Pulmonary arterial hypertension: a new era in management

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ABSTRACT

- Pulmonary arterial hypertension (PAH) is a heterogeneous condition with a wide range of causes.
- The diagnosis is often delayed or missed.
- PAH is covert in its early stages, when its detection and treatment should have the most impact.
- Access in Australia to effective PAH therapies has lagged behind that in other affluent countries.
- New agents for PAH, now becoming available, improve symptoms and reduce pulmonary resistance, with some demonstrating an ability to reverse remodelling of the right ventricle.
- Best management of PAH is comprehensive and multidisciplinary. Centres of excellence are needed in geographically strategic areas.
- Aggressive efforts must be made to diagnose PAH and to facilitate access to effective therapies.

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PULMONARY ARTERIAL HYPERTENSION (PAH) is generally considered a rare and rapidly lethal condition with poor prognosis and few or no treatment options.[1,2] However, PAH is a generic term that includes elevated pulmonary vascular resistance due to a wide range of causes (Box 1).[3] PAH is defined as a mean pulmonary arterial pressure of >25 mmHg at rest and >30 mmHg with exercise. Primary pulmonary hypertension has an estimated incidence of 2 per million population (possibly higher), with PAH associated with other diseases showing a higher incidence.[3] PAH is often not detected until the late and highly symptomatic stage. There is increasing recognition that PAH associated with other diseases (eg, connective tissue diseases such as scleroderma, airways diseases, interstitial lung disease and sleep apnoea) contributes to exercise intolerance and is a threat to survival. Perhaps in the past, with few treatment options, late diagnosis of PAH was not critical. With new drugs demonstrating efficacy in PAH, an active effort is required to diagnose its presence early, when these treatments may have greater effect.

Symptoms

Symptoms of mild-to-moderate PAH may be insidious. In the early stages, breathlessness, palpitations, fatigue and a pounding heart may be misinterpreted as lack of fitness or cardiac ischaemia. As PAH progresses, ankle oedema and later right-sided congestion (elevated jugular venous pressure, ascites, hepatomegaly, peripheral oedema) occur. Syncope is evident late in the disease. Unless the diagnosis is considered and actively sought, it may be missed.[4]

Diagnosis

The most useful investigations are echocardiography and respiratory function tests. The echocardiogram may show a hypertrophied, dilated or hypokinetic right ventricle, tricuspid regurgitation and elevated pulmonary arterial pressure. The left ventricle usually contracts normally, but may be encroached upon by the enlarged right ventricle. In the absence of a tricuspid regurgitation jet, pulmonary arterial pressure cannot be determined on echocardiography and the diagnosis is not excluded using this test. Respiratory function tests show a disproportionate reduction in carbon monoxide diffusion in the lung (DLCO) (around 50% of predicted in moderate PAH), with at most a mild-to-moderate restrictive lung defect. The reduction in DLCO is greater than that seen with comparably symptomatic left heart failure.

The definitive test for PAH is right heart catheterisation, providing a direct measure of pulmonary pressures. Several Australian centres perform this as an outpatient procedure, via the right internal jugular vein under local anaesthetic. Anticoagulation does not need to be ceased and fasting is not required. Repetitive straight leg raising to increase cardiac demand may uncover early cases in which PAH is only present during exercise. The six-minute walk test is informative and safe in assessing response to treatment and has a strong independent association with mortality.[5] Once PAH has been detected, a comprehensive search for causes should be undertaken (Box 2).

Screening

Patients with family history of primary PAH may have a genetic predisposition to PAH, although the predictive value of the *BMPR2* gene, which has been associated with the

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1: Common causes of pulmonary arterial hypertension*

1. Pulmonary arterial hypertension

Primary pulmonary arterial hypertension:

- Sporadic
- Familial (up to 25%)

Pulmonary arterial hypertension related to:

- Connective tissue diseases (CREST syndrome, scleroderma, mixed connective tissue disease)
- HIV
- Congenital heart disease, Eisenmenger's syndrome
- Portopulmonary hypertension
- Anorexigens
- Primary pulmonary hypertension of the newborn

