THE CURRENT TREATMENT OF PULMONARY HYPERTENSION

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Overview

Pulmonary vascular hypertension in general is a progressive, nearly always fatal condition that until recently has had very few treatment options. Our understanding of the pulmonary vascular disease process has opened the window to earlier screening techniques, diagnosis, and treatment options. However, all current treatment options are complex and expensive and therefore require clinical support strategies often necessitating specialized pulmonary hypertension treatment centers.

Whether idiopathic or secondary, pulmonary arterial hypertension is characterized by the deregulated proliferation of pulmonary artery endothelial cells and intimal smooth muscle cells, both resistant to cellular apoptosis. Early recognition of such disregulation may lead to earlier diagnosis and treatment and thus alteration in the disease process. Screening of high-risk populations such as those with connective tissue disorders, HIV disease, congenital heart disease, portal hypertension, and those exposed to certain drugs and toxins such as methamphetamines and the diet drugs Dexfenfluramine and Fenfluramine is of utmost importance. Similarly, early symptom recognition in these high-risk groups is essential to earlier diagnosis and treatment.

Risk Factors for Pulmonary Hypertension

Pulmonary artery pressures greater than 30-40 mm Hg systolic with mean pulmonary artery pressures greater than 25 mm Hg and pulmonary capillary wedge pressure less than 15 mm Hg classify as elevated. Pulmonary hypertension may be associated with pulmonary venous occlusive disease or pulmonary capillary hemangiomatosis. Between 6 and 12% of patients with idiopathic pulmonary hypertension have a family history with autonomic dominant gene expression for bone morphogenetic protein receptor II (BMPR2). Scleroderma, lupus, and rheumatoid arthritis are all associated with pulmonary hypertension at a rate of 33%, 14%, and 21% respectively, and 3% of pulmonary emboli patients develop pulmonary hypertension.

When secondary to valvular heart disease, hypertensive diastolic or systolic cardiomyopathy, or pulmonary embolic disease, the primary treatment strategy is to treat the causative factors first. If despite these corrective measures the pulmonary hypertension persists, often secondary to pulmonary vascular endothelial remodeling, pharmacologic intervention may be warranted.

Diagnostic Approaches

Although cardiac 2D-echo Doppler is critical to screen and noninvasively follow patients with pulmonary hypertension, accurate pressure measurements to exclude cardiac causes almost always require at least an initial right and left heart catheterization. The limitation of 2D-echo in the early disease stages is that pulmonary hypertension may exist before a pulmonic valve leak can be detected to accurately window and measure pulmonary artery pressures. If elevated, the initial right heart catheterization can also be used to test for responsiveness to vasodilator therapies such as calcium channel blockers, nitric oxide, or intravenous prostacyclin administration.

Response to therapy has been defined as a fall in mean pulmonary artery pressure by at least 10 mm Hg, or a drop in systolic pulmonary artery pressure to 35-40 mm Hg, with stable to increased cardiac output. Responders to calcium channel blockade may be started on calcium channel blockers and followed carefully, while nonresponders may be considered candidates for endovascular vasodilator therapy with one of the endothelial receptor antagonists, prostacylin agents, or the phosphodiesterase-5 inhibitors.

All pulmonary hypertension patients should also have a baseline ECG, blood work with CBC to exclude polycythemia, and an over-

night oximeter measurement with or without a formal sleep study to exclude nocturnal hypoxemia as a contributory cause to pulmonary vasoconstriction. If the screening cardiac echo is normal in patients at risk for pulmonary hypertension, transesophageal cardiac echo should be considered if cardiac catheterization is not done to rule out left-to-right intracranial shunts and to obtain accurate pulmonary pressures.

Once endovascular injury and resultant cellular proliferation of both endothelial and smooth muscle cells has occurred, various mediator pathways are altered. Increased activity is seen in endothelin-1, serotonin, thromboxane A2, and endothelial growth factors as well as various inflammatory mediators. Reduced activity is seen in endogenous prostacyclin, prostacyclin synthase, nitric oxide, nitric oxide synthase, vasoactive inhibitory protein, and fibrinolysis. These alterations in the pulmonary vascular bed create the opportunity for a multi-step approach to managing and treating pulmonary hypertension much as the stepwise approach to congestive heart failure has evolved (Figure 1).

