Pulmonary arterial hypertension

New treatments and the prospect of cure

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Pulmonary arterial hypertension (PAH) is a life-threatening cardiopulmonary disorder for which, not so long ago, the only effective treatment option was transplantation. Due to tremendous scientific progress over the past decade, many effective drug therapies are now available to treat this devastating condition.

Pulmonary arterial hypertension (PAH) is a severe cardiopulmonary condition caused by obstructive remodelling of the small pulmonary arteries.[1] Progressive obstruction of these arteries leads to a rise in pulmonary vascular resistance, which eventuates in right heart failure and, if untreated, death. In the past, PAH was considered a rare and lethal condition with a poor prognosis, and few or no treatment options were available apart from transplantation.[2] PAH is often not detected until the late and highly symptomatic stage when survival is already very limited.[3] With multiple targeted therapies now demonstrating efficacy in PAH, early diagnosis is key to ensure best outcomes for patients with this devastating condition.

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Definition of pulmonary arterial hypertension

PAH is a specific subgroup (Group 1) of pulmonary hypertension. It should not be confused with the generic term pulmonary hypertension, which refers to the pathophysiological state of elevated pulmonary artery pressure. The current clinical classification of pulmonary hypertension is summarised in Box 1.[4] In Australia,

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Key points

- **Pulmonary arterial hypertension (PAH) is a life-threatening disease of the small pulmonary arteries that progresses to right heart failure and death if untreated.**
- **Early diagnosis and timely initiation of therapy are crucial to good outcomes. PAH must be considered in any patient with unexplained breathlessness.**
- **Unexplained breathlessness should be viewed just as seriously as chest pain.**
- **Echocardiography and lung function testing are the most useful initial tests for suspected PAH. Definitive diagnosis requires right heart catheterisation.**
- **Annual screening for PAH should be undertaken in high-risk patient groups, such as those with systemic sclerosis or past repair of a septal defect.**
- **Many efficacious drug therapies are available and combination therapy is now the evidence-based standard of care.**
- **Access to the best drug therapies is only available at expert PAH centres, and early referral is recommended.**

the estimated prevalence of PAH is approximately 15 cases per 100,000 population.[5] It should be emphasised that left heart disease (Group 2) and lung disease (Group 3) are the most common causes of pulmonary hypertension.

PAH is termed idiopathic when no causative factors are identified but can also be heritable, induced by drugs and toxins (such as methamphetamine or dasatinib) or be secondary to conditions such as connective tissue disease (particularly systemic sclerosis and systemic lupus erythematosus), congenital heart disease, portal hypertension and HIV infection.

The diagnosis of PAH can only be made by invasive haemodynamic measurements at right heart catheterisation as the pulmonary artery wedge pressure is essential to the diagnosis. PAH is defined by a mean pulmonary artery pressure of 25 mmHg or more together with wedge pressure 15 mmHg or lower and pulmonary vascular resistance above 3 Wood units, as in Box 2.[6]

Pathophysiology

Underlying all forms of PAH is vasculopathy of the small pulmonary arteries. PAH is characterised by an increase in the vasoconstrictors thromboxane and endothelin-1 and a reduction in the vasodilators nitric oxide and prostacyclin.[7] Excessive endothelial and smooth muscle cell proliferation, intimal fibrosis and in situ thrombosis result in structural reduction in the lumen size of the small pulmonary arteries. The right ventricle ultimately fails to cope with the sustained elevation in pulmonary vascular resistance and right heart failure ensues. Right heart function is the main determinant of prognosis in PAH, and right heart failure is the leading cause of death.[8,9]

The three major pathogenic pathways in PAH are the prostacyclin pathway, the endothelin-1 pathway and the nitric oxide pathway. Targeted PAH therapy (discussed later) targets these pathways (Box 3).

