Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a term used to classify a variety of conditions that have in common an injury to the pulmonary vasculature that produces elevations in pulmonary arterial pressure. There have been considerable advances in our understanding of the pathogenesis and treatment of PAH over the past decade. The article reviews the classification of diseases associated with PAH, the current understanding of its pathogenesis, and the contemporary approach to therapy.

Keywords: endothelin; prostacyclin; pulmonary hypertension

Pulmonary arterial hypertension (PAH) is a condition characterized by vascular growth and proliferation, leading to increased vascular resistance and right heart dysfunction. PAH can be idiopathic (IPAH; previously known as primary pulmonary hypertension, PPH) or associated with other conditions or exposures, including connective tissue diseases, HIV infection, portal hypertension, and anorexigenic drug ingestion. A recently developed classification for pulmonary hypertension is shown in Table 1.

The past decade has witnessed dramatic advances in the treatment of PAH, with five medical therapies targeting specific pathways that are believed to play pathogenic roles, and which are receiving regulatory approval worldwide, and several additional therapies undergoing clinical trials. Despite these achievements, however, PAH remains a serious, life-threatening condition. Early recognition and an understanding of the selection and timing of therapeutic options remain critical elements in the optimal management of patients with this disorder.

PATHOGENESIS

Although the specific mechanisms responsible for the development of PAH remain unknown, a number of mechanisms have been proposed. The histopathologic features of PAH suggest that endothelial injury and proliferative stimuli are fundamental processes. Mutations in the bone morphogenetic protein receptor 2 (BMPR2), a member of the transforming growth factor (TGF-β) superfamily, are present in most cases of familial PAH (1, 2). Mutations associated with PAH also occur in Alk/endoglin, a TGF receptor that also causes hereditary hemorrhagic telangectasia (3). These genes appear to play a central role in apoptosis, or programmed cell death; inherited or acquired abnormalities in regulation or transcription could promote angiogenesis. However, fewer than 20% of individuals with a BMPR2 mutation develop PAH; accordingly, other genes, genetic polymorphisms, and environmental factors are likely needed to initiate the disease (4–6).

Additional studies have demonstrated abnormalities in other pathways that may contribute to the pathogenesis of PAH. These include enhanced expression of the serotonin transporter, diminished expression of the enzymes responsible for synthesis of nitric oxide (NO) and prostacyclin, altered potassium channels, and increased production of several growth factors, including endothelin, vascular endothelial growth factor, and platelet-derived growth factor (7). Many of these observations have already translated into targeted therapies for PAH, with the probability that more will be investigated in the future.

CLINICAL PRESENTATION AND DIAGNOSTIC APPROACH

Most patients with PAH present with exertional dyspnea, which is indicative of an inability to increase pulmonary blood flow with exercise (8). Exertional chest pain, syncope, and edema are indications of more severely impaired right heart function. Unfortunately, establishing the diagnosis of PAH is frequently delayed, due to the subtle findings on physical examination and the nonspecific symptoms experienced by most patients.

The diagnosis of PAH can be made on clinical grounds, based on a comprehensive evaluation that includes pulmonary function testing, connective tissue serology, echocardiography, complete cardiac catheterization, $\dot{V}/\dot{Q}$ lung scanning, and/or pulmonary angiography (9). Rarely is histopathology required to establish a diagnosis or determine the etiology; furthermore, biopsy carries substantial risk in this population.

Echocardiography is usually the first diagnostic test suggesting the presence of pulmonary vascular disease, typically showing evidence of right heart chamber enlargement, abnormal motion of the interventricular septum, and tricuspid insufficiency.

The pulmonary artery systolic pressure can be estimated noninvasively using Doppler techniques, although these measurements are not as accurate as invasively measured pulmonary artery pressures.

Chest radiographs may demonstrate enlarged central pulmonary arteries and right heart dilation, in addition to providing etiologic clues such as evidence of parenchymal or airways disease or signs of left-sided cardiac disease.

The electrocardiogram shows right axis deviation and right ventricular hypertrophy with a strain pattern. Electrocardiographic changes are generally not helpful in assessing disease severity or prognosis.

