

Pulmonary Arterial Hypertension: Current Diagnosis and Management

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Introduction

Primary pulmonary hypertension (PPH) is a disease affecting the pulmonary vascular bed that results in sustained pulmonary hypertension for which there is no apparent cause. The incidence of PPH has been estimated at 1–2 cases per million in the general population but is increased in patients with portal hypertension, HIV infection and with the use of appetite suppressants. Pulmonary arterial hypertension (PAH) also occurs in association with collagen vascular diseases (scleroderma, systemic lupus erythematosus) and congenital systemic to pulmonary shunts. The classification of pulmonary hypertension has recently been revised at a symposium sponsored by The World Health Organization (Table 1). Historically, the prognosis of PPH has been poor. The National Institutes of Health Registry estimated a median survival of 2.8 years among the 194 patients enrolled. The survival rates at 1, 3 and 5 years were 68%, 48% and 34%, respectively. Mortality was closely associated with parameters of right ventricular function. This registry formulated an equation using three variables (mean pulmonary artery pressure, mean right atrial pressure and cardiac index) to predict survival, which was later prospectively validated. The most common causes of death are progressive right ventricular failure and sudden death. Pneumonia and pulmonary embolus are particularly life threatening in patients with pulmonary hypertension.

Diagnostic Evaluation

The diagnosis of PAH is sometimes very difficult to make. The major obstacle in establishing the diagnosis early is the non-specific nature of the symptoms. In the NIH Registry of PPH, the mean length of time from the onset of symptoms to diagnosis was approximately 2 years. Dyspnea was the most common initial presenting symptom and was reported by nearly all patients at some point in the disease process. Fatigue was another common early symptom. Other symptoms include angina, syncope and edema. Common findings on physical examination include: elevated jugular venous pressure, reduced carotid volume, right ventricular heave, loud pulmonic component of the second heart sound, murmur of tricuspid regurgitation, right-sided fourth heart sound, ascites and edema. Physical exam findings of other disorders associated with PAH including manifestations of collagen vascular disease, liver disease and congenital heart disease may be present.

Table 2 displays diagnostic tests that are commonly performed for the evaluation of PPH. The electrocardio-



gram may show right ventricular enlargement and a right ventricular strain pattern (Figure 1). Chest x-rays commonly show enlarged pulmonary arteries (Figure 2). Right ventricular enlargement may be appreciated on the lateral view. An echocardiogram is vitally important to evaluate for left heart, valvular disease and congenital heart defects. It is also useful to estimate the severity of the pulmonary hypertension and to evaluate the size of the right heart chambers (Figure 3). Ventilation perfusion scans are important to rule out thromboembolic disease. In the setting of PPH, the ventilation perfusion scan may be normal or may reveal a patchy distribution of tracer. In contrast, in the setting of thromboembolic disease, there are multiple larger perfusion defects (Figure 4). If the perfusion scan or spiral CT is inconclusive, pulmonary arteriography should be performed to evaluate for the possibility of thromboembolic disease. Patients with pulmonary hypertension due to large, bilateral thromboembolic disease should be evaluated for pulmonary thromboendarterectomy. Although high risk, carefully selected patients may realize an improvement in exercise tolerance and quality of life. Pulmonary function tests are crucial to evaluate for lung disease. There is generally a mild restrictive pattern but no evidence of obstruction. The diffusing capacity of carbon monoxide may be reduced. Because exercise tolerance correlates well with severity of pulmonary hypertension and prognosis, it is also important to obtain a treadmill test or 6-minute walk test. Serologic studies are often performed to screen for connective tissue diseases. A positive antinuclear antibody is common in the setting of PPH, although higher titers and specific antibody patterns should raise the suspicion of collagen vascular diseases. HIV testing is also indicated.

