Pulmonary arterial hypertension (PAH) is a chronic and serious disease characterized by a progressive increase in pulmonary vascular resistance (PVR) leading ultimately to right ventricular failure and death. Despite the fact that we now have numerous therapeutic options based on advances in our understanding of the underlying pathobiology, there remains no cure for this devastating condition. A high index of clinical suspicion and early diagnosis remain imperative to maintain the best chances of improving and preventing deterioration in exercise tolerance, functional capacity, quality of life and survival for these patients.

**Definition and classification**

The normal pulmonary vasculature can accommodate increases in cardiac output with little or no increase in pressure. Pulmonary hypertension (PH) is defined as an elevation of mean pulmonary artery pressure (PAP) > 25 mmHg at rest. The clinical classification of PH was recently refined at the Fourth World Symposium in Dana Point, California in February 2008, but retains the original broad categories of:
- PAH,
- PH with left heart disease,
- PH with lung diseases and/or hypoxemia and
- PH due to chronic thromboembolic disease.\(^1\)

PAH includes idiopathic pulmonary arterial hypertension (IPAH), formerly known as primary PH and PAH associated with selected conditions that result in disease similar to IPAH in many respects (Table 1). The treatment approach can differ substantially between each of the broad categories and thus an accurate diagnosis is essential. The following discussion focuses on PAH.

**Pathophysiology**

A combination of genetic predisposition and exposure to risk factors is thought to lead to the development of PAH. Several aggravating mediators have been implicated in the disease process, including:
- endothelin-1,
- serotonin,
- thromboxane A\(_2\),
- angiopoietin-1 and
- clotting, growth and inflammation factors.

Simultaneously, decreased activity of potentially protective factors can be found in PAH, most notably prostacyclin, nitric oxide and vasoactive intestinal peptide. Imbalances in these mediators result in vasoconstriction, *in situ* thrombosis and remodeling of the pulmonary microvasculature, which ultimately leads to increased PVR.\(^2\) The prostacyclin, endothelin and nitric oxide pathways have become targets of therapy for three classes of PAH-specific compounds that have been demonstrated to be
beneficial in randomized controlled trials (RCTs) and a number of other candidate mechanisms are being pursued.

### Diagnosis

PAH should be considered in the differential diagnosis of:
- unexplained dyspnea,
- decreased exercise tolerance, or
- syncope.

Incidental findings suggestive of PH or right ventricular enlargement on physical examination, chest radiographs or ECGs should trigger further investigations. An underlying family history of PAH or other risk factors such as connective tissue disease, portal hypertension or anorexigen exposure should also prompt a high index of suspicion and screening.

Signs and symptoms of PAH relate to progressive increases in PVR. In the initial asymptomatic phase, cardiac output is maintained as PVR increases. Patients then start to note progressive dyspnea on exertion as cardiac output during exercise is no longer maintained against a continually increasing PVR. They may also complain of fatigue, palpitations, presyncope and chest pain. In later stages, patients develop signs and symptoms of right heart failure with edema and ascites. CV examination reveals a loud pulmonic component of $S_2$, widely split $S_2$, right ventricular $S_3$, $S_4$ and heave. Murmurs of tricuspid and pulmonic regurgitation may be heard and jugular venous pressure can be elevated.

The diagnosis of PAH is one of exclusion. Non-PAH causes of PH such as significant lung disease, left heart disease and thromboembolic disease must be excluded before considering therapies for PAH. This is not only because of the distinct natural history and prognosis associated with a diagnosis of PAH, but also because of the differ-

### Table 1

#### Clinical classification of PH

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>1. Pulmonary arterial hypertension (PAH)</td>
<td>- Idiopathic pulmonary arterial hypertension - Familial pulmonary arterial hypertension - Associated PAH with: - Collagen vascular disease - Congenital systemic-to-pulmonary shunts - Portal HTN - HIV infection - Drugs and toxins - Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)</td>
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<tr>
<td>2. Pulmonary HTN with left heart disease</td>
<td>- Left-sided atrial or ventricular heart disease - Left-sided valvular heart disease</td>
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<tr>
<td>3. Pulmonary HTN associated with lung diseases and/or hypoxemia</td>
<td>- Chronic obstructive pulmonary disease - Interstitial lung disease - Sleep-disordered breathing - Alveolar hypoventilation disorders - Chronic exposure to high altitude - Developmental abnormalities</td>
</tr>
<tr>
<td>4. Pulmonary HTN due to CTEPH</td>
<td>- Thromboembolic obstruction of proximal pulmonary arteries - Thromboembolic obstruction of distal pulmonary arteries</td>
</tr>
<tr>
<td>5. Miscellaneous</td>
<td>- Sarcoidosis - Histiocytosis X - Lymphangiomatosis - Compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)</td>
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</table>

*Modified from the Venice Classification*
ent treatment approaches indicated for PAH compared to non-PAH forms of PH. For example, patients with chronic thromboembolic pulmonary hypertension (CTEPH) can have improvement, or sometimes be cured, of their PH with a surgical procedure (pulmonary thromboendarterectomy). It is also important to note that PAH drugs can result in clinical deterioration if used off-label. For example, PAH drugs can precipitate pulmonary edema in the presence of left ventricular dysfunction.

