**Pulmonary Arterial Hypertension Expert Column**

# Early Diagnosis and Treatment of Pulmonary Arterial Hypertension

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## Introduction

Pulmonary arterial hypertension (PAH) is one of the most important and potentially life-threatening disorders of the pulmonary circulation and is defined as a systolic pulmonary artery pressure of > 35 mm Hg or, alternatively, as a mean pulmonary artery pressure of > 25 mm Hg at rest or > 30 mm Hg with exertion.[1] PAH is characterized by progressive increases in pulmonary vascular resistance, which, untreated, can lead to right ventricular failure and death.[2] PAH is a disorder of diverse etiologies, and its diagnosis and treatment can prove challenging. PAH can develop in up to 50% of patients with scleroderma, 10% to 15% of patients with systemic lupus erythematosus (SLE), and 5% to 10% of patients with chronic liver disease. Patients with a history of exposure to diet pills have a significantly increased risk of developing PAH, as do patients with HIV or a history of thromboembolic disease.[1] The main presenting symptom of dyspnea is nonspecific, and PAH is as likely to be encountered by general practitioners as it is by pulmonologists, cardiologists, rheumatologists, and other specialists. A Doppler echocardiogram is the screening test of choice for patients in whom there is a clinical suspicion of PAH.

Presently, our ability to diagnose PAH patients with earlier-stage disease such as New York Heart Association (NYHA) Class I or II is hampered by our inability to identify the condition until symptoms become severe. Until recently, there were few therapies to offer early-stage patients, and given the side effects of those therapies, treatment was reserved for only the sickest patients. In 1995, intravenous epoprostenol became the first US Food and Drug Administration (FDA)-approved therapy for PAH after clinical trials were performed primarily in patients with NYHA III or IV symptoms. Most published reports of diagnosis and treatment of patients with PAH are populated with patients with advanced disease at the time of presentation (NYHA Class III or IV), but new clinical trials in patients with NYHA I or II symptoms may help us learn more about the natural history of PAH and ascertain the role of early interventions. Currently, it is not known for certain whether establishing an early diagnosis of PAH can improve survival, but it can undoubtedly lead to improvements in symptoms and quality of life.[2] In asymptomatic patients, the utility of screening tests (eg, an echocardiogram) has not yet been established; in asymptomatic patients felt to be at risk for familial PAH (FPAH), the clinical role of genetic screening has not yet been determined.

## History

The diagnosis of PAH should begin with a thorough history in which underlying etiologies and possible contributing factors are sought. While it was once classified as either primary pulmonary hypertension (PPH) or secondary pulmonary hypertension, a newer system of classification ( Table 1 ) more accurately reflects the pathogenesis of PAH and should be used as a guide for making the diagnosis.[3] In the new classification, PPH is replaced by idiopathic PAH (IPAH). The term "pulmonary hypertension" refers simply to the hemodynamic state shared by many conditions. For instance, a patient with pulmonary hypertension in the setting of left-sided heart disease is classified as pulmonary venous hypertension, not PAH, and would warrant an assessment for causes of the LV dysfunction and appropriate treatment based on that. A patient who presents with a finding of pulmonary hypertension by echocardiogram and a known history of thromboembolism may merit a workup that focuses on the possibility of thromboembolism as the cause for their pulmonary hypertension.