Cardiac catheterization is essential in the evaluation of all patients with suspected PAH to confirm diagnosis and establish the severity. In addition to an elevated pulmonary artery pressure, other altered hemodynamics may include an elevated right atrial pressure and a depressed cardiac output. In the NIH Registry, the mean right atrial pressure was 9.7 mm Hg, mean pulmonary artery pressure was 60 mm Hg, cardiac index was 2.3 L/min and pulmonary vascular resistance index was 26 Wood units \times m². In the setting of PAH, the pulmonary capillary wedge pressure is normal. Acute vasodilator testing with short-acting vasodilators such as adenosine, nitric oxide or prostacyclin is commonly performed in the cardiac catheterization laboratory and is useful in making treatment decisions.

Medical Management

Considerable progress in therapy has been made since the NIH registry of the 1980s. PPH is a progressive disease for which there is no cure. One of the main goals of therapy, however, is to prevent progression and induce regression of

Table 1. Classification of Pulmonary Hypertension Adapted from the World Health Organization, 1998

- Pulmonary arterial hypertension
 - Primary pulmonary hypertension
 - Sporadic
 - Familial
 - Related to:
 - Collagen vascular disease
 - Congenital systemic to pulmonary shunts
 - Portal hypertension
 - HIV infection
 - Anorexigens
 - Persistent pulmonary hypertension of the newborn
- Pulmonary venous hypertension
- Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia
- Pulmonary hypertension caused by chronic thrombotic and/or embolic disease
- Pulmonary hypertension associated with miscellaneous diseases

the disease. In the past decade, the vasodilators have been studied most extensively. Because of the pathogenic importance of vasoconstriction, this was a reasonable approach. More recently, novel therapies aimed at endothelial dysfunction have been investigated. Treatment of right heart failure is also important as it improves quality of life.

Diuretics are frequently used to reduce excessive edema in patients with right heart failure. They are particularly useful when hepatic congestion, ascites and edema are present. In refractory cases, more than one diuretic is required. In some instances, patients must be treated with intravenous diuretics. Digoxin can increase cardiac output and reduce circulating neurohormones. Anticoagulant therapy has been associated with an improved survival in one prospective and one retrospective study. Although the effectiveness of warfarin anticoagulation in patients with PPH has never been tested in a prospective randomized long-term trial, based on the known pathogenesis of PPH and the available data, the use of low-dose warfarin maintaining an INR of 2.0–2.5 times control is recommended for all patients with PPH. Patients with hypoxemia, either at rest or with exercise, should receive supplemental oxygen.

Calcium-Channel Blockers

Although many drugs have been utilized for vasodilatation in the setting of PPH, calcium-channel blockers have been

Table 2. Diagnostic Evaluation of PPH

- Blood Tests
 - ANA
 - HIV
 - TFTs
 - Liver profile
- Electrocardiogram
- Chest x-ray
- Lung scan or spiral CT
- Echocardiogram
- Treadmill or 6-minute walk
- Pulmonary function tests
- Cardiac catheterization

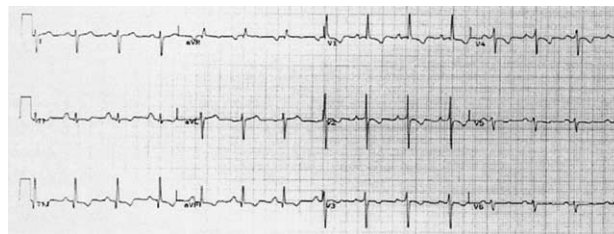


Figure 1. Electrocardiogram demonstrating right axis deviation, right ventricular enlargement and right bundle branch block.

most widely tested for this purpose and appear to produce a more consistent reduction in pulmonary artery pressure and pulmonary vascular resistance than other vasodilators. Approximately 20% of patients with PPH will respond to calcium-channel blockers. This favorable response is usually predicted by the response to a short-acting vasodilator such as adenosine, epoprostenol or nitric oxide at the time of cardiac catheterization. A substantial decline in mean pulmonary artery pressure, to normal or near normal levels, defines a vasodilator response. A reduction in pulmonary vascular resistance as the result of an increase in cardiac output without substantial fall in mean pulmonary does not correlate with response to calcium-channel blockers. Of a group of 17 patients who responded to high-dose calcium-channel blockers, Rich et al. reported a 94% 5-year survival rate compared to a 36% survival rate among patients who did not respond to therapy. Long-acting nifedipine, diltiazem or amlodipine are currently the most commonly used calcium-channel blockers. Dosing is posed on the hemodynamic response and high doses (up to 270 mg nifedipine, 720 mg diltiazem, 30 mg amlodipine) are frequently re-

