Drugs 2001; 61 (13): 1945-1956
0012-6667/01/0013-1945/$27.50/0

Current Management of Primary Pulmonary Hypertension

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Contents

Abstract

Primary pulmonary hypertension (PPH) is a rare disorder with an annual incidence of 1 to 2 per million people. The aetiology of this disorder is unknown, but it appears to result from an abnormal interaction of environmental and genetic factors leading to a vasculopathy. The pulmonary arteries in these patients exhibit a spectrum of pathological lesions ranging from the early medial hypertrophy to the end-stage fibrotic plexiform lesions. This characteristic pathology is also observed in pulmonary hypertension resulting from connective tissue disease (particularly systemic sclerosis), HIV infection, portal hypertension and certain toxins.

PPH is a condition that is difficult to diagnose and treat, with a median survival of 2.8 years in historical studies. One of the difficulties in treating patients with PHH is that the subacute nature of disease presentation often prevents an accurate diagnosis during the early stages of the illness. Progressive dyspnoea on exertion is the most common presenting symptom. Diagnostic evaluation should include electrocardiography, chest radiograph and echocardiography, and laboratory and other studies to evaluate for secondary causes (e.g. pulmonary function tests,

chest computed tomography and ventilation/perfusion scans, pulmonary arteriogram, cardiopulmonary testing, right heart catherisation).

PHH is a disorder for which there is no known cure. Current medical and surgical treatment options for patients with PHH include anticoagulation, vasodilators and transplantation. Calcium channel antagonists are currently the oral drugs of choice for the treatment of patients with New York Heart Association (NYHA) Class II disease. These agents, in particular the dihydropyridine compounds, have beneficial effects on haemodynamics and right ventricular function, and possibly increased survival. Epoprostenol is administered by intravenous infusion, and studies have demonstrated short- and long-term improvements in symptoms, haemodynamics and survival. It is well tolerated and has become the treatment of choice for patients with NYHA Class III and IV disease.

Inotropic agents are used as a bridge to transplant, which is indicated in patients who do not respond to maximal medical therapy. Experience has shown that single lung, double lung and heart-lung transplantation are approximately of equal efficacy. Currently, single lung transplant appears to be the procedure of choice.

Newer agents, such as sildenafil, beraprost and bosentan, are presently being evaluated for the treatment of this disorder. Future study should include elucidation of the pathogenic mechanisms in the development of this vasculopathy, which will hopefully lead to the development of improved treatment options for patients with PHH.

Primary pulmonary hypertension (PPH) is a rare disorder with an annual incidence of 1 to 2 per million people.[1] This disorder is defined clinically by the presence of a mean pulmonary artery pressure (PAP) >25mm Hg at rest or >30mm Hg with exercise, accompanied by a pulmonary vascular resistance (PVR) >160 dynes/sec cm^{-5} and a pulmonary capillary wedge pressure (PCWP) <15mm Hg.[2] In addition to this clinical definition, patients with PPH histologically exhibit a primary pulmonary arteriopathy characterised by varying degrees of medial and intimal hypertrophy, intimal fibrosis and *in situ* thrombosis, the aetiology of which remains unclear (fig. 1).[1,3]

PPH is a disorder which affects women more frequently than men (1.7 : 1), most commonly in the fourth decade of life. As patients usually present with vague symptoms, it can take 18 to 24 months to make this diagnosis, usually, when the patient has severe limitations from the disease. Because of limited treatment options, the prognosis has been poor, with an historical median survival of 2 years after diagnosis.[1] One of the major developments over the past ten years has been new treatment options for patients with PPH that not only improve symptomatology but also survival. It is theorised that, over time, these treatments will significantly alter the natural history of PPH. This review considers the current classification of pul-

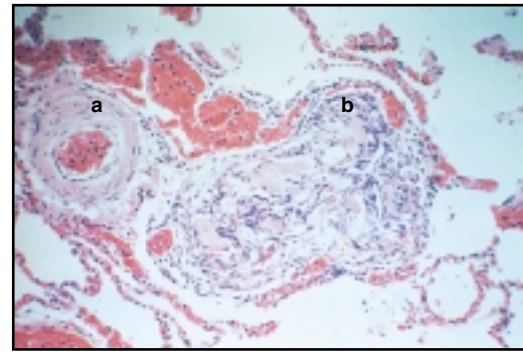

Fig. 1. Histological section of the lungs of a patient with primary pulmonary hypertension (PPH) (haematoxylin and eosin stained, 63X). This section demonstrates the characteristic vascular lesions of PPH: (**a**) hypertrophy of the vascular media; (**b**) plexiform lesion.

monary hypertension (PH) and relates this to diagnostic and treatment regimens for patients with PPH.

