Pulmonary Hypertension: A Review of the Aetiology, Pathophysiology and Management

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ABSTRACT

Pulmonary hypertension (PH) is defined as a systolic pulmonary artery pressure (PAP) above 30 mmHg and a mean PAP above 25 mmHg. Pulmonary hypertensive diseases (PHDs) encompass a myriad of conditions that cause pulmonary hypertension (PH), hence the Evian Classification was developed for the categorization of the various causes. Pulmonary hypertensive diseases are complex conditions that are difficult to treat and in the case of primary pulmonary hypertension, there is no known cure. Dyspnoea on exertion is the main symptom. This usually worsens as the disease progresses and can lead to syncope as a result of right ventricular failure. Prostacyclin has been the mainstay of treatment for decades, but several new drugs and alternate methods of treatment are currently available.

Hipertensión Pulmonar: Revisión de su Etiología, Patofisiología y Tratamiento

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RESUMEN

La hipertensión pulmonar (HP) se define como presión arterial pulmonar sistólica (PAP) por encima de 30 mmHg y una PAP por encima de 25 mmHg. Las enfermedades hipertensivas pulmonares (EHPs) comprenden un sinnúmero de condiciones que causan hipertensión pulmonar (HP), razón por la cual fue desarrollada la Clasificación de Evian para la categorización de las diversas causas. Las enfermedades pulmonares hipertensivas son condiciones complejas que son difíciles de tratar y en el caso de la hipertensión pulmonar primaria, no se conoce cura. La disnea al realizar un esfuerzo es el síntoma principal. Esta condición por lo regular empeora a medida que la enfermedad progresa, y puede llevar al síncope como resultado del fallo del ventrículo derecho. Durante décadas, la prostaciclina ha sido el soporte principal del tratamiento, pero varios medicamentos nuevos y métodos de tratamiento alternativos se hallan disponibles en el presente.

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INTRODUCTION

Normal pulmonary arterial pressures (PAPs) are usually one-fifth that of systemic pressures, with the pulmonary artery systolic and mean pressure ranges being 15–30 mmHg and 10–15 mmHg respectively, and the pulmonary vascular resistance (PVR) being 20–150 dynes/s/cm^5. Pulmonary hypertension (PH) is a complex disorder caused by a number of disease entities that are clinically quite difficult to distinguish from each other but are easily distinguished on histologic examination of lung tissue. Pulmonary hypertension is characterized by an increase in the PAPs and the PVR. The systolic PAP is above 30 mmHg, the mean PAP above 15 mmHg, and the PVR above 150 dynes/s/cm^5 (1–3). The myriad of conditions that cause PH are grouped together as pulmonary hypertensive diseases (PHDs). A search of the literature did not yield a numerical value for mild, moderate and severe PAP, but severe is stated to be a pulmonary systolic pressure of over 50 mmHg or a mean of three times the normal value (1, 3). The revised World Health Organization Classification of PHDs and the functional assessment classification are shown in [Tables 1 – 3]. There is also the New York Heart Association clinical classification (1, 12).

Patients with primary PH have no identifiable underlying cause while secondary PH is due to pulmonary, cardiac or systemic diseases. Pulmonary causes include: fibrosis, emphysema, inflammatory conditions that cause scarring of the lung and chronic thromboembolism (3–11). Cardiac causes include congenital (atrial and ventricular septal de-

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fects, patent ductus arteriosus) and acquired heart disease *eg* rheumatic fever induced mitral valve stenosis and to a lesser extent mitral valve incompetence and aortic valve stenosis (2–4, 8–12) [Tables 1–3].

