# Diagnosis and treatment of pulmonary arterial hypertension

Richard Channick, MD[a],*, Timothy L. Williamson, MD[b]

[a]Division of Pulmonary and Critical Care, University of California, San Diego, 9300 Campus Point Drive,
La Jolla, CA 92037, USA
[b]Division of Pulmonary and Critical Medicine Care Medicine, University of Kansas Hospital,
3901 Rainbow Boulevard, Kansas City, KS 66160, USA

Pulmonary arterial hypertension (PAH) is characterized by an elevated pulmonary vascular resistance (PVR) that, in the absence of intervention, progresses to right ventricular failure and death. When defined clinically as a mean pulmonary artery pressure greater than or equal to 25 mm Hg at rest or 30 mm Hg with exercise, idiopathic PAH has been estimated to affect at least 1 to 2 persons per million population [1], although secondary forms of the disease are much more common.

The World Health Organization (WHO) classification of pulmonary hypertension (PH) is reviewed in detail in the article by McLaughlin et al. This classification is based on expert consensus opinion reached at the WHO Symposium on Pulmonary Hypertension in Evian, France in 1998. It divides PH into five categories, including PAH, pulmonary venous hypertension, PH associated with respiratory diseases, PH associated with embolic disease, and PH caused by diseases that directly affect the pulmonary vasculature, such as sarcoidosis. Experts recently convened again in Venice, Italy in 2003 [1]. Among the modifications from the Venice meeting is that pulmonary hypertension without a known association or cause is no longer referred to as primary pulmonary hypertension (PPH), but instead as idiopathic (sporadic) PAH (IPAH) with a separate category for familial PAH (FPAH). Because of the body of literature

that has employed the term PPH, this article uses both terms interchangeably. In addition to IPAH, PAH can occur in association with other conditions such as connective tissue disease, congenital heart disease, portal hypertension, HIV, and prior ingestion of stimulant drugs such as fenfluramines, amphetamines, or cocaine. Of the various categories, only PAH is discussed in this article. The evaluation of pulmonary hypertension, however, should ascertain its proper cause and classification, because many of the treatment options for PAH discussed here are not necessarily efficacious and may be deleterious in patients with pulmonary hypertension secondary to other disorders.

Although long considered a disease of pulmonary vasoconstriction, PAH should now more correctly be considered a disease of proliferation. Voelkel and Cool further review the pathology of this disorder elsewhere in this issue. Briefly, PAH is characterized by increased pulmonary arterial thickness, dilated capillaries, and plexiform lesions that obstruct the vessel lumen [2]. Additionally, patients are at risk for in situ thrombosis secondary to increased platelet aggregation as a consequence of decreased nitric oxide and prostacyclin production [3].

Survival in PAH without intervention is dismal. A National Institutes of Health registry followed patients with PPH (idiopathic PAH) between 1985 and 1988, in an era that preceded currently available therapeutic agents [4]. Survival rates at 1, 3, and 5 years were 68%, 48% and 34%, respectively, with a median survival from diagnosis of 2.8 years.

* Corresponding author.
*E-mail address:* rchannick@ucsd.edu (R. Channick).

Findings correlated with poorer prognosis included WHO functional class III or class IV (Box 1), presence of Raynaud's phenomenon, increased right atrial pressure, increased pulmonary artery pressure, decreased cardiac index, and decreased diffusion [4]. In another study multivariate analysis suggested pericardial effusion, enlarged right atrium, 6-minute walk distance, and mixed venous oxygen saturation as predictors of adverse outcomes [5]. Not all causes of PAH portend the same survival. Patients with PAH associated with the scleroderma spectrum of diseases, for example, have a worse prognosis than those with idiopathic PAH (PPH) [6]. Pulmonary veno-occlusive disease is associated with perhaps the worst survival, with 1-year mortality following diagnosis exceeding 70% [7].

### Diagnosis

The diagnosis of PAH requires a high index of suspicion, because presenting symptoms are often protean and common to a multitude of cardiopulmonary disorders. The goals of the PAH evaluation are severalfold: to establish the correct cause of dyspnea, to exclude treatable causes of PAH, to document the presence and severity of pulmonary hypertension and right ventricular dysfunction, to recognize the extent of functional impairment, and to use this information to help formulate a therapeutic regimen. The tools for accomplishing these tasks are largely those used daily by physicians to quantify and qualify other cardiopulmonary disorders, namely clinical findings, lung function testing, radiographic studies, echocardiograms, heart catheterization, and exercise testing. During the diagnostic process special attention should be paid to excluding chronic thromboembolic disease, because a potentially corrective surgical procedure exists for this disorder [8,9].

The symptoms of PAH are nonspecific. Dyspnea is nearly universal as the disease progresses, but fatigue, chest pain, syncope, and near syncope are also common [10]. Given the vague nature of symptoms, it is not surprising that the time from symptom onset to definitive diagnosis averages 2 or more years [10].

The cardinal findings on physical examination in PAH are an accentuated second heart sound and a tricuspid regurgitation murmur, but both findings may be variably present. As pulmonary hypertension progresses, signs of right-heart failure may ensue as evidenced by jugular venous distention, a right ventricular heave, lower extremity edema, hepatomegaly, and ascites. During the physical examination particular attention should also be paid to findings suggestive of diseases known to be associated with PAH, such as collagen vascular disorders and chronic liver disease, because prognosis and treatment may vary by underlying cause. Additionally, the presence or absence of pulmonary flow murmurs should be noted, because these murmurs are highly suggestive of chronic thromboembolic disease, pulmonary vasculitis, or pulmonic stenosis, and have not been reported in PAH from other causes [9].