1. Clinical Classification of Primary Pulmonary Hypertension (PPH)

In the past, PH had been classified as either primary (idiopathic) or secondary to another disease state. However, it has been clear that within the classification of secondary PH, there existed conditions with similar histopathology and response to treatment as PPH. This prompted a re-classification of PH at the World Health Organization (WHO) meeting of 1998 (table I).[4]

1.1 PPH

1.1.1 Sporadic

This disorder most commonly affects women in their fourth decade as described in the opening paragraphs.

1.1.2 Familial

Approximately 100 families worldwide with genetic predilection for PPH have been identified. Familial PPH is present in approximately 6% of all patients and has a similar female to male gender ratio, age of onset and natural history as the sporadic form. Transmission appears to be autosomal dominant with incomplete penetrance often leading to skipped generations.[4,5] One of the genes responsible for this disorder has been identified as *PPH 1* (locus 2q 31-32), but lifetime prevalence is <20% even if the gene is present.[4] In asymptomatic family members, abnormalities in the 2q 31-32 locus have been associated with abnormal elevation in PAP in response to exercise.[6] This suggests that clinical screening of asymptomatic family members by stress Doppler echocardiography may be a means to identify patients at risk for the development of PPH. Further investigation has correlated mutations in the bone morphogenetic protein receptor gene II (*BMPR II*) with the vascular proliferative lesions observed in PPH, suggesting that this is the same as *PPH 1*.[7] Although the role of *BMPR II* in the pathogenesis of PPH has not

Table I. WHO classification of pulmonary hypertension[4]

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
others
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 veno-occlusive 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 secondary to chronic thrombotic and/or embolic disease
Thrombembolic obstruction of proximal pulmonary arteries
Obstruction of distal pulmonary arteries
pulmonary embolism
in situ thrombosis
sickle cell disease
Pulmonary hypertension secondary to disorders directly affecting the pulmonary vasculature
Inflammatory
schistosomiasis
sarcoidosis
other
Pulmonary capillary haemangiomatosis

been clarified, this will probably be an area of intense interest in the future.

1.2 Other Conditions Associated with Pulmonary Hypertension (PH)

1.2.1 Connective Tissue Disorders

A primary arteriopathy occurs most commonly in patients with limited systemic sclerosis (SSc) the CREST variant (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, teleangectasias) in which up to 80% will have histopathological changes consistent with PH at autopsy.[8-10] Histology consistent with PH has also been demonstrated in systemic lupus erythematosis (SLE), mixed connective tissue disease (MCTD) and rheumatoid arthritis (RA).[1] There is a high association between the presence of connective tissue disorder-related PH and the presence of Raynaud's phenomenon, suggesting that there may be similarities in the vasculopathies present in each of these disorders. Because of the high incidence of PH in this patient group and the difficulty in making an early diagnosis, the WHO conference recommended annual echocardiograms to evaluate pulmonary pressures in all patients with limited SSc, regardless of symptoms.[4]

1.2.2 HIV Infection

An association between HIV infection and PH was first reported in 1991; a review of 1200 patients with HIV infection noted an incidence of PPH of 0.5%.[11] Although PH occurs with greater frequency in individuals who use intravenous drugs, no clear aetiological link has been established with either foreign body emboli or portal hypertension related to cirrhosis from hepatitis B or C infection, each of which has been associated independently with PH.

