Pulmonary Hypertension: New Perspectives

The World Health Organization symposium offers a new treatment-oriented classification of pulmonary hypertension based on an improved understanding of its pathophysiology. Regardless of the etiology, severe or unrelieved pulmonary hypertension leads to right heart failure. Symptoms and signs of pulmonary hypertension are often subtle and nonspecific. As a result, a significant delay between the onset of symptoms and the diagnosis of pulmonary hypertension is common. Echocardiography with Doppler flow is the most useful study to evaluate patients suspected of having pulmonary hypertension. The suspected diagnosis of pulmonary hypertension should then be confirmed by right heart catheterization. If present, further evaluation may include oxygen assessment, pulmonary function testing, high resolution computed tomography of the chest, and ventilation-perfusion lung scanning. Treatment of pulmonary hypertension requires uncommon expertise. General measures include correction of the underlying cause, reversal of hypoxemia and judicious use of diuretics. Advances in vasodilator therapy have increased treatment options beyond calcium channel blockers and intravenous epoprostenol. Lung transplantation remains an option for select patients with pulmonary hypertension not responding to medical management. (CHF. 2003;9:155–162) ©2003 CHF, Inc.

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The pulmonary circulation is normally a low-pressure, low-resistance circuit due to its large cross-sectional area and high capacitance. Pulmonary hypertension is defined as a mean pulmonary arterial pressure >25 mm Hg at rest or 30 mm Hg with exercise at catheterization. The significance of elevated pulmonary arterial pressure is that it increases impedance to right ventricular ejection. This increased afterload, if severe or unrelieved, leads to right heart failure.

Pulmonary hypertension has traditionally been divided into two forms: primary and secondary. The etiology of primary pulmonary hypertension (PPH) is unknown. In secondary pulmonary hypertension, a myriad of respiratory, cardiac, and extrathoracic disorders presumably explain the pulmonary hypertension. However, pulmonary vascular disease with clinical and pathologic features identical to PPH can occur in association with several conditions. As a result, this nomenclature becomes unclear. Recently, a new diagnostic classification was proposed by a World Health Organization symposium (Table I).[1] In this categorization, forms of pulmonary hypertension are grouped according to shared pathobiologic processes. For instance, pulmonary arterial hypertension refers to a disease spectrum that includes PPH and pulmonary hypertension that cannot be distinguished from PPH.

Pathogenesis and Classification

The pulmonary vasculature is the exclusive target of disease in PPH, although its pathogenesis remains speculative. The most widely accepted mechanism suggests that PPH is a disease of predisposed individuals in whom various stimuli may initiate the development of pulmonary arteriopathy. Vasoconstriction, vascular-wall remodeling and thrombosis in situ all play a role.[2]

Vascular tone is increased in PPH. A decrease in the ratio of the metabolites of the vasodilator prostacyclin to those of the vasoconstrictor thrombaxane exists.[2] Levels of the potent vasoconstrictor endothelin-1 are increased.[2] Impaired function and expression of voltage-gated potassium channels on smooth muscle cells have been noted.[2] This may initiate and maintain vasoconstriction. Vascular remodeling is

also a prominent feature of PPH. Intimal fibrosis and medial hypertrophy are well recognized. Production of extracellular matrix including collagen and elastin is increased.[2] Thrombosis in situ is often found in the pulmonary arterioles.[2] Platelet activity is enhanced; levels of serotonin, plasminogen activator inhibitor and fibrinopeptide are elevated; and thrombomodulin levels are decreased.[2]

PPH is rare, with an incidence of 1 to 2 cases per million people in the general population. The disease is most prevalent in the third and fourth decade of life where it is more common in women than men (ratio: 1.7 to 1).[3] Familial PPH, an autosomal dominant disorder with incomplete penetrance, accounts for 6% of all cases of PPH. The gene involved, *BMPR2*, encodes a transforming growth factor β type II receptor that influences angiogenesis and apoptosis.[4]

Entities other than PPH associated with pulmonary arterial hypertension include collagen vascular disease, systemic arterial-to-pulmonary artery shunts, portal hypertension, human immunodeficiency virus (HIV) infection, and anorexic agents. The exact mechanism by which these risk factors lead to pulmonary arterial hypertension is unknown. Since only a minority of persons with these risk factors develop pulmonary hypertension, individual susceptibility is likely to have an important function.