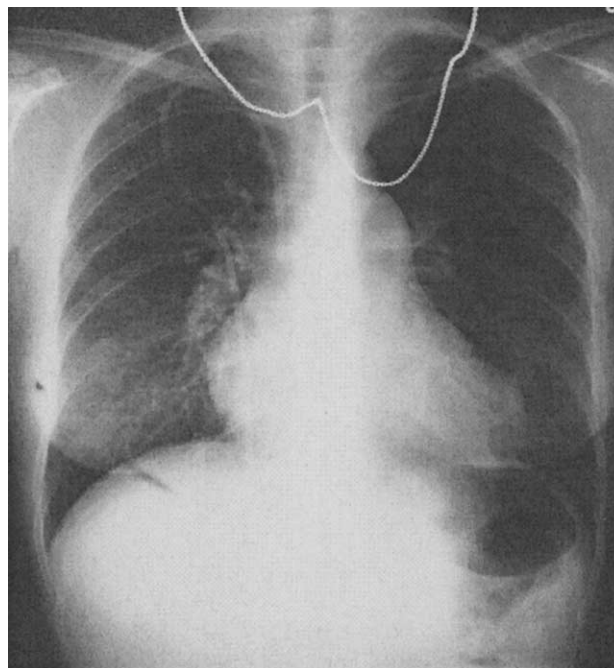


Figure 2. Chest x-ray demonstrating enlarged pulmonary arteries and cardiomegaly.

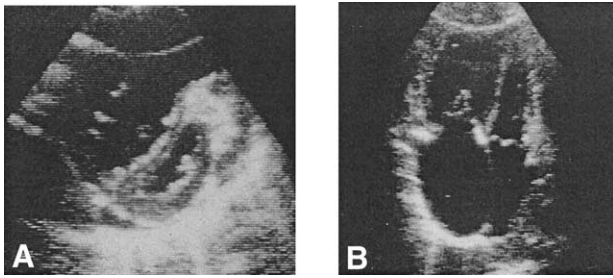


Figure 3. Echocardiogram: (A) Short axis view demonstrating right ventricular enlargement and flattening of the interventricular septum. (B) Four-chamber view demonstrating marked right atrial and right ventricular enlargement. The left heart chambers are small.

quired. Verapamil should be avoided due to its negative inotropic effects. Because of the dramatic impact that this therapy has had on patients who respond, most patients with PPH should be considered for acute vasodilator testing to determine if calcium-channel blockers would be warranted. Calcium-channel blockers must be used with great caution. Some patients, such as those who are clinically unstable, should not be challenged. Calcium-channel blockers should almost always be instituted with invasive hemodynamic guidance. An increase in right atrial pressure and/or decline in cardiac output warrants discontinuation of therapy. When used without the benefit of hemodynamic monitoring, calcium-channel blockers may worsen right ventricular failure resulting in premature death. Patients who respond should receive long-term treatment with an appropriate dose of calcium-channel blockers, but still require careful follow up to monitor both the safety and

efficacy of treatment. Patients who initially tolerate calcium-channel blockers but subsequently deteriorate should have them discontinued.

Prostacyclins

Prostacyclin is a metabolite of arachidonic acid that is produced primarily in the vascular endothelium. Patients with PPH have a reduction in prostacyclin synthase. The major pharmacologic actions of prostacyclin include potent vasodilatation of the pulmonary and systemic arterial and venous beds and inhibition of platelet aggregation. Intravenous prostacyclin (epoprostenol, Flolan [GlaxoSmithKline, Research Triangle Park, NC]) is currently commercially available. Prostacyclin analogues that are under investigation include the subcutaneous analogue treprostinil, the oral analogue Beraprost (United Therapeutics, Silver Spring, MD), and the inhaled analogue Iloprost (Schering AG, Berlin, Germany).