1.2.3 Anorectic Agents

The association between use of anorectic agents and PH was first described in the late 1960s when an epidemic of PH was noted in Europe after the introduction of aminorex.[12] Although this drug was removed from commercial availability, the structurally related compounds fenfluramine and dexfenfluramine were subsequently developed in the 1980s. Use of these agents has also been associated with an increase in the incidence of PPH, particularly in individuals who have taken the drug for more than 6 months.[13,14]

1.2.4 Portal Hypertension

An infrequent association exists between the presence of portal hypertension and PH. Hadengue et al.[15] in 1991 documented that 10 of 507 (2%) patients with portal hypertension had concomitant PH. The mechanism of this association is unclear but cirrhosis without the presence of portal hypertension seems insufficient for development of PH.

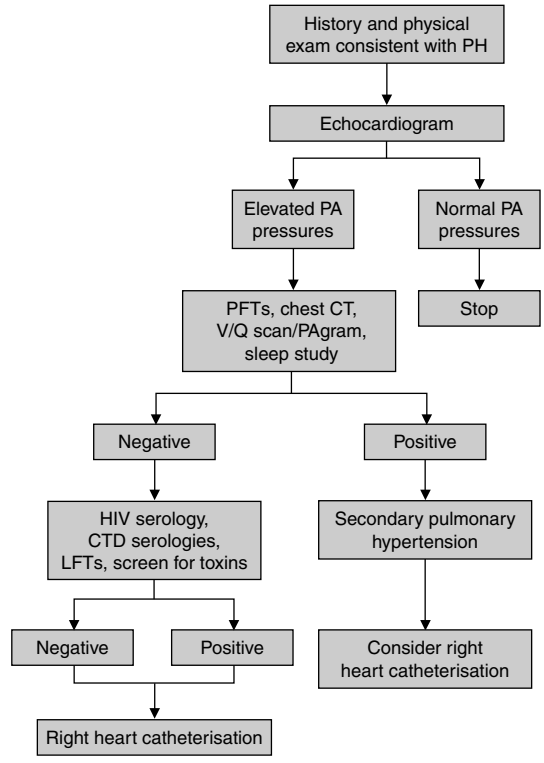

Fig. 2. Algorithm for the diagnostic evaluation of a patient with pulmonary hypertension. **CT** = computed tomography; **CTD** = connective tissue disease; **HIV** = human immunodeficiency virus; **LFTs** = liver function tests; **PA** = pulmonary artery; **PAgram** = pulmonary arteriogram; **PFTs** = pulmonary function tests; **PH** = pulmonary hypertension; **V/Q scan** = ventilation/perfusion scan.

2. Diagnostic Evaluation

2.1 History and Physical Examination

One of the difficulties in treating patients with PPH is that the subacute nature of disease presentation often prevents an accurate diagnosis during the early stages of the illness (fig. 2). It is not unusual for 18 to 24 months to pass before the diagnosis is made.[16] Progressive dyspnoea on exertion is the most common presenting symptom, occurring in 60% of patients at initial presentation and affecting nearly 100% as the disease progresses. Other symptoms usually present with more advanced disease include fatigue, chest pain which may be anginal in nature, syncope, and signs suggestive of right-sided congestive heart failure including weight gain, increased abdominal girth and lower extremity oedema. Physical examination will often reveal a pronounced pulmonic component of the second heart sound, a right ventricular heave, and a right-sided fourth heart sound as early findings.[3] Later in the course of the disease, a right-sided third heart sound, tricuspid insufficiency, elevated jugular venous pressure, cyanosis and oedema may be present. Physical examination should also include evaluation for signs associated with connective tissue disease, liver cirrhosis or HIV infection.

2.2 Electrocardiogram

The electrocardiogram may demonstrate changes consistent with right ventricular (RV) hypertrophy (RVH), including right axis deviation and right atrial (RA) enlargement (cor pulmonale).[17]

2.3 Chest Radiograph

Although a chest radiograph may be normal in up to 10% of individuals with PH, it can often provide clues to the presence of elevated right-sided pressures.[16] Prominence of the main pulmonary arteries is apparent in 90% of patients and peripheral pruning of the vessels occurs in approximately 50%.[16] Moreover, radiographic evidence of RVH can be observed in patients with advanced disease.