Many collagen vascular diseases have been associated with pulmonary hypertension.[5] This includes systemic lupus erythematosus, scleroderma, CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) syndrome, rheumatoid arthritis, Sjogren's syndrome, dermatomyositis/polymyositis, and mixed connective tissue disease. Pulmonary hypertension may be the presenting manifestation and can precede the diagnosis of autoimmune disease by several years. Most often pulmonary hypertension develops because of pulmonary fibrosis. However, in some cases the pulmonary interstitium is preserved and the pulmonary vessels have histologic features resembling PPH.

Through vascular recruitment and distensibility, the pulmonary circulation can accommodate moderate increases in blood flow with minimal increase in pulmonary arterial pressure. However, when pulmonary blood flow is extreme and pulmonary vascular capacity is reached, any further increase in flow will generate pulmonary hypertension. This occurs most commonly in congenital anomalies involving systemic to pulmonary shunts. Irreversible pathologic changes in the pulmonary vasculature similar to PPH may occur depending upon the quantity and duration of volume and pressure overload.

Elevated pulmonary arterial pressure is not uncommon in advanced liver disease.[6] The mechanisms are at least three-fold: 1) a high pulmonary flow state due to a hyperdynamic circulation; 2) volume overload possibly related to impaired left ventricular contractility; and 3) a condition that leads to the histologic abnormalities identical to PPH. Only the third description should be labeled portopulmonary hypertension.

Chronic HIV infection is related to the development of pulmonary arterial hypertension.[7] However, no correlation exists between CD_4 counts or prior respiratory infections and its development. Pulmonary arterial hypertension does appear to be more rapidly progressive in patients with HIV than in those without this risk factor.

The use of anorexic agents for more than three months is associated with a >30 times increased risk of pulmonary arterial hypertension.[8] Importantly, pulmonary hypertension may present several months after discontinuation of the agent. Aminorex, fenfluramine, dexfenfluramine, and amphetamines have all been implicated. The pathogenic mechanism of pulmonary hypertension associated with appetite suppressants is unclear, although alteration of the serotonin pathway has been proposed.[9] Serotonin is known to be a potent pulmonary vasoconstrictor and stimulator of smooth muscle proliferation.

Pulmonary venous hypertension is a potential consequence of any condition that impedes pulmonary venous drainage. Left ventricular dysfunction and mitral valve disease result in pulmonary hypertension primarily by raising left atrial pressure and therefore obstructing pulmonary venous drainage. This necessitates an increase in pulmonary arterial pressure to maintain flow through the pulmonary circulation. More direct hindrance to pulmonary venous flow occurs in association with unusual conditions such as fibrosing mediastinitis and pulmonary venoocclusive disease.

Alveolar hypoxia causes pulmonary vasoconstriction by a variety of actions on endothelium and smooth muscle. This increased pulmonary vascular resistance can be further compounded by reactive polycythemia. Chronic mountain sickness and sleep apnea syndromes[10] are illustrative of pulmonary hypertension associated with hypoxemia.

Advanced interstitial lung disease or chronic obstructive pulmonary disease (COPD) may cause pulmonary hypertension through hypoxia-induced vasoconstriction and obliteration of capillary beds. Acidosis, also a pulmonary vasoconstrictor, may augment the effects of hypoxia.[11] As a result, acute exacerbations of COPD leading to hypoxia and uncompensated hypercarbia can markedly elevate pulmonary arterial pressure.