Pulmonary function tests are often obtained during the course of an evaluation of dyspnea but have no findings specific for PAH. Diffusion is often only modestly decreased (69 $\pm$ 25) [10]; more severe diffusion defects may indicate concurrent parenchymal disease. A pattern of mild

---

**Box 1. World Health Organization functional class in pulmonary artery hypertension**

Class I: Patients in with pulmonary hypertension, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. Patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. Patients are comfortable at rest, but less than ordinary physical activity cause undue dyspnea or fatigue, chest pain, or near syncope.

Class IV: Patients with pulmonary hypertension resulting in inability to perform any physical activity without symptoms. Patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

obstructive lung disease has been described in severe PAH [11].

Radiographic studies may be most useful to exclude competing explanations for dyspnea and, if PAH is present, to aid in excluding secondary causes. Chest radiographs may suggest interstitial or obstructive lung disease and demonstrate enlarged pulmonary arteries or cardiomegaly.

CT scans may likewise exhibit enlarged pulmonary arteries and parenchymal lung disease but may also help detect chronic thromboembolic pulmonary hypertension, pulmonary veno-occlusive disease, pulmonary vascular tumors, or extrinsic compression of the pulmonary vessels.

Lung perfusion scanning has a pivotal role in the evaluation of PAH, because it may reveal segmental and subsegmental defects consistent with chronic thromboembolic disease, prompting further evaluation by pulmonary angiography. High-probability perfusion scans, although highly suggestive of possible chronic thromboembolic disease, have also been reported in pulmonary veno-occlusive disease [12]. In contrast, lung perfusion scans in PAH are either normal or demonstrate a diffuse, mottled appearance.

### Echocardiography

Echocardiography is a relatively inexpensive, noninvasive tool for estimating pulmonary artery pressures and detailing cardiovascular anatomy and function. In addition to providing an estimation of peak pulmonary artery pressure, echocardiography may provide useful assessments of chamber and valve morphology, presence of congenital heart disease, left ventricular systolic and diastolic function, and intracardiac or intrapulmonary shunting [13]. Pericardial effusions are common (present in more than half of patients with severe PAH), and although they often are not hemodynamically significant, they may carry prognostic significance, with an association with right-heart failure, impaired exercise tolerance, and a poor 1-year survival [14]. Typical findings in severe PAH may include tricuspid regurgitation, right ventricular or atrial enlargement, and elevated pulmonary artery pressures. Several studies, however, have shown that the accuracy of echocardiography is limited when compared with direct measurement of pulmonary artery pressure by right-heart catheterization. Arcasoy and colleagues [15] examined 374 lung transplant candidates who underwent both procedures. Estimation of systolic pulmonary artery pressures by

echocardiography was possible in only 44% of the patients, with a correlation coefficient of 0.69. In 52% of patients studied, the differences between measurements on right-heart catheterization and echocardiography were greater than 10 mm Hg, and 48% of patients classified as having pulmonary hypertension on echocardiography were found to be misclassified after right-heart catheterization. Similarly, Cotton et al [16] looked at 78 liver transplant candidates. Systolic pulmonary artery pressures were significantly higher when measured by echocardiography than when measured by right-heart catheterization, with a correlation coefficient of only 0.46, and a positive predictive value of 37.5%. Negative predictive value, however, was nearly 92%. Daniels et al present a full discussion of echocardiography in pulmonary vascular disease elsewhere in this issue.

### Right-heart catheterization

Given its limitations, echocardiography should not be used to diagnose PAH definitively. Right-heart catheterization remains the standard for determining pulmonary artery pressures and should always be performed before initiation of costly or invasive therapy. In addition to direct quantification of pulmonary hemodynamics (which are correlated with prognosis [4]), right-heart catheterization may help exclude congenital heart disease, establish the presence and contribution of left-sided heart disease, and quantify vasodilator reserve (discussed further in the section on calcium-channel blockers). The details of the right-heart catheterization procedure are discussed elsewhere in this issue.

### Functional assessment

Functional impairment in PAH may be identified subjectively or objectively. Subjectively, the WHO functional classification detailed in Box 1 categorizes patients by reported exercise tolerance. Although this classification system is not perfect, most PAH practitioners are familiar with its application, and it is widely used in research and therapeutic algorithms. Cardiopulmonary exercise testing provides an objective assessment of functional status correlates closely with mortality: a peak $Vo_{2max}$ less than 10.4 mL/kg/min independently predicts decreased survival [17]. Cardiopulmonary exercise testing, however, is expensive, time consuming, difficult to perform for many patients with advanced disease, and not universally available. For these reasons submaximal

exercise testing to determine functional status is desirable. The 6-minute walk has been used as a reliable, well-validated examination in assessing exercise capacity. Simply, patients walk a premeasured course, at their own pace and without encouragement or direction from technicians, and the distance walked is measured. The 6-minute walk distance has been shown to be correlated with survival, with a distance less than 332 m associated with increased mortality [18]. The test is inexpensive, widely available, not overly burdensome to patients or providers, and reproducible. Six-minute walk testing has often served as the primary outcome endpoint in clinical trials of new therapies for PAH.