2.4 Echocardiogram

An echocardiogram is the best screening examination for patients with suspicion of elevated pulmonary pressures. In addition to evaluating the patient for the presence of left-sided cardiac dysfunction, valvular disease and intracardiac shunts due to congenital heart disease, an approximate calculation of the peak RV pressure can be made. Furthermore, if tricuspid regurgitant flow is sufficient, the peak systolic PA pressure can be estimated. PPH patients will typically demonstrate RVH or RV dilation, RA enlargement, and, as the disease progresses, a decrease in the size of the left ventricular cavity as a result of leftward displacement of the interventricular septum. Pulmonic and tricuspid insufficiency will often be present on Doppler examination.[18] In advanced disease, the inferior vena cava will be distended and will not collapse during inspiration.

2.5 Laboratory Studies

To evaluate the patient for other causes of PH, laboratory evaluation for connective tissue disease (particularly SSc and SLE), HIV infection, and hepatic dysfunction should be performed.

2.6 Other Studies

Other studies should be conducted to evaluate the patient for secondary causes of PH.

2.6.1 Pulmonary Function Tests

Pulmonary function tests should be performed to exclude the presence of significant obstructive or restrictive lung disease which, if associated with hypoxaemia, will result in elevated PA pressures. In patients with PPH, either restrictive or obstructive physiology can be observed, although the most common finding is an isolated decline in the diffusing capacity for carbon monoxide as a result of a low blood volume of the pulmonary capillaries.[16]

2.6.2 High Resolution Computed Tomography

High resolution computed tomography (CT) can evaluate the lung parenchyma for the presence of interstitial lung disease, or for findings consistent with pulmonary veno-occlusive disease or pul-

monary capillary haemangiomatosis, each of which may result in secondary PH. If suspicion for chronic or recurrent pulmonary thromboembolism is high, a helical CT scan can be used for visualisation of the central pulmonary arteries. Although usually unnecessary and not routinely performed, magnetic resonance imaging with angiography can be used alternatively to view the lung parenchyma and the pulmonary vasculature.

2.6.3 Ventilation-Perfusion Scintigraphy/Pulmonary Angiography

Ventilation-perfusion scintigraphy and pulmonary angiography are performed to evaluate the patient for the presence of chronic thromboembolic disease. In general, occlusion of >70% of the pulmonary vessels is necessary before PAP is elevated. In patients with PPH, these scans will be normal or reveal patchy defects,[3,16] whereas in patients with chronic thromboembolic disease, multiple larger perfusion defects will be observed. If the lung scan is inconclusive, pulmonary arteriography may be necessary in order to determine definitively the existence of thromboembolic disease.

2.6.4 Cardiopulmonary Exercise Testing

Exercise testing is not required to make the diagnosis of PH. However, the six-minute walk test has been used extensively in clinical trials in patients with PPH to objectively evaluate the symptomatic response to therapy.[19]

2.6.5 Right Heart Catheterisation

Although the non-invasive studies elaborated in this section will screen patients and provide information to help distinguish between primary and secondary PH, the actual measurement of pulmonary haemodynamics can only be realised by right heart catheterisation. Echocardiograms are notoriously inaccurate in measuring PAP, thus limiting their usefulness as a diagnostic tool and as a means to evaluate therapeutic interventions. Right heart catheterisation allows for direct assessment of RA, RV and PA pressures as well as measurement of pulmonary capillary wedge pressure (PCWP) and cardiac output (CO). Thus, this study should be used not only for diagnosis of PH but also in determining the acute and long term response to pharmacological interventions.

3. Treatment of PPH

PPH is a disorder for which there is no known cure. However, treatment has dramatically improved over the last 10 to 15 years providing options that offer both symptomatic improvement and prolonged survival. In certain patients, particularly those with anorexigen-associated PPH, there can be a spontaneous remission upon withdrawal of the offending agent.[13] In most patients, medical and/or surgical therapy is warranted, particularly for those patients with New York Heart Association (NYHA) Class III or IV disease. The mainstays of medical therapy include anti-coagulation, vasodilators, and oxygen therapy if hypoxemia is present (fig.3).

Data from the US National Registry of patients with PPH demonstrate that the haemodynamic variables most predictive of prognosis are those reflective of RV function; RA pressure, pulmonary artery pressure (PAP) and cardiac index (CI).[20] Vasodilator therapy has been used in this patient group with the goal of reversing the pulmonary vasoconstrictive process to improve RV function, decrease symptoms and improve exercise tolerance, and prolong survival.[21] Unfortunately, many of the agents used failed to achieve these goals without significant toxicity, such as systemic hypotension and hypoxaemia. This section (3) reviews the current state of medical and surgical treatment options for patients with PPH.

