PRIMARY PULMONARY HYPERTENSION

WAQAS AHMED, SABEEN RAZAQUE**, AYESHA KHALID****

INTRODUCTION

Primary pulmonary hypertension (PPH) is a rare disease characterized by elevated pulmonary artery pressure without a demonstrable cause. Defined as a mean pulmonary artery pressure (PAP) >25mmHg at rest or >30mmHg during exercise[1]. PPH is also termed pre-capillary pulmonary hypertension or, more recently, idiopathic pulmonary arterial hypertension (IPAH). The diagnosis is usually made after excluding other etiologies that may cause secondary pulmonary hypertension (Table-1). Dresdale and colleagues first reported a hemodynamic account of PPH in 1951[2]. Internationally, the incidence of primary pulmonary hypertension ranges from 1 to 2 cases per million people in the general population[3]. Prior to the 1990s, therapeutic options were limited. The recent emergence of prostacyclin analogues, endothelin receptor antagonists, and other novel drug therapies has greatly improved the outlook for patients with PPH and PPH-like diseases. PPH occurs at a female-to-male ratio ranging from 2-9:1, depending on the treatment center sampled. No racial predilection is recognized. PPH typically develops in younger women of childbearing age. However, it can also affect women in their fifth and sixth decades of life or older. The mean age at presentation for PPH is fourth decade[4].

FAMILIAL AND GENETIC VARIANT:

A subset of the patients with PPH has a familial variant. Familial primary pulmonary hypertension accounted for 6 percent of the 187 cases in the NIH registry[4]. The histopathological and clinical features of the familial form of the disease are identical to those of the sporadic form,[5] although, not unexpectedly, the diagnosis is made earlier in the familial form. The familial form is inherited as an autosomal dominant trait and is associated with a pattern of "genetic anticipation"; a worsening of disease in subsequent generations, manifested by greater severity or earlier onset[6].

Some cases may be related to sporadic genetic defects. The most common genetic defect in these cases is related to the BMPR-II gene. Mutations in transforming growth factor (TGF)-ß receptor 2, an important growth regulatory gene, have been described by Yeager and colleagues in endothelial cells in PPH. Such mutations have been proposed to impair the TGF-ß signaling system, an important growth suppressor, thus assisting in cell proliferation[7,8].

CLINICAL PRESENTATION:

The average time from symptom onset to diagnosis has been reported to be approximately 2 years. In about 10 percent of patients, the diagnosis is not established until after three years of symptoms[4]. Early symptoms are nonspecific. Women are more likely to be symptomatic than men. The most common symptoms reported in a national prospective study by Rich, et al in 1987 were dyspnea (60%), weakness (19%) and recurrent syncope (13%)[4].

Physical findings in PAH can be quite variable. A loud P2 component of second heart sound which may demonstrate fixed or paradoxic splitting in the presence of severe right ventricular dysfunction. Occasionally, the second heart sound may be palpable. Murmurs of tricuspid regurgitation & pulmonary regurgitation (Grahams Steell) are usually audible. A right ventricular heave may also be palpable. Jugular venous pulsations may be elevated in the presence of volume overload, right ventricular failure, or both. Large V waves are often present because of the commonly present severe tricuspid regurgitation.

Other findings may include hepatomegaly with palpable pulsations of the liver and an abnormal

* *Department of Cardiology, Shifa International Hospital, Islamabad correspondence.*

** *Department of Cardiology, Shifa International Hospital, Islamabad.*

*** *Consultant Cardiologist, Shifa International Hospital, Islamabad.*

abdominal-jugular reflex. Ascites is not uncommonly present in untreated patients or in patients with worsening decompensated right heart failure. Pulmonary examination may be unremarkable. Variable degree of dependent edema may be present.