## Treatment

In the past 2 decades an exponential growth of interest and research in PAH has engendered several therapeutic options that were not available as recently as 5 years ago. The ideal goals of treatment are to improve symptoms and survival using the least invasive therapies possible. Given the expanding therapeutic options in PAH, it is important to understand which patients are appropriate for which therapy. Used inappropriately, many of the available PAH therapies have the potential for adversely affecting patient outcome, so the dictum of *primum non nocere* must be paramount. For example, using PAH medications in patients with even modest degrees of left ventricular systolic or diastolic dysfunction can worsen clinical status. It is recommended that right-heart catheterization be performed before initiating therapy with most agents specific for the treatment of PAH, because right-heart catheterization is a powerful resource to determine contributions of left-sided heart disease and also provides indirect evidence of right ventricular compensation, knowledge that is useful in selecting the appropriate therapeutic regimen. Patients with WHO functional class III and class IV symptoms should be considered for referral to a center with specific focus and expertise in the management of pulmonary vascular disorders.

### General treatments

### Lifestyle modification

Treatment should be directed toward both pharmacologic interventions and lifestyle modification, with avoidance of behaviors that might increase morbidity or mortality. This disease often afflicts women of childbearing age, and these patients should be strongly counseled to avoid pregnancy, because the mortality in patients with PAH who become pregnant has been reported to be as high as 30% to 56% [19,20]. Patients are often concerned about the level of activity that they are allowed to undertake. In general, patients should be encouraged to stay active to prevent deconditioning but cautioned to not overexert themselves to the point of severe dyspnea, chest pain, or syncope. Given the adverse effect of altitude on the pulmonary vasculature, patients with PAH should avoid altitudes higher than approximately 4000 feet.

### Supportive therapies

Despite limited evidence of their value, a number of nonspecific supportive therapies are frequently used in PAH, especially as right-heart failure ensues. The decision to initiate any of these treatments must be made on an individualized basis.

*Oxygen.* Hypoxemia should be recognized and treated, both at rest and with exercise. When given acutely, 100% oxygen has been demonstrated to reduce mean pulmonary artery pressure and PVR modestly and to increase the cardiac index [21]. Few data exist regarding the long-term benefits of oxygen in this disorder, but extrapolating the positive effect of oxygen therapy on survival in patients with chronic obstructive pulmonary disorder [22], it seems reasonable that hypoxemia should be recognized and treated at rest and with exercise. Additionally, nocturnal oxygen desaturation is common in PAH [23], even in the absence of concurrent sleep-disordered breathing, and adequate oxygenation at night should be assured as well.

*Wafarin.* Warfarin therapy is standard in patients with IPAH (PPH) and is often recommended in other forms of PAH based on two retrospective studies demonstrating a modest survival benefit. PAH may be complicated by in situ thrombosis, and low-level anticoagulation with warfarin is often used in an effort to help prevent this process. Two studies have established a beneficial effect on mortality [24,25]; one of these studies also exhibited improvement in quality-of-life indices [24]. Patients with chronic indwelling intravenous catheters and right-to-left intracardiac shunting may

be especially strong candidates for chronic anti-coagulation.

*Digoxin.* Digoxin is often added to the regimen of patients with right-heart failure. In 17 patients examined in the catheterization laboratory, digoxin was shown to improve cardiac output somewhat and to decrease norepinephrine levels [26]. Long-term data on its efficacy in PAH are lacking, however.

*Diuretics.* Diuretics are also commonly used in PAH to decrease intravascular volume and to improve dyspnea. It is postulated that improvements in right ventricular geometry may decrease septal intrusion into the left ventricle, improving left-ventricular function as well.

### Specific therapies

In properly selected patients the therapies discussed here have been shown to modify the course of PAH significantly and to improve symptoms, hemodynamics, and survival.

#### Calcium-channel blockade

Acute vasodilator challenge testing during right-heart catheterization may identify the small percentage of patients with PAH who have disease characterized primarily by vasoconstriction. Appropriate testing agents include inhaled nitric oxide, adenosine, and prostacyclin. The definition of a vasodilator responder has varied, but using a definition of a decrease in PVR of greater than 20%, Rich and colleagues [25] found 26% of patients to be responders. These patients were treated for up to 5 years with high doses of calcium-channel blockers (nifedipine with an average daily dose of 172 mg and diltiazem with an average daily dose of 720 mg). At 5 years 94% of responding patients were alive, compared with 55% of patients who were not responders. A recent retrospective study by Sitbon et al [27] suggests that only half of acute vasodilator responders will benefit long term. In this study only 6% of all patients did well functionally when treated with calcium-channel blockers alone. These patients were those who achieved nearly normal pulmonary arterial pressures (mean, <37 mm Hg) and PVR (<5 Wood units) with adequate cardiac output during the vasodilator test. Similarly, Raffy et al [28] examined 91 consecutive patients undergoing vasodilator challenge with epoprostenol. Patients were classified by the magnitude of their response in depression of total pulmonary resistance: those with a depression of less than 20% were categorized as nonresponding, those with a depression of 20% to 50% as moderately responding, and those with a depression above 50% as highly responding. Two-year survival rates for these groups were 38%, 47%, and 62%, respectively ($P < 0.05$).

Use of calcium-channel blockers for PAH should be reserved for the small subset of patients who exhibit near normalization of pulmonary artery pressures during vasodilator challenge with a preserved cardiac output. Long-term clinical response should be closely monitored, and treatment should be escalated if deterioration occurs. It thus seems that calcium-channel blockers are rarely beneficial and should be used only in patients with a significant acute vasodilator response and never in nonresponders. Calcium-channel blockers with significant negative inotropic effect, such as verapamil, should be avoided. Treatment with calcium-channel blockade should be avoided in patients who do not respond at vasodilator challenge, because serious adverse events have been reported in these patients [29]. Systemic hypotension in the setting of a fixed right ventricular cardiac output may lead to decreased right coronary perfusion, with potential to cause syncope, chest pain, or even death.