Therapeutic Options

From 1992 to 2002, there was poor survival with single-agent therapy. Combination studies such as BREATHE-2 (bosentan plus epoprostenol) showed lower pulmonary vascular resistance compared to placebo, and STEP-1 (bosentan plus inhaled iloprost) showed improved six-minute walk tests and slower time to worsening. The PACES study added Viagra to iloprost and showed improved six-minute walk tests. Other studies found varying degrees of success with combination agents. For example, the TRIUMPH study combined inhaled treprostinil and bosentan, the VISION trial combined inhaled iloprost and sildenafil, the FREEDOM trial combined oral treprostinil with bosentan and sildenafil, and the COMPASS trials combined bosentan and sildenafil.

Three main pharmaceutical classes are currently available to treat pulmonary hypertension. The first is endothelin receptor antagonists, of which there are three. Bosentan (Tracleer) is a dual receptor ETA and ETB antagonist at a dose of 62.5 mg to 250 mg BID approved after the BREATHE-1 trial. Sitaxsentan (Thelin) is approved in Canada and Europe for BID dosing with similar efficacy to bosentan. Both agents have a potential for transaminase elevation, and liver function tests need to be monitored. Ambrisentan (Letairis) is an oral, once-daily ETA selective agent with no liver toxicity yet seen in a dose of 5 mg or 10 mg daily in the ARIES-1 and ARIES-2 trials. Endothelin seems particularly active in connective tissue disease associated pulmonary hypertension. Bosentan has been shown to be effective in both scleroderma and lupus associated pulmonary hypertension.

The second pharmaceutical class is PDE-5 inhibitors, which raise the intrinsic vasodilator activity of endothelial cyclic GMP by inhibiting the phosphodiesterase 5 enzyme that is responsible for cGMP degradation. Sildenafil (Viagra) and sildenafil citrate (Revatio) were both approved in 2005 for clinical use. Raising intrinsic cGMP levels leads to nitric oxide-mediated ongoing pulmonary vasodilation as the mechanism for lowering pulmonary artery pressures. In the SUPER I trial where 38% of the participants were NYHA II and 58% NYHA III, 20 to 80 mg TID orally of sildenafil showed improved six-minute walk tests and reduced pulmonary artery pres-

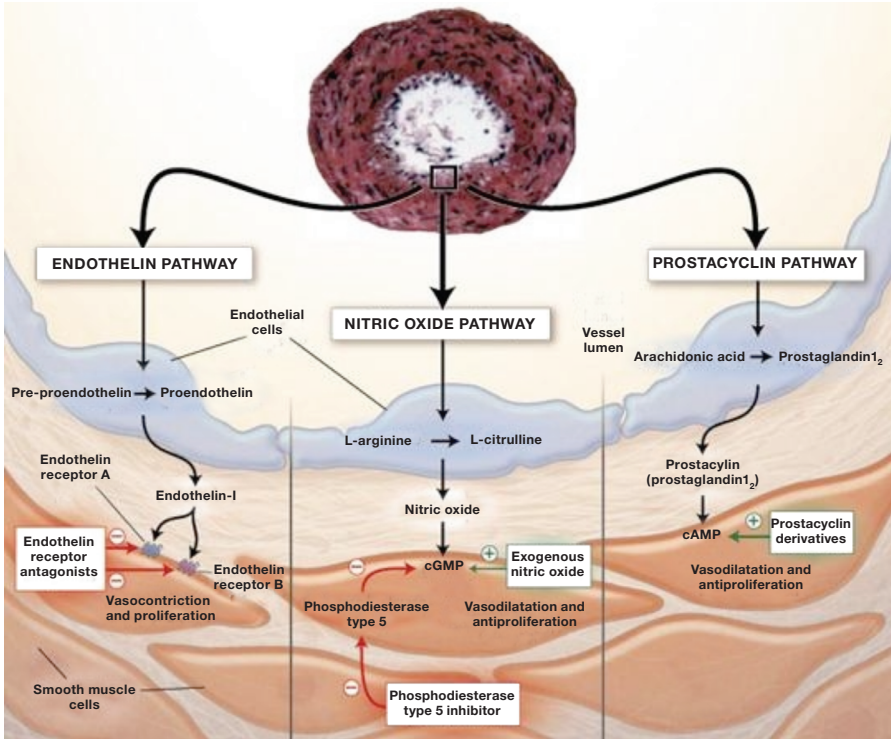

Figure 1. Pulmonary vasoactive target pathways.[5]