Clinical presentation

Symptoms of mild to moderate PAH are often insidious. Patients may present to

1. Classification of pulmonary hypertension, focusing on pulmonary arterial hypertension[4]*

Group 1
Pulmonary arterial hypertension
- 1.1 Idiopathic
- 1.2 Heritable (*BMPR-2, ALK-1, ENG, SMAD9, CAV1, KCNK3*, unknown)
- 1.3 Drug- and toxin-induced
- 1.4 Associated with: connective tissue disease, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis

Group 1'
Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

Group 1''
Persistent pulmonary hypertension of the newborn

Group 2
Pulmonary hypertension due to left heart disease

Group 3
Pulmonary hypertension due to lung diseases and/or hypoxia

Group 4
Chronic thromboembolic pulmonary hypertension

Group 5
Pulmonary hypertension with unclear and/or multifactorial mechanisms

* 5th World Symposium on Pulmonary Hypertension 2013, Nice, France. Only the disorder categories in Group 1, PAH, have been included; the full classification is available in *J Am Coll Cardiol* 2013; 62: D34-D41.[4]

Abbreviations: *ALK-1* = anaplastic lymphoma kinase gene; *BMPR-2* = bone morphogenic protein receptor type 2 gene; *CAV1* = caveolin-1 gene; *ENG* = endoglin gene; HIV = human immunodeficiency virus; *KCNK3* = potassium channel super family K member-3 gene; PAH = pulmonary arterial hypertension; SMAD9 = SMAD family member 9 gene.

2. Haemodynamic definition of pulmonary arterial hypertension[6]

Pulmonary arterial hypertension (PAH) is a subgroup of pulmonary hypertension. It is characterised by the following haemodynamic parameters found at right heart catheterisation:

- mean pulmonary artery pressure (MPAP) ≥25 mmHg at rest (i.e. pulmonary hypertension)
- pulmonary artery wedge pressure (PAWP) ≤15 mmHg (i.e. pre-capillary), and
- pulmonary vascular resistance (PVR) >3 Wood units.

The unit used for PVR is Wood units, and the value can be derived from the PAP and cardiac output (CO) measurements:
PVR = (MPAP – PAWP)/CO

Definitive diagnosis of PAH is only possible with right heart catheterisation.

general practitioners, respiratory physicians, cardiologists or rheumatologists, all of whom need to have a high awareness of the potential gravity of dyspnoea.

In the early stages, breathlessness, palpitations, fatigue and a pounding heart may be dismissed as lack of fitness because clinical examination may be normal. As PAH progresses, right-sided congestion, elevated jugular venous pressure, ascites, hepatomegaly and peripheral oedema occur. Exertional syncope represents a sinister symptom, and in late stages, atrial flutter is not uncommon.

Unless the diagnosis is considered and actively sought, it will often be missed or misdiagnosed as more common conditions such as asthma or chronic obstructive pulmonary disease. The presence of an underlying condition known to be associated with PAH, such as systemic sclerosis, should raise particular suspicion. Unfortunately, most patients with PAH are still diagnosed late, with advanced New York Heart Association (NYHA) Functional Class III–IV status. An Australian study showed that the mean time from symptom onset to definitive diagnosis in idiopathic PAH was 47 ± 34 months.[10] Ongoing efforts for community awareness of PAH as a potential cause of otherwise 'unexplained breathlessness' are needed to ensure timely diagnosis. Unexplained breathlessness should be taken just as seriously as undiagnosed chest pain.

Diagnosis

The most useful initial investigations in a patient with suspected PAH are echocardiography and lung function tests, including diffusion capacity measurement (Table 1 and Box 4 [Figures 1 to 4]). Echocardiography may show a hypertrophied, dilated or hypokinetic right ventricle, tricuspid regurgitation and elevated pulmonary artery pressure. The left ventricle should be normal. Pulmonary artery pressure is usually estimated from the tricuspid regurgitation jet velocity, but if there is no tricuspid regurgitation, measurement of pulmonary artery pressure is not possible. Echocardiography may be normal in patients with early PAH.