3.1 Anticoagulation

Anticoagulation has been recommended as adjunctive therapy for patients with PPH on the basis of two small studies, one retrospective[22] and one prospective,[23] which suggest that such use prolongs survival. There are several possible mechanisms for the increased risk of thromboembolic disease in these patients. First, the relative decrease in physical activity, particularly with late-stage disease, places these patients at risk for the development of deep venous thromboses and subsequent

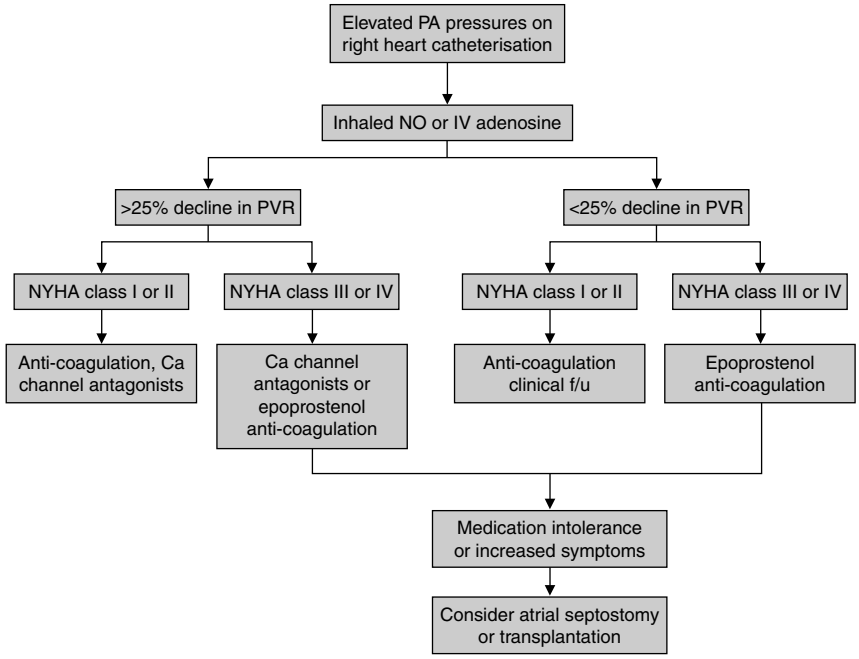

Fig. 3. Algorithm for treatment strategies for patients with primary pulmonary hypertension. **Ca** = calcium; **f/u** = follow-up; **IV** = intravenous; **NO** = nitric oxide; **NYHA** = New York Heart Association; **PA** = pulmonary artery; **PVR** = pulmonary vascular resistance.

pulmonary emboli. Secondly, it is hypothesised that decreased pulmonary blood flow results in an increase in microthrombi in the pulmonary vasculature of these patients. Although these may not be the primary events responsible for the elevation of pulmonary pressures observed in PPH, they may have a contributory effect.

3.2 Vasodilators

To assess the response to vasodilators accurately, initiation of these drugs should be performed with a pulmonary artery catheter in place. When assessing the haemodynamic response to vasodilators, the most important variable is the change in pulmonary vascular resistance (PVR) as this reflects RV function, whereas changes in PAP do not.[21] A therapeutic response to a vasodilator in most trials is considered a decline in PVR by ≥25%.[2,24,25]

3.2.1 Adenosine and Nitric Oxide

To predict which patient will have a therapeutic response to vasodilators, a trial for vasoreactivity is generally performed, usually with either inhaled nitric oxide (NO) or intravenous adenosine.[3] Sitbon et al.[26] demonstrated that 37% of patients with PPH had a significant haemodynamic response to inhaled NO; this predicts an acute response to epoprostenol (prostacyclin). As NO is rapidly metabolised within the pulmonary circulation, there is no systemic hypotension associated with the use of this medication. The short half-life and need for continuous inhalation limits its efficacy for long term use, although it has been used long-term in a small number of patients.[27]

Adenosine has also been used as a screening agent for pulmonary vascular reactivity;[28] unfortunately, its extremely short half-life makes long-term use impractical.