Pulmonary hypertension may result from obstruction of flow through the pulmonary arterial tree after pulmonary embolism. Subsequent to pulmonary embolism, the normal right ventricle can sustain its output after an abrupt increase in mean pulmonary arterial pressure up to 50 mm Hg. A higher acute pressure increase will cause the right ventricle to fail. Therefore, a massive pulmonary embolus may cause right ventricular failure, but not severe pulmonary hypertension. A pulmonary arterial pressure >50 mm Hg suggests a chronic process with resultant right ventricular hypertrophy. Chronic thromboembolism can provoke severe pulmonary hypertension if thrombi fail to undergo recanalization or lysis. This occurs in <1% of patients with thromboembolic disease.[12]

Clinical Manifestations

Patients with pulmonary hypertension often present with nonspecific symptoms. These symptoms are often difficult to dissociate from symptoms due to a known underlying pulmonary or cardiac disorder. As a result, a significant delay between the onset of symptoms and the diagnosis of pulmonary hypertension is common.

Dyspnea on exertion, fatigue, and syncope are the most common presenting symptoms. These reflect an inability to increase cardiac output when appropriate. Chest pain is prevalent in pulmonary hypertension despite normal coronary arteries. This is likely due to angina from right ventricular ischemia or pain directly related to pulmonary artery stretching.

Hemoptysis, due to the rupture of distended pulmonary vessels, is rare but potentially life-threatening. Hoarseness may result from compression of the recurrent laryngeal nerve by the enlarged pulmonary artery. Raynaud's phenomenon occurs in approximately 2% of patients with PPH, but is more common in pulmonary hypertension related to connective tissue disease.[5]

Physical examination abnormalities tend to be localized to the cardiovascular system. A careful exam will often detect signs of both pulmonary hypertension and right ventricular hypertrophy. Compatible findings include jugular venous distention, a right ventricular heave, an accentuated second heart sound in the pulmonic area, and a tricuspid insufficiency murmur. Hepatomegaly and peripheral edema are signs of advanced pulmonary hypertension.

Diagnostic Assessment

A high index of suspicion combined with a meticulous history and physical examination is paramount in the evaluation of patients with pulmonary hypertension. Careful attention should be given to prior medical conditions, all drug use (both legal and illegal), family history, and an extensive review of systems.

The electrocardiogram (ECG) may demonstrate signs of right ventricular hypertrophy or right atrial enlargement in pulmonary hypertension. ECG findings include right axis deviation, P-pulmonale, right bundle branch block, and R/S ratio >1 in lead V_1. The higher the pulmonary artery pressure, the more sensitive is the ECG.[13] Chest radiograph is inferior to ECG in detecting pulmonary hypertension. Although insensitive, a right descending pulmonary artery diameter >16 mm on standard chest x-ray is specific for pulmonary hypertension.[13]

Patients with symptoms, signs, ECG, or chest radiograph suggestive of pulmonary hypertension should undergo two-dimensional echocardiography with Doppler flow. Echocardiography is the most useful screening test to detect pulmonary hypertension[14] and to exclude underlying congenital, valvular, or myocardial disease.

Echocardiographic screening for pulmonary hypertension is based on identification of the tricuspid regurgitant jet (TR), absent in normal individuals. Measurement of TR velocity (m/sec) provides an estimate of the backward flow between the right ventricle and right atrium. The modified Bernoulli equation [$\Delta p=4(TR^2)$] converts this flow measurement into a pressure gradient. By adding this pressure gradient to an estimate of right atrial pressure, the right ventricle peak systolic pressure is determined. The right ventricle peak systolic pressure approximates pulmonary artery systolic pressure obtained by catheterization.[14]

All patients with suspected pulmonary hypertension on echocardiography should undergo comprehensive evaluation to clarify the etiology. The goal of this diagnostic approach is to identify or exclude treatable causes, keeping in mind the differential diagnosis (Table I). Initial laboratory evaluation includes a complete blood count, prothrombin time, partial thromboplastin time, hepatic profile and serologic studies for collagen vascular disease if suggested by history or physical examination. Specific autoantibodies might include antinuclear and anti-DNA (systemic lupus erythematosus), anti-Scl-70 and antinucleolar (scleroderma), anticentromere (CREST syndrome), rheumatoid factor (rheumatoid arthritis), anti-Ro and anti-La (Sjogren's syndrome), anti-Jo-1 (dermatomyositis/polymyositis) and anti-U_1 RNP (mixed connective tissue disease). HIV testing should be considered in all patients, especially those with a compatible history or risk factors.