Table 1: Revised clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension (PAH)
   - 1.1. **Idiopathic** (IPAH)
   - 1.2. Familial (FPAH)
   - 1.3. Associated with (APAH):
     - 1.3.1. Collagen vascular disease
     - 1.3.2. Congenial systemic-to-pulmonary shunts**
     - 1.3.3. Portal hypertension
     - 1.3.4. HIV infection
     - 1.3.5. Drug and toxins
     - 1.3.6. **Other** (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary haemorrhagic telangiecctasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
   - 1.4 **Associated with significant venous or capillary involvement**
     - 1.4.1. Pulmonary veno-occulsive disease (PVOD)
     - 1.4.2. Pulmonary capillary haemangiomatosis (PCH)
   - 1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary Hypertension associated with left heart disease
   - 2.1. Left-sided atrial or ventricular heart disease
   - 2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxaemia
   - 3.1. Chronic obstructive pulmonary disease
   - 3.2. Interstitial lung disease
   - 3.3. Sleep-disordered breathing
   - 3.4. Alveolar hypoventilation disorders
   - 3.5. Chronic exposure to high altitude
   - 3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   - 4.1. Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2. Thromboembolic obstruction of distal pulmonary arteries
   - 4.3. Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)
5. **Miscellaneous**
   Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

The table is the revised World Health Organizations classification done by Simonneau *et al* and presented in Venice in 2003 (12). ** See Table 2

Table 2: Guidelines for classification of congenital systemic to pulmonary shunts

1. Type
   - Simple
     - Atrial septal defect (ASD)
     - Ventricular septal defect (VSD)
     - Patent ductus arteriosus
     - Total or partial unobstructed anomalous pulmonary venous return
   - Combined
     - Describe combination and define prevalence defect if any
   - Complex
     - Truncus arteriosus
     - Single ventricle with unobstructed pulmonary blood flow
     - Atrioventricular septal defect
2. Dimensions
   - Small (ASD ? 2.0 cm and VSD ? 1.0 cm)
   - Large (ASD > 2.0 cm and VSD > 1.0 cm)
3. Associated extracardiac abnormalities
4. Correction status
   - Noncorrected
   - Partially corrected (age)
   - Corrected: spontaneously or surgically (age)

By Simonneau *et al* (12)

Table 3: World Health Organization functional assessment classification

Class I:	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.
Class II:	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class III:	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class IV:	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

By Rubin LJ (1)

At the University Hospital of the West Indies (UHWI), 132 patients were diagnosed with PH over the period 2000 to 2006. Seventy per cent were due to cardiac causes; 35 congenital and 57 acquired, 9% due to pulmonary, 8% to primary pulmonary and 13% to other systemic causes (personal communication with the Medical Records Department). The authors however believe that PH is underreported at UHWI.

The Pathobiology and Pathophysiology of Pulmonary Hypertension

Pulmonary Hypertension can also be divided in terms of clinical severity and outcome into two main forms – mild-to moderate and severe. Mild-to-moderate PH characteristically occurs secondary to parenchymal pulmonary diseases such as interstitial lung diseases, emphysema or chronic hypoxia. The pathogenesis of this type of PH has been attributed to either damage to the peripheral pulmonary arterial circulation or to the vasoconstrictive or vascular remodelling effects of chronic hypoxia. The fact that the pulmonary vascular remodelling has been found to be reversible with oxygen therapy and resolution of the underlying lung disease, suggests that it is an adaptive phenomenon (13, 14).

The severe form of PH is usually irreversible and fatal in outcome. This includes primary pulmonary hypertension (PPH), PH due to anorexigens (appetite suppressant agents *eg* fenfluramine and amphetamine), human immunodeficien-

Table 4: Drugs currently approved for the treatment of pulmonary arterial hypertension in the United States of America and Europe

Drugs	Method of administration	Recommended Doses
Epoprostenol (PGI_2)	Continuous intravenous	Start at 2-4 ng/Kg/minute Increase in increments to 45 ng/Kg/minute
Iloprost (a PGI_2 analogue)	Aerosol – nasally	100–150 mcg/kg/day
Remodulin/treprostinil (a PGI_2 analogue)	Continuous intravenous and subcutaneous	Start at 1.25ng/Kg/minute Increase in increment of 2.5 ng/Kg/minute per week to a maximum of 40 ng/Kg/minute
Bosentan (an endothelin-receptor antagonist)	Orally	Start at 62.5 mg twice daily Increase stepwise to a maximum of 250 mg/day
Sildenafil citrate (Revatio) (a phosphodiesterase-5 – inhibitor)	Orally	Start at 20 mg thrice daily Increase stepwise as necessary