Intravenous Prostacyclin

Flolan (GlaxoSmithKline) was the first FDA-approved therapy for PPH. In 1996, Barst et al. reported the results of a prospective randomized, multicenter, open trial comparing the effects of continuous intravenous epoprostenol plus conventional therapy with that of conventional therapy alone in 81 patients with New York Heart Association Functional Class III or IV PPH. The primary end point of distance walked in 6 minutes improved in the 41 patients treated with epoprostenol (from 315 meters at baseline to 362 meters at 12 weeks) while it decreased in the 40 patients treated with conventional therapy alone (270 meters at baseline compared to 204 meters at 12 weeks). There were also improvements in hemodynamic parameters. Mean changes in pulmonary vascular resistance in the epoprostenol and control groups were -21% and $+9\%$, respectively ($p > 0.001$). There was also a significant difference in survival as eight patients died during the study, all of whom had been randomly assigned to the conventional therapy group. ($p = 0.003$) Shortly thereafter, intravenous epoprostenol (Flolan, GlaxoSmithKline) was approved by the FDA for use in patients with Functional Class III or IV PPH. We then reported our long-term results of epoprostenol therapy in 27 patients with PPH over a period of 16.7 months. Twenty-six patients had improvement in symptoms and hemodynamic parameters. The mean pulmonary artery pressure decreased by 20% and the pulmonary vascular resistance decreased by 53% compared to baseline. In addition, the long-term effects of epoprostenol exceeded the acute pulmonary vasodilator response achieved in all but one patient. Importantly, even patients with little or no response to acute vasodilator testing at the time of cardiac catheterization experienced a substantial reduction in pulmonary vascular resistance after long-term therapy with epoprostenol. Shapiro et al. demonstrated improved survival in patients treated with epoprostenol. The 1-, 2- and 3-year survival rates in their patients were 80%, 76% and

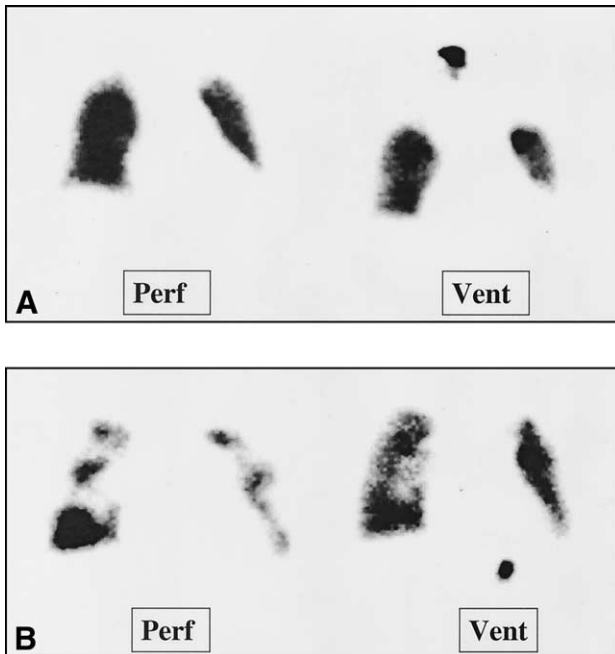


Figure 4. Ventilation perfusion scans: (A) Primary pulmonary hypertension and (B) Chronic thromboembolic disease. Note the large unmatched perfusion defects.

49%, respectively, which was superior to historical control subjects.

