REVIEW ARTICLE

Biodrugs 2001; 15 (12): 801-817
1173-8804/01/0012-0801/$22.00/0

Current Management of Primary Pulmonary Hypertension

Tine L.M. De Backer, Jan-Peter Smedema and *Stéphane G. Carlier*

Department of Cardiology, Thoraxcentre, Erasmus Medical Centre Rotterdam, Rotterdam, The Netherlands

Contents

Abstract

Primary pulmonary hypertension (PPH) is a rare disorder of the lung vasculature characterised by an increase in pulmonary artery pressure. Although the aetiology of this disease remains unknown, knowledge of the pathophysiology of the disease has advanced considerably. Diagnosis of PPH is largely by exclusion. The clinical symptoms associated with PPH are aspecific and similar to those seen in other cardiovascular and pulmonary diseases. Electrocardiography, echocardiography, pulmonary function tests, and a lung perfusion scan are necessary to exclude secondary forms of pulmonary hypertension and also help to confirm the diagnosis of PPH. A definite diagnosis of PPH is established by right-heart catheterisation which gives a precise measure of the blood pressure in the right side of the heart and the pulmonary artery, right ventricular function and cardiac output. Once a diagnosis of PPH is established, treatment involving drug therapy or surgery is commenced on the basis of the New York Heart Association functional class. Conventional treatment consists of lifetime administration of anticoagulants, oxygen, diuretics, and digoxin. Vasodilator therapy with calcium channel antagonists is indicated in patients who are 'vasoreactive' to acute vasodilator challenge as assessed by right-heart catheterisation. Promising results are obtained by continuous intravenous administration of epoprostenol (prostacyclin). Newer therapies for PPH include prostacyclin analogues, endothelin receptor antagonists, nitric oxide, phosphodiesterase-5 inhibitors, elastase inhibitors, and gene therapy. Surgical treatment consists of atrial septostomy, thromboendarterectomy, and lung or heart-lung transplantation.

Primary pulmonary hypertension (PPH) is a rare condition with an estimated prevalence of 1 to 2 per million people.[1] The disease is often diagnosed rather late because the clinical symptoms are aspecific and the clinical findings on physical examination are subtle. However, the natural history of PPH is progressive with a fatal outcome.[2,3] Since the 1970s, this condition has received more attention as a result of an increased incidence of PPH in patients treated with aminorex fumarate, an anorectic drug.[4] Although the cause of PPH itself is unknown, the pathology, risk factors and the genetics of the disease are well characterised. Diagnosis and assessment of the disease have become easier and more accurate as a result of advanced technology.

Medical and/or surgical therapies have made an important contribution to quality of life and survival in patients with PPH. This review reflects the current state of accepted international medical practice and clinical research in the area of PPH.

1. Definition

According to the National Institutes of Health (NIH), PPH is defined as a disorder of the pulmonary vasculature in which the blood pressure in the pulmonary artery increases above normal for no apparent reason and is associated with changes in the pulmonary vasculature resulting in an augmented resistance to the blood flow from the right heart.[5] Clinical diagnostic criteria for PPH, based on the NIH registry, include a mean pulmonary arterial pressure (PAP) greater than 25mm Hg at rest or greater than 30mm Hg during exercise, nor-

mal capillary wedge pressure, and the absence of secondary causes.

2. Epidemiology

PPH is a rare condition, with an estimated prevalence of 1 to 2 per million individuals and is twice as common in women as in men.[1] Childhood PPH occurs with equal frequency in both sexes.[6] Necropsy studies have shown a prevalence of 1300 per million.[7] In the US, an estimated 500 to 1000 new patients with PPH are diagnosed each year. The incidence of PPH among users of certain appetite suppressants may be as high as 25 to 50 per million per year.[8] The disease can develop at any age (mean age at diagnosis is 36 years) the age in men being slightly higher than that in women; race has no influence on the risk of PPH.[6]

Familial PPH is encountered in approximately 10% of patients.[9] The natural history of PPH is usually progressive and fatal. In patients who are not treated, median survival is less than 3 years.[2]

3. Pathology

The pathological findings in PPH are not unique or diagnostic, and include smooth muscle hypertrophy of the pulmonary vasculature, intimal hyperplasia, and *in situ* thrombosis. PPH has three distinct pathological patterns.[5]

3.1 Arteriopathy

Arteriopathy is found in approximately 85% of patients.[10] Some patients with isolated medial hypertrophy of the pulmonary vasculature have shown an isolated increase in the medial muscle in muscular arteries and muscularisation of arterioles without intimal or luminal obstructive lesions and plexiform lesions.

Plexogenic pulmonary arteriopathy has been noted in approximately 45% of patients. The latter arteriopathy is characterised by plexiform and dilatation lesions of the pulmonary vasculature accompanied by medial hypertrophy, eccentric or concentric laminar and non-laminar thickening of the intima, fibrinoid necrosis, arteritis and thrombotic lesions.

PPH patients with thrombotic pulmonary arteriopathy show thrombi, eccentric or concentric laminar and non-laminar intimal thickening, and varying degrees of medial hypertrophy of the pulmonary vasculature.

Patients with isolated pulmonary arteritis have active or healed arteritis limited to the pulmonary arteries, in the absense of systemic arteritis, varying degrees of medial hypertrophy, intimal fibrosis and thrombotic lesions in the pulmonary vasculature.

3.2 Venopathy

Veno-occlusive disease is characterised by intimal proliferation and fibrosis of the intrapulmonary veins and venules. Medial hypertrophy, eccentric and concentric non-laminar intimal fibrosis, and fibrinoid necrosis of pulmonary arteries are also present.[11]

3.3 Microangiopathy

Microangiopathy is characterised by infiltrating thin-walled blood vessels throughout the pulmonary parenchyma, pleura, bronchi, and the walls of pulmonary veins and arteries accompanied by intimal and medial hypertrophy of pulmonary arterioles and arteries.

The plexiform lesion consists of a mass of disorganised blood vessels with proliferating endothelial cells, smooth muscle cells, myofibroblasts and macrophages, and arises from pre-existing pulmonary arteries. The plexiform lesion, once considered pathognomonic for PPH, is also found in a variety of secondary forms of pulmonary hypertension. It is unclear whether it represents impaired proliferation or angiogenesis of the pulmonary vasculature. Patients with plexogenic pulmonary arteriopathy seem to be on average 10 years younger and appear to have a worse prognosis than those with thrombotic arteriopathy.[10]

The pathological findings in PPH can be graded on a 6-point scale, which was originally devised for patients with pulmonary hypertension and

cardiac septal defects at birth.[12] There is, however, a lack of correlation between this grading system and patient survival or PAP.[10,13]

4. Pathophysiology of Primary Pulmonary Hypertension (PPH)

The aetiology of PPH is unknown. The current concepts of pathogenesis focus on individual genetic susceptibility and a trigger that leads to vascular intimal injury with secondary intimal hypertrophy, fibrosis and dysfunction.[14-16] The stimuli that may trigger PPH are diverse and include ingested toxins, drugs, infectious disease and inflammatory disorders (table I).

Figure 1 depicts the pathophysiology of PPH. Endothelial cell injury leads to an imbalance between the production of vasodilators and vasoconstrictors, resulting in vasoconstriction and medial hypertrophy.[14-16,29] Immunohistochemical studies have shown that vascular endothelial cells have decreased expression of nitric oxide (NO) synthase (eNOS; NOS III) and prostacyclin synthase, while the expression of endothelin-1 is increased.[14,15,30,31]

Increased expression of endothelin in the pulmonary arteries has been demonstrated in both primary and secondary pulmonary hypertension.[15,30]

Platelet activation releases vasoconstrictors (serotonin, thomboxane A_2) and growth factors and leads to *in situ* thrombosis.[16,29,32] Abnormal fibrinolysis and elevated plasminogen activator inhibitor-1 and fibrinopeptide A plasma levels were found in a number of patients, consistent with the presence of procoagulant and inadequate fibrinolytic activity of plasma.[33-37]

Pulmonary hypertension was reversible in a patient with an inherited platelet storage disease and increased plasma levels of serotonin, following the administration of ketanserin, a serotonin receptor antagonist.[38]

