

# Diagnosis and Management of Pulmonary Arterial Hypertension: Implications for Respiratory Care

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**Pulmonary arterial hypertension (PAH) is a pathological condition of the small pulmonary arteries. PAH is characterized histopathologically by vasoconstriction, vascular proliferation, in situ thrombosis, and remodeling of all 3 levels of the vascular walls. These pathologic changes result in progressive increases in the mean pulmonary-artery pressure and pulmonary vascular resistance, which, if untreated, leads to right-ventricular failure and death. PAH can be associated with multiple conditions or risk factors (eg, collagen vascular diseases, liver disease, human immuno-**

deficiency virus, congenital heart disease, or ingestion of certain medications or toxins) or it can be idiopathic. Up to 10% of the idiopathic cases are familial. Regardless of the etiology, the clinical presentation, histopathologic lesions, and response to therapy are all similar. Early in the disease process, the signs and symptoms of PAH are often subtle and nonspecific, making diagnosis challenging. Patients most often present with progressively worsening dyspnea and fatigue. An extensive evaluation is indicated to diagnose PAH, decipher its etiology, and determine long-term treatment goals. Transthoracic echocardiogram is an excellent screening tool to evaluate PAH, but every patient requires a right-side heart catheterization to help stage the disease and guide therapy. Prior to a decade ago, clinicians were only able to offer symptomatic therapy to this challenging group of patients. Earlier diagnosis, rapidly advancing understanding of the pathogenesis, and an increasing number of treatment options have changed the course of PAH, which was once thought to be invariably fatal. *Key words: pulmonary arterial hypertension, pulmonary hypertension, pulmonary vascular disease, right heart failure, cor pulmonale.* [Respir Care 2006;51(4):368–381. © 2006 Daedalus Enterprises]

### Introduction

Pulmonary arterial hypertension (PAH) is the most challenging chronic disorder of the pulmonary vasculature. It is a disease of the small pulmonary arteries and is associated with substantial morbidity and mortality from progressive increase of pulmonary vascular resistance and consequent right-heart dysfunction secondary to sustained elevation of the pulmonary-artery pressure. PAH was once thought of as an invariably fatal disease, but with better understanding of its pathogenesis, substantial progress in diagnostic techniques, and the development of new treatment options, the outcomes are improving.

PAH may occur as a primary disease or as a complication of various systemic, cardiac, or pulmonary conditions. The nonspecific nature of its symptoms often delays accurate diagnosis, making it difficult to offer medical or surgical therapy in the early course of disease when these therapies may be most efficacious. A thorough diagnostic evaluation is required to evaluate the presence and severity of the disease and to provide insight on which therapy may be most useful in an individual patient.

The complexity of this disorder requires input from several members of the health-care team, including physicians, nurses, respiratory therapists (RTs), and social work-

ers, to accurately evaluate, diagnose, and treat patients who are afflicted.

### Definition

*Pulmonary hypertension* is an observation, not a single diagnosis or disease. It encompasses a diverse group of conditions that lead to elevated pulmonary pressure. It is defined clinically as an increase in the pulmonary vascular pressure that is caused by conditions that are associated with an increase in the pulmonary arterial pressure or both the arterial and venous pressure.<sup>1</sup> Hemodynamically, it is defined as an increase in the mean pulmonary arterial pressure to > 25 mm Hg at rest or > 30 mm Hg during exercise.<sup>2</sup>

PAH is a condition in which the pulmonary arterial pressure and pulmonary vascular resistance are elevated in conjunction with a normal pulmonary capillary wedge pressure.

### Normal Physiology

The normal pulmonary circulation is a high-capacitance, low-resistance system. The pulmonary vasculature is able to accommodate a greater than 6-fold increase in cardiac output (flow) with relatively small increases in pulmonary-artery pressure, by recruiting closed vessels and distending open vessels. Even though the blood flow to the lungs is greater than the flow to any other organ, normal mean pulmonary-artery pressure remains less than one sixth of mean systemic arterial pressure. Associated with this low transmural pressure, the pulmonary arteries are larger in caliber and have thinner vessel walls than their systemic counterparts, and they possess little resting vascular tone.

In accordance with this low-pressure circuit, the right ventricle is normally accustomed to a relatively low afterload, even with stress. It is a thin muscle, with limited contractile reserve. The principles underlying the manage-

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ment of PAH and implications for prognosis in severe disease are associated with the right ventricle's limited capacity in working against high vascular resistance.<sup>3</sup>

### Pathophysiology

The pathology of PAH involves both what is pathologic at the pulmonary arterial vessel level as well as what consequences this has on the myocardium of the right heart. Persistently elevated pulmonary pressure, as seen in PAH, causes increased pulmonary vascular resistance. As a consequence of unrelieved pulmonary hypertension, regardless of the cause, there is progressive systolic-pressure overload of the right ventricle, which then becomes hypertrophied and dilated, which ultimately leads to right-heart failure (cor pulmonale).

Hemodynamically, PAH is the combination of an elevated pulmonary-artery pressure and a decreased cardiac output with a normal wedge pressure. As the disease progresses, the cardiac output progressively decreases as the right ventricle begins to fail. Symptoms begin with exercise, as the cardiac output is not able to increase with the increased demand. As the ventricle starts to fail, the patient becomes more symptomatic with less exertion, leading to gradual deterioration.<sup>4</sup>

### Pathogenesis

The pathogenesis of PAH is not completely elucidated, but recent important advances on the genetics and molecular and pathologic mechanisms of PAH have identified pathways involved in the development of PAH. Although the initiating event leading to the progressive increase in pulmonary vascular resistance remains unknown, several important contributing mechanisms have been acknowledged. The most recent thinking is that a combination of these molecular and pathologic mechanisms plus an underlying genetic predisposition and risk factors lead to PAH.<sup>5</sup>

Originally, it was thought that PAH was secondary only to extensive vasoconstriction of the small pulmonary arteries. We now know that, although vasoconstriction is involved, pulmonary vascular proliferation and remodeling are also key and maybe even more important mechanisms of pathogenesis.