The symptoms of PAH are nonspecific but are generally due to impaired oxygen transport and decreased cardiac output. Dyspnea is present in most PAH patients at the time of presentation.[4] Exercise intolerance is a frequent complaint and, in most PAH patients, it has an insidious onset. Many patients with PAH describe a gradual decline in exercise tolerance over months to years that they attribute to a lack of fitness or depression or weight gain. Some will describe an acute worsening or "onset" of symptoms following a physical stress such as childbirth or a routine illness or surgery from which they never seem to have recovered. Many patients are labeled by healthcare providers with an incorrect diagnosis for several years before PAH is correctly diagnosed. Careful questioning about the nature of dyspnea can help exclude more common respiratory or cardiac conditions such as asthma or coronary artery disease. As PH may be associated with other diseases and conditions, queries about other symptoms should be made. For example, symptoms such as orthopnea and paroxysmal nocturnal dyspnea may point to pulmonary venous congestion due to left-sided cardiac disease, while a history of snoring or apnea may raise the possibility of sleep-disordered breathing as a causative factor.[1] Patients with PAH related to connective tissue diseases may complain about painful joints or rashes. Patients who give a history of childhood heart murmur or blue baby syndrome may have PAH due to congenital systemic to pulmonary shunts. Angina and syncope are fairly common symptoms in patients with PAH but are nonspecific. As PAH progresses, signs of progressive right heart failure such as hepatic congestion (suggested by an enlarged liver), peripheral edema, and ascites will appear, usually accompanied by worsening exercise tolerance and fatigue.

Since there is a known genetic predisposition to PAH, any family history of sudden death, PAH, or conditions known to be related to PAH (such

as connective tissue disease) should be explored.[1] Because there is a known link between PAH and certain exposures to toxins, infections, and inflammatory states, patients should be queried on their past or present use of diet pills or amphetamines. Patients at risk for HIV should be offered HIV testing. Portopulmonary hypertension can occur in patients with chronic liver disease; therefore, patients should be questioned about risk factors for liver disease such as hepatitis B and C or alcohol abuse. A history suggestive of thrombophilia such as excessive fetal loss in young women or a known history of thrombembolism should be explored; though chronic thromboembolic pulmonary hypertension (CTEPH) is relatively rare, a surgical cure for CTEPH is possible if diagnosed early. All patients should be assigned to an NYHA functional class based on their symptoms, as functional class has been shown to be useful in assessing prognosis as well as response to therapy in patients with PAH ( Table 2 ).[5]

### Physical Examination

The physical examination is relatively insensitive in terms of diagnosing PAH but may be helpful to the clinician seeking to exclude other possibilities while honing in on the diagnosis. A low resting oxygen saturation when present can be suggestive of PAH, among many conditions, but when particularly low may suggest a shunt as may occur with congenital heart disease and PAH. Central and/or peripheral cyanosis and clubbing on examination may further support this diagnosis. In the National Institutes of Health (NIH) registry trial, 20% of patients with a diagnosis of IPAH were noted to be cyanotic on presentation.[4] However, patients with normal resting oxygen saturation should undergo exercise oximetry, where any decline in saturation with exercise should raise concerns for a potentially serious cardiopulmonary illness, including PAH.

Patients with severe chest wall deformity or kyphoscoliosis, obesity, or a small hypopharynx may suffer from a hypoventilatory disorder leading to PH. On physical exam, the lungs of patients with IPAH are generally clear on auscultation. Wheezes, rhonchi, or rales should raise the possibility of other lung diseases such as asthma, bronchitis, or fibrosis. The so-called "wet rales" of congestive heart failure should suggest left-sided heart disease, not PAH. In the NIH registry, an accentuated pulmonary component of the second heart sound was noted in > 90% of patients.[4] In the later stages of PAH, when right ventricular failure is more likely, signs and symptoms such as a right ventricular gallop (right sided S4), prominent jugular venous distention, an enlarged liver or spleen, ascites, or peripheral edema may be found. Skin changes suggestive of a mixed connective disorder such as rashes, skin tightening, or telangiectasias may be helpful findings on physical examination.

### Diagnostic Tests

In patients in whom there is a clinical suspicion of PAH, the diagnosis should be confirmed with an echocardiogram. The echocardiogram not only helps establish the diagnosis but can delineate the etiology and offer prognostic information as well. Echocardiograms can detect valvular heart disease, left ventricular dysfunction, and intracardiac shunts.[1] In order to estimate a right ventricular systolic pressure by echocardiogram, tricuspid regurgitation (TR) must be present. In the absence of the ability to provide a quantitative assessment of right sided pressures using the TR jet, the presence of certain qualitative signs on echocardiogram can prove helpful in the diagnosis of pulmonary hypertension. These qualitative signs include right atrial and right ventricular enlargement and septal bowing or flattening. When present, pericardial effusions have been shown to be associated with advanced disease and poor outcome.[2] It is not yet clear that exercise echocardiograms can or should play a role in the diagnosis of early or relatively asymptomatic patients.