Intravenous epoprostenol has also been evaluated for treatment of PAH related to the scleroderma spectrum of diseases. In a randomized open label controlled trial at 17 pulmonary hypertension referral centers in the United States, 111 patients with moderate-to-severe PAH due to the scleroderma spectrum of diseases were randomized to receive epoprostenol plus conventional therapy or conventional therapy alone. The primary end point of exercise capacity as determined by distance walked in 6 minutes improved from 270 meters at baseline to 316 meters at 12 weeks in the group treated with epoprostenol but decreased from 240 meters to 192 meters in the group treated with placebo ($p < 0.001$). There was a reduction in mean pulmonary artery pressure and pulmonary vascular resistance and an increase in cardiac index in patients treated with IV epoprostenol. This study did not demonstrate a survival improvement.

Epoprostenol is administered through a permanent intravenous catheter and delivered by an ambulatory infusion system. The delivery system is complex and requires the patients to learn the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump and care of the permanent intravenous catheter. Side effects related to epoprostenol therapy are common and include headache, flushing, nausea, diarrhea and an unusual type of jaw discomfort, which occurs with the first bite or two of a meal. Other chronic side effects include thrombocytopenia, weight loss, foot pain, gastropathy and ascites. In most patients, the symptoms are minimal and well tolerated. Other complications related to epoprostenol therapy include infection of the central venous catheter and interruptions of therapy. The expected local central line infection rate is in the range of 0.22–0.68 per patient per year and that of bacteremia is 0.39 per patient per year. Even a brief interruption in therapy can result in rebound pulmonary hypertension and has been fatal in some instances. Epoprostenol is very expensive. In the United States the average cost is \$60,000 per year.

Dosing of epoprostenol is problematic. Early on it was noted that tolerance to the beneficial effects of epoprostenol seemed to occur. This led to the practice of clinicians progressively increasing the dose in anticipation of symptoms. In 1999, we made the observation that patients treated with chronic epoprostenol therapy may suffer adverse effects related to high cardiac output states. We studied 12 patients on chronic epoprostenol therapy with intolerable side effects and high cardiac output. All patients underwent successful reduction in the dose of epoprostenol (mean dose reduction 39%) without a change in pulmonary artery pressure. Although the cardiac output went down to the normal range, all patients retained their clinical benefit without a return intolerance of the drug. Importantly, patients had less side effects related to epoprostenol.

Prostacyclin Analogues

Because of the complexity with delivery of intravenous epoprostenol, the associated infections and other potentially severe adverse events, an alternative mode of delivery is desirable. Clinical studies have suggested that subcutaneously delivered treprostinil (Remodulin, United Therapeutics) may also be efficacious in the treatment of PAH. A parallel placebo-controlled 12-week trial in 470 patients with PAH demonstrated improvements in 6-minute walk distance, symptoms and hemodynamics in patients treated with treprostinil vs. those treated with placebo. There was a significant improvement in the primary end point of 6-minute walk distance of 17 meters. Importantly, improvements in 6-minute walk distance were related to the dose of treprostinil. The group in the highest quartile of dose (13.8 ng/kg/min) had a 35-meter improvement in 6-minute walk distance. Most patients experience pain and/or erythema at the site of the subcutaneous infusion. In some patients this can be severe and limit dose escalation. Numerous remedies have been used in an attempt to control this infusion site reaction but none has been uniformly successful. Current recommendations include local therapies such as warm and cold packs and non-steroidal anti-inflammatory agents. An Advisory Panel for the FDA has recently recommended that the agency approve treprostinil. A final FDA decision should be available soon.

Beraprost is an orally active epoprostenol analogue that has been used primarily in Japan for the treatment of PPH. A retrospective analysis compared survival in 24 patients treated with oral Beraprost vs. 34 patients treated with conventional therapy. Kaplan-Meier survival curves demonstrated that the 1-, 2- and 3-year survival rates for the Beraprost group were 96%, 86% and 76%, respectively as compared to 77%, 47% and 44% in the group receiving conventional therapy (log-rank test, $p < 0.05$). A European trial evaluating Beraprost has recently concluded and results should be available soon. The results of a trial evaluating Beraprost in the United States should be available in mid-2002.