A decrease in oxygen tension depolarises the membrane of smooth muscle cells by inhibition of the potassium channels, thereby leading to a secondary intracellular influx of calcium and pulmonary vasoconstriction.[39] Patients who have PPH may present with pulmonary oedema when exposed to hypoxia, such as in high altitudes.[40] Recently, it was demonstrated that aminorex and fenfluramine also depolarise the membrane of smooth muscle cells of pulmonary arterioles.[41] Inhibition of the voltage-regulated (Kv) potassium channels can also produce pulmonary vasoconstriction in patients with PPH.[42,43]

Increased expression of growth factors such as vascular endothelial growth factor and transforming growth factor-β (TGFβ) 2 and 3, and angiotensin converting enzyme have been shown to play a role in pulmonary vascular remodelling.[44-46]

About 10% of patients with PPH show an autosomal dominant pattern of inheritance.[6,9] The clinical transmission of the gene might be based on expanded trinucleotide repeats and involve abnormal promoter or modifier gene functions. The low

Table I. Stimuli that may trigger primary pulmonary hypertension (PPH)

Definite	Very likely	Possible	Unlikely
Drugs and toxins associated with PPH			
Aminorex[4]	Amphetamine	Meta-amphetamines[17]	Antidepressants
Fenfluramine[18]	L-tryptophane[19]	Cocaine[20]	Oral contraceptives
Dexfenfluramine[21]	Glue (toluene)[22]	Chemotherapeutic agents[23]	Estrogen therapy
Toxic rapeseed oil[24]			Cigarette smoking
Demographic and medical conditions associated with PPH			
Gender		Pregnancy[25]	Obesity
		Systemic hypertension	
Diseases associated with PPH			
HIV1 infection[26]	Portal hypertension/liver disease[27]		Thyroid disorders[28]
	Collagen vascular diseases		

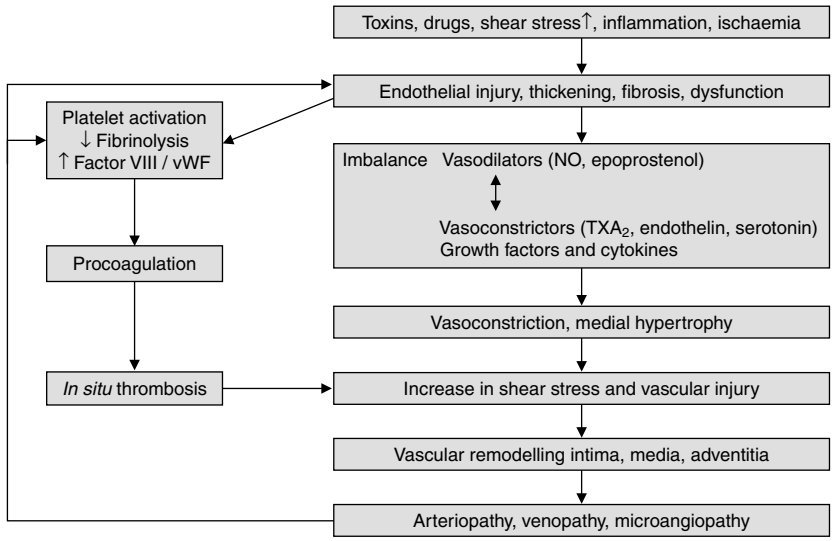

Fig. 1. The pathogenesis and pathophysiology of primary pulmonary hypertension (PPH). **NO** = nitric oxide; **TXA_2** = thromboxane A_2; **vWF** = von Willebrand's factor.

penetrance of this gene confers only about a 10 to 20% likelihood of developing the disease.[47]

In familial primary pulmonary hypertension, the age of onset of the disease is variable. Furthermore, there are fewer males born to PPH families compared with the general population, indicating decreased fertilisation or increased loss of male fetuses.[48] The clinical and pathological features of familial and sporadic PPH are identical. A complete family history should be obtained for every patient with PPH in order to explore the possibility of familial disease. The likelihood of a first degree relative being affected, when only a single person in a family has PPH, is estimated at 0.6 to 1.2%. In the case where two members of a family are affected with PPH, this risk increases to 5 to 10%. Children of an affected parent have a 5 to 10% lifetime risk of developing the disease.[49]

Recently, the gene for PPH was mapped to 2q31-33 and mutations were reported in the BMPR2 gene, which encodes the type II bone morphogenetic protein receptor.[50-53] It is a cell-surface receptor belonging to the superfamily of receptors for ligands of TGFβ family. Binding of ligands results in phosphorylation of cytoplasmic transcription factors, which alter gene transcription. Bone morphogenetic proteins 2 and 7 have been shown to inhibit vascular smooth muscle-cell proliferation and to induce apoptosis in some cell types in culture.[54,55] PPH may result from impaired control of cellular proliferation. Endothelial and smooth muscle cells are unable to respond to injury normally and proliferate, narrowing the precapillary arteries and forming the plexiform lesion.

Trembath et al. investigated the genetic basis of lung disease in patients with hereditary haemorrhagic telangiectasia, as such patients may have pulmonary disease indistinguishable from PPH. They found that pulmonary hypertension in association with hereditary haemorrhagic telangiectasia can involve mutations in activin-receptor-like kinase 1 (ALK 1), which is located on chromosome 12q13. These mutations are associated with diverse effects such as the vascular dilatation characteristic of hereditary haemorrhagic telangiectasia and the occlusion of small pulmonary arteries characteristic of PPH.[56]

5. Survival and Natural History of PPH

For patients with PPH who are not treated with vasodilators or anticoagulation, the median period of survival after diagnosis is 2.8 years.[1,57] Predictors of survival include haemodynamic indicators of disease severity such as mean pulmonary arterial pressure (PAP), right atrial pressure, cardiac index, and mixed venous oxygen saturation, as well as New York Heart Association (NYHA) functional class, anticoagulant therapy and response to vasodilators.[1] Anticoagulants double the 3-year survival rate, and patients who respond to calcium channel antagonists have a 5-year survival rate of 95%.[58] The 5-year survival rate in patients with NYHA functional class III and IV and treated with epoprostenol (prostacyclin) was twice that of matched historical controls (54 and 27%).[59]

6. Diagnosis and Assessment

6.1 Symptoms and Physical Findings

It is difficult to determine the onset of PPH based on the age at which the diagnosis is made or the severity of symptoms. PPH is more common in women between the ages of 21 and 40 years; however, anyone at any age can be affected. Initial symptoms may be very minor, so that diagnosis may be delayed for several years until symptoms become worse. Early clinical symptoms are tiredness, shortness of breath, dizziness, and fainting. Other clinical signs include oedema of the lower limbs, bluish lips and skin, angina-like chest pain, palpitations and dysphonia (Ortner's syndrome). Advanced disease is associated with severe clinical symptoms precipitated with minimal activity or even at rest.

Since the symptoms and signs of PPH can also be found in other cardiovascular syndromes and lung diseases, a definite diagnosis of PPH is difficult to make in a routine medical examination. The mean time between the onset of the symptoms and disease diagnosis is 2 years.

The most common clinical sign is tachypnoea, a weak pulse and peripheral cyanosis, indicative of low cardiac output. Pulmonary auscultation is normal. Cardiac auscultation reveals an increased second heart sound at the pulmonary site, a murmur from tricuspidal regurgitation or, less often, from pulmonary regurgitation. Oedema, hepatomegaly, hepato-jugular pulse and ascites are present in patients with advanced stage disease. [5,60]

A retrospective study in 40 patients with PPH (mean age 43.5 years) showed a prevalence of hypothyroidism (defined as a thyroid-stimulating hormone level of >5.5 U/L, intake of thyroid supplement, or a low thyroxine level) in 22.5% of patients, which is much more than in the general population of the same age. The authors concluded that patients with PPH should be investigated for the possibility of hypothyroidism.[61] A small study examined ocular findings associated with PPH, retrospectively. It was found that elevated venous pressure in PPH was responsible for delayed choroidal perfusion and reduced venous blood outflow leading to venous stasis retinopathy and choroidal detachments in PPH patients.[62]

The current standard for the diagnosis of PPH consists of a thorough history and physical examination, as well as technical investigations.

6.2 Technical Investigations

A tentative diagnosis of PPH can be made after the following investigations (figure 2).

6.2.1 Electrocardiogram

The electrocardiogram may show right auricular and ventricular hypertrophy with strain and may show evidence of underlying cardiac disease, if present. Cardiopulmonary function tests, such as cyclo-ergometry or treadmill testing, can be performed to evaluate the functional class and haemodynamic status during exercise.