Electrocardiograms (ECGs) should also be performed in patients with suspected PAH; though not specific for PAH, typical findings on ECG include right ventricular strain, right ventricular hypertrophy, and right axis deviation. Laboratory evaluation should include tests for mixed connective tissue disease, liver disease, thrombophilias, and other conditions associated with PAH.

Chest radiographs may support the diagnosis of PAH or may lead to the diagnosis of other underlying diseases. In the NIH Registry on Primary Pulmonary Hypertension,[6] the main findings on chest radiograph in patients with PAH were enlarged hilar and pulmonary arterial shadows.[4] Enlargement of the right ventricle, suggested by filling of the retrosternal space on lateral chest radiographs, is also consistent with PAH. Except in the case of accompanying parenchymal lung disease (eg, a patient with PAH and interstitial lung disease due to scleroderma), the lungs on chest x-ray are typically clear in PAH. In PAH patients with late-stage disease, ascites with pleural effusions may be seen on chest x-ray. Ventilation/perfusion scans should be performed in all patients with PAH; a normal V/Q scan rules out thromboembolism but an abnormal one warrants further testing with pulmonary angiography.[7]

The role of computed tomography (CT) angiography in excluding the diagnosis of CTEPH is currently under study, but CT scans of the chest may be useful in other ways as they can assess for the presence or absence of parenchymal lung diseases such as pulmonary fibrosis or emphysema. Pulmonary function tests (PFTs) and arterial blood gas should be performed in all patients; in patients with systemic sclerosis, regular PFTs with measurements of diffusing capacity may aid in the early detection of PAH.[8] An assessment of functional status using a 6-minute walk test should be performed in all patients with PAH.

Cardiac catheterization is the gold standard for the diagnosis of PAH. It aids in the diagnosis by excluding other etiologies such as left heart disease and provides important prognostic information for patients with PAH. Vasodilator testing using short-acting agents such as adenosine, inhaled nitric oxide, or epoprostenol should be performed during cardiac catheterization to identify the small subset of patients who may benefit from long-term therapy with calcium channel blockers (CCBs).[1] CCBs should not be used as agents for vasodilator testing during catheterization. Historically, a positive vasodilator response has been defined as a fall in both mean pulmonary artery pressure (PAP) and pulmonary vascular resistance of at least 20% from baseline values. Newer recommendations have defined a positive vasodilator response as a decrease in mean PAP of at least 10 mm Hg to < 40 mm Hg with an increased or unchanged cardiac output compared with baseline values.

### Vasodilator Treatments

#### CCBs

CCBs are useful only in the subset of patients with a positive vasodilator response during cardiac catheterization as defined above.[9] Among

PAH patients, only 10% or fewer have a positive acute vasodilator response and thus warrant consideration for long-term treatment with these agents. The use of oral CCB therapy in PAH should be limited to these patients, and their general use should be discouraged, especially in patients with right heart failure.[10]

**Prostanoids**

Intravenous (IV) epoprostenol was the first FDA-approved therapy for PAH in 1995. Since that time, 2 other prostanoid agents, treprostinil and inhaled iloprost, have been approved for use in patients with PAH. Long-term IV epoprostenol therapy has been shown to improve hemodynamics, exercise tolerance, functional class, and survival in patients with PAH.[11,12] Most of the pivotal trials of epoprostenol were in ill patients (NYHA III or IV) with IPAH or PAH associated with scleroderma.[13] However, its successful use in treating other types of PAH has also been described in the literature. Because it has a very short half-life and requires a constant IV infusion via an indwelling catheter and portable pump, its use can be complicated and requires referral to a clinical center of excellence for initiation and management.