The characteristic histopathologic appearance of PAH is obstruction of the small pulmonary arteries described as a plexogenic lesion.<sup>6</sup> This obstruction is a result of dysfunctional endothelial cells, smooth-muscle cells, and fibroblasts causing proliferation.<sup>7</sup> Vasoconstriction, remodeling of the vessel wall, and in situ thrombosis can also result from the dysfunction of these cells.

Pulmonary vascular tone is modulated by the normally balanced activity of endothelium-derived vaso-mediators,

mainly nitric oxide and prostacyclin (both potent vasodilators and anti-proliferative agents) and endothelin-1 and thromboxane A<sub>2</sub> (both potent vasoconstrictors and proliferative cytokines). Dysfunctional pulmonary-artery endothelial cells produce less endogenous nitric oxide and prostacyclin and produce more endothelin-1 and thromboxane A<sub>2</sub>.<sup>8-10</sup>

In situ thrombosis with recanalization is often present. These lesions are not embolic, and are probably due to abnormal endothelial activity, abnormal platelet activation, and a hypercoagulable state.<sup>11</sup>

The characteristic lesion of PAH is the plexiform lesion, which is a dilated pulmonary artery in which the normal structure is replaced by an intraluminal plexus of endothelial cells and slit-like vascular channels.<sup>12</sup> These lesions are seen in all forms of PAH.

Survival in PAH without intervention or therapy is dismal. A National Institutes of Health registry followed patients with primary pulmonary hypertension between 1985 and 1988, when there were no therapeutic agents. Survival rates at 1, 3, and 5 years were 68%, 48%, and 34%, respectively. The median survival from time of diagnosis was 2.8 years.<sup>13</sup>

### Classification

While there are several classification schemes for PAH, the most useful scheme now assigns patients to a clinical classification based on the presence or absence of associated clinical disorders, and a functional classification, based on the severity of the symptoms.

#### Clinical Classification

Pulmonary hypertension was previously classified as either *primary* or *secondary* pulmonary hypertension, depending on the absence or presence of identifiable causes of increased pulmonary pressure.<sup>14</sup> The diagnosis of primary pulmonary hypertension was made after an extensive diagnostic workup to exclude other causes. This classification was descriptive in nature, but lacked clinical practicality. It was unsatisfactory because it grouped together a wide range of distinct diagnoses (secondary pulmonary hypertension), without regard to clinical presentation or pathogenesis, while it set apart those diagnoses in the secondary group which were similar in both pathogenesis as well as in treatment options to primary pulmonary hypertension. The 2003 World Symposium on Pulmonary Hypertension set forth a new classification system that categorizes pulmonary hypertension on the basis of shared clinical attributes (Table 1). It classifies pulmonary hypertension into 5 groups, based largely on diagnostic and treatment implications. This new clinical classification is vital in helping clinicians evaluate individual patients, stan-

Table 1. Pulmonary Hypertension Classification System From the 2003 World Symposium on Pulmonary Hypertension

1. Pulmonary Arterial Hypertension
1.1. Idiopathic pulmonary arterial hypertension
1.2. Familial pulmonary arterial hypertension
1.3. Associated with pulmonary arterial hypertension
1.3.1. Collagen vascular disease
1.3.2. Congenital systemic to pulmonary shunts
1.3.3. Portal hypertension
1.3.4. Human immunodeficiency virus
1.3.5. Drugs and toxins
1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hemoglobinopathies, hereditary hemorrhagic telangiectasia, myeloproliferative disease, splenectomy)
1.4. Associated with venous or capillary involvement
1.4.1. Pulmonary veno-occlusive disease
1.4.2. Pulmonary capillary hemangiomatosis
1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary Hypertension With Left Heart Disease
2.1. Left-sided atrial or ventricular heart disease
2.2. Left-sided valvular heart disease
3. Pulmonary Hypertension Associated With Lung Disease and/or Hypoxemia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Sleep-disordered breathing
3.4. Alveolar hypoventilation disorders
3.5. Long-term exposure to high altitude
3.6. Developmental abnormalities
4. Pulmonary Hypertension Due to Chronic Thrombotic/Embolic Disease
4.1. Thromboembolic obstruction of proximal pulmonary arteries
4.2. Thromboembolic obstruction of distal pulmonary arteries
4.3. Nonthrombotic pulmonary embolism
5. Miscellaneous

standardize diagnoses, design clinical studies, and modify treatment.<sup>15</sup> This classification system has 5 categories:

1. Pulmonary arterial hypertension (PAH). This category includes 3 subgroups: idiopathic PAH (IPAH), familial PAH, and PAH that is frequently associated with specific conditions or risk factors. These entities all share similar clinical, morphologic, and histopathologic characteristics, as well as clinical responsiveness to pulmonary vasodilator therapy.

2. Pulmonary hypertension related to left-heart disease. This category consists of left-sided, valvular, or myocardial diseases that require therapies directed at improving myocardial performance or relieving valvular defects, rather than pulmonary vasodilator therapy.

3. Pulmonary hypertension related to lung disease or hypoxemia. The predominant cause of this pulmonary hypertension is inadequate oxygenation, caused by lung disease (interstitial or obstructive), impaired control of breathing, or high altitude. The increase in mean pulmonary-

artery pressure is generally modest (< 35 mm Hg). This pulmonary hypertension may also be caused by or exacerbated by obstructive sleep apnea.

4. Chronic thrombotic or embolic pulmonary hypertension. This category includes (1) chronic thromboembolic pulmonary hypertension due to proximal organized clot in major pulmonary arteries and (2) PAH secondary to small peripheral emboli. If the clot is proximal, it can be treated surgically with a pulmonary endarterectomy to remove the clot. These patients may present similarly to PAH and may benefit from vasodilator therapy. Patients with idiopathic pulmonary hypertension (Group 1) may also develop proximal or distal clots.