6.2.2 Chest X-Ray

The chest x-ray is abnormal in 90% of patients with PPH and often shows dilation of the proximal pulmonary arteries with pruning, and dilation of the right heart. Additional cardiac, pulmonary and thoracic wall and/or spinal abnormalities can be present in patients with secondary pulmonary hypertension. [63]

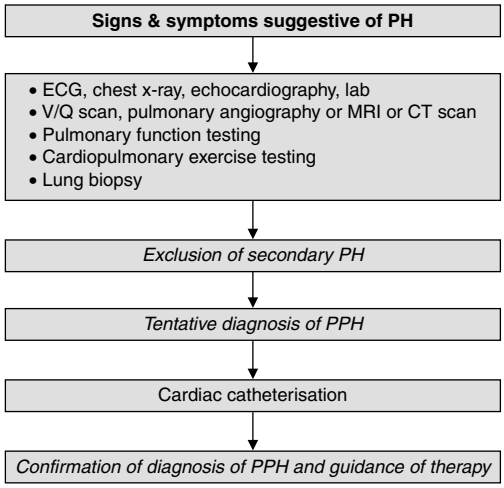

Fig. 2. Algorithm for the assessment of primary pulmonary hypertension (PPH). **CT** = computed tomography; **ECG** = electrocardiogram; **lab** = laboratory investigations; **MRI** = magnetic resonance imaging; **PH** = pulmonary hypertension; **V/Q** scan = ventilation-perfusion scan.

6.2.3 Echocardiography

Doppler echocardiography is an important non-invasive technique that will exclude left-sided heart disease (e.g. mitral stenosis, myxoma), congenital heart disease or pericardial diseases. In PPH it will confirm enlargement of the right heart, right ventricular hypertrophy, and evaluate right ventricular performance, paradoxical septal movement, tricuspid and pulmonary valve regurgitation, shortened right ventricular outflow tract acceleration time, and flow reversal in the hepatic vein. Doppler echocardiography is useful for monitoring pulmonary arterial pressures, for measuring the peak flow velocity of the tricuspid regurgitation and for calculating the instantaneous PAP utilising the Bernouilli equation.[64]

6.2.4 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) gives information on the right atrial, ventricular and pulmonary artery morphology and on right ventricular function.[65]

6.2.5 Computed Tomography

Computed tomography (CT) of the chest gives information similar to that with MRI. High-resolution CT also gives an indication of the lung parenchyma and the presence of pulmonary veno-occlusive disease.[66]

6.2.6 Ventilation-Perfusion Scan

A ventilation-perfusion (V/Q) scan needs to be performed to exclude proximal thromboemboli. In contrast to the multiple larger perfusion defects typical of chronic, major vessel thromboembolic pulmonary hypertension, PPH has a patchy perfusion defect pattern.[67]

6.2.7 Pulmonary Angiography

Pulmonary angiography can be performed to differentiate PPH from thromboembolic PH. However, the procedure is risky in patients with pulmonary hypertension, and several conditions must be fulfilled to keep this risk as low as possible (table II).[68,69]

6.2.8 Pulmonary Function Tests and Cardiopulmonary Function Testing

Pulmonary function tests and cardiopulmonary function testing will be performed mainly to evaluate possible intrinsic pulmonary disease and to assess the haemodynamic status of the patient. Patients with PPH often have restricted lung function due to increased stiffness of the lungs induced by structural changes and increased pressure in the

Table II. Prerequisite conditions for performing pulmonary angiography in patients with primary pulmonary hypertension

Be sure of the indication to do a pulmonary angiography
Patients need to be in a stable condition
Patients should be devoid of systemic hypotension or haemodynamically significant arrhythmias
Renal failure or other organ failure are contraindications
Femoral veins should not be used for access because of risk of emboli
Oxygen should be administered during the entire procedure of pulmonary angiography
Use of analgesia should be kept at a minimum
Optimal positioning of the patient and correct radiological technique are essential to minimise the number of injections administered
Ensure stable positioning of the catheter
Non-ionic contrast agents are recommended

pulmonary arteries. On average, the vital capacity in patients with PPH is 86% of the expected value. Diffusion of carbon monoxide is slightly dereased (60 to 80% of normal range) and arterial blood gas analysis shows mild hypoxaemia and respiratory alkalosis. Cardiopulmonary function testing gives information on the clinical status and on functional capacity and may have prognostic significance.[70] There is a decrease in the peak oxygen uptake ($\dot{V}O_{2max}$). The 6-minute walk test is usually preferred. The maximal distance walked is directly related to the severity of the disease.

6.2.9 Laboratory Examinations

Laboratory examinations should consist of a complete blood cell count, documentation of autoantibodies for exclusion of connective tissue diseases (antinuclear antibodies, anti-Ku antibodies) antibodies to HIV-1, renal, liver and thyroid function tests, and arterial blood gases.[71]

6.2.10 Lung Biopsy

Although pathological assessment of the lung may give insights into the histopathological characteristics of conditions associated with pulmonary hypertension, lung biopsy is risky and is not used routinely for the diagnosis of PPH. Lung biopsy usually does not provide additional clinically useful information over careful noninvasive and haemodynamic assessment, in most patients. It may be desirable in specific cases of secondary PH.[49]

6.2.11 Right Heart Catheterisation

A definite diagnosis of PPH is established by right-heart catheterisation. Heart catheterisation gives data on right atrial pressure, right ventricular systolic and end-diastolic pressure, PAPs, pulmonary capillary wedge pressure, mixed venous oxygen saturation, cardiac output, differentiating PPH from other cardiac disorders. PPH is primarily a disease of the small muscular pulmonary arteries and arterioles that are < 500 to 1000μm in diameter. These histological findings have been confirmed by bedside haemodynamic evaluation of pulmonary artery occlusion pressure decay curves, which suggest that there are no structural changes important enough to increase the resistance of larger diameter pulmonary arteries.[72]

Acute testing of the vasodilating capacity of the pulmonary vessels is recommended.[73] Vasodilators currently used to assess vasoreactivity are intravenous epoprostenol (prostacyclin), intravenous adenosine and inhaled nitric oxide (NO). Patients who are responsive to acute vasodilator testing [>10% decrease in mean PAP and > 30% decrease in pulmonary vascular resistance (PVR)] may benefit from therapy with oral calcium channel antagonists.[58]

7. Treatment

Since PPH is a rare and complex disorder, it is recommended that patients are referred to a centre with experience in the management of the disease.

7.1 Medical Therapy

7.1.1 General Measures

Precautions should be taken to prevent aggravation of the disease state. Pulmonary infections must be aggressively treated and vaccination against influenza virus infection must be considered. Exercise may lead to sudden death. Isometric exercises must be limited and exercise in general must be guided by clinical symptoms such as angina and syncope. Vasoconstrictive stimuli such as high altitude must be avoided since they worsen PPH or may lead to pulmonary oedema.[40] Oxygen supplementation may be advisable when flying in airplane cabins, since they are pressurised to a corresponding altitude of 1500 to 2500m. Pregnancy is poorly tolerated in women with PPH and should be avoided by effective birth control methods. Some studies suggest that oral contraception can worsen pulmonary hypertension.[25,74] The latter fact has however, not been confirmed in more recent studies in which women used oral contraceptives containing a lower dosage of estrogens.[6,8,57]

7.1.2 Anticoagulation

Patients with PPH are at increased risk of thromboembolic events. Patients receiving anticoagulants show improved survival compared with patients not receiving anticoagulants.[57] Lifelong

anticoagulation with an international normalised ratio (INR) of 2 to 3 and regular monitoring are recommended. When contraindications to warfarin exist, dose-adjusted heparin is a suitable alternative, maintaining the activated partial thromboplastin time (aPTT) at 1.3 to 1.5 times the normal value.[57,75]

7.1.3 Diuretics

Diuretics are useful in patients with right-heart failure to reduce the increased intravascular volume and hepatic congestion. However, the right heart is highly preload dependent and exaggerated diuresis should be avoided, since this can lead to a drop in cardiac output and compromise the use of vasodilators. Diuretic therapy is started at low dosages and the dosage is increased as guided by physical findings and renal function.[76,77]

7.1.4 Digoxin

The efficacy of cardiac glycosides in PPH in humans is unknown and the risk of toxicity is increased in the presence of hypoxaemia and diuretic-induced hypokalaemia. Therefore, the use of digoxin in the treatment of PPH is mostly restricted to patients with concomitant left ventricular heart failure. Digoxin may compensate the possible negative inotropic effects of concomitant calcium antagonist therapy.[76,78]