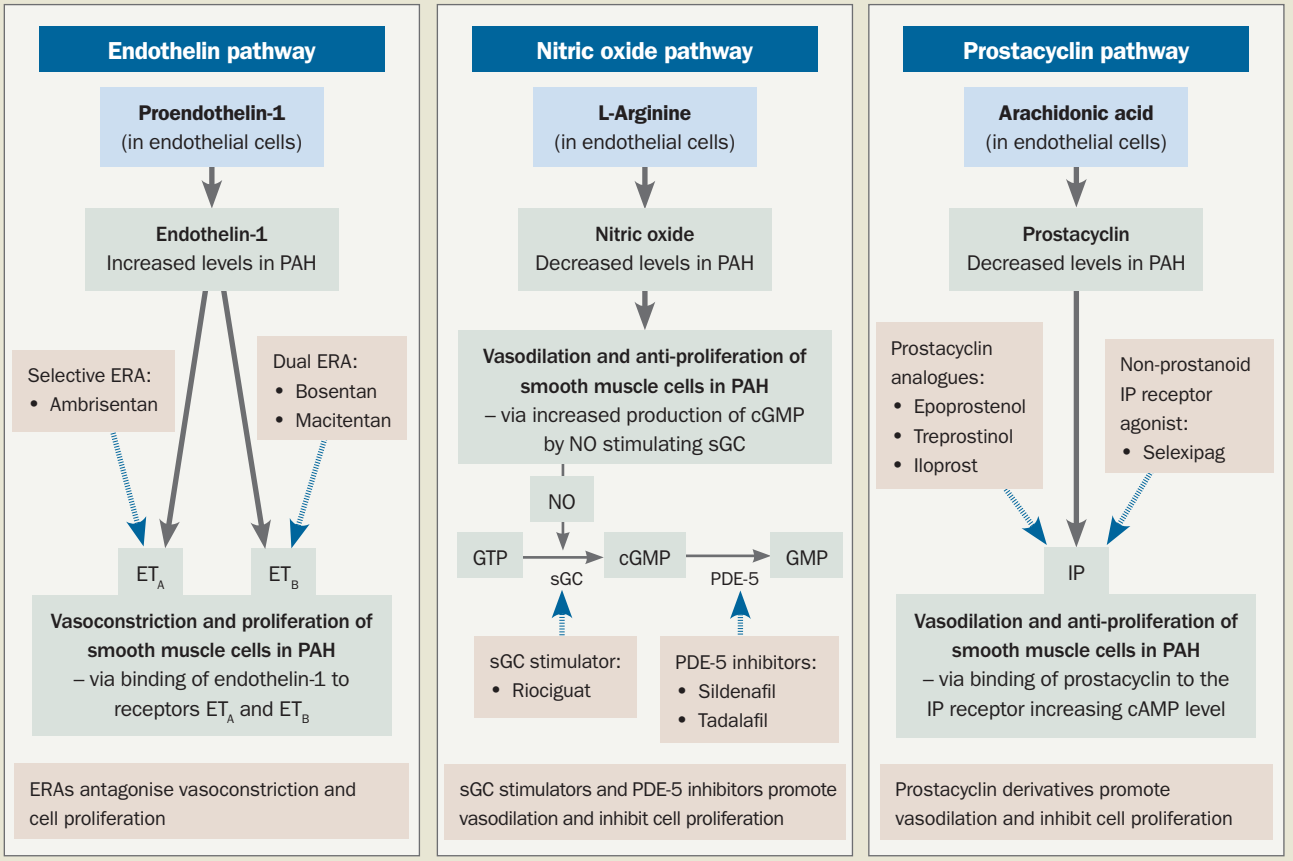
Lung function tests show a disproportionate reduction in diffusing capacity for carbon monoxide (DLCO) with relative preservation of spirometry and lung volumes. The DLCO is usually moderately reduced in patients with PAH, although it may be normal in early disease. A mild restrictive lung defect may be present in some patients.

The only definitive test for the diagnosis of PAH is right heart catheterisation, in which the pulmonary artery pressure, pulmonary artery wedge pressure, right atrial pressure and cardiac output are directly measured and acute vasoreactivity testing may be undertaken.[6] Vasoreactivity testing is only performed in patients with idiopathic, heritable or drug-induced PAH and identifies the small subset (less than 10%) with vasoreactive idiopathic PAH; a positive response is indicated by a large reduction in pulmonary artery pressure

3. Pathogenesis of pulmonary arterial hypertension and therapeutic targets

The three major pathogenic pathways in PAH are the endothelin pathway, the nitric oxide pathway and the prostacyclin pathway. These pathways are the targets of current PAH therapy.