#### Treatment sequence

Currently, the WHO functional class of patients largely guides therapy. Supportive therapy is used as indicated. In patients with functional class I and class II symptoms, specific therapy is not indicated, because the cost and risk of therapy in these patients has not been justified. Patients who are WHO functional class III should be considered for oral therapy, and patients whose disease progresses on oral therapy and patients with advanced class IV symptoms should be considered for intervention with prostacyclin. Unfortunately, cost and insurance coverage can also influence the selection of available agents: the cost of bosentan therapy can exceed US $25,000 per year, and the costs of epoprostenol and treprostinil therapy can each exceed US $100,000 per year. Although interest is growing in testing combination therapy, limited data are currently available.

#### Endothelin receptor antagonists

Endothelin is a smooth muscle mitogen and vasoconstrictive agent. Its production is increased in pulmonary hypertension [30] and is strongly

correlated with pulmonary hemodynamics and 6-minute walk data [31]. Effects are mediated through endothelin-A and endothelin-B receptors that are variably distributed throughout the lung. Both receptors may contribute to pulmonary artery smooth muscle cell proliferation and vascular remodeling [32]. Blockade of these receptors has generated significant interest as a therapeutic target.

Bosentan (Tracleer) is a nonselective endothelin receptor antagonist that has proven efficacy in two double-blinded, multicenter, placebo-controlled trials. It is currently the only oral medication approved in the United States for PAH. In a pilot study, Channick and colleagues [33] randomly assigned 32 patients with idiopathic PAH or PAH associated with the scleroderma spectrum of disease to treatment with bosentan (62.5 mg twice daily for 1 month followed by 125 mg twice daily) or placebo in a study lasting 12 weeks. Six-minute walk distance improved by 70 m in the treatment group but declined by 6 m in the placebo group. Cardiac index improved, and PVR decreased, with associated improvements in Borg Dyspnea Index scores and functional class. Three patients in the placebo group withdrew from the study because of worsening clinical status. A larger follow-up study (BREATHE-1, the Bosentan Randomized Trial of Endothelin Antagonist Therapy) enrolled 213 WHO functional class III or class IV patients with idiopathic PAH or PAH associated with connective tissue disease and followed them for 16 weeks [34]. Six-minute walk distances again improved, as did Borg Dyspnea Index scores and WHO functional class. Although the preliminary study exhibited adverse events that did not differ from placebo [33], BREATHE-1 found that some patients suffered a significant elevation of hepatic transaminases [34]. These elevations resolved in all patients with dose reduction or discontinuation of bosentan, but the finding reflects the need for at least monthly monitoring of liver function tests in patients who receive this drug.

When bosentan was introduced as a treatment for PAH, there was concern that delaying therapy with prostacyclin would adversely affect survival. Recent survival data with bosentan offer some reassurance that this is not the case. McLaughlin and colleagues [35] reported long-term follow-up of 169 patients with PPH who had been enrolled in the initial bosentan trials. Observed survival was compared with predicted survival using an equation based on initial NIH registry data encompassing variables such as cardiac index, mean pulmonary artery pressure, and mean right atrial pressure. Actual survival in patients receiving bosentan at 1, 2, and 3 years was 96%, 89% and 86%, respectively, compared with predicted survivals of 69%, 57%, and 48%, respectively, at the same time intervals.

Bosentan (Actelion Pharmaceuticals Ltd., Allschwil, Switzerland, 2003) is a class X drug in pregnancy, because animal studies have identified it as a teratogen. Female patients of childbearing age should be tested for pregnancy before starting treatment with bosentan and should use two forms of contraception, including a barrier method, because bosentan may affect the efficacy of oral contraceptive. Patients taking bosentan should not receive concurrent glyburide because an increased risk for elevations in transaminases has been associated with this combination, and they should not receive concurrent cyclosporine because markedly elevated bosentan levels have been reported with coadministration of both drugs.

The Food and Drug Administration (FDA) approved bosentan for use in WHO functional class III or class IV patients. Efficacy of this drug may not be seen for 2 to 3 months after initiation of therapy, and it should not be used as sole therapy for patients with advanced class IV disease who need a more immediate response. Bosetan is, however, the only currently approved oral therapy for PAH and should be considered first-line therapy for patients with WHO functional class III symptoms.

*Prostacyclins*

Prostacyclin (PG$_{I2}$) is produced by the vascular endothelium and has important vasodilatory, antiplatelet aggregation, and antiproliferative effects. The production of prostacyclin synthase, the enzyme necessary for prostacyclin synthesis, is decreased in patients with PAH [3], as is the excretion of stable metabolites of PG$_{I2}$ [36].

Replacement of prostacyclin, therefore, is a reasonable therapeutic option from a pathophysiologic standpoint. The agent with which there is the most experience is epoprostenol (Flolan). Epoprostenol is a synthetic salt of prostacyclin that has an extremely short half-life, 3 to 5 minuets, on average. Because of its short half-life, it must be given by continuous infusion through an indwelling venous catheter. In addition to the previously mentioned effects of endogenous prostacyclin, chronic epoprostenol administration also improves right ventricular function and geometry

[37] and improves the net balance between pulmonary endothelin-1 clearance and release [38].