Although initially it was thought that a response to either NO or adenosine was predictive of subsequent response to epoprostenol, more recent work suggests that this underestimates the number of patients who will be responders and that the long term effect of epoprostenol is independent of an acute vasodilator response.[16,29] Currently, trials for vasoreactivity are most predictive of subsequent response to calcium channel antagonists,[30] suggesting that patients who respond to calcium channel antagonists may, pathologically, have earlier, less fibrotic vascular lesions of their pulmonary arteries.

3.2.2 Calcium Channel Antagonists

Calcium channel antagonists are currently the oral drugs of choice for treatment of PPH. Rich and Brundage[30] demonstrated in 1987 that these agents, primarily the dihydropyridine compounds, had beneficial effects on haemodynamics and RV function in patients with PPH, confirming previous work by Rubin.[31] Moreover, in some studies, it has been noted in responders that there may be an increase in survival.[23]

Unfortunately, there are several factors limiting the widespread use of calcium channel antgonists in patients with PPH. First, a significant haemodynamic effect is observed in less than 30% of patients studied.[23,30] Secondly, the much higher doses which are required to lower PVR (up to 960 mg/day of diltiazem or 240 mg/day of nifedipine) are often associated with systemic effects, such as depressed myocardial contractility and hypotension, which require cessation even in patients who are acute responders.[1] Even so, their relatively low cost and ease of administration make the calcium channel antagonists a therapeutic option for responders with NYHA Class II disease. In isolated instances, patients with NYHA Class III or Class IV disease have been treated successfully with these agents.

3.2.3 Epoprostenol

Epoprostenol, the synthetic form of prostaglandin (PG)I_2, was first demonstrated by Higenbottam in the 1980s to have selective vasodilatory effects on the pulmonary vasculature.[32] Since that time, several studies have demonstrated that continuous intravenous infusion of epoprostenol results in short- and long-term improvements in symptoms, haemodynamics and survival for up to 3 years.[20,33,34] In addition to its role as a potent vasodilator, epoprostenol decreases platelet aggregation and migration, which may play a beneficial role in treating the potential pro-thrombotic state of PPH.[35,36] Epoprostenol may also play a role in vascular remodelling during long-term administration since even individuals without an acute response to this drug may demonstrate significant improvement in haemodynamic response over time.[20,33] Moreover, in responders, the extent of the haemodynamic response improves over time.[20,33] In addition to its effects on pulmonary haemodynamics, long-term use of epoprostenol has been associated with reversal of echocardiographic evidence of RVH, which again suggests that there may be some remodelling effects on the myocardium.[37]

Epoprostenol has been well tolerated long-term and because of its efficacy, has become the treatment of choice for patients with NYHA Class III or IV PPH.[2] The dosage required long-term is highly variable among patients. The major shortcoming with the use of epoprostenol is the need for long term intravenous access for the continuous infusion and the subsequent slight increased risk of infection. In addition, for reasons that are not clear, patients develop tolerance to the medication with long-term use requiring an increasing dosage over time. These factors, as well as the extremely high cost of epoprostenol, have led to evaluation of a subcutaneous form of this agent. However, results are too preliminary at this stage to make recommendations for the use of epoprostenol by the subcutaneous route.[38]

3.2.4 Iloprost

The use of the stable prostacyclin analogue, iloprost, by inhalation has been used to mitigate some of the problems associated with intravenous epoprostenol. Two small, uncontrolled trials have demonstrated acute and long-term improvement in haemodynamics and symptoms in patients with NYHA Class III or IV disease.[39,40] Sustained

haemodynamic effects have been demonstrated for up to 1 year; however, the effect of iloprost on mortality has not been well established.[40] The lack of a controlled trial comparing the use of iloprost to intravenous epoprostenol and its unavailability in the US makes recommendations regarding its use too preliminary at this point.

3.2.5 Other Vasodilators

Angiotensin converting enzyme (ACE) inhibitors, peripheral α-adrenergic agonists, β-blockers, nitrates, and direct vasodilators such as diazoxide and hydralazine have all been tried in the treatment of patients with PPH. Unfortunately, even if an acute haemodynamic response was observed with any of these agents, the effect was not sustained.[29,41-43] As such, these agents have all been abandoned as potential therapeutic options for patients with PPH.