In PAH, there is upregulation of vasoconstricting endothelin-1 and decreased production of vasodilatory nitric oxide and prostacyclin. The endothelin pathway can be blocked by either selective or nonselective endothelin-1 receptor antagonists; the nitric oxide pathway can be increased by inhibition of phosphodiesterase type-5 or stimulation of soluble guanylate cyclase; and the prostacyclin pathway can be enhanced by administration of prostanoid analogues or nonprostanoid IP receptor agonists.



Abbreviations: ET_A and ET_B = endothelin receptors A and B; ERA = endothelin-1 receptor antagonist; cGMP = cyclic guanosine monophosphate; GMP = guanosine monophosphate; GTP = guanosine triphosphate; IP = prostacyclin receptor; NO = nitric oxide; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase.

following nitric oxide (or other short-acting vasodilator) challenge.[11,12] Right heart catheterisation is most easily performed as an outpatient procedure, via the right internal jugular vein approach with local anaesthetic. Anticoagulation does not need to be ceased and fasting is not required. Cardiac magnetic resonance imaging is rapidly growing in usefulness in patients with PAH to detect undiagnosed intracardiac shunts and patent ductus arteriosus, and to assess the right ventricle in detail.

Once PAH has been confirmed by right heart catheterisation, a comprehensive search for an underlying cause should be undertaken (Table 1). It is also important that other causes of pulmonary hypertension listed in Box 1 (such as chronic thromboembolic pulmonary hypertension and chronic lung disease) are excluded by appropriate investigations.

Screening in high-risk groups

As PAH has an insidious onset and the disease is mostly recognised late in its natural history, patient groups that are at high risk for the development of PAH need to be screened regularly. Patients with systemic sclerosis have a 10% lifetime risk of developing PAH,[13] and should be monitored with annual echocardiography and/or lung function testing.[11] N-terminal pro-brain natriuretic peptide has also been shown to be a useful complementary test for the screening for PAH in these patients.[14]

Table 1. Key investigations in the diagnostic work-up of patients with pulmonary arterial hypertension

Investigation	Key use and interpretation
Echocardiography	• The most important screening test for PAH • Echo will reveal elevated pulmonary artery pressure and signs of right ventricular dysfunction • Left ventricular systolic function is usually preserved • A normal echo does not exclude PAH
Electrocardiogram	• Signs of right heart strain in PAH • Ischaemic changes may suggest coronary artery disease • A normal ECG does not exclude PAH
Chest x-ray	• Enlarged central pulmonary arteries and/or enlarged right heart chambers in PAH • A normal x-ray does not exclude PAH
Ventilation–perfusion scintigraphy	• Mismatched perfusion defects suggest thromboembolic disease • More sensitive than CT pulmonary angiogram in detecting chronic thromboembolic PH • Both CT pulmonary angiogram and V/Q should be performed; these tests are complementary
CT pulmonary angiography	• Enlarged main pulmonary artery and enlarged right heart chambers in PAH • CT pulmonary angiogram may detect signs of chronic thromboembolic disease • Lung disease can be detected with high resolution chest CT
Lung function test	• Isolated reduction in DLCO is seen in PAH • Mild restrictive ventilatory defect may be seen in PAH • Severe reduction in spirometry or lung volumes suggests lung disease
Sleep study	• Identify and treat sleep disordered breathing and nocturnal desaturation (which may exacerbate PAH)
Six-minute walk distance	• A simple test to assess exercise capacity and monitor therapeutic response • Six-minute walk distance correlates with prognosis in PAH
Connective tissue disease screen and HIV serology	• Search for an underlying cause of PAH
N-terminal pro-brain natriuretic peptide	• Elevated NT-pro BNP occurs in PAH due to right ventricular strain • NT-pro BNP is prognostic and used to monitor patients
Coronary angiography or CT coronary angiography	• If coronary artery disease is suspected clinically or risk factors for coronary artery disease are present
Right heart catheterisation	• Required for definitive diagnosis of PAH • Acute vasoreactivity testing can be performed with any short-acting vasodilator

Abbreviations: CT = computed tomography; DLCO = diffusing capacity of the lung for carbon monoxide; NT-pro BNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; V/Q = ventilation–perfusion ratio.