Epoprostenol has been investigated in a variety of patient populations. In 81 patients with idiopathic PAH (PPH) and WHO functional class III and class IV symptoms followed for a 12-week period, epoprostenol improved 6-minute walk distances from 315 to 362 m, whereas patients in the control group deteriorated from 270 to 204 m over the study period [39]. Quality-of-life indices were improved, as were pulmonary hemodynamics, albeit modestly. There were eight deaths, all in the placebo group.

The response to epoprostenol of patients with PAH associated with the scleroderma spectrum of disease has also been examined in a randomized, controlled fashion in 111 patients, also over a 12-week period [40]. Exercise capacity, dyspnea scores, and functional class improved in the treatment group. There was no demonstrated difference in survival, although the study was not powered to do so.

A recent Cochrane review synthesized the results of seven randomized, controlled trials using intravenous prostacyclin or one of its analogues and found that over a 12-week period prostaglandins seem to improve exercise capacity, functional class, and several cardiopulmonary hemodynamic variables [41]. In addition to these beneficial effects, epoprostenol has been shown to affect survival positively in studies involving both adults and children [42–44].

Epoprostenol, however, has a number of unfavorable characteristics that limit more widespread applicability. Its short half-life requires continuous intravenous administration, necessitating indwelling central venous access and the associated risks of catheter-related sepsis, cellulitis, thrombosis, pneumothorax, catheter dislodgement, and hemorrhage [39,40]. Additionally, adverse effects related to the drug itself are common and include jaw pain, diarrhea, flushing, headaches, nausea, vomiting, and anorexia [39,40]. Caution should be exercised when considering epoprostenol administration for subsets of PAH patients who have a significant fixed downstream obstruction such as pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis. Case reports in both disorders report pulmonary edema that complicates epoprostenol delivery [45,46].

Despite its significant drawbacks, epoprostenol is potentially life saving and is among the quickest acting of agents currently available. In the treatment algorithm described later, it is reserved for WHO functional class IV patients and (rarely) for WHO functional class III patients who are not candidates for less-invasive therapy.

Because the instability of epoprostenol requires placement of an indwelling catheter for continuous infusion, with the subsequent risk of complications, there is much interest in providing prostacyclin therapy through alternate mechanisms of delivery. Treprostinil (Remodulin) is a prostaglandin analogue that is stable at room temperature (unlike epoprostenol, which must be kept cool) and has a much longer half-life than epoprostenol that permits subcutaneous administration of this drug. Treprostinil is delivered by continuous subcutaneous infusion in a manner similar to continuous insulin administration. The delivery pump is roughly the size of a pager and can be worn inconspicuously by the patient.

Two studies have demonstrated the safety and efficacy of treprostinil. Initial pilot studies compared intravenous treprostinil with intravenous epoprostenol, subcutaneous treprostinil with intravenous treprostinil, and subcutaneous treprostinil with placebo [47]. Intravenous treprostinil, subcutaneous treprostinil, and epoprostenol produced similar reductions in PVR (approximately 20%). When compared with placebo, subcutaneous treprostinil produced statistically significant improvement in 6-minute walk distance (increase of $37 \pm 17$ m versus a decline of $6 \pm 28$ m in the placebo arm) and trends toward improved cardiac index and reduced PVR.

A larger multicenter, randomized trial focused on 470 patients with idiopathic PAH, PAH associated with connective tissue disease, and PAH associated with congenital systemic to pulmonary shunts [48]. Patients with WHO class II, class III, or class IV symptoms were enrolled. After 12 weeks there was a 16-m difference in median 6-minute walk distances between treatment and placebo groups, and dyspnea indices improved in treated patients. Eighty-five percent of patients, however, reported significant pain at the infusion site, and 8% of patients withdrew from the study because of pain. Other typical adverse effects common to prostacyclin analogues, such as diarrhea, jaw pain, flushing, and lower extremity pain, were also reported.

In the United States, the FDA has approved treprostinil for patients with PAH characterized by WHO class II, class III, and class IV symptoms. Improvements in 6-minute walk distances, however, do not reach the magnitude demonstrated by

eoprostenol, and to the authors' knowledge, no significant improvement in mortality has been demonstrated with treprostinil. Site pain is a significant problem for patients receiving this drug and limits its utility in the management of PAH. Although approved for most classes of symptoms, treprostinil should primarily be reserved for patients with class IV symptoms who are not candidates for continuous intravenous infusion of epoprostenol and for patients with class III symptoms for whom treatment with currently available oral therapies is not appropriate.

Two other prostacyclin analogues have been investigated and used outside the United States, but neither is currently available in the United States. Iloprost is a nebulized prostaglandin with demonstrated beneficial effects on functional class, 6-minute walk distance, and hemodynamics [49–51]. A mild cough, minor headache, jaw pain, and nausea were reported adverse effects in these studies. Because of its short half-life, iloprost must be administered six to nine times per day.

Beraprost is an oral prostacyclin analogue that is approved in Japan for PAH patients. The largest trial examined 130 WHO functional class II and class III patients and showed a difference in 6-minute walk distance of 25.1 m between treatment and placebo groups, improved Borg dyspnea index, and no change in hemodynamics or functional class [52]. Adverse effects included headache, flushing, jaw pain, diarrhea, leg pain, and nausea.

Table 1 summarizes the drugs used in treating PAH.