PATHOPHYSIOLOGY:

The pathophysiology of PPH is not well understood. But three elements combine to produce increased vascular resistance in patients with primary pulmonary hypertension: vasoconstriction, vascular-wall remodeling, and thrombosis in situ. An insult (e.g., hormonal, mechanical etc.) to the endothelium may occur, possibly in the setting of increased susceptibility to pulmonary vascular injury (the multiple hit theory), resulting in a cascade of events characterized by vascular scarring, endothelial dysfunction, and intimal and medial (smooth muscle) proliferation. Early in the disease, as the pulmonary artery pressure increases, thrombotic pulmonary arteriopathy occurs. Thrombotic pulmonary arteriopathy is characterized by in situ thrombosis of small muscular arteries of the pulmonary vasculature. Thrombosis may result from injury to the endothelium, abnormal fibrinolysis, enhanced procoagulant activity, and platelet abnormalities[9]. In later stages, as the pulmonary pressure continues to rise, plexogenic pulmonary arteriopathy develops. This is characterized by a remodeling of the pulmonary vasculature with intimal fibrosis and replacement of normal endothelial structure[10,11].

An imbalance between prostacyclin and thromboxane was first suggested by Christman et al, who found decreased urinary levels of 2, 3-dinor-6-keto-prostaglandin F1 , a metabolite of prostacyclin, as well as increased level of 11-dehydro-thromboxane B2, a thromboxane A2 metabolite, in patients with PPH as well as secondary pulmonary hypertension. Endothelial cells are the primary sites of prostacyclin synthase protein expression in the pulmonary circulation[12]. Tuder and colleagues reported decreased expression of prostacyclin synthase in small and medium-sized pulmonary arteries of patients with severe pulmonary hypertension[13].

Impaired synthesis of the endothelium-derived vaso-relaxant nitric oxide and enhanced production of the endothelium-derived vasoconstrictor endothelin have also been associated with pulmonary hypertension[14,15]. Whether these abnormalities are the cause or the result of the disease, however, remains uncertain.

DIAGNOSTIC EVALUATION:

ECG usually reveals right atrial enlargement, right axis deviation, right ventricular hypertrophy, and characteristic ST depression and T-wave inversions in the anterior leads. Some patients have few or no abnormal ECG findings; thus, normal ECG results do not exclude a diagnosis of PPH.

Chest radiography is usually the first diagnostic step in the evaluation of a patient with dyspnea; however, for many patients with PPH, the findings do not help reveal the underlying etiology of the pulmonary hypertension. Chest radiography is useful for excluding interstitial and alveolar processes that may cause hypoxia-mediated pulmonary vasoconstriction. Echocardiography is extremely useful for assessing right and left ventricular function, estimating pulmonary systolic arterial pressure, and excluding congenital anomalies and valvular disease. Pulmonary hemodynamics are markedly deranged, with increases in pulmonary-artery pressure to levels three or more times normal, elevated right heart pressure, and depressed cardiac output[4]. Pressures on the left side of the heart are usually normal, although extreme dilation of the right heart chambers can compress the left chambers to a degree that limits filling and produces small increases in diastolic pressures.

High-resolution chest CT scanning and ventilation-perfusion lung scanning are frequently obtained to help exclude interstitial lung disease and thromboembolic disease.

Pulmonary angiography may occasionally be required to help definitively exclude thromboembolic disease. While considered a high-risk procedure in patients with elevated pulmonary arterial pressures and/or right ventricular failure, a carefully performed study is generally safe[21].

Pulmonary function and cardiopulmonary exercise testing helps in the assessment of ventilatory efficiency and mechanical lung function can help differentiate intrinsic pulmonary vascular disease

from cardiac deconditioning and restrictive or obstructive lung disease. In patients with PPH, values for peak exercise oxygen consumption, oxygen pulse, and ventilator equivalents (ratio of expired volume to carbon dioxide output at the anaerobic threshold) during exercise are abnormal to varying degrees.

Right heart catheterization is considered gold standard test to definitively confirm a PPH diagnosis. Catheterization is also performed to determine vasoreactivity , which may have implications in the initiation and titration of vasodilator therapy. When the etiology of pulmonary hypertension is still in doubt, a lung biopsy may be necessary.

OTHER TESTS:

* Antinuclear antibody (ANA): When performing a workup of a patient with possible PPH, excluding autoimmune disorders is important. However, up to 40% of patients with PPH have been reported to have a positive ANA and have no other clinical manifestations of autoimmune disease[4].
* Thyroid-stimulating hormone: Screening for thyroid abnormalities during the initial workup for PPH should be done because these abnormalities are common in patients with PPH. Thyroid abnormalities may be the cause of or contribute to symptoms similar to PPH. In addition, hyperthyroidism itself may lead to an elevation in pulmonary artery pressure.
* HIV testing: HIV-positive patients have a higher rate of PPH compared with the general population.
* Leuchte and colleagues suggested that plasma BNP levels are closely related to the functional impairment of PPH patients and parallel the extent of pulmonary hemodynamic changes and right heart failure. Serial measurements of plasma BNP concentrations may help improve the management of PPH patients[17].