Patients who have had a cardiac septal defect repaired should also be screened annually for life.

Treatment of PAH

Basic measures

Judicious use of diuretics is indispensable in patients with PAH to relieve symptoms of fluid retention. Oxygen should be prescribed to correct arterial hypoxaemia.

Anticoagulation with vitamin K antagonists has traditionally been used for PAH to prevent in situ thrombosis, and has been shown to reduce mortality in patients with idiopathic PAH by at least 40% in retrospective cohort studies.[1] Anticoagulation should be considered generally in the absence of significant bleeding risks, but should be avoided in patients with systemic sclerosis, who may be more prone to gastrointestinal bleeding, and in those with Eisenmenger syndrome.

Exercise rehabilitation under the close supervision of physiotherapists with experience in PAH has been shown to improve exercise capacity and quality of life.[15] Pregnancy is contraindicated in severe PAH and reproductive counselling is mandatory for women of childbearing age. Some therapies for PAH are teratogenic, for example endothelin receptor antagonists. Calcium channel blockers (off-label use) should only be used in the small subset of idiopathic PAH patients who display acute vasoreactivity at right heart catheterisation.[11]

Targeted PAH therapy

Numerous drugs have now been approved in Australia and elsewhere for the treatment of PAH. These drugs target the many pathogenic pathways implicated in PAH pathogenesis, the three major pathways and their targeted drugs being (Box 3):

- endothelin pathway – ambrisentan, bosentan and macitentan
- nitric oxide pathway – sildenafil, tadalafil and riociguat
- prostacyclin pathway – epoprostenol, treprostinil, iloprost and selexipag.

All targeted PAH therapies vasodilate the pulmonary vasculature and modify vascular proliferation. There is currently no data to support the use of PAH drugs for the

4. Imaging investigations in pulmonary arterial hypertension

Echocardiography is the most useful noninvasive imaging investigation for suspected pulmonary arterial hypertension (Figures 1 and 2).

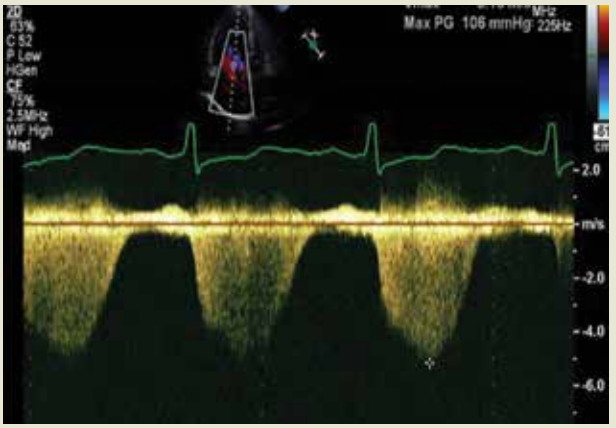


Figure 1. Echocardiography – continuous wave Doppler interrogation of the tricuspid regurgitation jet. A markedly elevated peak velocity of 5.2 m/s is shown, with a corresponding right ventricular to right atrial pressure gradient of 106 mmHg. This patient has severe idiopathic PAH with elevated pulmonary artery pressure to systemic levels found at right heart catheterisation.