7.1.5 Oxygen Therapy

Hypoxaemia contributes to the pulmonary vascular damage due to hypoxic pulmonary vasoconstriction. Oxygen is administered only when there is significant arterial oxygen desaturation (arterial O_2 saturation < 90%, oxygen partial pressure in arterial blood (PaO_2) < 60mm Hg) at rest or during exercise. However, oxygen therapy will only be beneficial if there is a decrease in the mixed venous oxygen content or a decrease in the ventilation : perfusion ratio, but will not improve the hypoxia related to a shunt. Oxygen lowers the PAP and increases the oxygen delivery while the systemic arterial pressure remains unchanged, reducing stimuli for hypoxic vasoconstriction and secondary erythropoiesis. Patients with severe right-sided heart failure and hypoxaemia at rest need continuous oxygen therapy. The goal of oxygen therapy is to obtain and maintain an arterial oxygen saturation above 90 to 92%. The systemic arterial oxygen saturation is an important factor for survival.[76,79]

7.1.6 Vasodilators

Vasodilator treatment is recommended in patients who are 'vasoreactive' to acute vasodilator therapy.[13,76,80-82] The rationale for the use of vasodilator drugs is to reduce vasoconstriction, leading to a reduction in right ventricular afterload and an increase in right ventricular output. Several systemic vasodilators such as nifedipine,[83,84] diltiazem,[85] amlodipine,[86] hydralazine,[87,88] nitroprusside,[89] nitrates,[90] and epoprostenol [91-95] also have pulmonary vascular effects. The aim of vasodilator treatment is to reduce PAP and to increase cardiac output without symptomatic systemic hypotension. This effect is achieved in about 25% of the patients. In approximately 50% of the patients, cardiac output increases without a decrease in PAP. In the remaining patients, vasodilators are strictly contraindicated because of the potential lethal risk of severe reduction in systemic blood pressure (systemic hypotension) associated with either a decrease or an increase in PAP, and a decrease, an increase or no change in cardiac output.

The course of PPH varies widely. Therefore, therapy must be individualised. During right-heart catheterisation, a short-acting titratable vasodilator such as intravenous epoprostenol[96,97] adenosine[98,99] or acetylcholine[100,101] is administered to establish vasoreactivity. Approximately 25 to 30% of the patients who experience a reduction in PAP and resistance with or without an increase in cardiac output will respond to oral calcium channel antagonists.[58,102] The dose of nifedipine is titrated upwards, hourly, until the maximal haemodynamic effect is obtained or until adverse effects appear. Sustained-release nifedipine 120 to 240 mg/day is often prescribed. In the presence of a resting tachycardia or significant systemic hypotension, diltiazem 120 to 900 mg/day is preferred.

The adverse effects of calcium channel antagonists consist of a reduction in cardiac output,

systemic hypotension, and oedema. The latter symptoms have to be differentiated from right-heart failure. In certain patients, worsening of the arterial hypoxaemia can occur because of an increase in the V/Q mismatch, by increasing right to left shunting through a patent foramen ovale, or by decreasing the mixed venous saturation as a result of a decrease in systemic perfusion.

Nitrates,[90] hydralazine,[87,88] diazoxide,[103-105] and ACE inhibitors[106,107] have been used in the management of PPH, but data are limited and the clinical usefulness of these drugs is limited because of frequent systemic hypotension.

If oral vasodilator therapy is not indicated or is not beneficial, or if patients with PPH become refractory to treatment with calcium channel antagonists, a low dose of intravenous epoprostenol may be administered via a Hickman catheter and infusion pump.[91-95,108] Intravenous epoprostenol is a very potent pulmonary vasodilator and a potent platelet inhibitor. The starting dose is 2 to 12 ng/kg/min as a function of tolerance. Continuous intravenous epoprostenol increases exercise tolerance[109] and survival, and is a bridge to transplantation. The complications induced by epoprostenol therapy are mostly associated with the delivery system and include catheter-related infections, thrombosis and temporary interruption of the infusion. Clinically relevant adverse effects are flushing (in all patients), dose-dependent headache, indigestion (may be a precursor to a vasovagal reaction), and diarrhoea. All these adverse effects resolve spontaneously within 5 to 10 minutes of stopping the administration of epoprostenol. Long term epoprostenol treatment with upward dose titration can lead to increased cardiac output, which returns to normal with a reduction in the drug dose. Dosage adjustments can be performed without rebound pulmonary hypertension or worsening of the clinical condition.[110] One case report described the development of nonspecific interstitial pneumonitis in a young woman after long-term treatment (5 years) with prostacyclin.[111]

7.2 Surgical Therapy for PPH

7.2.1 Atrial Septostomy

This palliative procedure is considered investigational and may present an option for selected patients with severe PPH who experience recurrent syncope and/or right ventricular failure, despite maximal medical therapy.[112,113] A study by researchers in Mexico City, reported prolonged survival in a group of 15 patients with PPH treated with this surgical procedure.[114] A right-to-left shunt in the atria allowed decompression of the right heart and improved filling and function of the left ventricle.[112,113] Atrial septostomy may also serve as a bridge to transplantation in patients with PPH that has not responded to maximal medical therapy.

The procedure-related mortality is high, and atrial septostomy should therefore be attempted only by persons with experience. Predictors of procedure-related failure or death are a mean right atrial pressure of more than 20mm Hg, a PVR index of more than 55 U/m^2, or a predicted 1-year survival rate less than 40%.[115] Candidates for atrial septostomy should have a systemic arterial oxygen saturation greater than 90% on room air. The procedure should be performed in a stepwise manner, creating the smallest possible septal defect that will produce haemodynamic changes. The endpoint should be a 5 to 10% reduction in systemic arterial oxygen saturation. Before and after septostomy, transfusion of packed red blood cells or the use of erythropoietin may be necessary to increase oxygen delivery. Long-term anticoagulation is also recommended.

7.2.2 Transplantation

Transplantation is an effective treatment for patients with advanced pulmonary hypertension, resulting in a significant improvement in quality of life and life span.[116] Since 1981, approximately 1000 patients worldwide have undergone single-lung, double-lung or heart-lung transplantation for pulmonary hypertension. Ages of transplant recipients have ranged from 2 months to 61 years. PPH recipients of single-lung transplants have a greater mortality rate compared with patients undergoing

transplantation for other conditions, However, recipients of double-lung or heart-lung transplants have shown mortality rates comparable to those seen in patients undergoing transplantation for other conditions.[117] The major long-term complication of lung transplantation, obliterative bronchiolitis, occurs more often in patients who undergo transplantation because of PPH.[118] Recurrence of PPH after transplantation has not been reported. One-, 3- and 5-year survival rates of 70 to 75%, 55 to 60% and 40 to 45%, respectively, have been reported after transplantation in patients with PPH.[119] Patients in NYHA functional class III to IV and those not responding to medical therapy, particularly epoprostenol, should be referred for transplantation. The current median waiting time to transplantation is 18 months because of donor shortage and an ever-increasing number of patients with PPH requiring transplantation.

8. Newer and Future Therapies for PPH

8.1 Prostanoids

Stable analogues of epoprostenol for subcutaneous administration, oral intake or inhalation are under development.

Uniprost, a prostacyclin analogue, is administered subcutaneously by a small pump, remains stable at room temperature, and is associated with a lower risk of infections. McLaughlin and Rich[120] observed a decrease in mean PAP, a decrease in PVR and an increase in cardiac output, after the administration of uniprost to patients with PPH. However, uniprost may not be as effective as epoprostenol and skin reactions can develop.[120]

Beraprost is a prostacyclin analogue that is well absorbed after oral administration and has a short half-life and therefore needs frequent administration. Short-term beneficial effects on haemodynamics and exercise tolerance have been shown. Beraprost improves survival in outpatients with PPH compared with conventional therapy only.[121] A multicentre, prospective, randomised clinical trial in 110 patients with primary and secondary pulmonary hypertension (NYHA classes II to IV) is ongoing. There are no data available yet.

Terbogrel is a thromboxane synthetase inhibitor and receptor antagonist administered orally, with positive effects on pulmonary haemodynamics. However, an international study by Christman et al.[122] was prematurely stopped because of a high incidence of leg pain in the treated group.