5. Miscellaneous. This category involves pulmonary hypertension from inflammatory processes or mechanical obstruction (eg, schistosomiasis, sarcoidosis). Studies indicate that some patients in this group will also respond, to some degree, to vasodilator therapy.

This discussion will focus solely on the first diagnostic category, PAH, which includes IPAH, familial PAH, and PAH associated with specific conditions or risk factors. In general, however, when evaluating a patient with pulmonary hypertension, the diagnostic evaluation needs to include studies to either rule in or rule out the other causes (ie, Groups 2 through 5), because the treatment options differ substantially.

### Idiopathic Pulmonary Arterial Hypertension

IPAH (previously known as primary pulmonary hypertension) is PAH that occurs without an identifiable cause. IPAH is rare, with an incidence of only 1–2 cases per million people in the general population.<sup>16</sup> IPAH is more prominent in women (2.7-to-1 predominance). The median age at presentation is the third-to-fourth decade of life.<sup>17</sup> IPAH can occur sporadically or as an inherited condition (familial IPAH).

### Familial PAH

Familial PAH is an autosomal-dominant disease with genetic linkage to chromosome 2q33.<sup>18</sup> Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor gene. Different mutations of this gene were found in many families diagnosed with primary pulmonary hypertension. These mutations cause uncontrolled proliferation of vascular smooth muscle.<sup>19</sup> Familial PAH can account for up to 6–10% of IPAH patients.

### PAH Associated With Specific Conditions and Risk Factors

PAH also occurs in association with specific conditions and risk factors, including connective-tissue diseases, human immunodeficiency virus (HIV), hemoglobinopathies (including sickle-cell disease, liver disease, and congenital heart disease), and ingestion of certain drugs and toxins.

**Drugs and Toxins.** PAH has definitively been linked to several drugs and toxins and is associated with the ingestion of others. Appetite suppressants, including aminorex, fenfluramine, and dexfenfluramine, have the strongest relationship with PAH. The course, prognosis, and treatment are similar to that of IPAH.<sup>20</sup> Appetite-suppressant-induced PAH occurs in < 1% of patients exposed, but there is a 10-fold risk increase with use exceeding 3 months.<sup>21</sup> Other likely causes of drug- or toxin-induced PAH include toxic rapeseed oil, L-tryptophan, chemotherapeutic agents, amphetamines, and cocaine.<sup>16</sup> Progression of drug- or toxin-induced PAH and response to therapy are similar to that of IPAH.

**Liver Disease.** One to 6 percent of patients with advanced liver disease have portopulmonary hypertension. Portal hypertension, not the hepatic disorder itself or its severity, is thought to be the main determining risk factor for developing PAH. The incidence of PAH in patients with portal hypertension is much higher than the estimated incidence of IPAH.

Clinically and histopathologically, the course of portopulmonary hypertension is similar to that of IPAH, but, hemodynamically, patients with portopulmonary hypertension can have a higher cardiac output and lower systemic vascular resistance secondary to their liver disease.

In the early era of liver transplant, the diagnosis of portopulmonary hypertension was, unfortunately, often made in the operating room during transplant. Sixty-five percent of patients who underwent liver transplant in one study were diagnosed, with a subsequent mortality of 36%.<sup>22</sup> Now, patients being evaluated for liver transplant undergo screening echocardiography and workup for pulmonary hypertension prior to being listed. If the pressure is elevated or there are signs of right-heart dysfunction on the screening echocardiogram, the patient will undergo right-heart catheterization.

Because of this substantially higher risk, liver transplantation is contraindicated in patients with portopulmonary hypertension whose pulmonary pressure and pulmonary vascular resistance are substantially increased. It is possible, however, in some patients, to decrease these indices with aggressive treatment, which usually includes the use of intravenous epoprostenol.<sup>23</sup> Some patients show improvement of portopulmonary hypertension after liver

transplantation, whereas others are unchanged or worsen.<sup>24</sup>

**Human Immunodeficiency Virus.** First reported in 1987, PAH has been diagnosed with increased frequency among HIV-infected patients. The incidence is suspected to be in the range of about 1 in 200 HIV-infected patients, making it 6–12 times more common than IPAH.<sup>25</sup>

The cause of the association between PAH and HIV is still unclear. There is speculation that the HIV virus induces pulmonary hypertension through activation of cytokine or growth-factor pathways. There is no association between viral load or cluster-of-differentiation-4 (CD4+) count or the severity of PAH.<sup>25</sup> Every group with risk factors for HIV can be affected, but intravenous drug users predominate in the literature. The presentation is similar both clinically and physiologically to IPAH.

There are uncontrolled studies that suggest that combination therapy of antiretrovirals and treatment for PAH positively affects the pulmonary-artery pressure as well as survival.<sup>26</sup> Therefore, patients should be aggressively treated for HIV as well as for PAH.

Viruses other than HIV may also induce pulmonary hypertension; human herpesvirus-8 is associated with PAH.<sup>27</sup>

**Hemoglobinopathies (Sickle-Cell Anemia).** PAH is a well recognized complication of sickle-cell disease. PAH associated with sickle-cell disease significantly reduces the survival rate of these patients, as compared to those without PAH. It is important in these patients to rule out left-heart disease with diastolic dysfunction, because it is treated differently than PAH. The pathogenesis is unclear but probably multifactorial. Proposed causes include a sickle-cell related vasculopathy with in situ thrombosis, chronic hypoxemia from parenchymal disease, and increased blood flow.<sup>28</sup> Pathological changes are similar as those in IPAH.