cy virus (HIV) infection, portal hypertension and the CREST syndrome. These conditions share the feature of obliteration of the PA lumina by proliferated endothelial cells. Dysfunction of the pulmonary artery (PA) endothelial cells is considered to be the key pathobiologic feature of severe PH, and is thought to be responsible for the initiation and progression of the disease. It has been discovered that a subset of families with PPH had a germline mutation in the bone morphogenetic protein (BMP) receptor-2. This is supportive evidence that genetic mutations may be the underlying trigger for severe PH, acting *via* an undetermined mechanism to cause: lung cell (endothelial and medial) proliferation, inhibition of apoptosis and increase growth factor expression (14). These observations highlight a non-vasoconstrictive hypothesis for the explanation of severe PH as compared to that for mild-to-moderate disease.

Characteristic structural changes that are identified in patients with severe PH, especially those with PPH are: (i) increased medial, intimal and adventitial thickness, (ii) appearance of muscle in the walls of normally non-muscular intraacinar arteries, (iii) concentric and eccentric intimal thickening, (iv) occlusion and recanalization of the smaller arterial lumens and (v) loss of peripheral artery which is associated with increased elastin. The end result of these structural changes is a reduction in pulmonary arterial volume and flow. Other features include dilated capillaries and the appearance of plexiform lesions. The latter is considered to be a pathognomonic pathologic feature of PPH, but it is also seen in patients with congestive heart disease (CHD), HIV- and scleroderma-induced pulmonary hypertension. However, not all patients with primary pulmonary hypertension exhibit plexiform lesions. Proliferated endothelial cells form the cellular basis of the plexiform, eccentric and concentric lesions as well as the obliterated vascular lumen resulting in disruption of blood flow (15).

Alterations in vasoactive mediators have also been suggested to contribute to the development and maintenance of pulmonary hypertension. The onset of mild-to-moderate PH has been suggested to result from an increase in vasoconstrictor agents such as thromboxane (Tx) and endothelin-1 (ET-1), and/or a loss or reduction in pulmonary vasodilators such as prostacyclin ($PG\text{-}I_2$) and nitric oxide (NO). Increased expression of ET-1 and decreased expression of prostacyclin synthase and endothelial (NO) synthase have been noted in the vasculature of patients with primary pulmonary hypertension. The vasoconstrictive agents have also been found to increase platelet aggregation and thrombosis which contribute to the maintenance and progression of the disease (14). Endogenous PGI_2 is synthesized mainly by the endothelial cells and is a potent vasodilator. It acts by binding to its membrane associated G-protein-coupled receptor of the vascular smooth muscle. This causes activation of adenylate cyclase and increased production of cyclic adenosine monophosphate (cAMP). Prostacyclin (PGI_2) is also the most potent endogenous inhibitor of platelet aggregation, and also seems to have cytoprotective and antiproliferative activities (16). The exact influence of these substances on the structural and functional changes seen in the various types of PH as well as the exact mechanism that initiate and maintain PH remains enigmatic.

The pathophysiologic factors which contribute to PH seen in long standing mitral or aortic valvular disease have been purported to include the following: (i) retrograde transmission of the increased left atrial pressure to the pulmonary

circulation, (ii) remodelling of the pulmonary vasculature which occurs in response to chronic obstruction to pulmonary venous drainage – the "fixed component" and (iii) pulmonary arterial vasoconstriction – the "reactive component" (11). It is this reactive component in both cardiac and non-cardiac causes of PH that is purported to be modulated by vasodilatory agents.

Clinical Features and Diagnosis

A meticulous history, careful physical examination, a high index of suspicion and the use of appropriate diagnostic tools are paramount for diagnosing PH. Dyspnoea on exertion is the most common presentation. This worsens as the disease progresses and may lead to syncope, anginal or atypical chest discomfort due to a limited ability to increase the cardiac output in response to increased metabolic demand. Jugular veinous distension and a prominent "a" wave in the jugular venous pulse, a left parasternal heave (due to right ventricular hypertrophy – RVH), a loud second (pulmonary-P2) heart sound and a right-sided fourth heart sound are pathognomonic clinical findings. A Graham Steell murmur of pulmonary hypertension may be heard. Signs of right heart dysfunction (hepatomegaly and peripheral oedema) are seen in severe cases. Prominence of the main pulmonary artery and hilar vessel enlargement are characteristic chest radiographic signs. Increase P-wave amplitude in lead ? and right axis deviation as a result of RVH are evident on ECG in moderate to severe cases. Pulmonary function tests will reveal a reduced capacity for gas (carbon monoxide) transfer due to obliteration of small pulmonary arteries. A respiratory or mixed respiratory-metabolic alkalosis with hypoxaemia is likely to occur in most patients. The hypoxaemia is increased with exercise and is due to the inability to increase cardiac output to match the metabolic needs (3, 17). The six-minute walk test is useful for clinical assessment of severity as well as response to treatment (18).