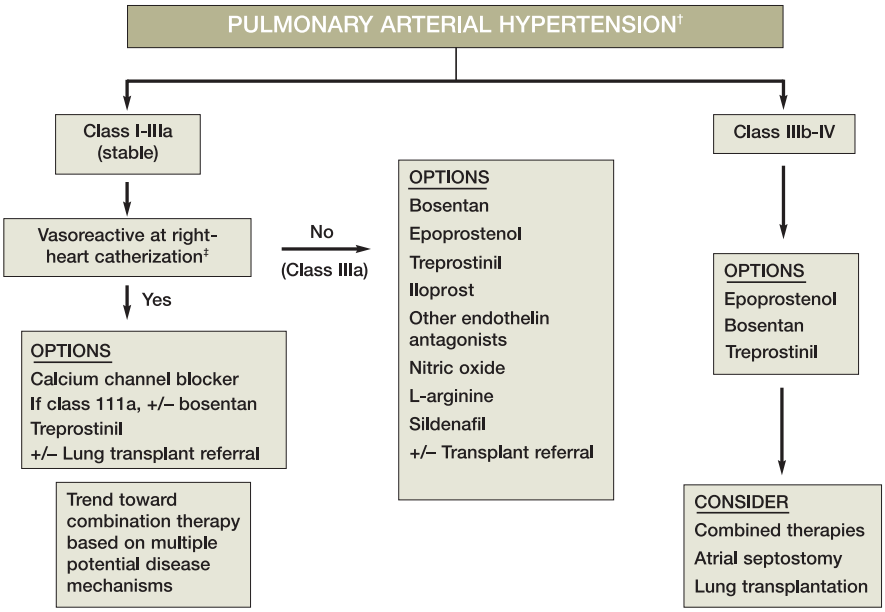

Figure 2. Current treatment algorithm for pulmonary hypertension.[7]

sures without serious side effects being noted at one year, with 94% alive in the SUPER II study.

The third pharmaceutical class is the prostacyclin agonist agents that are more difficult to administer due to their short half lives. These agents work to increase endothelial prostacyclin levels that then vasodilate the pulmonary microvasculature. Prostacyclin (iloprost), epoprostenol (Flolan), and treprostinil (Remodulin) are such agents. In the STEP trial, increased six-minute walk was documented in the 12 weeks of iloprost therapy. Similarly, intravenous epoprostenol or subcutaneous treprostinil were also shown to be effective.

Given the three main class mechanisms of action of these drugs, combination therapy studies are ongoing to better define optimal treatment regimens that extend life and improve functional class while minimizing side effects and symptoms. Reasonable treatment goals would be improved functional class to NYHA I or II, increased six-minute walk tests, lower pulmonary artery pressures and peripheral vascular resistance, and improved RV function if impaired.

Historically, calcium channel blockade was an early treatment, but it has two setbacks: many patients do not respond to them, and hypotension is a potentially dangerous side effect which often limits doses that would otherwise be effective. The most commonly used were nifedipine (Procardia) and later amlodipine (Norvasc). Some patients may benefit from the addition of anticoagulants to prevent in situ small vessel thrombosis from further obstructing the pulmonary vascular bed, or the addition of diuretics to mobilize the fluid retention often precipitated by either calcium channel blockers or endothelin receptor antagonists. Oxygen is a potent pulmonary vasodilator and should be used to maintain O_2 saturations above 90% both day and night as confirmed by day and overnight oximetry. Obese patients should always undergo a formal sleep study with oxygen and CPAP/BiPAP titration to correct hypoxemia.

Surgical treatments for pulmonary hypertension include pulmonary artery thromboembolectomy for those patients with large central chronic emboli not responsive to thrombolytics or anticoagulant therapy with or without vasodilator therapy. However, post-operative mortality can exceed 10% depending on the patient's condition and the experience of the center performing the operation. Preoperative pulmonary angiograms should be done to determine the exact burden and location of residual clots. Whether or not a good result is obtained, the patient must use anticoagulants for life to prevent further thrombotic or thromboembolic events. Lung transplantation is reserved for patients that fail other therapies and continue to progress to NYHA class III or IV. Atrial septostomy is reserved for those patients with severe end stage PAH and no other reasonably good treatment options.

Conclusion

In summary, various options now exist for single-agent and dual-combination therapy with vasoactive agents. Ideally, patients should be detected prior to becoming NYHA class III or IV and before irreversible endothelial damage occurs. Patients in class III and IV who initiate treatment should have it titrated with the goal of improving to class II or higher with at least two agents. Patients classified as NYHA I or II may be started on single-agent therapy and followed (Figure 2).

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