**Congenital Heart Disease.** PAH is a known complication of congenital heart disease. It is seen with cardiac defects that are associated with systemic-to-pulmonary connections (ie, ventricular septal defects, atrial septal defects). Histology findings identical to those of IPAH can be identified in these patients after a period of high pulmonary blood flow, which occurs because of left-to-right shunting. As the pulmonary vascular resistance approaches or exceeds the systemic vascular resistance, the shunt is reversed, leading to a right-to-left shunt (Eisenmenger's syndrome).<sup>29</sup> The development of PAH in congenital heart disease is related to the type and size of the defect. For example, about twice as many patients with ventricular septal defects will develop PAH as those with atrial septal defects.

The clinical course of PAH associated with congenital heart disease is somewhat different than that of IPAH. These patients may be cyanotic as a result of right-to-left shunt. Blood dyscrasias, including polycythemia and a tendency toward thrombosis, may be present. And, most importantly, survival in patients with PAH associated with congenital heart disease is usually better than in patients with IPAH,<sup>30</sup> probably because the right ventricle has had time to accommodate the progressive pressure increase.

**Connective-Tissue Disease.** PAH is a well-known and serious complication of various forms of connective-tissue diseases. In most cases it is histologically indistinguishable from IPAH. Compared to IPAH, however, patients with connective-tissue diseases may have an accelerated course, substantially lower cardiac output, may not respond as well to treatment, and may have worse survival.<sup>31</sup>

The occurrence of PAH has been reported to be associated with every known type of collagen vascular disease, but the frequency of PAH varies substantially. For example, PAH is a rare complication of rheumatoid arthritis, but occurs in 10–33% of patients with the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, and telangiectasia), which represents the main connective-tissue disease process associated with PAH.<sup>32</sup> It has been suggested that, because of the increased incidence of PAH among patients with the scleroderma spectrum of diseases, yearly screening echocardiograms should be performed.<sup>31</sup>

In patients with connective-tissue diseases, increased pulmonary pressure can be secondary to hypoxemia in association with interstitial fibrosis (restrictive lung disease), pulmonary venous hypertension secondary to left-heart systolic or diastolic dysfunction, or PAH. It is important to determine the etiology of the increased pulmonary pressure in these patients, because treatment is quite different for each process.

The association of PAH and connective-tissue disease markedly decreases survival. The 2-year survival of patients with scleroderma without pulmonary complications is 80%, whereas in those with PAH it is 40%.<sup>33</sup>

The pathogenesis of PAH in connective-tissue diseases has not yet been elucidated. Autoimmune processes have been postulated, but the mechanism is unclear. Treatment of the disease is identical to that for IPAH.

**Uncommon Etiologies of PAH.** Pulmonary veno-occlusive disease and pulmonary-capillary hemangiomatosis are both rare causes of PAH that fall into category 1 and that present clinically similarly to other forms of PAH. The course of the disease, however, is quite aggressive, leading to severe pulmonary hypertension and right-sided heart failure. Unlike the other forms of PAH, this form is usually not responsive to vasodilation treatment. These pa-

Table 2. World Health Organization Functional Classification for Patients With Pulmonary Hypertension

Class	Description
1	No limitation of usual physical activity. Ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or syncope.
2	Mild limitation of usual physical activity. No discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or pre-syncope.
3	Marked limitation of physical activity. No discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or pre-syncope.
4	Unable to perform any physical activity at rest, and may have signs of right-ventricular failure.

tients need to be referred to a lung-transplant center as soon as diagnosed.<sup>34</sup>

### Functional Classification

PAH is classified not only by the patient's clinical and diagnostic characteristics, but also in terms of functional assessment. The World Health Organization modified the New York Heart Association heart-failure functional classification system for patients with PAH, to categorize patients by reported exercise tolerance. This scheme offers important prognostic information and is used in most research and therapeutic algorithms.<sup>1,35</sup> Dyspnea and/or fatigue may be present at rest, and symptoms are increased by any activity (Table 2).

### Clinical Presentation and Symptoms

There is usually a substantial delay between the presence of initial symptoms and the diagnosis of PAH, because the symptoms of PAH are initially insidious and nonspecific. In general, the mean interval from the onset of symptoms to diagnosis is 2 years.<sup>36</sup> Dyspnea, especially on exertion, is the most common and universal symptom, which is present in the majority of patients on presentation. It worsens as the disease progresses. Fatigue is the next most common symptom, and in one study was found to be the initial symptom in 75% of the patients at diagnosis.<sup>2</sup> Many patients and clinicians initially attribute this symptom to deconditioning. Chest pain, which is probably the result of under-perfusion of the right ventricle, is present in almost half of these patients at some time during the disease. Dizziness, syncope, and hemoptysis can occur when the right heart begins to fail and the patient cannot maintain an appropriate cardiac output. These symptoms may not be apparent until the disease process is late in its course. Hoarseness has been reported late in the disease

and is caused by compression of the recurrent laryngeal nerve by an enlarged pulmonary artery (Ortner's syndrome).

### Physical Examination

The findings of PAH on physical examination may be subtle. Vital signs may reveal resting tachycardia and a reduced pulse pressure. Desaturation with exertion is the most common finding when assessing vital signs. The lung auscultation is most commonly unremarkable unless there is an associated pulmonary (interstitial or obstructive) process or left-heart disease co-existing with PAH. Characteristic findings on the cardiac examination in patients with PAH include increased jugular venous distention, an accentuated pulmonic component of the second heart sound, and a murmur (tricuspid regurgitation) that is louder during inspiration. Signs of right-heart dysfunction, including peripheral edema, ascites, hepatomegaly, and audible right-sided gallop, can all be observed in patients who present late in the disease process. Clubbing is not common in IPAH, and, when found, should alert the clinician to evaluate the patient for disorders associated with PAH (ie, congenital heart disease).<sup>37</sup>

### Diagnosis

The first and most critical step in making the diagnosis of PAH is to have enough of a heightened awareness to consider it as a diagnosis. Because it shares many symptoms of other disorders, a high index of suspicion is necessary for an accurate and timely diagnosis of PAH. The diagnosis should be considered in any patient with unexplained dyspnea on exertion, fatigue, or exercise limitation, those with clinical signs consistent with right-heart dysfunction (eg, peripheral edema, ascites), patients with symptoms and who have a process known to be associated with PAH and/or a family history of pulmonary hypertension.