Echocardiography is the most useful imaging modality for diagnosing PH and for excluding or confirming underlying cardiac disease. M-mode echocardiography will show a normal to small left ventricular end-diastolic internal dimension, right ventricular enlargement, paradoxical septal motion and partial systolic closure of the pulmonary valve in patients with no cardiac disease (17). Two-dimensional echocardiography with doppler study will show tricuspid valve regurgitation (TVR) and a peak TVR jet velocity of 28 m/second or more in the presence of normal (in mild to moderate cases) or elevated (in moderate to severe cases) right atrial pressure (RAP). The addition of the mean RAP to the peak tricuspid jet velocity gives an accurate noninvasive estimate of peak PAP (3, 18). Patients with PPH, generally have severe pulmonary hypertension, with a three-fold increase in the mean pulmonary artery pressure, mild to moderate elevation of the mean right atrial pressure with a normal pulmonary capillary wedge pressure (PCWP) and a moderate to severely reduced cardiac index (17).

Computed tomographic (CT) scanning of the chest with high resolution images is useful for detecting or excluding occult interstitial lung disease with mediastinal fibrosis. Ventilation – perfusion scanning will detect chronic thromboembolism. Cardiac (especially right heart) catheterization should be performed in patients with unexplained PH. It is particularly useful for: detecting occult shunts, confirming the type and severity of congential heart disease/s and detecting distal PA stenosis (3, 19).

Treatment

The goals of treatment are to: (i) treat the underlying cause, (ii) reduce symptoms and improve quality of life, (iii) slow the growth of the pulmonary smooth muscle cells and the development of thrombus, (iv) increase the supply of blood and oxygen to the heart, while reducing its workload (20). Treatment of the underlying cause is the first priority in patients with secondary PH, and if instituted early may correct the PH if it is not severe. Manipulating the imbalance between endothelial derived vasoconstrictors and vasodilators remains the cornerstone of treatment for the pulmonary pathology regardless of the severity or cause of pulmonary hypertension and particularly for primary pulmonary hypertension. Prostacyclin (prostaglandin I_2 – PGI_2, Flolan or epoprostenol) is the drug of choice. It is a potent short acting vasodilator and inhibitor of platelet aggregation. It is administered by continuous intravenous infusion and hence requires hospitalization especially at the initiation of treatment. An initial haemodynamic study is useful to predict patients who are likely to respond to long term vasodilator therapy. One method is via Swan-Ganz catheter measurement of pulmonary haemodynamics pre- and post-treatment with inhaled nitric oxide (NO) or an intravenous vasodilator. Exercise tolerance (as measured by the 6-minute walk test), symptoms and cardiopulmonary haemodynamic parameters have been shown to improve with prostacyclin (5, 19–25) and other treatment (6–8, 25–26).

Chronic/long term PGI_2 therapy has been so effective in some patients, it has caused deferral or cancellation of lung transplantation. In one centre, this was the case for seventy per cent of such candidates (16). Treatment is initiated in hospital at doses ranging from 2 to 4 ng/kg/minute and is increased at a rate limited by its side effects. The target dose for the first 2 to 4 weeks is usually about 10 to 15 ng/kg/minute. Periodic dose increase may still be required to maximize efficacy and to maintain clinical benefits because of tolerance to the drug. The optimal dose is said to range from 22 to 45 ng/kg/minute (16, 22 23). Patients are taught to prepare and infuse the drug in some centres, hence avoiding prolonged hospitalization, if they are stable (3, 16 21 23). Caution has been suggested regarding its use in patients with left-sided heart disease, pulmonary capillary haemangioma-

tosis and veno-occulsive disease. Pulmonary oedema has been reported and is presumably due to increase pulmonary perfusion in the presence of downstream vascular obstruction. Side effects include: headache, flushing, nausea, diarrhoea, arthralgia, jaw pain, cutaneous erythema, catheter related infection, sepsis, thrombosis and pump malfunction. The latter four are related to the use of a delivery system. Prostacyclin, its analogue and nitric oxide have been found to reduce symptoms significantly but they do not reverse the vascular changes associated with PH.