Iloprost is a more stable form of prostacyclin that requires nebulisation and frequent administration. It is effective as an acute vasodilator.[123,124] A randomised controlled trial in 200 patients with primary and secondary pulmonary hypertension (NYHA classes II to IV) is ongoing. Simultaneous pulsatile inhalation of NO and aerosolised iloprost has been recently described, with an additive beneficial effect on the reduction of pulmonary pressure.[125]

8.2 Endothelin Receptor Antagonists

The endothelin-A (ET-A) receptors on smooth muscle cells mediate vasoconstriction and smooth muscle-cell proliferation, while the endothelin-B (ET-B) receptors mediate clearance of endothelin from the circulation. On vascular endothelial cells, the ET-B receptor mediates vasodilatation by production of NO. Therefore, it may be preferable to block the ET-A receptor and to preserve the ET-B receptor in the treatment of pulmonary hypertension. Endothelin receptor antagonists may be selective or nonselective and ongoing clinical trials examining both types of receptors may reveal the exact role of these receptors related to PPH.[126-129]

Bosentan is an orally active endothelin receptor antagonist administered to patients with PPH. Compared with placebo, bosentan increases the 6-minute walking distance and cardiac index, and decreases mean PAP and mean PVR in patients with PPH.[128]

Sitaxsentan sodium is an orally active ET-A receptor antagonist. It increases the 6-minute walking distance and cardiac index, and decreases mean PAP and mean PVR in patients with PPH. Sitaxsentan sodium may also be of value in pulmo-

nary hypertension secondary to chronic heart failure.[129]

8.3 Nitric Oxide and Cyclic Guanosine Monophosphate

NO inhalation has also been used in the treatment of pulmonary hypertension.[130-135] Since NO is rapidly inactivated by haemoglobin, the vasodilating effect is restricted to the pulmonary vasculature, resulting in reduced PAP without systemic vasodilatation. NO, used in low doses with continuous monitoring, is a safe new therapeutic option in the treatment of PPH. A dose of 10 ppm is well tolerated and gives a maximal effect, similar to the effect of epoprostenol. [136] Unlike epoprostenol, NO does not induce any systemic adverse effects but a moderate increase in methaemoglobin levels can occur.[137] NO reverses pulmonary hypertension by dilation of the pulmonary vasculature. Experiments have shown that NO hyperpolarises pulmonary artery myocytes and decreases cytosolic calcium by activating Kv channels. NO is used in the treatment of neonates with pulmonary hypertension and hypoxia and is a short-term therapy for patients with the acute respiratory distress syndrome. Its long-term use and effects need to be investigated.

NO donors such as L-arginine and substance P have a beneficial effect on pulmonary haemodynamics.[138,139] These agents are under intense investigation.

Phosphodiesterase-5 (PDE-5) inhibitors also have potential in the treatment of pulmonary hypertension. Dipyridamole, a cyclic guanosine monophosphate (cGMP) phosphodiesterase inhibitor tested mostly in secondary forms of pulmonary hypertension, has proved effective in some patients.[140-143] Sildenafil is a selective, potent inhibitor of the enzyme cGMP-specific phosphodiesterase type 5, which inhibits the degradation of cGMP. It may have beneficial effects as a pulmonary vasodilator in patients with pulmonary hypertension, as reported recently in a child and an adult patient with PPH.[144,145] Sildenafil has also been shown to ameliorate withdrawal effects of inhaled NO.[146] Further prospective studies on the role of sildenafil in the management of PPH are necessary.

8.4 Elastase Inhibitors

Pulmonary hypertension is associated with increased elastase activity. Animal models have shown elastase inhibitors to have a positive effect on vascular remodelling.[147,148] These drugs are still experimental.

8.5 Potassium Channel Openers

In animal experiments, mostly rat models, potassium channel openers such as pinacidil have demonstrated relaxation of pulmonary arteries. Their vascular relaxant effects are not selective for the pulmonary vasculature but have also been observed in the aorta.[149,150] Further studies are necessary to define the place of K^+ channel openers in the treatment of PPH.

8.6 Gene Therapy

Genes carried by adenovirus vectors have been transfected into the airways and small pulmonary arteries by nebulisation. In experimental studies, genes, which carry prostacyclin synthase[151] and NOS[152] have resulted in a reduction of PAP. There are still some concerns about the possibility of sustained expression of the genes and the risk of inflammatory reactions to the vectors. Other vector types are currently being studied.[47,153-156]

9. Conclusion

PPH is a rare but severe disorder in mainly young to middle-aged individuals, and is characterised by raised PVR and PAP. The mean survival time from onset of symptoms is 2 to 3 years. The aetiology of PPH is unknown. However, several predisposing factors and a genetic predisposition have been reported. Pathogenesis mainly involves vasoconstriction of the pulmonary vasculature, vascular remodelling and *in situ* thrombosis caused by abnormal interactions between the pulmonary vascular endothelium, smooth muscle cells and platelets. These complex mechanisms associated

with disease pathogenesis are under investigation at cellular, biochemical and genetic levels and could lead to an improvement in conventional therapy and the advent of new drugs and delivery methods for the treatment of pulmonary hypertension. Newer promising treatments are prostacyclin analogues, endothelin receptor antagonists, NO, phosphodiesterase inhibitors and elastase inhibitors. Gene therapy holds great promise. There is a strong possibility that, in the future pulmonary hypertension could be managed by combined therapy. In the treatment of patients with PPH, quality of life issues are as important as prolongation of survival and improvement in pulmonary haemodynamics.

Acknowledgements

We thank Professor Dr R Naeije for his expert advice and comments. The authors received no funding for the preparation of this manuscript and have no conflicts of interest with any relevant pharmaceutical companies.

References

1. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med 1991; 115 (5): 343-9
2. Oakley CW. Primary pulmonary hypertension: case series from the United Kingdom. Chest 1994; 105 (2 Suppl): 29S-32S
3. Rubin LJ. Primary pulmonary hypertension. N Engl J Med 1997; 336 (2): 111-7
4. Kay JM, Smith P, Heath D. Aminorex and the pulmonary circulation. Thorax 1971; 26 (3): 262-70
5. Rubin LJ. Primary pulmonary hypertension. Chest 1993; 104 (1): 236-50
6. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987; 107 (2): 216-23
7. McDonnell PJ, Toye PA, Hutchins GM. Primary pulmonary hypertension and cirrhosis: are they related? Am Rev Respir Dis 1983; 127 (4): 437-41
8. Abenhaim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. N Engl J Med 1996; 335 (9): 609-16
9. Loyd JE, Primm RK, Newman JH. Familial primary pulmonary hypertension: clinical patterns. Am Rev Respir Dis 1984; 129 (1): 194-7
10. Pietra GG, Edwards WD, Kay JM, et al. Histopathology of primary pulmonary hypertension: a qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. Circulation 1989; 80 (5): 1198-206
11. Wagenvoort CA, Wagenvoort N. The pathology of pulmonary veno-occlusive disease. Virchows Arch A Pathol Anat Histol 1974; 364 (1): 69-79
12. Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease: a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation 1958; 18: 533-47
13. Palevsky HI, Schloo BL, Pietra GG, et al. Primary pulmonary hypertension: vascular structure, morphometry, and responsiveness to vasodilator agents. Circulation 1989; 80 (5): 1207-21
14. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med 1995; 333 (4): 214-21
15. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 1993; 328 (24): 1732-9
16. Veyssier-Belot C, Cacoub P. Role of endothelial and smooth muscle cells in the physiopathology and treatment management of pulmonary hypertension. Cardiovasc Res 1999; 44 (2): 274-82
17. Schaiberger PH, Kennedy TC, Miller FC, et al. Pulmonary hypertension associated with long-term inhalation of 'crank' methamphetamine. Chest 1993; 104 (2): 614-6
18. McMurray J, Bloomfield P, Miller HC. Irreversible pulmonary hypertension after treatment with fenfluramine. Br Med J (Clin Res Ed) 1986; 292 (6515): 239-40
19. Tazelaar HD, Myers JL, Drage CW, et al. Pulmonary disease associated with L-tryptophan-induced eosinophilic myalgia syndrome. Clinical and pathologic features. Chest 1990; 97 (5): 1032-6
20. Russel LA, Spehlmann JE, Clarke M, et al. Pulmonary hypertension in female crack users [abstract]. Am Rev Resp Dis 1992; 145: 717A
21. Cacoub P, Dorent R, Nataf P, et al. Pulmonary hypertension and dexfenfluramine. Eur J Clin Pharmacol 1995; 48 (1): 81-3
22. Devathasan G, Low D, Teoh PC, et al. Complications of chronic glue (toluene) abuse in adolescents. Aust N Z J Med 1984; 14 (1): 39-43
23. Lombard CM, Churg A, Winokur S. Pulmonary veno-occlusive disease following therapy for malignant neoplasms. Chest 1987; 92 (5): 871-6
24. Gomez-Sanchez MA, Saenz de la Calzada C, Gomez-Pajuelo C, et al. Clinical and pathologic manifestations of pulmonary vascular disease in the toxic oil syndrome. J Am Coll Cardiol 1991; 18 (6): 1539-45
25. Martinez JM, Comas C, Sala X, et al. Maternal primary pulmonary hypertension associated with pregnancy. Eur J Obstet Gynecol Reprod Biol 1994; 54 (2): 143-7
26. Petitpretz P, Brenot F, Azarian R, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection: comparison with primary pulmonary hypertension. Circulation 1994; 89 (6): 2722-7
27. Hadengue A, Benhayoun MK, Lebrec D, et al. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. Gastroenterology 1991; 100 (2): 520-8
28. Badesch DB, Wynne KM, Bonvallet S, et al. Hypothyroidism and primary pulmonary hypertension: an autoimmune pathogenetic link? Ann Intern Med 1993; 119 (1): 44-6
29. Herve P, Launay JM, Scrobohaci ML, et al. Increased plasma serotonin in primary pulmonary hypertension. Am J Med 1995; 99 (3): 249-54
30. Cacoub P, Dorent R, Carayon A. Thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med 1992; 327 (20): 1456-7; discussion 1458