The development of other prostacyclin products was fueled in part by the complicated nature of epoprostenol therapy. Treprostinil has a longer half-life than epoprostenol and the added advantage that it can be delivered subcutaneously. In the pivotal trial of treprostinil, 470 patients were enrolled in a 12-week, randomized, placebo-controlled trial. The trial included patients with a range of disease severity: NYHA II (12%), NYHA III (81%), and NYHA IV (7%). The underlying diagnoses of patients in the treprostinil trial were IPAH (58%), PAH associated with connective tissue disease (27%), and PAH associated with congenital heart disease (25%). There were improvements in hemodynamic indices and exercise capacity as measured by right heart catheterization and 6-minute walk test.[14] There was no impact of treprostinil in the congenital heart disease group, likely due to the short duration of the trial (12 weeks), and the inclusion of this group may have adversely impacted the study results overall. Subcutaneous treprostinil is associated with significant site pain, which may limit its use in certain patients. Recent approval of treprostinil for IV use will allow clinicians an alternative to IV epoprostenol, and though IV treprostinil has advantages over epoprostenol (a longer drug half-life and a smaller pump for drug delivery), it is unclear if it will offer the same long-term benefits demonstrated with epoprostenol.

Inhaled iloprost was recently approved by the FDA for use in patients with PAH. In the pivotal trial of this therapy, 203 patients were randomized to receive inhaled iloprost or placebo. Of the patients in this trial, 59% were NYHA III and 41% were NYHA IV at the time of enrollment. The majority of patients had a diagnosis of IPAH (50.5%); a considerable percentage had CTEPH (33%) and 13% had PAH associated with connective tissue disease. Patients in the treatment group showed a significant improvement in the primary outcome, which was a combined clinical variable, comprised of exercise capacity, NYHA class, and clinical deterioration.[15]

**Endothelin Receptor Antagonists (ERA)**

Recent trials of oral endothelin receptor antagonists (ERAs) have shown this new class of drugs to be effective in the treatment of PAH. Results of the first randomized controlled trial of the ERA bosentan were reported in 2002; subsequently, it won approval by the FDA for use in PAH patients. Patients in the 16-week bosentan trial were primarily patients with IPAH (70%) and NYHA III symptoms (94%); patients with scleroderma and SLE made up 20% and 10% of the patients studied, respectively. Compared with patients on placebo, patients on bosentan showed significant improvement in the primary end point, the 6-minute walk test. Patients on the drug also showed improvements in functional class and dyspnea scores.[16] There are several potential toxicities associated with bosentan, including liver function test abnormalities. Because of this concern, the FDA requires that liver function tests be performed monthly in patients who take it. It has also been associated with anemia so periodic blood counts should also be performed in patients taking the drug. Because of the potential teratogenic effects, the use of bosentan in women who are pregnant or likely to become pregnant is contraindicated.

Two other ERAs are currently under study but are not yet FDA approved. In a placebo-controlled trial published in 2004, the ERA sitaxsentan was shown to improve 6-minute walk test, functional class, and cardiac index in patients with PAH.[17] In that trial, 33% of the patients studied were NYHA Class II while the majority were NYHA III (66%); most patients had IPAH (53%), but patients with connective tissue disease-related PAH and PAH associated with congenital heart disease were also well represented. The most frequent adverse event noted was an increased plasma INR in patients taking warfarin; reductions in warfarin dosing were found to address this problem. Abnormal liver function tests have also been reported with use of this drug. A third ERA, ambrisentan, is currently in clinical trials in patients with PAH.

Use of the ERA class of drugs in patients with liver disease or in HIV patients on HAART therapy may be problematic because of the potential for hepatotoxicity and drug-drug interactions.