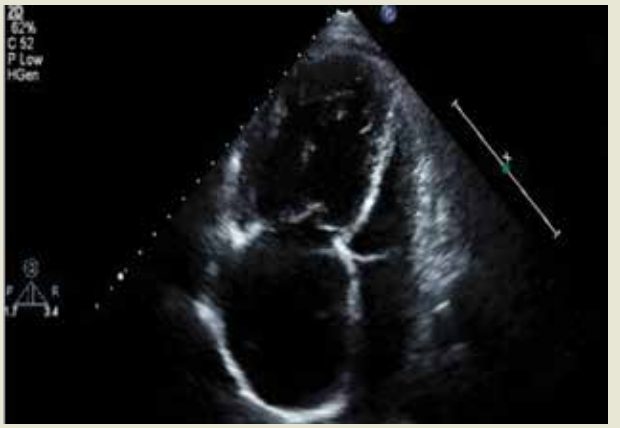


Figure 2. Echocardiography – apical 4-chamber view from the same patient. A grossly enlarged right ventricle and right atrium is shown, with bowing of the interventricular septum towards to the left ventricle, typical of severe pulmonary arterial hypertension.

Computed tomography (CT) pulmonary angiogram and ventilation–perfusion scintigraphy (V/Q scan) are other useful investigations in the diagnostic work up of a patient with suspected PAH (Figures 3 and 4).

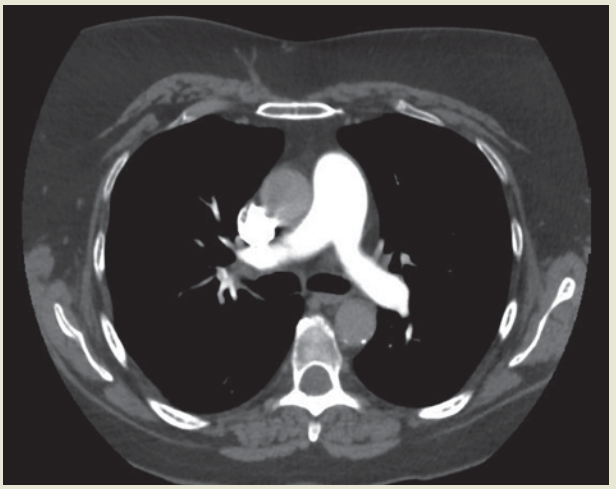


Figure 3. CT pulmonary angiogram of a patient with mild PAH. A dilated main pulmonary artery is shown. Patients with PAH should not have significant parenchymal lung disease or filling defects in the pulmonary arterial tree.

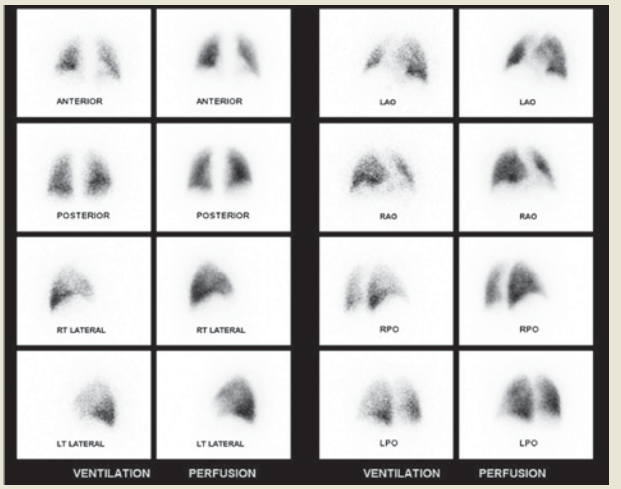


Figure 4. V/Q scan (normal) in a patient with PAH. A V/Q scan is typically normal in PAH and should not demonstrate perfusion defects. The presence of perfusion defects with ventilation mismatch in a patient with pulmonary hypertension is highly suggestive of chronic thromboembolic pulmonary hypertension rather than PAH.

treatment of pulmonary hypertension caused by left heart disease or lung disease, and specific PAH agents may be harmful if used in left heart disease. The mechanism of action, route of delivery, dosage, side effects and PBS listing of targeted therapies approved for PAH are summarised in Table 2.