3.2.6 Newer Therapies

Sildenafil, a highly specific oral inhibitor of phoshodiesterase-5, prevents breakdown of cyclic guanosine monophosphate (cGMP), potentially increasing NO bioavailability within the pulmonary vasculature. Case reports in adults and children with PH have reported increased pulmonary vasodilation acutely in response to this medication;[44,45] use of this agent may also potentiate the effects of inhaled NO.[46]

Beraprost, an oral PGI_2 analogue, has a longer half-life than intravenous epoprostenol, obviating the need for continuous infusion. Small studies of patients with PPH and PH secondary to congenital heart disease have demonstrated short-term improvement in haemodynamics when this medication is used alone or in conjunction with inhaled NO.[47,48]

Bosentan, an intravenous endothelin-1 receptor antagonist, has been used in a small study of patients with PPH or isolated SSc-associated PH.[49] Although a dose-dependent decrease in PVR and mean PAP was observed, the occurrence of systemic hypotension may limit its long-term use. Larger studies over a longer time period are needed before general recommendations can be made regarding the use of beraprost, sildenafil or bosentan.

3.2.7 Inotropic Agents

As right-sided heart failure is a main cause of mortality in patients with PPH, these agents have been used in patients with right-sided heart failure unresponsive to other drugs as a bridge to transplant. No long-term studies have evaluated use of digoxin in this patient group. Intravenous dobutamine or dopamine may acutely improve symptoms of right-sided heart failure, but the long-term effects of these agents are unknown.[4]

3.3 Surgical Treatment

In patients who do not respond to maximal medical therapy, another treatment option is the creation of an artificial atrial septal defect. Atrial septostomy has the benefit of providing, via creation of a right to left shunt, a means to improve left-sided CO with consequent improvements in oxygen delivery.[50-52] This counteracts the decrease in oxygen content that results from the creation of a right-to-left shunt. Unfortunately, the effect of this procedure on mortality has not been established. It is recommended that this procedure only be performed at centres experienced with the procedure, in severely symptomatic patients without other therapeutic options.[1]

3.3.1 Transplantation

Prior to the emergence of epoprostenol for treatment of severe PPH, heart-lung transplant was the treatment of choice for patients with NYHA Class III or IV disease. However, further experience has demonstrated that single lung, double lung and heart-lung transplant are approximately of equal efficacy in treating this disorder with a 1-year survival rate of 70 to 80% and 3-year survival of 60 to 70%.[1,53] In addition, single lung transplant results in right ventricular re-modelling within 3 to 6 months suggesting that there is no need for heart transplant in most of these patients.[54] Although concern has been raised that single lung transplant may produce dyspnea as a result of increased perfusion to the donor lung, this has not been the case.[53] On the basis of these findings, as well as the relative lack of organs available for transplant, single lung transplant appears to be the procedure

of choice. It is unclear at this point whether PPH recurs in the transplanted lung, but to date there has not been evidence to support this.

Although a direct comparison in survival between patients receiving epoprostenol and those receiving transplantation has not been performed, historical data suggest they may be similar. This suggestion of equal efficacy and the limited number of transplantable organs has led to the recommendation that epoprostenol should be first line therapy for treatment of PPH. Transplantation should be reserved for those who are unable to tolerate epoprostenol or for those who develop progressive RV failure while taking this agent.

4. Treatment of Other Causes of PH

On the basis of the similarities in histopathology which exist between PPH and the other primary vasculopathies associated with PH, it was hoped that a similar therapeutic benefit might be observed with vasodilator therapy in these patients. It is recommended that all patients with PH related to connective tissue disease, HIV infection, portal hypertension, or toxin ingestion receive lifelong anti-coagulation as prophylaxis against microthrombi that may occur in the setting of decreased pulmonary blood flow.