Arterial blood gas analysis should be performed to exclude hypoxia and acidosis as contributors to pulmonary hypertension. Importantly, normal resting oxygenation does not exclude exertional or nocturnal oxygen desaturation. Approximately 20% of patients with COPD and normal awake arterial oxygen tensions have nocturnal, nonapneic oxygen desaturation.[15] Exertional oxygen desaturation is also common. These episodes are ameliorated with supplemental oxygen. Consequently, exercise and sleep oximetry should be completed in all patients with pulmonary hypertension. A formal overnight polysomnogram is indicated if the clinical presentation suggests sleep apnea.

Pulmonary function tests are necessary to establish airflow obstruction or restrictive pulmonary physiology. Unless hypoxia is present, pulmonary hypertension cannot be attributed to these disorders unless pulmonary function is severely reduced. Computerized tomographic scanning of the chest with high-resolution images is useful to exclude occult interstitial lung disease and mediastinal fibrosis when pulmonary function tests and chest radiograph are nondiagnostic.

If the cause of the pulmonary hypertension remains unexplained, chronic thromboembolism should be excluded as it can mimic PPH clinically. Fortunately, the ventilation-perfusion lung scan is a reliable method of differentiating chronic thromboembolic pulmonary hypertension from PPH. One or more segmental or larger perfusion defects is a sensitive marker of embolic obstruction. The ventilation-perfusion scan is either normal or demonstrates patchy subsegmental abnormalities in PPH.[16]

If the ventilation-perfusion scan is suggestive of chronic thromboembolism, pulmonary angiography can be safely performed in order to confirm the diagnosis, define the extent of disease, and consider possible surgical thromboendarterectomy.[17] The role of helical computerized tomography of the pulmonary arteries remains unclear. Helical computerized tomography has high specificity but undefined sensitivity for the diagnosis of pulmonary embolism.[18]

Complete cardiac catheterization should be performed in all patients undergoing an evaluation of pulmonary arterial hypertension, and remains the gold standard for its diagnosis and quantification. Catheterization is particularly useful in the diagnosis of occult systemic to pulmonary shunts, congenital heart disease, and distal pulmonary artery stenosis.

Prognosis

The median duration of survival after diagnosis of PPH is 2.8 years,[19] but this is highly variable. In patients without hemodynamic evidence of right ventricular dysfunction, survival >10 years is possible with new treatment methods. The 6-minute walk test is predictive of mortality in patients with PPH and is useful for following a response to therapy.[20]

Prognosis in patients with other forms of pulmonary hypertension depends on the underlying disease as well as right ventricular function. For instance, patients with COPD and moderate airflow obstruction have a 3-year mortality of 50% after the onset of right ventricular failure.[21] Survival is influenced similarly in patients with interstitial lung disease and pulmonary hypertension.

Therapeutics

The treatment of pulmonary hypertension is complex and potentially dangerous. Patients benefit from referral to centers that specialize in the management of this problem. Table II lists possible treatment options for patients with pulmonary hypertension.

General Measures

A primary goal in the management of pulmonary hypertension is the early recognition and treatment of the underlying disease while it is still potentially reversible. To illustrate, pulmonary arterial hypertension associated with autoimmune disease may respond to corticosteroids or other immunosuppressive agents. If no permanent arteriolar vascular disease exists, abolition of a systemic to pulmonary shunt by corrective surgery restores pulmonary blood flow and pressure to normal. Mild to moderate portopulmonary hypertension does not appear to alter outcome after orthotopic liver transplantation.[22] Antiretroviral therapy may exert a beneficial effect on the course of pulmonary hypertension in the setting of HIV infection in some patients.[23] Improvement or resolution of pulmonary hypertension may be seen following discontinuation of anorexic medications, although this is uncommon.[24] Left ventricular dysfunction should be treated with afterload reducing agents, digoxin, diuretics, and revascularization if appropriate.

