herget J: Role of nitric oxide in the pathogenesis of chronic pulmonary hypertension. Physiol Rev 80:1337, 2000

4. Olschewski H, Olschewski A, Rose F, et al: Physiologic basis for the treatment of pulmonary hypertension. J Lab Clin Med 138:287, 2001

5. Olschewski H, Rose F, Grunig E, et al: Cellular pathophysiology and therapy of pulmonary hypertension. J Lab Clin Med 138:367, 2001

6. Meyrick B: The pathology of pulmonary artery hypertension. Clin Chest Med 22:393, 2001

7. Moser KM, Bloor CM: Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 103:685, 1993

8. McGoon MD: The assessment of pulmonary hypertension. Clin Chest Med 22:493, 2001

9. Nootens MT, Berarducci LA, Kaufmann E, et al: The prevalence and significance of a patent foramen ovale in pulmonary hypertension. Chest 104:1673, 1993

10. Belenkie I, Smith ER, Tyberg JV: Ventricular interaction: from bench to bedside. Ann Med 33:236, 2001

11. Vieillard-Baron A, Page B, Augarde R, et al: Acute cor pulmonale in massive pulmonary embolism: incidence, echocardiographic pattern, clinical implications and recovery rate. Intensive Care Med 27:1481, 2001

12. Vieillard-Baron A, Schmitt JM, Augarde R, et al: Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. Crit Care Med 29:1551, 2001

13. Goldhaber SZ: Echocardiography in the management of pulmonary embolism. Ann Intern Med 136:691, 2002

14. Arcasoy SM, Kreit JW: Thrombolytic therapy of pulmonary embolism: a comprehensive review of current evidence. Chest 115:1695, 1999

15. Romano PM, Peterson S: The management of cor pulmonale. Heart Dis 2:431, 2000

16. Borst MM, Leschke M, Konig U, et al: Repetitive hemodilution in chronic obstructive pulmonary disease and pulmonary hypertension: effects on pulmonary hemodynamics, gas exchange, and exercise capacity. Respiration 66:225, 1999

17. Schonhofer B, Barchfeld T, Wenzel M, et al: Long term effects of non-invasive mechanical ventilation on pulmonary haemodynamics in patients with chronic respiratory failure. Thorax 56:524, 2001

18. Galie N, Manes A, Branzi A: Medical therapy of pulmonary hypertension: the prostacyclins. Clin Chest Med 22:529, 2001

19. Rashid A, Lehrman S, Romano P, et al: Primary pulmonary hypertension. Heart Dis 2:422, 2000

20. Thomas AQ, Gaddipati R, Newman JH, et al: Genetics of primary pulmonary hypertension. Clin Chest Med 22:477, 2001

21. Lilienfeld DE, Rubin LJ: Mortality from primary pulmonary hypertension in the United States, 1979–1996. Chest 117:796, 2000

22. Humbert M, Nunes H, Sitbon O, et al: Risk factors for pulmonary arterial hypertension. Clin Chest Med 22:459, 2001

23. Michelakis ED, Weir EK: Anorectic drugs and pulmonary hypertension from the bedside to the bench. Am J Med Sci 321:292, 2001

24. Seoane L, Shellito J, Welsh D, et al: Pulmonary hypertension associated with HIV infection. South Med J 94:635, 2001

25. Tuder RM, Yeager ME, Geraci M, et al: Severe pulmonary hypertension after the discovery of the familial primary pulmonary hypertension gene. Eur Respir J 17:1065, 2001

26. Archer S, Rich S: Primary pulmonary hypertension: a vascular biology and translational research "work in progress." Circulation 102:2781, 2000

27. Salvi SS: Alpha$_1$-adrenergic hypothesis for pulmonary hypertension. Chest 115:1708, 1999

28. Botney MD: Role of hemodynamics in pulmonary vascular remodeling: implications for primary pulmonary hypertension. Am J Respir Crit Care Med 159:361, 1999

29. Farber HW, Loscalzo J: Prothrombotic mechanisms in primary pulmonary hypertension. J Lab Clin Med 134:561, 1999

30. Naeije R, Vachiery JL: Medical therapy of pulmonary hypertension: conventional therapies. Clin Chest Med 22:517, 2001

31. Channick RN, Rubin LJ: New and experimental therapies for pulmonary hypertension. Clin Chest Med 22:539, 2001

32. Ghofrani HA, Wiedemann R, Rose F, et al: Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. Ann Intern Med 136:515, 2002

33. Rubin LH, Badesch DB, Barst RJ, et al: Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 346:896, 2002

34. Barst RJ, Rich S, Widlitz A, et al: Clinical efficacy of sitaxsentan, an endothelin-A receptor antagonist, in patients with pulmonary arterial hypertension: open-label pilot study. Chest 121:1860, 2002

35. Nagaya N, Uematsu M, Oya H, et al: Short-term oral administration of L-arginine improves hemodynamics and exercise capacity in patients with precapillary pulmonary hypertension. Am J Respir Crit Care Med 163:887, 2001

36. Sandoval J, Rothman A, Pulido T: Atrial septostomy for pulmonary hypertension. Clin Chest Med 22:547, 2001

37. Trulock EP: Lung transplantation for primary pulmonary hypertension. Clin Chest Med 22:583, 2001

38. Gaine SP, Rubin LJ: Medical and surgical treatment options for pulmonary hypertension. Am J Med Sci 315:179, 1998

39. D'Alonzo GE, Barst RJ, Ayres SM, et al: Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med 115:343, 1991

40. Fedullo PF, Auger WR, Kerr KM, et al: Chronic thromboembolic pulmonary hypertension. N Engl J Med 345:1465, 2001

41. Fedullo PF, Auger WR, Channick RN, et al: Chronic thromboembolic pulmonary hypertension. Clin Chest Med 22:561, 2001

42. Sanchez O, Humbert M, Sitbon O, et al: Treatment of pulmonary hypertension secondary to connective tissue diseases. Thorax 54:273, 1999