Inhaled nitric oxide (in combination with oxygen) has been found to be: an effective, potent and selective vasodilator, inhibitor of platelet aggregation and vascular smooth muscle cell proliferation. The delivery system necessitates in-hospital administration. "Pulsed" inhalation, rather than continuous short-term therapy has been found to be particularly useful in patients with chronic obstructive pulmonary disease (4, 27).

A range of oral calcium channel blockers (CCB *eg* amlodipine, diltiazem, nicardipine and nifedipine) have been used over the past two decades with mixed clinical effect. The doses used are generally much higher than those used in the treatment of systemic arterial hypertension and coronary artery disease. In one observational study, only twenty per cent of adults and forty per cent of children with PHTN responded favourably (22). Patients with left heart disease and who are long term inhabitants of high altitude appear to respond more favourably than those with other types of PHDs (4). Generally, CCB therapy has not been found to be efficacious in patients who did not respond to acute vasodilator testing with inhaled nitric oxide, intravenous PGI_2 or intravenous adenosine. It is therefore recommended that it be not used empirically without demonstration of pulmonary vasoreactivity (3, 23). Calcium channel blockers may lower both the pulmonary and systemic vascular resistance, and can therefore cause marked systemic hypotension, worsening of the ventilation-perfusion mismatch and hence hypoxaemia. This is seen especially with verapamil (and less so with nifedipine) because of its negative inotropic effect (3, 4, 23).

Newer treatment agents have been shown to improve exercise tolerance and capacity and cardio-pulmonary haemodynamics (Table 2). Iloprost/prostenol is one such drug. It is a long acting chemically stable prostacyclin analogue, which is administered in an aerosolized form (100 – 150 mcg/day). Uniprost is another PGI_2 analogue and is administered via continuous IV infusion. Remodulin (treprostinil or UT-15) is a tricyclic benzidine PGI_2 analogue and is administered *via* continuous intravenous or subcutaneous infusion. These PGI_2 analogues also have antiplatelet aggregation effects. These have been used for all types of PHDs of varying severity (4, 23).

Beroprost sodium is the first chemically stable oral and active form of PGI_2. It has been used in Japan since 1995 (23, 24). Hydroxymethyglutaryl – CoA reductase inhibitors are being assessed in animal studies (23).

Antiproliferative agents which are targeted at abnormal endothelial function include, Bosentan which is a non-selective endothelium receptor (ET_A and ET_B) antagonist and sitaxsentan a highly selective ET_A receptor antagonist. Bosentan (Tracleer) is administered orally, usually at a starting dose of 62.5 mg twice daily and increased stepwise to a maximum of 250 mg/day. Abnormalities of liver function are the main complications. It may also cause flushing, headache and sore throat (28). Sitaxsentan (100–300 mg four times daily) and Ambrisentan (5 mg daily increasing to 10 mg daily) are newer agents that are on the market (23, 24). Relaxin is a pregnancy-induced hormone which promotes angiogenesis and vasodilatation.

Sildenafil citrate, a phosphodiesterase-5-inhibitor (PD5-I), promotes the accumulation of intracellular cyclic guanosine monophosphate (cGMP) and thereby enhances nitric oxide-mediated vasodilatation. It is thought to also have antiproliferative effects on pulmonary vascular smooth muscle cells (6–10, 29–31). The starting dose is 20 mg three times daily to a maximum dose of 100mg three to four times daily. Common side effects include headache, flushing, dyspepsia and diarrhoea. In June 2005, sildenafil citrate was approved by the FDA as a treatment for PHTN. Combination therapy with sildenafil citrate and Iloprost has also been used successfully (6, 29, 30).