TREATMENT:

A) ORAL VASODILATOR THERAPY:

Calcium-channel blockers (CCBs) like nifedipine and diltiazem have been shown to improve survival in patients with PPH.18 Until recently, CCBs had been the most widely used class of drugs for PPH. These drugs are thought to act on the vascular smooth muscle to dilate the pulmonary resistance vessels and lower the pulmonary artery pressure. Several studies report clinical and hemodynamic benefits from the use of long-term calcium channel blockade. The use of these drugs produces a reduction in pulmonary vascular resistance by increasing the cardiac output and decreasing pulmonary artery pressure. It also improves the quality of life and survival rate, in patients who are proven "responders" to such therapy. A cardiac index of less than 2 L/min/m2 or elevated right atrial pressure above 15 mm Hg is evidence that CCBs may worsen right ventricular failure and, thus, may be potentially harmful to patients with PPH.
In general, high doses of CCBs are used in patients with PPH; however, only patients with an acute vasodilator response to an intravenous or inhaled pulmonary vasodilator challenge (e.g., with adenosine, epoprostenol, nitric oxide) derive any long-term benefit from CCBs (this corresponds to <20% of patients with PPH). Similarly, patients without an acute vasodilator response to a vasodilator challenge have a worse prognosis on long-term oral vasodilator therapy compared with those who have an initial response.

Importantly, the absence of an acute response to intravenous or inhaled vasodilators does not preclude the use of intravenous vasodilator therapy. In fact, continuous intravenous vasodilator therapy is strongly suggested for these patients because CCBs are contraindicated.

It is important to perform vasoreactivity testing in patients with PPH prior to treatment. Intravenous epoprostenol[19] or adenosine[20] or inhaled nitric oxide[21] are used most commonly for acute vasodilator testing. Oxygen, nitroprusside, and hydralazine should not be used as pulmonary vasodilator testing agents.

Only up to 25% of patients with PPH demonstrate significant pulmonary vasoreactivity, treated with high dose CCB under hemodynamic monitoring. Oral nifedipine may be given every hour (diltiazem can be used if resting tachycardia is present) until a 20% decrease in pulmonary artery pressure and pulmonary vascular resistance is observed or systemic hypotension or other adverse effects preclude further drug administration.

Wilkinson et al. have shown that oral sildenafil may be beneficial as a selective pulmonary vasodilator in patients with primary pulmonary hypertension[22]. Sildenafil therapy, both in its intravenous and oral form, is well tolerated and appears to be safe in patients with pulmonary hypertension. Mid-term oral sildenafil therapy led to improved pulmonary hemodynamics and improved functional class and exercise tolerance[23]. A study in children suggested a potential role for sildenafil in the management of pulmonary hypertension[24, 25].

B) OTHER ORAL AGENTS

Digoxin is frequently used with intent to improve right ventricular function in patients with right ventricular failure. However, no randomized controlled clinical study has been performed to validate this strategy for patients with PPH.

Loop diuretics are routinely used to manage peripheral edema. Potassium-sparing diuretics may have a role in ameliorating the sometimes-intractable hypokalemia observed with daily diuretic use.

C) PROSTACYCLIN ANALOGUES:

The observation that epoprostenol produces acute hemodynamic effects in a substantial proportion of patients[26] led to its use in long-term therapy. Epoprostenol must be given by continuous intravenous infusion, since it has a short half-life in the circulation and is inactivated by the low pH of the stomach. The drug is delivered with a portable infusion pump attached to a permanent indwelling central venous catheter. In a three-month randomized, prospective trial, the infusion of epoprostenol improved hemodynamic characteristics, exercise tolerance, quality of life, and survival in patients in New York Heart Association functional classes III and IV, as compared with a group of similar patients receiving conventional therapy[27]. Beneficial long-term hemodynamic responses have also been reported, although the dosage required to sustain these effects increases with time[28]. The major adverse effects of long-term therapy with epoprostenol are attributable to the complex delivery system involved; they include pump malfunction, catheter-related infections, and thrombosis[27,28]. Drug-induced side effects are common and include jaw pain, cutaneous erythema, diarrhea, and arthralgias. Intermittent therapy with nebulized iloprost, a stable analogue of prostacyclin, may be feasible,[29] although the long-term effects of this approach have not been evaluated.