The initial assessment of PAH is to determine whether pulmonary hypertension is present, with a noninvasive evaluation (screening echocardiogram). If there is evidence of pulmonary hypertension, then an invasive method (right-heart catheterization) is required to confirm this finding and evaluate if it is hemodynamically consistent with PAH (ie, increased pulmonary vascular resistance with normal wedge pressure). This method is also used to evaluate the severity of the disease.

The evaluation then shifts to identifying the etiology of the PAH. This involves an extensive workup that requires multiple studies and laboratory tests to exclude disorders associated with PAH (Table 3).

### Laboratory Tests

A full panel of serum chemistries, thyroid-function tests, liver-function tests, and complete blood count are required

Table 3. Pulmonary Hypertension Diagnostic Workup

Laboratory Tests	
Rheumatoid factor	
Scleroderma (SCL-70)	
Anti-nuclear antibody (ANA)	
Human immunodeficiency virus (HIV)	
Hepatitis profile	
Complete blood count	
Prothrombin time with international normalized ratio (PT/INR)	
Full chemistries	
Liver-function tests	
Pregnancy test	
B-type natriuretic peptide (BNP)	
Thyroid-function panel	
Studies	
High-resolution computed tomogram of the chest	
Chest radiograph (posteroanterior and lateral)	
Full pulmonary function tests	
Echocardiogram with bubble study	
Doppler study of bilateral lower extremities	
Ventilation-perfusion study	
Sleep study	
Full right-heart catheterization with vasodilator study and possible exercise study	
Left-heart catheterization, if required	

in the evaluation of PAH. It is also important to send an autoimmune screening, consisting of antinuclear antibodies, including anticentromere antibodies, scleroderma (SCL70), and ribonucleoprotein, to screen for connective-tissue diseases. All patients must provide informed consent and undertake an HIV test. All of these studies are important when investigating whether there is a risk factor or condition associated with PAH.

Hyperuricemia occurs with high frequency in patients with PAH and has been shown to correlate with hemodynamics in patients with IPAH.<sup>38</sup>

Brain natriuretic peptide is elevated in right-ventricular-pressure overload and correlates with severity of right-ventricular dysfunction and mortality in PAH.<sup>39</sup>

### Sleep Study

If the history and/or overnight oximetry suggests obstructive sleep apnea, polysomnography should be considered to assess a possible contributory role in PAH.

### Pulmonary Function Tests

Pulmonary function tests are a common tool to evaluate dyspnea in general. There are no findings that are truly specific to PAH. A decreased diffusion capacity ( $69 \pm 25\%$  of predicted) will often be seen.<sup>2</sup> Mild restriction has also been reported.<sup>40</sup> If the PAH is associated with chronic

thromboembolic disease, there may also be an increase in the alveolar-arterial oxygen difference ( $P_{(A-a)O_2}$ ). Besides these, there are no other indices that are only consistent with PAH. It is important to evaluate the pulmonary function test results to rule out other pulmonary disorders such as restrictive (eg, interstitial lung disease) or obstructive (eg, chronic obstructive pulmonary disease) diseases.

### Six-Minute-Walk Test

The 6-min-walk test is a sub-maximal exercise test in which the patient walks as far as possible in 6 min. Oxygen saturation, heart rate, and distance walked are measured. The 6-min-walk distance has a strong independent association with mortality among patients with IPAH.<sup>41</sup> A distance < 332 m was associated with higher mortality in a recent study.<sup>41</sup> The 6-min-walk test is used in the initial workup of a patient with PAH to assess exercise performance and predict prognosis. Following serial 6-min-walk tests at follow-up visits is valuable in monitoring the patient's progress and evaluating response to therapy.

### Cardiopulmonary Exercise Test

Cardiopulmonary exercise testing may provide a more objective assessment of functional status, and may correlate with mortality; a peak oxygen consumption ( $\dot{V}_{O_2}$ ) < 10.4 mL/kg/min independently predicts survival.<sup>42</sup> The  $\dot{V}_{O_2}$  test, however, is difficult for patients to perform and is not always available. Currently, this test is used most often in clinical trials, but some experienced centers do use it routinely.

### Electrocardiogram

Electrocardiography is a noninvasive test used to evaluate patients with cardiovascular complaints. It is part of the initial workup to help exclude other diagnoses; however, it is important to realize that electrocardiography has a limited role in screening for PAH. For patients with established PAH, it may help identify acute arrhythmic or ischemic events. Electrocardiogram findings consistent with PAH include evidence of right-ventricular hypertrophy, right-atrial enlargement, right-axis deviation, right-ventricular strain, and right bundle-branch block. These findings are usually seen late in the course of the disease and are therefore inadequate for screening for early disease.

### Radiograph

Conventional chest radiograph is usually the initial study obtained in a patient with a suspected pulmonary disease. Chest radiographs are readily available to the clinician and



Fig. 1. Chest radiograph of a patient with pulmonary arterial hypertension. The pulmonary arteries are enlarged and there is "pruning" of the vessels peripherally.

relatively inexpensive, but are fairly insensitive and non-specific when evaluating PAH. Chest radiograph is useful early in the disease to help exclude other pulmonary diagnoses or secondary causes of pulmonary hypertension. As the disease progresses, there is enlargement of the central pulmonary arteries, and the peripheral pulmonary vessels are decreased in caliber (pruning of the pulmonary vasculature) with rapid tapering of the vessel (Fig. 1). Cardiomegaly is usually seen late in the disease.