31. Stewart DJ, Levy RD, Cernacek P, et al. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med 1991; 114 (6): 464-9
32. Christman BW, McPherson CD, Newman JH, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med 1992; 327 (2): 70-5
33. Inglesby TV, Singer JW, Gordon DS. Abnormal fibrinolysis in familial pulmonary hypertension. Am J Med 1973; 55 (1): 5-14
34. Eisenberg PR, Lucore C, Kaufman L, et al. Fibrinopeptide A levels indicative of pulmonary vascular thrombosis in patients with primary pulmonary hypertension. Circulation 1990; 82 (3): 841-7
35. Huber K, Beckmann R, Frank H, et al. Fibrinogen, t-PA, and PAI-1 plasma levels in patients with pulmonary hypertension. Am J Respir Crit Care Med 1994; 150 (4): 929-33
36. Tubbs RR, Levin RD, Shirey EK, et al. Fibrinolysis in familial pulmonary hypertension. Am J Clin Pathol 1979; 71 (4): 384-7
37. Hoeper MM, Sosada M, Fabel H. Plasma coagulation profiles in patients with severe primary pulmonary hypertension. Eur Respir J 1998; 12 (6): 1446-9
38. Herve P, Drouet L, Dosquet C, et al. Primary pulmonary hypertension in a patient with a familial platelet storage pool disease: role of serotonin. Am J Med 1990; 89 (1): 117-20
39. Weir EK, Archer SL. The mechanism of acute hypoxic pulmonary vasoconstriction: the tale of two channels. Faseb J 1995; 9 (2): 183-9
40. Naeije R, De Backer D, Vachiery JL, et al. High-altitude pulmonary edema with primary pulmonary hypertension. Chest 1996; 110 (1): 286-9
41. Weir EK, Reeve HL, Huang JM, et al. Anorexic agents aminorex, fenfluramine, and dexfenfluramine inhibit potassium current in rat pulmonary vascular smooth muscle and cause pulmonary vasoconstriction. Circulation 1996; 94 (9): 2216-20
42. Wang J, Juhaszova M, Conte JV, et al. Action of fenfluramine on voltage-gated K+ channels in human pulmonary- artery smooth-muscle cells [letter]. Lancet 1998; 352 (9124): 290
43. Yuan XJ, Wang J, Juhaszova M, et al. Attenuated K+ channel gene transcription in primary pulmonary hypertension. Lancet 1998; 351 (9104): 726-7
44. Schuster DP, Crouch EC, Parks WC, et al. Angiotensin converting enzyme expression in primary pulmonary hypertension. Am J Respir Crit Care Med 1996; 154 (4 Pt 1): 1087-91
45. Stenmark KR, Mecham RP. Cellular and molecular mechanisms of pulmonary vascular remodelling. Annu Rev Physiol 1990; 136: 881-90
46. Voelkel NF, Tuder R, Weir E. Pathophysiology of primary pulmonary hypertension: from physiology to molecular mechanisms. In: Rubin L, Rich S, editors. Primary pulmonary hypertension. New York: Marcel Dekker, 1997: 83-130
47. Archer S, Rich S. Primary pulmonary hypertension: a vascular biology and translational research 'work in progress'. Circulation 2000; 102 (22): 2781-91
48. Loyd JE, Butler MG, Foroud TM, et al. Genetic anticipation and abnormal gender ratio at birth in familial primary pulmonary hypertension. Am J Respir Crit Care Med 1995; 152 (1): 93-7
49. Rich S. Executive summary from the World Symposium on primary pulmonary hypertension 1998. World Health Organization website. Available at URL: www.who.int/ncd/cvd/pph.html [Accessed 1998 Sep 6-10]
50. Nichols WC, Koller DL, Slovis B, et al. Localization of the gene for familial primary pulmonary hypertension to chromosome 2q31-32. Nat Genet 1997; 15 (3): 277-80
51. Deng Z, Morse JH, Slager SL, et al. Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene. Am J Hum Genet 2000; 67 (3): 737-44
52. Lane KB, Machado RD, Pauciulo MW, et al. Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. The International PPH Consortium. Nat Genet 2000; 26 (1): 81-4
53. Morrell NW, Yang X, Upton PD, et al. Altered growth responses of pulmonary artery smooth muscle cells from patients with primary pulmonary hypertension to transforming growth factor-beta(1) and bone morphogenetic proteins. Circulation 2001; 104 (7): 790-5
54. Kimura N, Matsuo R, Shibuya H, et al. BMP2-induced apoptosis is mediated by activation of the TAK1-p38 kinase pathway that is negatively regulated by Smad6. J Biol Chem 2000; 275 (23): 17647-52
55. Soda H, Raymond E, Sharma S, et al. Antiproliferative effects of recombinant human bone morphogenetic protein-2 on human tumor colony-forming units. Anticancer Drugs 1998; 9 (4): 327-31
56. Trembath RC, Thomson JR, Machado RD, et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 2001; 345: 367-71
57. Fuster V, Steele PM, Edwards WD, et al. Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation 1984; 70 (4): 580-7
58. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992; 327 (2): 76-81
59. Gaine SP, Rubin LJ. Medical and surgical treatment options for pulmonary hypertension. Am J Med Sci 1998; 315 (3): 179-84
60. Primary pulmonary hypertension. National Institutes of Health (NIH). Division of Lung Diseases and Office of Prevention, Education, and Control. National Heart, Lung and Blood Institute. US Department of Health and Human Services, Public Health Service. 1992 Oct; NIH Publication No.: 92-3291
61. Curnock AL, Dweik RA, Higgins BH, et al. High prevalence of hypothyroidism in patients with primary pulmonary hypertension. Am J Med Sci 1999; 318 (5): 289-92
62. Saran BR, Brucker AJ, Bandello F, et al. Familial primary pulmonary hypertension and associated ocular findings. Retina 2001; 21 (1): 34-9
63. Pavlesky HI, Fishman AP. The management of primary pulmonary hypertension . JAMA 1991; 265: 1014-20
64. Bossone E, Duong-Wagner TH, Paciocco G, et al. Echocardiographic features of primary pulmonary hypertension. J Am Soc Echocardiogr 1999; 12 (8): 655-62
65. Meaney JF, Johansson LO, Ahlstrom H, et al. Pulmonary magnetic resonance angiography. J Magn Reson Imaging 1999; 10 (3): 326-38
66. Remy-Jardin M, Remy J. Spiral CT angiography of the pulmonary circulation. Radiology 1999; 212 (3): 615-36
67. Worsley DF, Palevsky HI, Alavi A. Ventilation-perfusion lung scanning in the evaluation of pulmonary hypertension. J Nucl Med 1994; 35 (5): 793-6
68. Nicod P, Peterson K, Levine M, et al. Pulmonary angiography in severe chronic pulmonary hypertension. Ann Intern Med 1987; 107 (4): 565-8