**Phosphodiesterase (PDE) Inhibitors**

Recently, the FDA approved the use of the oral PDE inhibitor sildenafil in the treatment of PAH. Results of the pivotal 12-week trial of this drug were presented in October 2004 at the CHEST meeting and showed that PAH patients taking the drug showed significant improvements in 6-minute walk test, functional class, and hemodynamics. There were 277 PAH patients in this study, 38% of whom were NYHA II and 58% of whom were NYHA III; 63% of patients had IPAH, 30% had PAH associated with connective disease, and 7% had PAH associated with congenital heart disease. The most common reported side effects were headaches, flushing, and dyspepsia. PDE inhibitors are contraindicated in patients taking any form of nitrates.

**Combination Therapy?**

The advent of new therapies that target multiple pathways involved in the pathogenesis of PAH raises the question of the role of combination therapy. Upcoming clinical trials may not only provide direct comparison between different vasodilator therapies but may also help address the role of combination therapy in the treatment of PAH. Provocative early studies have suggested a role for combining treatments for PAH, but it is not yet clear what regimens will be the most beneficial in which patients.[18]

## General Medical Treatments

It has been shown that in situ thrombosis can occur in some patients with PAH and may contribute to their disease.[9] Because of this, anticoagulation with warfarin is recommended for patients with IPAH unless otherwise contraindicated.[19] Diuretics are indicated in PAH patients with evidence of right heart failure; however, patients should have frequent monitoring of serum electrolytes and renal function. Low oxygen levels can cause pulmonary vasoconstriction and may contribute to worsening of PAH. It is best to maintain oxygen saturations > 90% in patients with PAH when and if possible. This can be achieved in most patients by supplemental oxygen therapy. Digoxin may prove useful in some PAH patients with refractory right heart failure, but serum drug levels should be followed carefully.

### Surgical/Interventional Therapies for PAH

In certain patients with PAH, surgical or catheter-based interventions may be indicated. Atrial septostomy is a procedure in which an intra-atrial right-to-left shunt is created to help decompress a failing right ventricle. This procedure, which results in significant hypoxemia but which can improve cardiac output, should be performed only in select PAH patients with disease that is unresponsive to medical management. Atrial septostomy should be performed only at institutions with significant clinical and procedural experience. Patients with suspected CTEPH should be referred to specialized centers for consideration of pulmonary thromboendarterectomy, a surgical procedure that has been shown to improve hemodynamics, functional status, and survival in appropriately selected patients. Patients with PAH who are NYHA Class III or IV should be referred to a transplant center for evaluation and consideration for lung or heart-lung transplantation.[20]

### Table 1. Revised Nomenclature and Classification of Pulmonary Hypertension

- Pulmonary arterial hypertension
    - IPAH (idiopathic pulmonary arterial hypertension)
    - FPAH (familial pulmonary arterial hypertension)
    - Collagen vascular disease
    - Congenital systemic to pulmonary shunts
    - Portal hypertension
    - HIV infection
    - Drugs and toxins
    - Other (glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, splenectomy, myeloproliferative disorders)
    - Associated with significant venous or capillary involvement
    - Pulmonary veno-occlusive disease
    - Pulmonary capillary hemangiomatosis
- Pulmonary venous hypertension
    - Left-sided atrial or ventricular heart disease
    - Left-sided valvular heart disease
- Pulmonary hypertension associated with hypoxemia
    - Chronic obstructive pulmonary disease
    - Interstitial lung disease
    - Sleep-disordered breathing
    - Alveolar hypoventilation disorders
    - Chronic exposure to high altitude
- Pulmonary hypertension due to chronic thrombotic and/or embolic disease
    - Thromboembolic obstruction of proximal pulmonary arteries
    - Thromboembolic obstruction of distal pulmonary arteries
    - Pulmonary embolism (tumor, parasites, foreign material)
- Miscellaneous
    - Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

### Table 2. New York Heart Association Functional Classification

- **Class I:** No symptoms with ordinary physical activity.

- **Class II:** Symptoms with ordinary activity. Slight limitation of activity.
- **Class III:** Symptoms with less than ordinary activity. Marked limitation of activity.
- **Class IV:** Symptoms with any activity or even at rest.

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