### Computed Tomogram

Chest computed tomography is an important diagnostic tool, because it provides excellent visualization of the pulmonary vasculature, pulmonary parenchyma, and mediastinal structures. A main-pulmonary-artery diameter > 29 mm is suggestive of (but not diagnostic for) pulmonary hypertension (Fig. 2).<sup>43</sup> In the setting of chronic thromboembolic pulmonary hypertension, thrombus may be seen within the pulmonary arteries.

### Ventilation-Perfusion Scan

Ventilation-perfusion scan can identify a potentially treatable cause of pulmonary hypertension. Segmental or subsegmental perfusion unmatched defects (a high-probability scan) would suggest a pattern consistent with chronic thromboembolic disease. A normal scan and a generalized diffused or mottled appearance are findings that are both consistent with PAH.<sup>44</sup>

### Echocardiogram

Doppler transthoracic echocardiography is the most commonly performed diagnostic study in patients with PAH,



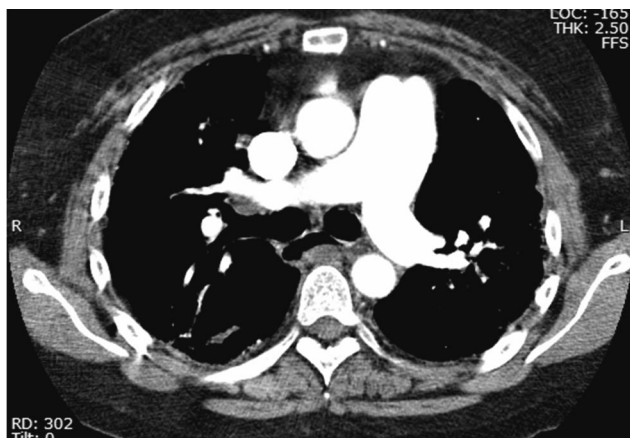


Fig. 2. Chest computed tomogram of a patient with pulmonary arterial hypertension. This patient's main pulmonary artery is enlarged (its diameter is even greater than the aorta), which is a typical tomogram finding in patients with moderate-to-severe pulmonary arterial hypertension.

and in most cases it is the first test to detect elevated right-ventricular pressure.<sup>45</sup> Echocardiography provides a rapid, noninvasive method to estimate the pulmonary-artery pressure, right-ventricular function, and valve and ventricular morphology. It is also useful in assessing left-ventricular systolic and diastolic function and intracardiac or intrapulmonary shunting. Pericardial effusions are not uncommon in the later stages of the disease, and can be assessed with echocardiography.<sup>46</sup> Echocardiogram findings consistent with PAH include elevated pulmonary-artery pressure (systolic pressure  $\geq 40$  mm Hg), tricuspid regurgitation, right-atrial and right-ventricular enlargement, flattening of the intraventricular septum, pericardial effusion, and patent foramen ovale.

Echocardiography can be used to differentiate various causes of pulmonary hypertension secondary to increased left-atrial pressure, including mitral and aortic valvular disease, cardiomyopathy, and constrictive pericarditis. Contrast echocardiogram, using intravenous agitated saline, can detect intracardiac shunts.

Echocardiography is also important in predicting the prognosis of patients with pulmonary hypertension. Raymond et al found that pericardial effusion, right-atrial enlargement, and interventricular septal distortion predicted adverse outcomes in pulmonary hypertension.<sup>46</sup> D'Alonzo et al reported worse survival in patients with PAH with increased pulmonary-artery pressure, right-atrial pressure, and decreased cardiac output.<sup>47</sup>

### Right-Heart Catheterization

Right-heart and pulmonary-artery catheterization is the accepted standard to establish the diagnosis and type of pulmonary hypertension. Current guidelines suggest that

all patients with suspected PAH undergo right-heart catheterization prior to initiation of treatment,<sup>15</sup> as it provides necessary diagnostic (eg, degree of hemodynamic impairment) and prognostic information.<sup>48</sup>

The goals of right-heart catheterization are to measure pulmonary-artery pressure directly, estimate pulmonary vascular resistance, determine cardiac output, evaluate for left-to-right shunt, determine the response to short-acting vasoactive agents, and assist with the titration of long-term vasodilators.

Many disorders associated with pulmonary hypertension can be elucidated by right-heart catheterization. For example, an elevated pulmonary wedge pressure may alert the clinician to evaluate the patient for left-heart disease caused by either systolic or diastolic dysfunction.<sup>49</sup> During the right-heart catheterization, an evaluation of oxygen saturation from the vena cava to the pulmonary artery can help diagnose an intracardiac left-to-right shunt.

### Vasodilator Testing

Patients with PAH who respond quickly to a pulmonary vasodilator have better survival.<sup>50</sup> The objective of the vasodilator test is to identify the small subset of patients who can be effectively treated with long-term oral calcium-channel blocker. The agents used for this testing are intravenous adenosine, intravenous epoprostenol, or inhaled nitric oxide. A positive response to vasodilator therapy is defined as a mean pulmonary-artery pressure decrease of  $\geq 10$  mm Hg, to a mean  $< 40$  mm Hg, with a concomitant increase in or maintenance of cardiac output.<sup>51</sup>

### Treatment

Over the last 10 years there has been a substantial increase in the number of medications in the armamentarium used to treat PAH, which has improved outcomes and survival. The approach to treating PAH can be divided into general (conventional) treatment measures and specific pharmacologic therapies. Selecting the most appropriate treatment for an individual patient is complex and requires familiarity with the disease process and the medications, including complicated drug-delivery systems, dosing regimens, adverse effects, and complications. Several ongoing clinical trials are evaluating various therapies and combinations of therapies. For these reasons, many patients are diagnosed and treated in referral centers that specialize in PAH.