69. Zuckerman DA, Sterling KM, Oser RF. Safety of pulmonary angiography in the 1990s. J Vasc Interv Radiol 1996; 7 (2): 199-205
70. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension: comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 2000; 161 (2 Pt 1): 487-92
71. Isern RA, Yaneva M, Weiner E, et al. Autoantibodies in patients with primary pulmonary hypertension: association with anti-Ku. Am J Med 1992; 93: 307-12
72. Kafi SA, Melot C, Vachiery JL, et al. Partitioning of pulmonary vascular resistance in primary pulmonary hypertension. J Am Coll Cardiol 1998; 31 (6): 1372-6
73. Gaine SP, Rubin LJ. Primary pulmonary hypertension. Lancet 1998; 352 (9129): 719-25
74. Oakley C, Somerville J. Oral contraceptives and progressive pulmonary vascular disease. Lancet 1968; 1 (7548): 890-3
75. Frank H, Mlczoch J, Huber K, et al. The effect of anticoagulant therapy in primary and anorectic drug- induced pulmonary hypertension. Chest 1997; 112 (3): 714-21
76. Palevsky HI, Fishman AP. The management of primary pulmonary hypertension. JAMA 1991; 265 (8): 1014-20
77. Moraes D, Loscalzo J. Pulmonary hypertension: newer concepts in diagnosis and management. Clin Cardiol 1997; 20 (8): 676-82
78. Rich S, Seidlitz M, Dodin E, et al. The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. Chest 1998; 114 (3): 787-92
79. Nagasaka Y, Akutsu H, Lee YS, et al. Longterm favorable effect of oxygen administration on a patient with primary pulmonary hypertension. Chest 1978; 74 (3): 299-300
80. Rubin LJ. Primary pulmonary hypertension: practical therapeutic recommendations. Drugs 1992; 43 (1): 37-43
81. Butt AY, Higenbottam T. New therapies for primary pulmonary hypertension. Chest 1994; 105 (2 Suppl): 21S-5S
82. Wanstall JC, Jeffery TK. Recognition and management of pulmonary hypertension. Drugs 1998; 56 (6): 989-1007
83. Phillips BG, Bauman JL, Schoen MD, et al. Serum nifedipine concentrations and response of patients with pulmonary hypertension. Am J Cardiol 1996; 77 (11): 996-9
84. Shimabukuro M, Chibana T, Yoshida H, et al. Sustained improvement of pulmonary haemodynamics with low-dose of nifedipine in primary pulmonary hypertension. Eur Heart J 1996; 17 (12): 1911-2
85. Kambara H, Fujimoto K, Wakabayashi A, et al. Primary pulmonary hypertension: beneficial therapy with diltiazem. Am Heart J 1981; 101 (2): 230-1
86. Woodmansey PA, O'Toole L, Channer KS, et al. Acute pulmonary vasodilatory properties of amlodipine in humans with pulmonary hypertension. Heart 1996; 75 (2): 171-3
87. Rich S, Ganz R, Levy PS. Comparative actions of hydralazine, nifedipine and amrinone in primary pulmonary hypertension. Am J Cardiol 1983; 52 (8): 1104-7
88. McGoon MD, Seward JB, Vlietstra RE, et al. Haemodynamic response to intravenous hydralazine in patients with pulmonary hypertension. Br Heart J 1983; 50 (6): 579-85
89. Scott JP, Higenbottam TW, Smyth RL, et al. Acute pulmonary hypertensive crisis in a patient with primary pulmonary hypertension treated by both epoprostenol (prostacyclin) and nitroprusside. Chest 1991; 99 (5): 1284-5
90. Mentzer SJ, Reilly JJ, DeCamp M, et al. Potential mechanism of vasomotor dysregulation after lung transplantation for primary pulmonary hypertension. J Heart Lung Transplant 1995; 14 (2): 387-93
91. Jones DK, Higenbottam TW, Wallwork J. Treatment of primary pulmonary hypertension intravenous epoprostenol (prostacyclin). Br Heart J 1987; 57 (3): 270-8
92. Higenbottam TW, Spiegelhalter D, Scott JP, et al. Prostacyclin (epoprostenol) and heart-lung transplantation as treatments for severe pulmonary hypertension. Br Heart J 1993; 70 (4): 366-70
93. Cremona G, Higenbottam T. Role of prostacyclin in the treatment of primary pulmonary hypertension. Am J Cardiol 1995; 75 (3): 67A-71A
94. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med 1996; 334 (5): 296-302
95. Barst RJ. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin. Heart 1997; 77 (4): 299-301
96. Galie N, Ussia G, Passarelli P, et al. Role of pharmacologic tests in the treatment of primary pulmonary hypertension. Am J Cardiol 1995; 75 (3): 55A-62A
97. Raffy O, Azarian R, Brenot F, et al. Clinical significance of the pulmonary vasodilator response during short-term infusion of prostacyclin in primary pulmonary hypertension. Circulation 1996; 93 (3): 484-8
98. Morgan JM, McCormack DG, Griffiths MJ, et al. Adenosine as a vasodilator in primary pulmonary hypertension. Circulation 1991; 84 (3): 1145-9
99. Nootens M, Schrader B, Kaufmann E, et al. Comparative acute effects of adenosine and prostacyclin in primary pulmonary hypertension. Chest 1995; 107 (1): 54-7
100. Palevsky HI, Long W, Crow J, et al. Prostacyclin and acetylcholine as screening agents for acute pulmonary vasodilator responsiveness in primary pulmonary hypertension. Circulation 1990; 82 (6): 2018-26
101. Conraads VM, Bosmans JM, Claeys MJ, et al. Paradoxic pulmonary vasoconstriction in response to acetylcholine in patients with primary pulmonary hypertension. Chest 1994; 106 (2): 385-90
102. Rich S, Kaufmann E. High dose titration of calcium channel blocking agents for primary pulmonary hypertension: guidelines for short-term drug testing. J Am Coll Cardiol 1991; 18 (5): 1323-7
103. Klinke WP, Gilbert JA. Diazoxide in primary pulmonary hypertension. N Engl J Med 1980; 302 (2): 91-2
104. Honey M, Cotter L, Davies N, et al. Clinical and haemodynamic effects of diazoxide in primary pulmonary hypertension. Thorax 1980; 35 (4): 269-76
105. Chan NS, McLay J, Kenmure AC. Reversibility of primary pulmonary hypertension during six years of treatment with oral diazoxide. Br Heart J 1987; 57 (2): 207-9
106. Rich S, Martinez J, Lam W, et al. Captopril as treatment for patients with pulmonary hypertension: problem of variability in assessing chronic drug treatment. Br Heart J 1982; 48 (3): 272-7
107. Leier CV, Bambach D, Nelson S, et al. Captopril in primary pulmonary hypertension. Circulation 1983; 67 (1): 155-61
108. McLaughlin VV, Genthner DE, Panella MM, et al. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med 1998; 338 (5): 273-7