43. Quismorio FP Jr, Sharma O, Koss M, et al: Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. Semin Arthritis Rheum 13:349, 1984

44. Coghlan JG, Mukerjee D: The heart and pulmonary vasculature in scleroderma: clinical features and pathobiology. Curr Opin Rheumatol 13:495, 2001

45. Badesch DB, Tapson VF, McGoon MD, et al: Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: a randomized, controlled trial. Ann Intern Med 132:425, 2000

46. Levy RD, Guerraty AJ, Yacoub MH, et al: Prolonged survival after heart-lung trans-

plantation in systemic lupus erythematosus. Chest 104:1903, 1993

47. Paul JF, Hernigou A, Lefebvre C, et al: Electron beam CT features of the pulmonary artery in Takayasu's arteritis. AJR Am J Roentgenol 173:89, 1999

48. Young ID, Ford SE, Ford PM: The association of pulmonary hypertension with rheumatoid arthritis. J Rheumatol 16:1266, 1989

49. Rubin LA, Geran A, Rose TH, et al: A fatal pulmonary complication of lupus in pregnancy. Arthritis Rheum 38:710, 1995

50. Chazova I, Robbins I, Loyd J, et al: Venous and arterial changes in pulmonary veno-occlusive disease, mitral stenosis and fibrosing mediastinitis. Eur Respir J 15:116, 2000

51. Swensen SJ, Tashjian JH, Myers JL, et al: Pulmonary venoocclusive disease: CT findings in eight patients. AJR Am J Roentgenol 167:937, 1996

52. Holcomb BW Jr, Loyd JE, Ely EW, et al: Pulmonary veno-occlusive disease: a case series and new observations. Chest 118:1671, 2000

53. Minter KR, Gladwin MT: Pulmonary complications of sickle cell anemia: a need for increased recognition, treatment, and research. Am J Respir Crit Care Med 164:2016, 2001

54. Dingli D, Utz JP, Krowka MJ, et al: Unexplained pulmonary hypertension in chronic myeloproliferative disorders. Chest 120:801, 2001

55. Dingli D, Utz JP, Gertz MA: Pulmonary hypertension in patients with amyloidosis. Chest 120:1735, 2001

56. Paciocco G, Bossone E, Erba H, et al: Reversible pulmonary hypertension in POEMS syndrome: another etiology of triggered pulmonary vasculopathy? Can J Cardiol 16:1007, 2000

57. Naeije R: Pulmonary circulation at high altitude. Respiration 64:429, 1997

58. Groves BM, Droma T, Sutton JR, et al: Minimal hypoxic pulmonary hypertension in normal Tibetans at 3,658 m. J Appl Physiol 74:312, 1993

59. Antezana AM, Antezana G, Aparicio O, et al: Pulmonary hypertension in high-altitude chronic hypoxia: response to nifedipine. Eur Respir J 12:1181, 1998

60. Bady E, Achkar A, Pascal S, et al: Pulmonary arterial hypertension in patients with sleep apnoea syndrome. Thorax 55:934, 2000

61. Sajkov D, Wang T, Saunders NA, et al: Daytime pulmonary hemodynamics in patients with obstructive sleep apnea without lung disease. Am J Respir Crit Care Med 159:1518, 1999

62. Sajkov D, Wang T, Saunders NA, et al: Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. Am J Respir Crit Care Med 165:152, 2002

63. Eltorky MA, Headley AS, Winer-Muram H, et al: Pulmonary capillary hemangiomatosis: a clinicopathologic review. Ann Thorac Surg 57:772, 1994

64. Dufour B, Maitre S, Humbert M, et al: High-resolution CT of the chest in four patients with pulmonary capillary hemangiomatosis or pulmonary venoocclusive disease. AJR Am J Roentgenol 171:1321, 1998

65. Gossage JR, Kanj G: Pulmonary arteriovenous malformations: a state of the art review. Am J Respir Crit Care Med 158:643, 1998

66. Swanson KL, Prakash UB, Stanson AW: Pulmonary arteriovenous fistulas: Mayo Clinic experience, 1982–1997. Mayo Clinic Proc 74:671, 1999

67. Maher CO, Piepgras DG, Brown RD Jr, et al: Cerebrovascular manifestations in 321 cases of hereditary hemorrhagic telangiectasia. Stroke 32:877, 2001

68. Kjeldsen AD, Oxhoj H, Andersen PE, et al: Pulmonary arteriovenous malformations: screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. Chest 116:432, 1999

69. Dutton JA, Jackson JE, Hughes JM, et al: Pulmonary arteriovenous malformations: results of treatment with coil embolization in 53 patients. AJR Am J Roentgenol 165:1119, 1995

70. Bartter T, Irwin RS, Nash G: Aneurysms of the pulmonary arteries. Chest 94:1065, 1988

71. Erkan F, Gul A, Tasali E: Pulmonary manifestations of Behçet's disease. Thorax 56:572, 2001

72. Kuwaki K, Morishita K, Sato H, et al: Surgical repair of the pulmonary trunk aneurysm. Eur J Cardiothorac Surg 18:535, 2000