Inhaled Iloprost has been studied in Europe. One uncontrolled long-term observational study demonstrated an improvement in cardiopulmonary hemodynamics and exercise capacity with aerosolized Iloprost. The cumbersome nature of this treatment, which requires inhalation approximately 9 times per day, may limit the practicality of its use.

Endothelin Receptor Antagonists

Endothelin-1 is a potent vasoconstrictor and smooth muscle mitogen. It likely contributes to the increase in pulmonary vascular tone in patients with PAH. Plasma endothelin-1 levels are elevated in patients with PPH and these levels correlate inversely with prognosis. Recently, the oral endothelin antagonists have been investigated in the setting of PAH. The first placebo-controlled study with the dual endothelin receptor antagonist Bosentan (Tracleer, Acte-

lion, Allschwil, Switzerland Inc., Mississauga, Ontario, Canada) in 32 patients with PPH or PAH related to the scleroderma spectrum of disease demonstrated an improvement in exercise tolerance and hemodynamics. The difference between groups in mean change at week 12 in 6 minute walk distance was 76 meters in favor of Bosentan (Actelion) ($p=0.021$). There were also significant improvements in cardiac index and pulmonary vascular resistance. An international multicenter, randomized double-blind placebo-controlled study was recently conducted at 27 centers in Europe, North America, Israel and Australia to evaluate the efficacy of Bosentan (Actelion) vs. placebo on exercise capacity in patients with PAH. Two hundred thirteen patients were enrolled in the 16-week trial. Patients treated with Bosentan (Actelion) experienced a significant improvement in 6-minute walk distance of 36 meters as compared to a small reduction of 8 meters in patients treated with placebo resulting in a mean treatment effect of 44 meters in favor of Bosentan (Actelion) ($p=0.0002$). The most concerning adverse effect associated with Bosentan (Actelion) is increased incidence of abnormal liver function tests. Patients treated with this drug should undergo liver function monitoring regularly. Recommendations to either reduce the dose or discontinue the drug are based on the degree of transaminase elevations. Hemoglobin must also be followed as there is a small incidence of anemia associated with Bosentan (Actelion). It should not be used during pregnancy, and because of drug interactions, it should not be used with cyclosporin A or glyburide. It may be used in combination with calcium-channel blockers. An ongoing clinical trial is evaluating the safety and efficacy of the combination of Bosentan (Actelion) and epoprostenol. It should soon be commercially available in the U.S.

Surgical Treatment of PPH

Lung transplantation has been performed successfully in patients with PPH for more than a decade. Because these patients have severe right ventricular dysfunction, it was originally believed that heart lung transplantation was the only transplantation option. More recently, bilateral lung transplantation and single lung transplantation have been performed successfully in patients with PPH. The immediate reduction in pulmonary artery pressure and pulmonary vascular resistance is associated with an improvement in right ventricular function. Bilateral lung transplantation is preferred at most centers because there is greater pulmonary vascular reserve should the patient sustain a rejection or infection. Single lung transplantation may be preferred in some situations because the operation is technically less challenging and the wait time is shorter. As with any type of

organ transplantation, the major long-term morbidity and mortality is related to the high incidence of rejection and opportunistic infections. In addition, lung transplantation carries a high risk of the development of bronchiolitis obliterans. In the era of epoprostenol, lung transplantation should be considered a treatment of last resort for PPH. However, due to the long wait time for lung transplantation at most institutions, it is prudent to evaluate and list a patient for transplantation at the time of diagnosis. If the patient responds well to medical therapy, they may go "inactive" on the transplantation list.

Conclusion

PAH is a complicated and progressive disease. Early diagnosis remains a major challenge. A small number of patients may respond to oral calcium-channel blockers and most patients respond well to intravenous epoprostenol. The oral endothelin receptor antagonist Bosentan will soon become a mainstay of therapy. Transplantation is indicated for patients with advanced disease and for those with a suboptimal response to medical therapy. Because of the complicated nature of this disease and its treatment, referral to a specialized pulmonary hypertension center is warranted.

Suggested Reading

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