Pulmonary function testing may demonstrate severe abnormalities in lung function that suggest the presence of parenchymal or airways disease. In IPAH, lung function tests are often slightly abnormal, with over half of all patients demonstrating a mild to moderate decrease in FEV_1 and FVC compared with age- and sex-matched control subjects. The diffusing capacity for carbon monoxide is frequently reduced; lung volume measurements may reveal an increase in residual volume, consistent with peripheral airway obstruction.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension and should be sought in all patients with clinically significant pulmonary hypertension because it is potentially curable with surgery. $\dot{V}/\dot{Q}$ lung scans in CTEPH typically show at least one segmental-sized or larger

(*Received in original form October 21, 2005; accepted in final form November 10, 2005*)

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Proc Am Thorac Soc Vol 3. pp 111–115, 2006
DOI: 10.1513/pats.200510-112JH
Internet address: www.atsjournals.org

TABLE 1. NOMENCLATURE AND CLASSIFICATION OF PULMONARY HYPERTENSION

Pulmonary arterial hypertension (PAH)
Sporadic (idiopathic PAH [IPAH])
Familial (FPAH)
Related to:
Collagen vascular disease
Congenital systemic to pulmonary shunts (large, small, repaired, or nonrepaired)
Portal hypertension
HIV infection
Drugs and toxins
Other (glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
Associated with significant venous or capillary involvement
Pulmonary venoocclusive 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)

Modified from Simonneau G, Galie N, Rubin LJ, *et al.* Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;43: 5S–12S.

mismatched perfusion defect (10). Scans suggestive of thromboembolic disease may also be seen in pulmonary artery sarcoma, large vessel pulmonary arteritis, extrinsic vascular compression, or pulmonary venoocclusive disease. Pulmonary angiography is the gold standard for diagnosing CTEPH and for determining operability, and should be performed in experienced centers when CTEPH is entertained.

Computed tomography (CT) scanning may suggest an etiology for PAH, such as severe airway or parenchymal lung diseases. In CTEPH, CT findings include right ventricular enlargement, dilated central pulmonary arteries, chronic thromboembolic material within the central pulmonary arteries, parenchymal abnormalities consistent with prior infarcts, and mosaic attenuation of the pulmonary parenchyma. Mosaic attenuation pattern predominantly in the lower lobes is also suggestive of pulmonary venoocclusive disease, an unusual form of pulmonary hypertension characterized by elevated pulmonary arterial pressure with a normal pulmonary capillary wedge and left ventricular diastolic pressures, evidence of venous congestion on chest radiograph, and a patchy appearance of tracer activity on a perfusion scan.

Complete cardiac catheterization is ultimately necessary to establish the diagnosis by excluding other cardiovascular conditions that can cause pulmonary hypertension, to assess its severity, and to guide management.

THERAPY FOR PAH

Therapy for PAH has recently been addressed in detail in two major consensus documents (11, 12), which share a similar evidence-based therapeutic algorithm.

Two small retrospective studies reported improved survival with oral anticoagulation in IPAH (13, 14). On the basis of these reports, and the knowledge that microscopic *in situ* thrombosis can occur in IPAH, anticoagulation of these patients with warfarin is recommended, targeting an international normalized ratio of approximately 1.5 to 2.5. Anticoagulation is controversial for patients with PAH due to other etiologies, such as scleroderma or congenital heart disease. Patients with PAH treated with chronic intravenous epoprostenol are generally anticoagulated in the absence of contraindications, due in part to the additional risk of catheter-associated thrombosis.

Diuretics are indicated for right ventricular volume overload. However, rapid and excessive diuresis may produce systemic hypotension and renal insufficiency. Serum electrolytes and renal function should be monitored closely.

Hypoxemia is a pulmonary vasoconstrictor, and supplemental oxygen should be used to maintain an oxygen saturation of greater than 90%. Supplemental oxygen use is more controversial in patients with Eisenmenger syndrome, but may decrease the need for phlebotomy and reduce the occurrence of neurologic complications.

Although not extensively studied in PAH, digitalis is sometimes used for refractory right ventricular failure. In addition, atrial flutter or other atrial dysrhythmias often complicate late-stage PAH with right heart dysfunction, and digoxin may be useful for rate control.

Vasodilator Testing and Calcium Channel Blockers

Patients with IPAH who acutely respond to vasodilators have improved survival with long-term use of calcium channel blockers (14). A variety of short-acting agents have been used to acutely test vasodilator responsiveness, including intravenous epoprostenol or adenosine, and inhaled NO. The recently formulated consensus definition of a positive acute vasodilator response in PAH is as follows: at least a 10-mm Hg fall in mean pulmonary artery pressure to less than or equal to 40 mm Hg, with an increased or unchanged cardiac output (11). Most experts believe that true vasoreactivity is uncommon, occurring in 10%

