INTRODUCTION

Most practicing cardiologists see patients with pulmonary hypertension (PH) on a regular basis. The explosion in knowledge of and treatment for PH over the past decade obligates cardiologists to be more cognizant of this disorder.

PH has been defined as a resting mean pulmonary arterial pressure (mPAP) >25 mm Hg, or >30 mm Hg with exercise. The subgroup of PH known as pulmonary arterial hypertension (PAH) adds the criterion that the pulmonary arterial wedge pressure must be ≤15 mm Hg.1

CLASSIFICATION

The clinical classification of PH has gone through a series of changes since the first version was proposed in 1973 at the first international conference on primary pulmonary hypertension endorsed by the WHO (Table 1).2 The initial classification designated only 2 categories, PPH or secondary PH. 25 years later, the 2nd World Symposium on PAH was held in Evian, France. The “Evian classification” attempted to create categories of PH that shared pathologic and clinical features as well as similar therapeutic options 3

The 3rd World Symposium on PAH was held in Venice, Italy, 5 years after the Evian conference. At this conference modest changes were made. The most notable change was to abandon the term PPH in favor of idiopathic pulmonary arterial hypertension (IPAH); familial PAH if there is a family history of PAH; or associated PAH if another cause, such as CTD or HIV, is present. The term “secondary PH” was abandoned since it did not help with diagnosis or in directing treatment.4

During the 4th World Symposium on PH held in 2008 in Dana Point, California, the general philosophy and organization of the Evian-Venice classifications was maintained, but modified it to clarify some areas that were unclear.

PATHOPHYSIOLOGY OF PH

Different pathological5-10 features characterize the diverse clinical PH groups.

• Group 1, PAH: The increase in PVR is related to different mechanisms, including vasoconstriction, proliferative and obstructive remodeling of the pulmonary vessel wall, inflammation, and thrombosis.

• Group 1’: includes mainly PVOD which involves septal veins and pre-septal venules with occlusive fibrotic lesions, venous muscularization, capillary proliferation (patchy), pulmonary oedema, occult alveolar haemorrhage, lymphatic dilatation and lymph node enlargement (vascular transformation of the sinus), and inflammatory infiltrates.

• Group 2, PH due to left heart disease.

• Group 3, PH due to lung diseases and/or hypoxia. The pathophysiological mechanisms involved in this setting are hypoxic vasoconstriction, mechanical stress of hyperinflated lungs, loss of capillaries, and inflammation.
NATURAL HISTORY AND PROGNOSTIC FACTORS

The natural history of IPAH was well described by the NIH registry in 1985 before the availability of any disease-specific therapy. The median survival was 2.8 years, with 1, 3, and 5-year survival rates of 68%, 48%, and 34%, respectively. Associated conditions influence outcomes: Patients with CTD and HIV-associated PAH tend to have a worse prognosis, whereas those with congenital heart disease–associated PAH tend to have a better prognosis.

Important prognostic indicators in PAH include symptoms, exercise endurance, and hemodynamics. Most of these prognostic variables are related to RV function. In the NIH registry, the median survival among patients presenting with class I and II symptoms was ~6 years versus 2.5 years for patients with class III symptoms and just 6 months for patients who presented with class IV symptoms. Two large retrospective series have confirmed the importance of functional class as a prognostic variable, even during treatment. Among IPAH patients treated with epoprostenol, prognosis was worse for patients who commenced therapy with more advanced symptoms. Moreover, in both series, patients who improved to class I or II status after 3 to 17 months of epoprostenol therapy had a better prognosis than patients who remained in class III or IV.

Exercise tolerance in PAH is commonly assessed by means of the 6-minute-walk distance (6MWD). In one of the first controlled trials, a 6MWD of <150 m was associated with a very poor prognosis. In a series of 178 IPAH patients treated with epoprostenol, those who walked further than the median value of 380 m after 3 months of therapy had a better prognosis than those who did not.

PROGRESS OF MEDICAL TREATMENT IN PULMONARY ARTERIAL HYPERTENSION

In 1891, Ernst von Romberg, a German physician, described an autopsy subject as having “pulmonary vascular sclerosis”; however, it is only since 1995 with the introduction of epoprostenol that disease-specific targeted medical therapies for PAH have become available. Furthermore, significant advances in the treatment of PAH have occurred during the past 15 years. Currently 9 medical therapies have received regulatory approval. These agents target the prostacyclin pathway, the nitric oxide pathway, and the endothelin pathway. Combination trials have demonstrated additive or synergistic benefit by targeting 2 or all 3 of these pathways (Figs. 1 and 2).