Experimental therapies

A number of therapies for PAH have shown promise in anecdotal case reports, small case series, or preliminary studies but have not yet been examined in a large-scale randomized trial and have not received FDA approval. Two endothelin receptor antagonists fall into this category. Sitaxsentan is an endothelin-A receptor antagonist investigated by Barst and colleagues [53] in a pilot study involving patients with idiopathic PAH or PAH associated with collagen vascular disease or congenital systemic to pulmonary shunts. Six-minute walk distances improved from $466 \pm 132$ m to $515 \pm 141$ m ($P = 0.006$), and there were modest improvements in mean positive airway pressure and PVR. There were, however, two cases of acute hepatitis, one of which was fatal. A larger, randomized trial is ongoing at this time. Other experimental endothelin antagonists, such as ambrisentan, are also in the preliminary phases of investigation.

Sildenafil (Viagra) is a phosphodiesterase-5 inhibitor that is gaining increasing attention for the treatment of pulmonary vascular disease. Sildenafil has potential vasodilatory properties mediated through cyclic GMP and cyclic AMP systems. Several small studies, short-term hemodynamic studies, and case reports have suggested beneficial results in pulmonary hypertension of various origins, with improvement in hemodynamics, exercise capacity, functional class, and dyspnea indices [54–58]. Sildenafil has also been used in combination with prostacyclins in small case series and in hemodynamic studies, also with encouraging results [59–61]. In a small open-label study, 16 patients with pulmonary fibrosis and pulmonary hypertension were randomly assigned to intravenous epoprostenol or sildenafil [62]. Both epoprostenol and sildenafil were found to reduce PVR, but epoprostenol in this setting

Table 1
Drugs used in treating pulmonary arterial hypertension

| Drug | Route | FDA Approval | Available in United States | Notes |
|---|---|---|---|---|
| Epoprostenol | Intravenous (continuous) | Yes—WHO class III/IV | Yes | Infection, catheter complications, rebound |
| Treprostinil | Subcutaneous (continuous) | Yes—WHO class II/III/IV | Yes | Infusion site pain |
| Iloprost | Inhaled (6–9 times/d) | No | No | Frequent inhalation |
| Beraprost | By mouth (4 times/d) | No | No | |
| Bosentan | By mouth (2 tunes/d) | Yes | Yes | Hepatic toxicity |
| Sitaxsentan | By mouth (1 time/d) | No | No | Experimental |
| Ambrisentan | By mouth (1 time/d) | No | No | Experimental |
| Sildenafil | By mouth (3 times/d) | Not for PAH | Yes | Off-label/experimental use |

*Abbreviations:* FDA, Food and Drug Administration; PAH, pulmonary arterial hypertension.

increased ventilation/perfusion mismatch and adversely affected arterial oxygenation. Sildenafil, in contrast, maintained ventilation/perfusion matching and raised arterial oxygenation. In original studies in patients with erectile dysfunction, the drug has been shown to be relatively safe, with headache, flushing, and dyspepsia the most commonly reported adverse effects [63]. Visual disturbances were also reported in this same series. Phase III trials are currently ongoing with sildenafil in the setting of PAH. For the time being, its use should be considered investigational.

A myriad of pathophysiologic defects in PAH are potential therapeutic targets, and it is conceivable that combination therapy acting on two or more targets could improve outcomes in this disease. Ongoing studies are scrutinizing this hypothesis.

A number of novel therapies have been suggested in PAH in animal models or small case reports. They include aerosolized adrenomedullin [64], oral dehydroepiandrosterone (DHEA) [65], simvastatin [66], and vasoactive intestinal peptide [67]. All are in the most preliminary stages of investigation and warrant further study before widespread clinical application.

*Surgical options in pulmonary hypertension*

Chronic thromboembolic pulmonary hypertension should be differentiated from pulmonary hypertension of other causes, because a potentially curative operative procedure exists for this entity. Chronic thromboembolic pulmonary hypertension and the surgery to treat it, namely pulmonary thromboendarterectomy, are beyond the scope of this article and are reviewed elsewhere in this issue.

Atrial septostomy was first described in 1983 [68] and is an option in patients with severe PAH who do not respond to maximal medical therapies. Sandoval and colleagues [69] reported their experiences with the procedure in a series of 15 such patients who underwent graded balloon dilation atrial septostomy. In the 14 patients who survived the procedure, right ventricular end diastolic procedure was immediately decreased, and cardiac output was improved, although at the expense of systemic oxygen desaturation secondary to the increased right to left shunting. Functional class and exercise capacity were improved as well. Atrial septostomy should be considered in patients with severe PAH and recurrent syncope or progressive right ventricular failure despite maximal medical therapy, as a bridge to transplantation if maximal medical therapy has failed, and as a palliative procedure when no other option exists [1]. It should be attempted only in institutions with experience in its use. Contraindications include patients with impending death, receiving maximal cardiopulmonary support, or with preprocedure systemic oxygen saturations of less than 90% [1].

PAH is a declining indication for lung and heart-lung transplantation compared with other indications for transplantation (constituting 4.5% of procedures over a 7-year period [70]), probably because of advances in the medical management of the disease. In the United States, most transplant centers perform bilateral single-lung transplantations for PAH, although a small percentage of centers perform single-lung transplantation for this disorder. Heart-lung transplantation is reserved for patients with PAH secondary to congenital systemic-to-pulmonary shunts that cannot be surgically corrected by isolated lung transplantation. Heart-lung transplantation in PAH is more frequently employed in Europe [70]. Early mortality is higher in patients with PAH than that in patients with other indications for transplantation, but overall survival approximates 83%, 73%, 57%, 45%, and 23% at 3 months, 1 year, 3 years, 5 years, and 10 years, respectively [70].