The first targeted PAH drug that demonstrated efficacy was intravenous epoprostenol, a prostacyclin derivative, which improved survival in patients with severe PAH over a 12-week period.[16] Due to its pharmacokinetic properties, it must be administered as a continuous infusion via a central access catheter and infusion

Table 2. Targeted therapies for pulmonary arterial hypertension

Drug class	Generic name	Route/dosage	Common side effects and considerations	Availability via PBS*
Prostacyclin analogue	Epoprostenol	Continuous intravenous; up to approx 30 ng/kg/min	• Flushing, jaw pain, headache, nausea, diarrhoea • Catheter-related infections	Available
	Treprostinil	Continuous subcutaneous; up to approx 50 to 60 ng/kg/min	• Flushing, jaw pain, headache, nausea, diarrhoea • Infusion site pain may limit dose escalation	Not available
	Iloprost	Inhaled; 5 µg, six to 12 times/day	• Flushing, jaw pain, headache, nausea, diarrhoea • Short half-life requires frequent inhalations	Available
Prostacyclin receptor agonist	Selexipag	Oral; starting dose 200 µg twice daily, up to 1600 µg twice daily	• Headache, diarrhoea, jaw pain, flushing	Not available
	Ambrisentan	Oral; 10 mg daily	• Headache, peripheral oedema, anaemia, nasopharyngitis, fluid retention, transaminitis • Teratogenic	Available
	Bosentan	Oral; 125 mg twice daily	• Headache, peripheral oedema, anaemia, nasopharyngitis, hepatotoxicity (transaminitis) may require cessation in ~5% of patients • Teratogenic	Available
	Macitentan	Oral; 10 mg daily	• Headache, anaemia, nasopharyngitis, fluid retention • Teratogenic	Available
Phosphodiesterase type-5 inhibitor	Sildenafil	Oral; 20 to 50 mg three times daily	• Headache, flushing, nasal congestion, dizziness, visual disturbance • Must not be combined with nitrates (severe hypotension) • Drug–drug interaction with bosentan via CYP3A4; concomitant administration decreases serum levels of both drugs	Available (Generic available)
	Tadalafil	Oral; 40 mg daily	• Headache, flushing, dizziness, visual disturbance • Must not be used with nitrates (severe hypotension)	Available
Soluble guanylate cyclase stimulator	Riociguat	Oral; up to 2.5 mg three times daily	• Headache, flushing, dizziness, haemoptysis • Must not be combined with nitrates or phosphodiesterase type-5 inhibitors due to increased risk of symptomatic hypotension • May cause fetal harm; contraindicated in pregnancy	Not available

* Currently, the PBS only reimburses single agent targeted PAH therapy.
Abbreviations: PAH = pulmonary arterial hypertension; PBS = Pharmaceutical Benefits Scheme.

pump. Although the administration of intravenous epoprostenol is complex, it remains the cornerstone of therapy for patients with severe PAH.

The development of oral agents for the treatment of PAH dramatically altered the care of patients with PAH through their convenience of dosing. The efficacies of the various oral agents targeting each of the three major pathogenic pathways described above have now been proven in large randomised controlled trials.[17-23]

Trial design has also evolved over time in PAH. The traditional primary endpoint of PAH drug trials was the six-minute walk distance, and a typical trial duration was three months. Recently, PAH drug trials have moved towards using long-term morbidity and mortality as the primary endpoint, clearly a more clinically relevant and robust endpoint than a surrogate endpoint such as the six-minute walk distance. For example, in the SERAPHIN study (Study with an Endothelin Receptor Antagonist in Pulmonary

Arterial Hypertension to Improve Clinical Outcome) of macitentan, the primary endpoint was the time from the initiation of treatment to the first morbidity/mortality event related to PAH (worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation or atrial septostomy) or death from any cause.[21] The SERAPHIN study showed that the dual endothelin-receptor antagonist macitentan at a fixed dose of 10 mg significantly reduced the primary endpoint of first morbidity/mortality event compared with placebo (hazard ratio [HR], 0.55; 97.5% confidence interval [CI], 0.39 to 0.76; p<0.001), with a median duration of treatment of 115 weeks.