Patients with severe PH are at risk of thromboembolic events due to the sluggish pulmonary blood flow, dilated right heart chambers, venous insufficiency and the sedentary lifestyle imposed by chronic hypoxia. Chronic anticoagulation therapy has been found to increase survival rates. Coumarin derivates (*eg* warfarin) remain the drug of choice and the target international normalized ratio (INR) is 1.5 to 2 (3, 23). A higher ratio (2 to 3) may be necessary in patients with PH secondary to chronic thromboembolic disease (29).

The role of cardiac glycosides (digoxin or lanoxin) in patients with severe PH remains controversial. It has been found to be beneficial in some patients with right ventricular failure (RVF) because of its positive inotropic effects (17, 29). Inotropic agents such as dobutamine, dopamine, milrinone and noradrenaline have caused significant improvement in patients with severe RVF. Diuretics are also used to reduce intravascular volume and hepatic congestion.

Long term oxygen therapy has increased survival rates. It also slows the progression of polycythemia and hence decreases the risk of thromboembolic events. Continuous long-term oxygen therapy is recommended when the arterial partial pressure (PaO_2) is less than or equal to 55 mmHg or the arterial saturation less than or equal to 88%. Oxygen supplement is recommended if a decrease in the PaO_2 of 10 mm Hg, or a decrease in SaO_2 of more than 5% occurs during sleep and if exercise is associated with a reduction of PaO_2 to 55 mm Hg or less, or SaO_2 to 88% or less. Patients with res-

piratory and cardiac disease may require oxygen therapy even with mild to moderate PH (23, 32).

Corticosteroids and other immunosuppressive agents have been beneficial especially in patients with interstitial pulmonary disease, but this treatment is primarily for the underlying disease (3). Other measures include avoidance or termination/discontinuation of aggravating conditions such as pregnancy, oral contraceptive agents, high altitude, appetite suppressant drugs and high salt intake (3, 23). The newest drug therapy, though still in the experimental phase is Imatinib mesylate (Gleevec). It is a tyrosine kinase inhibitor which has been used in certain types of cancer and found to be an antagonist to the platelet-derived growth factor (PDGF) [33, 34]. Statins have also been used because of the antiproliferative, anti-inflammatory and pro-apoptosis effects (34). Vasoactive intestinal peptide, L-arginine and selective serotonin receptor inhibitors are also being investigated.

Surgical treatment include repair of the structural cardiac or pulmonary anomalies, embolectomy or thromboendarterectomy (3). More invasive, temporary life-saving but not curative treatment in severe cases include atrial septostomy and lung transplantation. These should only be done in specialized centres. Atrial septostomy is the creation of an intra-atrial communication using a blade balloon or via graded balloon dilatation (35). The intra-cardiac shunting of blood causes decompression of the right ventricle and augments systemic blood flow, particularly during activity/ exercise. Patients are considered for lung or heart-lung transplantation if: (i) significant vasoreactivity does not occur with the challenging agents – adenosine, nitric oxide and epoprostenol; (ii) vasoreactivity cannot be reproduced with an oral calcium channel antagonist and (iii) if they are at a NYHA class III or IV. Bilateral lung transplantation seemed to be more successful than single lung transplantation (36). Bacterial and cytomegalovirus infection or pneumonia, obliterative bronchiolitis or bronchiolitis obliterans syndrome (BOS) and acute allograft rejection are major complications that can result in failure of the procedure and death of patients.

Gene therapy is also being considered but only animal data is available. This therapy involves the inhalation of survivin mutant. Survivin is an inhibitor of apoptosis and is expressed in the pulmonary artery of patients with PH but not in normal persons. The mutant form causes a decrease in PAPs and PVR (37). Studies are underway to assess whether stem cell transplantation combined with gene therapy can provide a cure (20).

The PHDs remain challenging conditions to treat but much progress has been made since the first WHO sponsored conference in 1973, which was a landmark in the understanding of PH. The paradigm for treatment of PAH continues to advance rapidly. Multicentre randomized clinical trials have provided a basis for evidence-based practice. The combined use of drugs with different mechanisms of action in order to maximize the clinical benefit is an emerging option for the treatment of PAH (24, 38, 39).

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