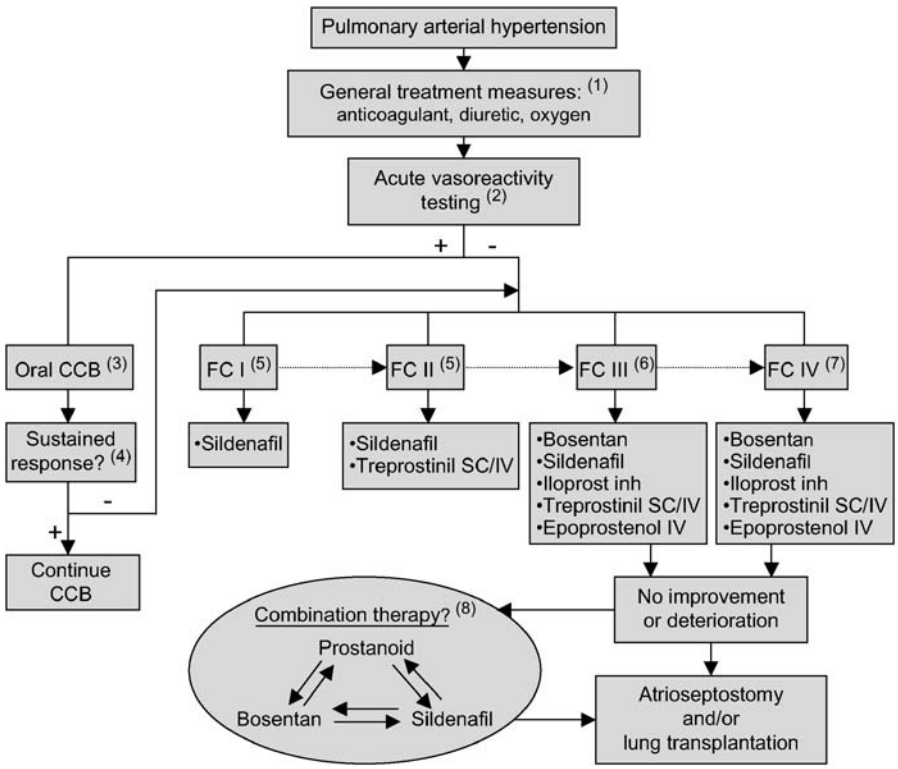

Figure 1. Treatment algorithm for pulmonary artery hypertension. Reprinted by permission from Lee SH, Rubin LJ. Current treatment strategies for pulmonary arterial hypertension. *J Intern Med* 2005;258:199–215.

of patients with IPAH and rarely in other forms of PAH. Vasoreactivity testing should be performed in experienced centers.

Only patients demonstrating a significant response to the acute administration of a short-acting vasodilator should be considered candidates for treatment with oral calcium channel blockers; treatment should be monitored closely, because maintenance of a response is not universal. Agents with negative inotropic effects, such as verapamil, should be avoided.

Prostanoids

Prostacyclin is a metabolite of arachidonic acid produced in vascular endothelium. It is a potent vasodilator, affecting both the pulmonary and systemic circulations, and has antiplatelet aggregator effects. A relative deficiency of endogenous prostacyclin may contribute to the pathogenesis of PAH (7).

In IPAH, continuous intravenously infused epoprostenol improved exercise capacity, assessed by the 6-min walk test, cardiopulmonary hemodynamics, and survival compared with conventional therapy (oral vasodilators, anticoagulation) (15). A similar study showed epoprostenol improved exercise capacity and hemodynamics in patients with PAH due to the scleroderma spectrum of disease (16). The beneficial effects of epoprostenol therapy are sustained for years in many patients with IPAH (17, 18).

Epoprostenol therapy is complicated by the need for continuous intravenous infusion. Due to its short half-life, the risk of rebound worsening with interruption of the infusion, and its irritant effects on peripheral veins, epoprostenol should be administered through an indwelling central venous catheter. Common side effects of epoprostenol therapy include headache, flushing, jaw pain, diarrhea, nausea, a blotchy erythematous rash, and musculoskeletal pain. Acute overdosage can lead to systemic hypotension, whereas chronic overdosage can produce a hyperdynamic circulatory state with high output cardiac failure. Serious complications include catheter-related sepsis and thrombosis. Although epoprostenol is approved by the U.S. Food and Drug Administration (FDA) for functional class III–IV patients with IPAH and PAH due to scleroderma, it is now generally reserved for patients with advanced disease refractory to oral therapies. Because of its complexity, patients should be referred to centers experienced with epoprostenol therapy.

Treprostinil is a stable prostacyclin analog with a half-life of 3 h. In a multicenter study of subcutaneously infused treprostinil in PAH, 6-min walk distance and hemodynamic parameters improved modestly with treprostinil compared with placebo (19). Common side effects include infusion site pain, headache, diarrhea, nausea, rash, and jaw pain. Treprostinil is approved by the FDA for subcutaneous or intravenous treatment of functional class II–IV PAH and is generally used when oral therapy has failed to produce benefit.

Iloprost is a stable prostacyclin analog with a serum half-life of 20 to 25 min. In a 3-mo multicenter trial, 2.5 or 5 μg iloprost administered six or nine times daily improved the 6-min walking distance and New York Heart Association (NYHA) functional class (20). Hemodynamic variables measured after iloprost inhalation were also improved at 3 mo. Cough, flushing, and headache occurred more frequently in the iloprost group. Inhaled iloprost is currently approved in Europe for patients with IPAH in functional class III and in the United States for patients with PAH in functional classes III and IV, and may be particularly useful as an adjunct to oral therapy.