Timing of lung transplantation is problematic. There is currently, in the United States, no priority for severity of patient illness, and priority is strictly related to time accrued while waiting for transplantation. Wait times average approximately 17 months but can be 36 months or longer [71]. Heart-lung transplant lists may have even longer wait times. Therefore, if a physician waits to refer a patient with severe PAH until the patient is in extremis, it is unlikely that the patient will survive to transplantation. Although the decision to refer for lung transplantation must be individualized to each patient, in general consideration for referral should be given to the patient who has "symptomatic, progressive disease which, despite medical or surgical treatment, leaves the patient in NYHA III or NYHA IV" [72]. From a practical standpoint, because the clinical course of patients with PAH can be quite variable, the authors refer patients for lung transplant evaluation if medical management necessitates the initiation of intravenous or subcutaneous prostaglandin administration.

## Summary

The diagnosis of pulmonary hypertension requires a high index of suspicion and careful attention to assessing the severity and classification of disease. Proper evaluation and understanding of determinants of severity in PAH are necessary to guide appropriate therapy. There are now highly effective therapies for PAH that have meaningfully improved the outcome for patients, and it likely that that the future is even brighter, with development of combination regimens and additional therapies that attack specific targets within the pulmonary vasculature and right ventricle. Despite the increasing availability of oral therapies for PAH, consideration should be given to referral of patients with functional class III and IV symptoms to specialized PAH centers that may have additional experience in the timing and nature of escalation of therapy when needed. Referral also may help concentrate a fairly rare population of patients to facilitate research that, one hopes, may lead to continued advances in the management of this disease. Although survival remains limited, the authors are encouraged by the interest and commitment to this disease that has engendered continued progress in the development of an armamentarium to fight it.

## References

[1] Simonneau G, Galiè N, Rubin L, Langleben D, Seeger W, Domenighetti G, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:55–125.

[2] Meyrick B. The pathology of pulmonary artery hypertension. Clin Chest Med 2001;22:393.

[3] Tuder RM, Cool CD, Geraci MW, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med 1999;159:1925.

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

[5] Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol 2002;39:1214.

[6] Kawut SM, Taichman DB, Archer-Chicko CL, et al. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. Chest 2003;123:344.

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

[8] Daily PO, Dembitzsky WP, Iversen S, et al. Current early results of pulmonary thromboendarterectomy for chronic pulmonary embolism. Eur J Cardiothorac Surg 1990;4:117.

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

[10] Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107:216.

[11] Meyer FJ, Ewert R, Hoeper MM, et al. Peripheral airway obstruction in primary pulmonary hypertension. Thorax 2002;57:473.

[12] Bailey CL, Channick R, Auger W, et al. "High probability" perfusion lung scans in pulmonary venoocclusive disease. Am J Respir Crit Care Med 2000;162:1974.

[13] McGoon MD. The assessment of pulmonary hypertension. Clin Chest Med 2001;22:493.

[14] Hinderliter AL, Willis PWt, Long W, et al. Frequency and prognostic significance of pericardial effusion in primary pulmonary hypertension. PPH Study Group. Am J Cardiol 1999;84:481.

[15] Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 2003;167:735.

[16] Cotton CL, Gandhi S, Vaitkus PT, et al. Role of echocardiography in detecting portopulmonary hypertension in liver transplant candidates. Liver Transpl 2002;8:1051.

[17] Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation 2002;106:319.

[18] Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000; 161:487.

[19] McCaffrey RN, Dunn LJ. Primary pulmonary hypertension in pregnancy. Obstet Gynecol Surv 1964;19:567.

[20] Weiss BM, Zemp L, Seifert B, et al. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am Coll Cardiol 1998;31:1650.

[21] Roberts DH, Lepore JJ, Maroo A, et al. Oxygen therapy improves cardiac index and pulmonary vascular resistance in patients with pulmonary hypertension. Chest 2001;120:1547.

[22] Group NOTT. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med 1980;93: 391.

[23] Rafanan AL, Golish JA, Dinner DS, et al. Nocturnal hypoxemia is common in primary pulmonary hypertension. Chest 2001;120:894.

[24] Frank H, Mlczoch J, Huber K, et al. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. Chest 1997; 112:714.

[25] Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76.

[26] Rich S, Seidlitz M, Dodin E, et al. The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. Chest 1998;114:787.

[27] Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Parent F, et al. Acute vasodilator responsiveness and long-term response to calcium-channel blockers in different forms of pulmonary artery hypertension [abstract A86]. In: Programs and abstracts of the 100th International Conference of the American Thoracic Society. Orlando, Florida: 2004. p. A210.

[28] Raffy O, Azarian R, Brenot F, et al. Clinical significance of the pulmonary vasodilator response during short-term infusion of prostacyclin in primary pulmonary hypertension. Circulation 1996;93:484.

[29] Sitbon O, Humbert M, Jagot JL, et al. Inhaled nitric oxide as a screening agent for safely identifying responders to oral calcium-channel blockers in primary pulmonary hypertension. Eur Respir J 1998;12:265.

[30] Stewart DJ, Levy RD, Cernacek P, et al. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med 1991;114:464.

[31] Rubens C, Ewert R, Halank M, et al. Big endothelin-1 and endothelin-1 plasma levels are correlated with the severity of primary pulmonary hypertension. Chest 2001;120:1562.

[32] Davie N, Haleen SJ, Upton PD, et al. ET(A) and ET(B) receptors modulate the proliferation of human pulmonary artery smooth muscle cells. Am J Respir Crit Care Med 2002;165:398.