Long-term therapy with epoprostenol produces sustained hemodynamic responses even in patients who have little or no response to acute infusion[27]. properties of the drug other than its vasodilator activity, including the inhibition of platelet aggregation and effects on vascular remodeling, may be responsible for these long-term effects. Thus, in contrast to oral vasodilators, which should not be used without evidence of a patient's vasoreactivity to acute challenge, therapy with epoprostenol may be initiated without an acute challenge. Epoprostenol has been used as a primary mode of therapy or as a bridge to transplantation. Several patients have been receiving epoprostenol by continuous infusion for almost 10 years with sustained clinical and hemodynamic benefits[32].

D) NEWER THERAPIES:

Bosentan, the endothelin-receptor antagonist, has been shown to reduce pulmonary artery pressure acutely in patients with pulmonary hypertension[30, 31]. Early reports indicate that bosentan increased exercise tolerance to a degree commensurate with that reported with prostacyclin infusion at a similar stage in the illness[32].

E) HOME OXYGEN:

Hypoxemia is a potent pulmonary vasoconstrictor, and can contribute to the progression of PPH. It is generally considered important to maintain oxygen saturations at > 90% at all times.

F) ORAL ANTICOAGULATION:

Anticoagulation has been recommended as therapy because there is an increased risk of thrombosis and thromboembolism in situ due to sluggish pulmonary blood flow, dilation of the right heart chambers, venous stasis, and the limitations in physical activity imposed by the disease. A retrospective analysis by Fuster and colleagues suggest that anticoagulation prolongs life[33]. When used, the international normalized ratio should be maintained at 1.5- to 2-times the control value, provided the patient has no contraindications to anticoagulation.

G) SURGERY:

A single- or double-lung transplant is indicated for

patients who do not respond to medical therapy[34, 35]. Simultaneous cardiac transplantation is not necessary in all patients. The timing of transplantation is a difficult challenge. Patients whose condition improves substantially with epoprostenol may wish to defer transplantation; those with little or no response to the drug are more likely to require transplantation, early[36].

Atrial septostomy is a palliative procedure that may afford some benefit to patients with deteriorating conditions, albeit at the cost of lower overall saturations[37].

PROGNOSIS:

The mortality rate for untreated PPH is approximately 50% at 3 years (this varies with severity at presentation). With epoprostenol therapy, this has increased to higher than 65% at 5 years. Data on long-term survival in patients treated with other pulmonary vascular therapies are emerging. Patients whose disease progresses and is unresponsive to medical treatments either undergo transplantation or die of progressive right-sided heart failure.

ACTIVITY LIMITATIONS:

Few data are available on cardiopulmonary rehabilitation. The generally accepted recommendation is that patients with pulmonary hypertension and heart failure may perform mild symptom-limited aerobic activity and avoid complete bed rest. Isometric exercises (weight-lifting) are contraindicated.

The hemodynamic stresses of pregnancy are poorly tolerated by women with PPH, and sudden deterioration, particularly in the immediate postpartum period, can be fatal[38]. Oral contraceptives are not recommended for birth control, since their use may exacerbate pulmonary hypertension[39].

Table-1: Causes of secondary Pulmonary Hypertension.

Causes of secondary Pulmonary Hypertension
1- Cor Pulmonale
2- Mitral Stenosis
3- Pulmonary Embolism
4- Pulmonic Stenosis
5- Sleep Apnea
6- Dilated Cardiomyopathy
7- Connective Tissue Diseases
* CREST@ variant of Scleroderma
* Systemic Lupus Erythematosis
* Mixed Connective Tissue Diseases
8- Anorexigens
* Fenfluramine
* Dexfenfluramine
9- Alpha adrenergic stimulants
* Cocaine
* Amphetamine
10- Human Immunodeficiency Virus(HIV) seropositivity

*CREST-calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia.

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