Previously, oral and inhaled agents targeting the prostacyclin pathway have not been clinically potent.[24,25] However, a novel orally bioavailable prostacyclin receptor agonist selexipag is now available. The phase 3 trial for this drug, the GRIPHON (Prostacyclin (PGI2) Receptor Agonist in Pulmonary Arterial Hypertension) study, showed its use was associated with a risk reduction of 40% for the primary composite endpoint of the first morbidity/mortality event (HR, 0.60; 95% CI, 0.46 to 0.78, p<0.0001).[23]

Given that the pathogenesis of PAH involves multiple pathways, combination therapy is a rational therapeutic approach, and there is now robust evidence that specific combinations of drugs can improve outcomes in PAH over and above monotherapy. Drawing from the success of combination therapy in left heart failure and cancer therapeutics, the recent phase 3–4 study AMBITION (Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension) study tested the hypothesis that upfront combination therapy was superior to monotherapy alone.[26] Treatment-naïve patients with PAH were randomised to upfront oral dual combination therapy with ambrisentan 10 mg (an endothelin receptor antagonist) and tadalafil 40 mg (a phosphodiesterase-5 inhibitor) versus initial monotherapy with either ambrisentan 10 mg or tadalafil 40 mg alone. The primary endpoint was the first event of clinical failure, defined as the first occurrence of a composite of death, hospitalisation for worsening PAH, disease progression or unsatisfactory long-term clinical response. The combination therapy resulted in a 50% relative reduction in the primary endpoint, compared with the pooled-monotherapy group (HR, 0.50; 95% CI, 0.35 to 0.72; p<0.001). The primary endpoint was driven by reduced hospitalisation for PAH, not by mortality rate. Greater improvements in the six-minute walk distance and lower N-terminal pro-brain natriuretic peptide levels were also observed in the combination-treated group at 24 weeks.

For most patients with PAH, dual combination therapy has now become standard of care.[27]

Triple combination therapy targeting all three major pathogenic pathways is now increasingly used for patients with severe disease at diagnosis or failure to respond to dual combination therapy.[28] Access to double or triple therapy is only available in expert PAH centres. Single drug therapy is no longer considered ethical in many aetiologies of PAH.

Another important current paradigm of PAH therapy is that disease stability is no longer regarded as an adequate treatment response, and the goal of therapy is to achieve improved exercise capacity (NYHA Functional Class I-II) and absence of right ventricular failure.[29]

Transplantation

Heart–lung transplantation for PAH was first performed in Australia at St Vincent's Hospital, Sydney in 1986. Transplantation is now required only for the minority of patients with advanced disease for whom medical therapy has failed. Bilateral lung transplantation is now used for PAH, as the right ventricle can recover following alleviation of high pulmonary vascular resistance with lung transplantation.[30]

Referral for pulmonary arterial hypertension

It is critical that patients with suspected PAH are referred to expert PAH centres for both diagnostic evaluation and treatment, given the complexities associated with accurate diagnosis and drug therapies.[31] Targeted PAH therapies are very expensive for the Pharmaceutical Benefits Scheme (PBS) and their correct usage is mandated by the PBS via a continuous review process. Only designated PAH centres may prescribe these medications, and the PBS will only fund one PAH agent at a time. Combination therapy (in line with best practice and international guidelines) is achieved via participation in clinical trials, compassionate access programs and some individual hospital funding. Expert PAH centres can provide access to combination therapy and are involved in clinical trials of novel therapies that are not available on the PBS.

A list of Medicare PAH designated centres can be found on the PHA Australia website (www.phaaustralia.com.au/content/medicare-pah-designated-centres).

Conclusion

For more than 15 years, expert PAH centres in Australia have treated thousands of patients with PAH with a wide range of treatments, often through clinical trials. Expert centres are available in each Australian state and territory and early referral of patients is welcomed. With the availability of new, effective agents, patients can be offered positive and reliable treatments with the chance of cure. As with most cardiovascular diseases, earlier detection and intervention improves outcomes. **CT**

References

A list of references is included in the website version of this article (www.cardiologytoday.com.au).

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Dr Lau has received speaking and consultancy fees from Actelion and Menarini Pharmaceuticals, and participated in clinical trials sponsored by Actelion, Bayer and GSK.

Dr Roche: None.

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