[33] Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001;358:1119.

[34] Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896.

[35] McLaughlin V, Sitbon O, Rubin LJ, et al. The effect of first line bosentan on survival of patients with primary pulmonary hypertension. Abstract, American Thoracic Society, 2003.

[36] Christman BW, McPherson CD, Newman JH, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med 1992;327:70.

[37] Hinderliter AL, Willis PWT, Barst RJ, et al. Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension. Primary Pulmonary Hypertension Study Group. Circulation 1997;95:1479.

[38] Langleben D, Barst RJ, Badesch D, et al. Continuous infusion of epoprostenol improves the net balance between pulmonary endothelin-1 clearance and release in primary pulmonary hypertension. Circulation 1999;99:3266.

[39] Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996; 334:296.

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

[41] Paramothayan NS, Lasserson TJ, Wells AU, et al. Prostacyclin for pulmonary hypertension. Cochrane Database Syst Rev CD002994, 2003.

[42] Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. Circulation 1999;99:1197.

[43] Kuhn KP, Byrne DW, Arbogast PG, et al. Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. Am J Respir Crit Care Med 2003;167:580.

[44] Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780.

[45] Humbert M, Maitre S, Capron F, et al. Pulmonary edema complicating continuous intravenous prostacyclin in pulmonary capillary hemangiomatosis. Am J Respir Crit Care Med 1998;157:1681.

[46] Palmer SM, Robinson LJ, Wang A, et al. Massive pulmonary edema and death after prostacyclin infusion in a patient with pulmonary veno-occlusive disease. Chest 1998;113:237.

[47] McLaughlin VV, Gaine SP, Barst RJ, et al. Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. J Cardiovasc Pharmacol 2003;41:293.

[48] Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002;165:800.

[49] Hoeper MM, Schwarze M, Ehlerding S, et al. Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med 2000;342:1866.

[50] Olschewski H, Ghofrani HA, Schmehl T, et al. Inhaled iloprost to treat severe pulmonary hypertension. An uncontrolled trial. German PPH Study Group. Ann Intern Med 2000;132:435.

[51] Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002;347:322.

[52] Galie N, Humbert M, Vachiery JL, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol 2002;39:1496.

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

[54] Bharani A, Mathew V, Sahu A, et al. The efficacy and tolerability of sildenafil in patients with moderate-to-severe pulmonary hypertension. Indian Heart J 2003;55:55.

[55] Ghofrani HA, Schermuly RT, Rose F, et al. Sildenafil for long-term treatment of nonoperable chronic thromboembolic pulmonary hypertension. Am J Respir Crit Care Med 2003;167:1139.

[56] Michelakis E, Tymchak W, Lien D, et al. Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: comparison with inhaled nitric oxide. Circulation 2002;105:2398.

[57] Molina J, Lucero E, Luluaga S, et al. Systemic lupus erythematosus-associated pulmonary hypertension: good outcome following sildenafil therapy. Lupus 2003;12:321.

[58] Sastry BK, Narasimhan C, Reddy NK, et al. A study of clinical efficacy of sildenafil in patients with primary pulmonary hypertension. Indian Heart J 2002;54:410.

[59] Ghofrani HA, Rose F, Schermuly RT, et al. Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. J Am Coll Cardiol 2003;42:158.

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

[61] Stiebellehner L, Petkov V, Vonbank K, et al. Long-term treatment with oral sildenafil in addition to continuous IV epoprostenol in patients with pulmonary arterial hypertension. Chest 2003;123:1293.

[62] Ghofrani HA, Wiedemann R, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet 2002;360:895.

[63] Goldstein I, Lue TF, Padma-Nathan H, et al. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil study group. N Engl J Med 1998;338:1397.

[64] Kandler MA, Von Der Hardt K, Mahfoud S, et al. Pilot intervention: aerosolized adrenomedullin reduces pulmonary hypertension. J Pharmacol Exp Ther 2003;306:1021.

[65] Bonnet S, Dumas-de-La-Roque E, Begueret H, et al. Dehydroepiandrosterone (DHEA) prevents and reverses chronic hypoxic pulmonary hypertension. Proc Natl Acad Sci U S A 2003;100:9488.

[66] Girgis RE, Li D, Zhan X, et al. Attenuation of chronic hypoxic pulmonary hypertension by simvastatin. Am J Physiol Heart Circ Physiol 2003;285: H938.

[67] Petkov V, Mosgoeller W, Ziesche R, et al. Vasoactive intestinal peptide as a new drug for treatment of primary pulmonary hypertension. J Clin Invest 2003;111:1339.

[68] Rich S, Lam W. Atrial septostomy as palliative therapy for refractory primary pulmonary hypertension. Am J Cardiol 1983;51:1560.

[69] Sandoval J, Gaspar J, Pulido T, et al. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension. A therapeutic alternative for patients nonresponsive to vasodilator treatment. J Am Coll Cardiol 1998;32:297.

[70] Trulock E, Edwards L, Taylor D, et al. The registry of the International Society for Heart and Lung Transplantation: Twentieth Official Adult Lung and Heart-lung Transplant Report–2003. J Heart Lung Transplant 2003;22:625.

[71] Pielsticker EJ, Martinez FJ, Rubenfire M. Lung and heart-lung transplant practice patterns in pulmonary hypertension centers. J Heart Lung Transplant 2001;20:1297.

[72] Physicians American Society for Transplant Physiciano, American Thoracic Society, European Respiratory Society, et al. International guidelines for the selection of lung transplant candidates. Am J Respir Crit Care Med 1998;158:335.