4.1 Vasodilator Therapy

Because of the small number of patients with PH related to connective tissue disease, HIV infection, portal hypertension or toxin ingestion, studies evaluating the use of vasodilators have been very limited. However, in SSc-associated PH, the only agents with demonstrated efficacy are inhaled NO and intravenous epoprostenol.[55-58] In this patient group, inhaled NO is used primarily as a screening agent for vasoreactivity as its long-term effects on SSc-associated PH are unknown.[55] We have demonstrated both acute and long term improvement in symptoms and haemodynamics in patients with SSc-associated PH with continuous epoprostenol for up to 3 years.[56] Badesch et al.[57] demonstrated improved symptoms after 12 weeks of treatment but no clear effect on survival. Humbert et al.[58] demonstrated long term improvement in survival in patients with connective tissue disease treated with epoprostenol.[58] Similar therapeutic effects have been demonstrated by Aguilar and Farber[59] in a small group of patients with HIV-associated PH. As the treatment options for patients with pulmonary arterial hypertension are extremely limited, a trial with intravenous epoprostenol is warranted in the appropriate individuals (those with NYHA Class III or IV disease in whom PH is their life-limiting disease process).

5. Survival

As documented by the US National Registry of PPH patients, the natural history of PPH is that of a progressive illness with a very poor prognosis. Survival correlates inversely with symptomatology with patients in NYHA Class I or II having a median survival of 58 months and those with Class IV disease surviving less than 6 months.[20] The haemodynamic variables associated with the poorest prognosis include RA pressure >20mm Hg, mean PAP >85mm Hg, and CI <2.0 L/min (fig. 4).[20]

Intravenous epoprostenol has been associated with improved 1-, 2- and 3-year survival rates for patients with PPH in NYHA Class III or IV with

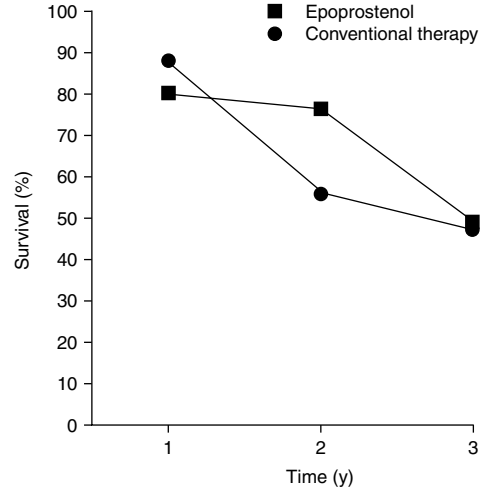

Fig. 4. Kaplan-Meier survival curves of patients with primary pulmonary hypertension (PPH) treated with epoprostenol and those treated with conventional methods.[34]

survival rates of 80, 78 and 50%, respectively.[34] Intravenous epoprostenol may also result in improved survival in the treatment of other forms of PH but data are too preliminary to make a definitive conclusion at the present time. In most patients, the cause of death is progressive right-sided heart failure or sudden cardiac death.[2]

6. Conclusions and Future Directions

Pulmonary arterial hypertension comprises a group of disorders which result in elevated pulmonary pressures secondary to a primary vasculopathy. Although the aetiology of these disorders remains unclear, it may be as a result of a combination of genetic and environmental factors. The characteristic plexiform lesion can be observed histologically in patients with PPH as well as those with other forms of PH. This appears to be an end-stage lesion which may be less responsive to vasodilator therapy.

Although the prognosis for this disorder has been historically poor, newer therapies such as intravenous epoprostenol and transplantation have had beneficial effects on symptoms, haemodynamics and mortality. Newer drug therapies including oral, inhaled and subcutaneous forms of prostacyclin, phosphodiesterase inhibitors and endothelin-1 receptor antagonists are presently being evaluated for their potential roles in the treatment of this disorder.[39,40,44-49]

Future work includes elucidation of the pathogenic mechanisms in the development of the vasculopathy through the use of genetic material from those with the familial form of the disease and explanted tissue from patients who undergo transplantation. This will lead to the development of improved treatment options for patients with PPH that are both easier to administer and result in greater survival.

Acknowledgements

The authors would like to acknowledge the physicians and nurses of the Medical Intensive Care Unit at Boston Medical Center for their assistance in the care of patients.

Dr Klings is funded by American Lung Association Research Training Fellowship RT-030-N and American Heart Association Beginning Grant In Aid 0160150T. Dr Farber is funded by American Heart Association Grant In Aid 0150155N. There are no conflicts on interest involving the authors of this manuscript.

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