### Conventional Therapy

**Supplemental Oxygen.** Patients with PAH have chronic hypoxemia secondary to decreased cardiac output. Hypox-

emia is a known pulmonary-artery vasoconstrictor, so supplemental oxygen is used in PAH patients to maintain oxygen saturation (above 90%) during both rest and exercise.<sup>52</sup> Supplemental oxygen improves pulmonary pressure in hypoxemic patients.<sup>52</sup>

**Diuretics.** Careful regulation of intravascular volume is a vital aspect of treating PAH. Increased filling pressure can further distend an already dilated right ventricle, which, in turn, can worsen function and decrease cardiac output. Decreasing right-ventricular preload with diuretics is a mainstay for patients with some right-heart dysfunction secondary to PAH. Diuresis improves hepatic congestion, ascites, and peripheral edema.<sup>53</sup> These medications must be used with caution so as not to decrease preload too quickly. Electrolytes and renal function need to be followed closely while patients are receiving diuretics.

**Cardiac Glycosides.** The use of long-term oral cardiac glycosides is controversial, because the long-term benefit has not been well validated. These agents do have some benefit in patients who have PAH and atrial fibrillation, and in those who may have some left-ventricular dysfunction with cor pulmonale.<sup>50,51</sup>

**Anticoagulation.** Anticoagulation is recommended (if there are no contraindications) as a part of the general treatment regimen for patients with PAH. In 2 studies, anticoagulation increased survival.<sup>50,54</sup> However, there have not been any prospective randomized placebo-controlled trials. Anticoagulation is effective in both decreasing the likelihood of thromboembolic complications because of decreased activity and in reducing in situ intra-arterial microvascular thrombosis, which are found pathologically in patients with PAH. Warfarin is the agent of choice, and most experts recommend adjusting the dose to an international normalized ratio (INR) of 1.5–2.5.

### Specific Treatments

There have traditionally been very few therapeutic options for the treatment of PAH, but the number of specific treatment options has increased substantially, paralleling our increasing understanding of the pathologic and molecular mechanisms of the disease. Recent developments have concerned 3 pathobiological pathways: the prostacyclin pathway, the endothelin pathway, and the nitric oxide pathway. These therapies differ in their mechanisms, indications, routes of delivery, and adverse-effect profiles. In appropriately selected patients, these specific therapies substantially modify the course of PAH, improving symptoms and hemodynamics.

**Calcium-Channel Blockers.** In 1992, McLaughlin et al<sup>55</sup> found a benefit from calcium-channel blockers in the treatment of a small subset of patients who have IPAH. Patients who had a significant response to short-term administration of vasodilator (intravenous epoprostenol or adenosine, or inhaled nitric oxide) had better 5-year survival when treated with oral calcium-channel blockers than did (1) those who did not respond and (2) the patients in the National Institutes of Health registry of patients with primary pulmonary hypertension. Since that time it has been found that very few patients with IPAH or PAH fit this category: 13% have short-term benefit and only 7% have sustained benefit from calcium-channel blockers. These patients had marked improvement in pulmonary hemodynamics in the vasodilator study; their mean pulmonary arterial pressure decreased by > 10 mm Hg, to < 40 mm, while their cardiac output increased or was maintained.<sup>56</sup> For the remaining patients, calcium-channel blockers will be ineffective or will worsen clinical status, so other therapies must be evaluated.

**Prostacyclin Therapy.** Prostaglandin I-2 (prostacyclin) is a metabolite of arachidonic acid, produced by the vascular endothelium. It is a potent vasodilator, relaxing vascular smooth muscle by increasing the level of cyclic adenosine monophosphate. It is also a strong platelet inhibitor and antiproliferative agent. It has some inotropic activity. Prostacyclin synthase, the enzyme required for prostacyclin synthesis, is decreased in patients with PAH,<sup>10</sup> and this deficiency is the rationale for replacement prostanoids.

Intravenous prostacyclin (epoprostenol) was first used to treat primary pulmonary hypertension in the early 1980s and the Food and Drug Administration (FDA) approved its use in 1995. It is the only PAH medication that has been shown to have a survival benefit in a randomized clinical trial.<sup>55</sup> No long-term randomized trial of epoprostenol has been conducted, but a cohort analysis of patients on epoprostenol clearly demonstrated clinical benefits for patients in New York Heart Association functional classes III and IV, as compared with historical control groups.<sup>57</sup> Intravenous epoprostenol increases exercise tolerance, hemodynamics, and long-term survival.

The drawbacks of intravenous epoprostenol are that it is complicated to deliver, it can be uncomfortable, and it is expensive. Common adverse effects include jaw pain, headache, diarrhea, flushing, leg pain, and vomiting. More serious complications are related to the delivery system. It has a short half-life in circulation (3 min) and is inactivated by a low pH, so it must be administered via continuous intravenous infusion through a permanent tunneled central venous catheter. Ice packs must be used to keep the infusate cold, because the drug is unstable at room temperature. Patients are at risk for catheter-related complications such as infection and thrombosis. Abrupt discon-

tinuation of the drug and subsequent rebound pulmonary hypertension may result in acute right-heart failure if the line is occluded or dislodged.

**Prostacyclin Analogues.** The complexity of epoprostenol therapy has led to the development of prostacyclin analogues. These analogues are more stable and have a longer half-life, which allows them to be delivered via alternate routes.<sup>58</sup> These medications may have the same spectrum of adverse effects as epoprostenol, but the effects differ substantially in severity.

Treprostinil is a stable prostacyclin analogue, with a half-life of 55–117 min.<sup>58</sup> It is administered either subcutaneously through a small pump (similar to those used to deliver insulin) or intravenously through a central catheter.