Because hypoxia is a potent pulmonary vasoconstrictor, identification and reversal of hypoxemia is a cornerstone of therapy for pulmonary hypertension. Low-flow supplemental oxygen selectively dilates the pulmonary vasculature and prolongs survival in hypoxemic patients.[25]

A low sodium diet and judicious use of diuretics can be helpful in reducing volume overload in patients with pulmonary hypertension and right ventricular failure. However, because the right heart is dependent upon preload, care should be taken to avoid excessive diuresis and further reduction in cardiac output.

Table I. The World Health Organization Diagnostic Classification of Pulmonary Hypertension

PULMONARY ARTERIAL HYPERTENSION
Primary pulmonary hypertension
Sporadic
Familial
Related to:
Collagen vascular disease
Congenital systemic to pulmonary shunts
Portal hypertension
HIV Infection
Drugs/toxins
Anorexigens
Other
Persistent pulmonary hypertension of the newborn
Other
PULMONARY VENOUS HYPERTENSION
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Extrinsic compression of central pulmonary veins
Fibrosing mediastinitis
Adenopathy/tumors
Pulmonary venoocclusive disease
Other
PULMONARY HYPERTENSION ASSOCIATED WITH DISORDERS OF THE RESPIRATORY SYSTEM AND/OR HYPOXEMIA
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Neonatal lung disease
Alveolar-capillary dysplasia
Other
PULMONARY HYPERTENSION DUE TO CHRONIC THROMBOTIC AND/OR EMBOLIC DISEASE
Thromboembolic obstruction of proximal pulmonary arteries
Obstruction of distal pulmonary arteries
Pulmonary embolism (thrombus, tumor, ova and/or parasites, foreign material)
In-situ thrombosis
Sickle cell disease
PULMONARY HYPERTENSION DUE TO DISORDERS DIRECTLY AFFECTING THE PULMONARY VASCULATURE
Inflammatory
Schistosomiasis
Sarcoidosis
Other
Pulmonary capillary hemangiomatosis

HIV=human immunodeficiency virus
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Medical Therapy

Oral calcium channel blockers may alleviate pulmonary vasoconstriction and prolong life in approximately 20% of patients with PPH. Unfortunately, there is no simple way to predict who will respond. Consequently, it is imperative to evaluate pulmonary vasoreactivity during right heart catheterization prior to selecting long-term therapy. The most suitable drugs for testing acute vasodilator response are potent, short acting, and titratable. Prostacyclin, adenosine, or nitric oxide can all be used for acute vasodilator testing. A minimal acceptable response would be a reduction in mean pulmonary artery pressure of 10 mm Hg associated with either no change or an increase in cardiac output.[1] Long-term therapy with high-dose oral calcium channel blockers can produce sustained hemodynamic responses and increase survival in patients with acute vasoreactivity.[26] However, oral calcium channel blockers can have pronounced systemic hypotensive effects. Patients who do not have an acute vasodilator response are unlikely to benefit from chronic oral calcium antagonists.

Epoprostenol (prostacyclin) is the single most important advance in the treatment of PPH. It may also be effective in select patients with pulmonary arterial hypertension related to collagen vascular disease, congenital heart disease and portopulmonary hypertension.[27,28] Epoprostenol is a potent, short-acting vasodilator and inhibitor of platelet aggregation that is produced by vascular endothelium. PPH patients treated with continuous intravenous infusion of epoprostenol have improved exercise capacity, quality of life, hemodynamics, and long-term survival compared to those treated with conventional therapy.[29] Lack of an acute vasodilator response to epoprostenol does not preclude a long-term benefit. Although the delivery system for continuous infusion is complex, most patients are able to learn how to prepare and infuse the drug. Dose-related side effects are common and include flushing, headache, jaw pain, nausea, foot pain and diarrhea. As tachyphylaxis develops, the dose of epoprostenol is slowly increased. Titration involves balancing the symptoms of drug excess against those of inadequately treated pulmonary hypertension. Abrupt cessation of long-term infusion is poorly tolerated and potentially catastrophic.

The side effects and inconvenience of continuous intravenous epoprostenol infusion make other routes of administration attractive. Subcutaneous, inhaled, and oral forms of prostacyclin analogs are being evaluated.

Treprostinil is a stable prostacyclin analog administered subcutaneously through an ambulatory

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