Table 2 lists the investigations which are commonly employed to arrive at a diagnosis of PAH. The ECHO is the key investigation which suggests an elevated pulmonary arterial pressure, but the Doppler estimate of right ventricular systolic pressure is prone to many pitfalls and ultimately requires confirmation by right heart catheterization. It should be emphasized that the ECHO estimates systolic pressures, not mean pressures and typically elevations of > 45 mmHg to 50 mmHg are abnormal. Of course, the ECHO not only helps to exclude left heart and valvular disease, but ancillary signs of PH including right ventricular dilatation and impaired function are often useful.

If PAH is suspected, the patient should be referred to a specialized centre where right heart catheterization and vasodilator studies can be performed. This step is mandatory for a variety of reasons, including the identification of approximately 10% of patients who are acute vasoresponders and can essentially be cured of their disease with high-dose calcium channel blockers (CCBs). Most patients with PAH do not benefit from CCBs and in many cases, these drugs can be harmful.

It is important to note that PAH drugs can result in clinical deterioration if used off-label.

**Treatment**

If the diagnosis of PAH is confirmed, general measures can include:
- diuretics,
- digoxin and
• anticoagulation with warfarin.
As alluded to above, there are three novel classes of medications now available to target PAH—prostanoids, endothelin receptor antagonists (ERAs) and phosphodiesterase-5 (PDE-5) inhibitors.

Prostanoids
Prostanoids exert their effect on PAH by inducing vascular smooth muscle relaxation and by inhibiting smooth muscle proliferation and platelet aggregation. Epoprostenol, an intravenous prostacyclin, is approved for IPAH patients and PAH related to connective tissue disease. While considered the most potent and effective treatment for PAH, epoprostenol is costly and complicated to use, requiring a continuous IV infusion and daily preparation by the patient. Side-effects include:
• central venous catheter complications and infections,
• jaw pain,
• diarrhea,
• nausea,
• joint pain and
• systemic hypotension.
The prostanoid treprostinil has a less complex delivery system than epoprostenol (it can be given subcutaneously by a portable mini-pump without the complications of an indwelling central line) and does not require patient preparation. Oral and inhaled prostanoids are currently being studied and are under development.

Most patients with PAH do not benefit from CCBs and in many cases, these drugs can be harmful.

ERAs
ERAs block the receptors that, when activated by endothelin-1, induce potent vasoconstriction and smooth muscle proliferation. Drugs in this class have the advantage of being administered orally.
The nonselective ERA bosentan is the best studied oral agent and has been shown to improve exercise capacity as measured by:
• the six-minute walk test,
• Borg dyspnea score,
• New York Heart Association/World Health Organization (NYHA/WHO) functional class and
• time to clinical worsening.
In the large RCT, only 6% of bosentan-treated patients had deteriorated by week 28, compared to 20% of placebo-treated patients. The drug’s major side-effect is hepatotoxicity, which occurs in approximately 10% of patients. It is also a potent teratogen, so its use should be accompanied by meticulous contraception in women with childbearing potential.
The selective ERA sitaxsentan has also been demonstrated to improve similar end-points in short-term studies. It has a comparable efficacy to that of bosentan, although some reports have found the drug to be associated with a lower incidence of liver function abnormalities. Another ERA, ambrisentan, appears to be very similar to bosentan and sitaxsentan based on initial reports.

PDE-5 inhibitors
PDE-5 inhibitors induce vasodilation by selectively inhibiting the enzyme that degrades cyclic guanosine monophosphate, a vasodilation-enhancing second messenger in the nitric oxide pathway. The PDE-5 inhibitor sildenafil citrate was recently approved for the treatment of PAH. As with the other agents, this drug also has anti-proliferative properties. The pivotal study of this drug found that treatment significantly improved six-minute walk distance, hemodynamics and functional
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classification. The most common side-effects were:
- nose bleeds,
- headache,
- dyspepsia,
- flushing and
- insomnia.
Tadalafil, a longer acting PDE-5 inhibitor, has also been studied in PAH, although results of large clinical trials are still pending.

Even though recent advances have improved survival and quality of life for this tragic group of patients over the last two decades, PAH is still an incurable disease.

A number of open-label, long-term studies have suggested that the benefits conferred by prostanoids, ERAs and PDE-5 inhibitors observed in short-term clinical trials can be maintained over extended periods—up to several years for some agents. However, many patients do deteriorate despite treatment with one of these agents and close follow-up with consideration for combination therapy is therefore necessary. Because of methodological limitations, it is not entirely clear how many patients can expect the most durable responses with individual medications, although it is clear that the benefits obtained are insufficient and further improvements are required. Even though recent advances have improved survival and quality of life for this tragic group of patients over the last two decades, PAH is still an incurable disease. Lung transplantation is ultimately a consideration and although medical therapy seems to delay the need for transplantation, it remains a necessary option for many patients.

References