109. Wax D, Garofano R, Barst RJ. Effects of long-term infusion of prostacyclin on exercise performance in patients with primary pulmonary hypertension. Chest 1999; 116 (4): 914-20
110. Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. J Am Coll Cardiol 1999; 34 (4): 1184-7
111. Kesten S, Dainauskas J, McLaughlin V, et al. Development of nonspecific interstitial pneumonitis associated with long-term treatment of primary pulmonary hypertension with prostacyclin. Chest 1999; 116 (2): 566-9
112. Nihill MR, O'Laughlin MP, Mullins CE. Effects of atrial septostomy in patients with terminal cor pulmonale due to pulmonary vascular disease. Cathet Cardiovasc Diagn 1991; 24 (3): 166-72
113. Kerstein D, Levy PS, Hsu DT, et al. Blade balloon atrial septostomy in patients with severe primary pulmonary hypertension. Circulation 1995; 91 (7): 2028-35
114. Sandoval J, Gaspar J, Pulido T, et al. Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension: a therapeutic alternative for patients nonresponsive to vasodilator treatment. J Am Coll Cardiol 1998; 32 (2): 297-304
115. Rich S, Dodin E, McLaughlin VV. Usefulness of atrial septostomy as a treatment for primary pulmonary hypertension and guidelines for its application. Am J Cardiol 1997; 80 (3): 369-71
116. Reitz BA, Wallwork JL, Hunt SA, et al. Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. N Engl J Med 1982; 306 (10): 557-64
117. Pasque MK, Trulock EP, Kaiser LR, et al. Single-lung transplantation for pulmonary hypertension: three-month hemodynamic follow-up. Circulation 1991; 84 (6): 2275-9
118. Glanville AR, Burke CM, Theodore J, et al. Primary pulmonary hypertension: length of survival in patients referred for heart-lung transplantation. Chest 1987; 91 (5): 675-81
119. Annual report of the US scientific registry for transplantation recipients and the organ procurement and transplantation network-transplant data: 1988-1996. Richmond (VA): United Network for Organ Sharing, 1997
120. McLaughlin VV, Rich S. Severe pulmonary hypertension: critical care clinics. Crit Care Clin 2001; 17 (2): 453-67
121. Nagaya N, Uematsu M, Okano Y, et al. Effect of orally active prostacyclin analogue on survival of outpatients with primary pulmonary hypertension. J Am Coll Cardiol 1999; 34 (4): 1188-92
122. Christman BW, Barst RJ, Dias VC, et al. Effects of a thromboxane synthetase inhibitor/receptor antagonist (TSI/TRA) on endogenous prostanoid synthesis, exercise capacity and hemodynamics in patients with PPH. Circulation 2000; 102 (18 Suppl II): II-100
123. Olschewski H, Ghofrani HA, Schmehl T, et al. Inhaled iloprost to treat severe pulmonary hypertension: an uncontrolled trial. German PPH Study Group. Ann Intern Med 2000; 132 (6): 435-43
124. Wensel R, Opitz CF, Ewert R, et al. Effects of iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. Circulation 2000; 101 (20): 2388-92
125. Schaar J, Oldenburg O, Caspari G, et al. A new treatment of pulmonary hypertension: simultaneous pulsatile inhalation of nitric oxide and iloprost [abstract]. J Am Coll Cardiol 2001; 37 (2 Suppl A): 243A
126. Nootens M, Kaufmann E, Rector T, et al. Neurohormonal activation in patients with right ventricular failure from pulmonary hypertension: relation to hemodynamic variables and endothelin levels. J Am Coll Cardiol 1995; 26 (7): 1581-5
127. Schiffrin EL. Endothelin and endothelin antagonists in hypertension. J Hypertens 1998; 16 (12 Pt 2): 1891-5
128. Williamson DJ, Wallman LL, Jones R, et al. Hemodynamic effects of Bosentan, an endothelin receptor antagonist, in patients with pulmonary hypertension. Circulation 2000; 102 (4): 411-8
129. Givertz MM, Colucci WS, LeJemtel TH, et al. Acute endothelin A receptor blockade causes selective pulmonary vasodilation in patients with chronic heart failure. Circulation 2000; 101 (25): 2922-7
130. Rossaint R. Nitric oxide: a new area in intensive care. Presse Med 1994; 23 (18): 855-8
131. Al-Alaiyan S, Neiley E. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn refractory to high-frequency ventilation. Crit Care 1999; 3 (1): 7-10
132. Roberts JD, Zapol WM. Inhaled nitric oxide. Semin Perinatol 2000; 24 (1): 55-8
133. Clark RH, Kueser TJ, Walker MW, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. Clinical Inhaled Nitric Oxide Research Group. N Engl J Med 2000; 342 (7): 469-74
134. Riley MS, Porszasz J, Engelen MP, et al. Responses to constant work rate bicycle ergometry exercise in primary pulmonary hypertension: the effect of inhaled nitric oxide. J Am Coll Cardiol 2000; 36 (2): 547-56
135. Krasuski RA, Warner JJ, Wang A, et al. Inhaled nitric oxide selectively dilates pulmonary vasculature in adult patients with pulmonary hypertension, irrespective of etiology. J Am Coll Cardiol 2000; 36 (7): 2204-11
136. Sitbon O, Brenot F, Denjean A, et al. Inhaled nitric oxide as a screening vasodilator agent in primary pulmonary hypertension: a dose-response study and comparison with prostacyclin. Am J Respir Crit Care Med 1995; 151 (2 Pt 1): 384-9
137. Young JD, Sear JW, Valvini EM. Kinetics of methaemoglobin and serum nitrogen oxide production during inhalation of nitric oxide in volunteers. Br J Anaesth 1996; 76: 652-6
138. Mehta S, Stewart DJ, Langleben D, et al. Short-term pulmonary vasodilation with L-arginine in pulmonary hypertension. Circulation 1995; 92 (6): 1539-45
139. Schulze-Neick I, Penny DJ, Rigby ML, et al. L-arginine and substance P reverse the pulmonary endothelial dysfunction caused by congenital heart surgery. Circulation 1999; 100 (7): 749-55
140. Thebaud B, Saizou C, Farnoux C, et al. Dypiridamole, a cGMP phosphodiesterase inhibitor, transiently improves the response to inhaled nitric oxide in two newborns with congenital diaphragmatic hernia. Intensive Care Med 1999; 25 (3): 300-3
141. Jiang ZY, Costachescu T, Derouin M, et al. Treatment of pulmonary hypertension during surgery with nitric oxide and vasodilators. Can J Anaesth 2000; 47 (6): 552-5
142. Ivy DD, Kinsella JP, Ziegler JW, et al. Dipyridamole attenuates rebound pulmonary hypertension after inhaled nitric oxide withdrawal in postoperative congenital heart disease. J Thorac Cardiovasc Surg 1998; 115 (4): 875-82
143. Fullerton DA, Jaggers J, Piedalue F, et al. Effective control of refractory pulmonary hypertension after cardiac operations. J Thorac Cardiovasc Surg 1997; 113 (2): 363-8; discussion 368-70

144. Abrams D, Schulze-Neick I, Magee AG. Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension. Heart 2000; 84 (2): E4
145. Prasad S, Wilkinson J, Gatzoulis MA. Sildenafil in primary pulmonary hypertension [letter]. N Engl J Med 2000; 343 (18): 1342
146. Atz AM, Wessel DL. Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. Anesthesiology 1999; 91 (1): 307-10
147. Ye CL, Rabinovitch M. Inhibition of elastolysis by SC-37698 reduces development and progression of monocrotaline pulmonary hypertension. Am J Physiol 1991; 261 (4 Pt 2): H1255-67
148. Cowan KN, Heilbut A, Humpl T, et al. Complete reversal of fatal pulmonary hypertension in rats by a serine elastase inhibitor. Nat Med 2000; 6 (6): 698-702
149. Wanstall JC, Kay CS, O'Donnell SR. Pinacidil-induced relaxation in pulmonary arteries isolated from pulmonary hypertensive and normotensive rats and pre-contracted with different spasmogens. Pulm Pharmacol 1994; 7 (6): 401-8
150. Kwan YW, To KW, Lau WM, et al. Comparison of the vascular relaxant effects of ATP-dependent K+ channel openers on aorta and pulmonary artery isolated from spontaneously hypertensive and Wistar-Kyoto rats. Eur J Pharmacol 1999; 365 (2-3): 241-51
151. Nagaya N, Yokoyama C, Kyotani S, et al. Gene transfer of human prostacyclin synthase ameliorates monocrotaline- induced pulmonary hypertension in rats. Circulation 2000; 102 (16): 2005-10
152. Budts W, Pokreisz P, Nong Z, et al. Aerosol gene transfer with inducible nitric oxide synthase reduces hypoxic pulmonary hypertension and pulmonary vascular remodeling in rats. Circulation 2000; 102 (23): 2880-5
153. Champion HC, Bivalacqua TJ, Toyoda K, et al. In vivo gene transfer of prepro-calcitonin gene-related peptide to the lung attenuates chronic hypoxia-induced pulmonary hypertension in the mouse. Circulation 2000; 101 (8): 923-30
154. Albelda SM, Wiewrodt R, Zuckerman JB. Gene therapy for lung disease: hype or hope? Ann Intern Med 2000; 132 (8): 649-60
155. Li SL, Zhang XY, Ling H, et al. A VSV-G pseudotyped HIV vector mediates efficient transduction of human pulmonary artery smooth muscle cells. Microbiol Immunol 2000; 44 (12): 1019-25
156. Heistad DD. Gene transfer to blood vessels: a research tool and potential therapy. Am J Hypertens 2001; 14 (6 Pt 2): 28S-32S

Correspondence and offprints: *Tine L.M. De Backer*, Department of Cardiology, Thoraxcentre , Erasmus Medical Centre Rotterdam, Dr Molewaterplein 40, Rotterdam, 3015 GD, The Netherlands.
E-mail: t_de_backer@hotmail.com