Endothelin Receptor Antagonists

Endothelin-1 (ET-1) is a potent vasoconstrictor and smooth muscle mitogen that may contribute to increased vascular tone and proliferation in PAH (7). ET-1 expression, production, and concentration in plasma and lung tissue are elevated in PAH, and levels correlate with disease severity (7).

A small multicenter study demonstrated significant improvement in 6-min walking distance, cardiopulmonary hemodynamics, and functional class with bosentan, a dual ET_A/ET_B receptor

antagonist, compared with placebo (21). Asymptomatic increases in hepatic aminotransferases were observed in two bosentan-treated patients, but normalized without discontinuation or change of dose.

Similar improvements in exercise capacity, symptoms, and clinical worsening were seen in the larger Bosentan Randomized Trial of Endothelin Antagonist Therapy of Pulmonary Hypertension (BREATHE-1) study (22). Due to the risk of hepatic toxicity, the FDA requires that liver function tests be performed at least monthly. Bosentan may also cause anemia, edema, and teratogenicity. The ET antagonists as a class may produce testicular atrophy and male infertility. Bosentan is approved in the United States for NYHA class III–IV PAH and in Europe for NYHA class III PAH.

Two selective ET_A receptor antagonists, sitaxsentan and ambrisentan, are currently completing phase III clinical trials, and remain investigational agents (23, 24).

Phosphodiesterase-5 Inhibitors

The vascular effects of NO depend on its augmentation of cyclic guanosine monophosphate (cGMP) content in vascular smooth muscle. The effects of intracellular cGMP are short-lived, due to the rapid degradation of cGMP by phosphodiesterases (PDEs). PDE5 is strongly expressed in the lung, and PDE5 gene expression and activity are increased in chronic pulmonary hypertension.

Sildenafil is a highly specific PDE5 inhibitor currently approved for erectile dysfunction. Sildenafil acutely reduces pulmonary artery pressure in patients with PAH (25) and both augments and prolongs the effects of inhaled NO, preventing rebound pulmonary vasoconstriction after acute withdrawal of inhaled NO (26). Combining sildenafil with aerosolized iloprost caused a greater and more prolonged decrease in pulmonary vascular resistance than either agent alone (27). A multicenter clinical trial has been recently completed (28). Sildenafil has recently been approved for use in the United States for PAH.

Interventional/Surgical Therapies

Atrial septostomy involves the creation of a right-to-left interatrial shunt to decompress the failing pressure- and volume-overloaded right heart (29). Where advanced medical therapies are available, atrial septostomy is seen largely as a palliative procedure, or as a stabilizing bridge to lung transplantation (30). In regions of the world lacking access to advanced medical therapies, atrial septostomy may be the best treatment option available (29). Patient selection, timing, and appropriate sizing of the septostomy are crucial to optimizing outcomes.

Lung transplantation is particularly challenging in PAH (31), and is usually reserved for patients deteriorating despite best available medical therapy. Survival in patients with PAH undergoing lung transplantation is approximately 66 to 75% at 1 yr (32). Most centers prefer bilateral lung transplantation for PAH (32, 33).

An algorithm for the treatment of PAH is presented in Figure 1.

The development of treatments for PAH has created the challenge of how to best monitor the effects of long-term therapy. Noninvasive markers of disease severity, such as the 6-min walk test and assessment of NYHA functional class, are useful in determining stability or deterioration (34). Echocardiographic indices of right heart size and function may also be useful in noninvasively monitoring therapy (35–37). Repeat cardiac catheterization should be considered when noninvasive measures suggest deterioration and alternative therapies are being considered, because the choice of therapy may be governed by the severity of hemodynamic abnormality. Biomarkers, such as brain natriuretic peptide and troponin, or physiologic studies, such as cardiopulmonary stress testing (38), are also being used to monitor clinical course.

Conflict of Interest Statement: L.J.R. has served as a consultant and investigator for Actelion ($75,000), Pfizer ($15,000), Schering ($20,000), Myogen ($20,000), CoTherix ($20,000), LungRx ($75,000), Nitrox ($10,000), and Mondobiotech ($5,000). He has received lecture fees from Actelion ($10,000) and his institution has received grants for clinical trials from Actelion ($200,000), Pfizer ($100,000), CoTherix ($30,000), Myogen ($30,000), and LungRx ($50,000). He serves as Chair of the Data Safety Monitoring Board for the Pediatric Pulmonary Hypertension Clinical Trials for Pfizer ($5,000), as Chair of the Scientific Advisory Board for LungRx for which he receives United Therapeutics stock options, and as Chair of the Scientific Advisory Board for Actelion ($5,000).

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