CONVENTIONAL TREATMENTS

Diuretics role has been limited to patients manifesting RV failure. However, patients with advanced PAH can have increased left ventricular filling pressures that contribute

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**Table 1 Updated clinical classification of PH (Dana Point, 2008)**

1. Pulmonary arterial hypertension (PAH)
   - 1.1 Idiopathic
   - 1.2 Heritable
     - 1.2.1 BMPR2
     - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
     - 1.2.3 Unknown
   - 1.3 Drugs and toxins induced
   - 1.4 Associated with (APAH)
     - 1.4.1 Connective tissue diseases (CTD)
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart disease
     - 1.4.5 Schistosomiasis
     - 1.4.6 Chronic haemolytic anaemia
   - 1.5 Persistent pulmonary hypertension of the newborn
     - 1.5.1 Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
   - 2 Pulmonary hypertension due to left heart disease
     - 2.1 Systolic dysfunction
     - 2.2 Diastolic dysfunction
     - 2.3 Valvular disease
   - 3 Pulmonary hypertension due to lung diseases and/or hypoxia
     - 3.1 Chronic obstructive pulmonary disease
     - 3.2 Interstitial lung disease
     - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
     - 3.4 Sleep-disordered breathing
     - 3.5 Alveolar hypventilation disorders
     - 3.6 Chronic exposure to high altitude
     - 3.7 Developmental abnormalities
   - 4 Chronic thromboembolic pulmonary hypertension
   - 5 PH with unclear and/or multifactorial mechanisms
     - 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
     - 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
     - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
     - 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 = activin receptor-like kinase 1; BMPR2 = bone morphogenetic protein receptor 2, HIV = human immunodeficiency virus.
norepinephrine in cardiac output and a significant reduction in circulating Short-term IV digoxin in IPAH produces a modest increase INR of 2.0 to 3.0. Experts recommend warfarin anticoagulation targeted to an of clinical judgment was improved from 21% to 49%. Most survival of anticoagulated patients selected on the basis of PAH. Prostacyclins have been found to be effective in the therapy of IPAH. Continuous IV infusion of epoprostenol has been shown in RCT to improve quality of life and symptoms related to PH. The long-term effects of epoprostenol in PH include its vasodilator and antithrombotic effects. Patients may have a reduction in PVR of ≥50%, even if no acute hemodynamic effects are noted. Epoprostenol is administered through a central venous catheter that is surgically implanted and delivered by an ambulatory infusion system. Most complications are due to the delivery system and include catheter-related infections and temporary interruption of the infusion because of pump malfunction, which causes rebound pulmonary hypertension. Side effects related to epoprostenol are flushing, headache, nausea, diarrhea, and a jaw discomfort that occurs with eating. In most patients, these symptoms are minimal and well tolerated.

The experience with epoprostenol in patients with IPAH for more than 10 years has been reported by two large centers. Survival rates markedly improved; predictors of survival included NYHA class, exercise tolerance, and acute vasodilator responsiveness. Both studies provided important data for identifying patients who would do well over the long term, versus those in whom transplantation should be considered.

Treprostinil is a stable prostacyclin analogue that has pharmacological actions similar to those of epoprostenol, but differs in that it is chemically stable at room temperature and neutral pH and has a longer half-life. It is administered through continuous S/C infusion. In a large RCT in patients with PH, it was effective in increasing 6MWD, decreasing dyspnea, and hemodynamics.

Iloprost, an inhalational analogue of prostacyclin. In RCT, inhaled iloprost was shown to have an acute effect on hemodynamics similar to those of inhaled nitric oxide and when given chronically, causes improvement in 6MWD, and in hemodynamics. Because of the short half-life of iloprost, however, it requires frequent (up to 12/day) inhalations.

Beraprost is an orally active prostacyclin analogue that has been evaluated in RCT trials in patients with PAH. In one large European trial (ALPHABET study), beraprost improved exercise capacity and symptoms over a 12-week period but had no significant effect on hemodynamics or functional class. A similar trial conducted in the United States, however, showed similar efficacy at 12 weeks, only to document the loss of effectiveness over 1 year. At present, beraprost is only approved for use in Japan.

ENDOTHELIN RECEPTOR BLOCKERS (ERA)

ET-1 exerts vasoconstrictor and mitogenic effects and is activated in PAH. Three endothelin receptor blockers have been approved for PAH. Although there have never been direct comparative trials, all three appear to have similar efficacy.