Subcutaneous treprostinil improves dyspnea, hemodynamic indices, and 6-min-walk distance, compared to placebo. Pain at the site of infusion is the most pronounced adverse effect. In one study, pain led to a discontinuation of the drug in 8% of the patients. A select group of patients can be safely transitioned from intravenous epoprostenol to subcutaneous treprostinil.<sup>59</sup>

An important advantage of intravenous treprostinil is that it has a much longer half-life than epoprostenol. If there were an unintentional disruption of the medication, it might be better tolerated. It does not need to be cooled, as it is stable at room temperature.

Iloprost is a stable prostacyclin analogue, with a half-life of 25 min. It is the first approved inhalable prostacyclin. It has a relatively short duration and it needs to be delivered in 6–9 inhalations per day (every 2–2.5 h, while the patient is awake). It was found to improve the 6-min-walk distance, the New York Heart Association functional class, and hemodynamic variables after a 3-month clinical trial.<sup>60</sup> The adverse effects are cough, flushing, and headache.

**Endothelin-Receptor Antagonists.** Endothelin-1 is a potent vasoconstrictor and smooth-muscle mitogen that plays an important pathogenetic role in the development and progression of PAH by modulating both vasoconstriction and proliferation.<sup>61</sup> Two endothelin receptor isoforms, endothelin-A (ET-A) and endothelin-B (ET-B), have been identified. ET-A receptors are found in the pulmonary vascular smooth-muscle cells, and ET-B receptors are located both on the pulmonary vascular endothelial cells and smooth-muscle cells.<sup>62</sup>

Activation of the ET-A receptors promotes vasoconstriction and proliferation of vascular smooth-muscle cells. Activation of ET-B on the smooth-muscle cells leads to vasoconstriction, but some studies suggest that activation of ET-B may play a protective role by producing nitric oxide and prostacyclin and clearing circulating ET-1. It is still unclear whether it is preferable for a medication to

block both of these receptors or to selectively block ET-A receptors.<sup>62</sup>

The first FDA-approved oral endothelin receptor antagonist, bosentan, is a dual ET-A/ET-B endothelin-receptor antagonist. It has shown to be safe and efficacious for the treatment of PAH, and it improves 6-min-walk distance, Borg dyspnea index, and functional class, and increases the time to clinical worsening.<sup>63,64</sup>

Sitaxsentan and ambrisentan are 2 selective ET-A blockers. These 2 agents are both finishing phase III clinical trials and awaiting FDA approval.<sup>65</sup>

All of the agents in this class are metabolized by the liver, and they may induce an increase in aminotransaminase levels. Liver-function tests must be conducted monthly when using these agents. All of the endothelin-receptor antagonists are teratogenic. Female patients of childbearing age also require monthly serum B-HCG pregnancy tests.

**Nitric Oxide.** Nitric oxide is an endogenous vasodilator that directly relaxes vascular smooth muscle by stimulating soluble guanylate cyclase and increases production of intracellular cyclic guanosine monophosphate.<sup>66</sup> PAH is associated with decreased production of nitric oxide, so nitric oxide has been proposed as a potential therapy. It is used for acute vasoreactive testing during right-heart catheterization, and in intubated patients with PAH. It is unlikely that nitric oxide will be used in the near future for long-term use, because delivering nitric oxide is cumbersome.

**Type 5 Phosphodiesterase Inhibitors.** Sildenafil, a highly selective phosphodiesterase (PDE-5) inhibitor, offers a strategy for increasing the activity of endogenous nitric oxide in PAH patients. Sildenafil was recently approved by the FDA as an oral therapy for PAH. Its mechanism of action is enhancement of endogenous nitric oxide effects by inhibiting breakdown of cyclic guanosine monophosphate. The increase in this nucleotide induces relaxation and anti-proliferative effects on vascular smooth-muscle cells. It improves functional status, pulmonary hemodynamics, and 6-min-walk distance.<sup>67</sup>

### Combination Therapy

It may be that the optimal approach to treating PAH is a combination of the above agents. This approach can be used for patients who do not respond to the initial monotherapy or who initially benefit but then deteriorate on a single agent. Multiple ongoing clinical trials are evaluating different combinations of agents.

## Lung Transplantation

Great strides in medical therapy over the last few years have improved survival for PAH patients. However, even though these medications have altered the clinical features and course of the disease in many patients, they are not a cure. Many patients already have moderate-to-severe disease when diagnosed, and not all patients respond favorably to medical therapy. There are also patients whose condition gradually worsens despite escalating pharmacologic therapy and patients who cannot tolerate medical therapy. For these patients, lung transplantation may significantly improve hemodynamics, functional class, survival, and quality of life.<sup>68</sup>

Lung transplantation is reserved for patients who have failed medical therapy. Identifying and selecting appropriate candidates and timely referral is challenging but critical for successful transplantation. Lung transplantation for any disease process is limited by chronic allograft rejection and infection; however, progressive improvements in outcomes have established lung transplantation as an efficacious treatment for PAH.

### Implications for the Respiratory Therapist

PAH is an infrequent disease in the general population, but RTs will see and care for these patients throughout their training and careers. The RT will have responsibility for these patients throughout the hospital, pulmonary-function-laboratory, and out-patient office settings. In the intensive care unit, RTs will provide support and expertise with patients who require nitric oxide (either via mask or mechanical ventilation) for PAH. The RT is also needed to assist with patients undergoing right-heart catheterization and vasodilator testing when nitric oxide is used.

PAH patients require pulmonary function tests for their initial evaluation and are often followed with serial tests if they have coexistent restrictive or obstructive lung disease.

The RT will also be involved with treating PAH via inhalation therapy (iloprost), which is being used more frequently.

The support and knowledge of RTs in these and with other interactions with these patients is imperative to make progress in continuing to identify and treat this disease process.

### Summary

The diagnosis and management of PAH has evolved substantially in the past decade, before which PAH was believed to be untreatable and invariably fatal. Earlier diagnosis, advanced understanding of the pathogenetic and molecular pathways, and a rapidly growing armamentarium

have all assisted in changing the course of this challenging disease.

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