Bosantan is a non-selective ET receptor blocker. 9 RCTs using 1 of 3 ERAs as monotherapy have been performed.
in PAH patients, bosentan was evaluated in 4 RCTs in PAH patients, including 1 RCT performed in a cohort of patients with the Eisenmenger syndrome and 1 RCT performed in a cohort of patients with only mildly symptomatic PAH. Overall, bosentan improved exercise capacity, functional class, hemodynamic status, echocardiographic and Doppler variables, and time to clinical worsening. The approved dosage of bosentan is 125 mg twice daily.

**Sitaxsentan** is an orally active ETₐ-selective endothelin receptor blocker that can be given once daily at a 100 mg dose. It has been assessed in PAH patients in 2 RCTs, both of which demonstrated improvement in exercise capacity and hemodynamic status.

**Ambrisentan** is an orally active ETₐ-selective endothelin receptor blocker that can be given once daily at a 5-mg dose, which can be increased to 10 mg if the drug is well tolerated. It has been evaluated in RCTs. Results showed improvements...
in exercise capacity and clinical events that seem similar to the results observed with the other 2 ERAs.

On the basis of the results of RCTs using ERAs, the incidence of elevated hepatic transaminases >3 times the upper limit of normal seems to be ~10, 4, 2% with bosentan, sitaxsentan, and ambrisentan respectively. They have interactions with warfarin that require careful monitoring of the INR and dose adjustments when used together.

**COMBINATION THERAPY**

Combination treatment has been evaluated to address the multiple pathobiologic mechanisms of PH. The combination of oral bosentan and IV epoprostenol was investigated in 1 small study, with inconclusive results. The addition of inhaled iloprost to background oral bosentan demonstrated improved hemodynamic status and clinical events in 1 RCT; however, these results were not confirmed in an open trial. In another study, the addition of oral sildenafil to background IV epoprostenol demonstrated improved exercise capacity, hemodynamic status, and clinical events; furthermore, the addition of oral sildenafil to background IV epoprostenol increased survival versus IV epoprostenol alone.

In the pivotal tadalafil RCT, ~50% of the patients had oral tadalafil added to background oral bosentan; it improved exercise capacity, hemodynamic status, and clinical events. Inhaled treprostinil has also been studied as add-on therapy to either background bosentan or sildenafil; in both combinations, the addition of inhaled treprostinil improved exercise capacity. These studies support the efficacy of combination treatment in patients who remain symptomatic on monotherapy. The optimal combination on the basis of overall risk-benefit considerations remains unknown.

**EARLY INTERVENTION**

For functional class II or III patients, the role of early aggressive intervention, either as monotherapy or in conjunction with either a PDE-5 inhibitor and/or an ERA, remains unknown. Although the first RCTs in PAH focused primarily on functional class III and IV patients, results from a more recent RCT evaluating the efficacy of bosentan in only mildly symptomatic PAH patients support early intervention. In addition, prespecified subgroup analyses of the sildenafil, tadalafil, and ambrisentan RCTs did not show any significant differences in the therapeutic efficacy of these drugs between patients in WHO functional classes II and III.
INVASIVE TECHNIQUES

Atrial septostomy is a palliative procedure, the rationale of which is based on experimental and clinical observations suggesting that intraatrial defect allowing right-to-left shunting in the setting of severe PH might be of benefit. Indications for the procedure include recurrent syncope and/or RV failure, despite maximum medical therapy, as a bridge to transplantation, or when no other option exists.

Heart-Lung and Lung Transplantation has been performed successfully in patients with PH since 1981. Currently, bilateral lung transplantation has become the procedure of choice. Hemodynamic studies have shown a moderate reduction in PAP and PVR associated with improvement in RV function. The 1-year survival rate is 70-75%, the 2-year survival rate is 55-60%, and the 5-year survival rate is between 40-45%.

Transplantation should be reserved for patients with PH when they are in NYHA functional Class III/IV despite therapy with conventional treatment, or when no other option exists.

META-ANALYSIS TO ASSESS EFFECT ON MORTALITY

Meta-analysis of 25 RCTs in 3363 PH patients showed a reduction in mortality ranging 38-43% after an average treatment period of 14.3 weeks. A subgroup analysis showed that all three classes of PH-approved drugs achieved a similar favorable reduction in mortality, although no statistical significance was achieved individually.

CONCLUSIONS

The epidemiology of PAH is changing. Remarkable advances in understanding the pathobiology and clinical care in PAH have resulted in improved exercise capacity and survival. Despite such important progress, however, neither exercise capacity nor survival is normal. Controlled studies have only just begun to evaluate the role of combinations of therapies, as well as the utility of genetic and other biomarkers. It is hoped that such studies will allow for better targeting of therapy to individual patients who have PH.

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