2. Pulmonary venous hypertension

- Left heart diseases and left ventricular dysfunction
- Pulmonary veno-occlusive disease

3. Disorders of the respiratory system

- Chronic obstructive pulmonary disease
- Interstitial lung diseases
- Sleep disordered breathing

4. Chronic thromboembolic pulmonary hypertension

5. Disorders directly affecting pulmonary vasculature

* Adapted from the WHO Classification of pulmonary arterial hypertension.

disease, is not yet well defined.[6] Up to 15% of patients with scleroderma (especially limited scleroderma) ultimately develop PAH, and annual screening with DLCO measurement and echocardiography is advisable.

Treatment

PAH can be treated specifically (pulmonary thromboendarterectomy) or generically. Chronic thromboembolic pulmonary hypertension is increasingly recognised as an important cause of secondary PAH, for which pulmonary thromboendarterectomy may provide definitive treatment.[7] PAH secondary to sleep apnoea may respond to continuous positive airway pressure.[8] PAH complicating connective tissue disease is recognised as an independent predictor of poorer prognosis in these conditions.[9] Treatment here should be along similar lines to that used in primary pulmonary hypertension.

Until recently, access to effective drug treatment for severe PAH has been very limited in Australia. Heart–lung transplantation for primary pulmonary hypertension was first performed at St Vincent's Hospital, Sydney, in 1986. This was the first putative "curative" therapy for this condition, but is now appropriate only for patients with advanced disease for whom medical therapy has failed. There is, however, an increasing selection of vasodilator and remodelling agents becoming available, providing promise of effective long term medical alternatives.[10-14] British guidelines for the diagnosis and treatment of PAH were recently published and treatment algorithms are under development internationally.[15]

2: Investigations in pulmonary arterial hypertension

- Echocardiogram
- Respiratory function tests: lung volumes, CO diffusion capacity
- Chest x-ray
- Ventilation perfusion scan
- High resolution computed tomography (CT) scan of lungs
- CT pulmonary angiogram
- Connective tissue disease screen (antinuclear antibodies, anti-dsDNA antibodies, anti-neutrophil cytoplasmic antibodies ± antitopoisomerase [SCL-70] ± antifibrillarin [anti-RNP])
- Thrombophilia screen (anticardiolipin antibody, lupus inhibitor, protein C, protein S, factor V Leiden, methyl tetrahydrofolate reductase mutation)
- Sleep study
  - ➤ ± contrast CT pulmonary angiogram
  - ➤ ± coronary angiogram (consider >40 years old)
- Right heart catheterisation for definitive diagnosis. (In PAH, mean pulmonary arterial pressure will be >25 mmHg at rest and >30 mmHg with exercise)

Medical therapies

The pathophysiological basis of PAH is an increase in vasoconstrictor substances (thromboxane, endothelin) and a reduction in vasodilatory substances (nitric oxide, prostacyclin) with smooth muscle cell proliferation and in situ thrombosis, resulting in structural reduction in pulmonary arterial lumen size and, ultimately, plexigenic arteriopathy.

Medical therapies for PAH (Box 3) consist of agents which modify one or more of these pathogenetic mechanisms:

- anticoagulation (to prevent in situ thrombosis or thromboembolism; eg, warfarin, prostacyclin analogues);
- vasodilators (eg, prostacyclin analogues, which increase intracellular cyclic AMP, calcium antagonists, endothelin antagonists, bosentan, and phosphodiesterase 5 inhibitors, which increase cyclic GMP); and
- long term antifibrotic and remodelling agents (prostacyclin analogues and bosentan).

Atrial septostomy

For patients refractory to vasodilator therapy, atrial septostomy may be considered. The aim of this intervention is to relieve right-sided congestion and augment systemic cardiac output. Experience with this procedure in Australia is extremely limited, but its value has been suggested in a number of small studies in other countries.[24]

Natural history

PAH is often a lethal condition or contributes to a poor outlook, with the prognosis directly related to the severity of the associated right ventricular dysfunction.[2] Once right ventricular failure ensues, the median survival for patients without treatment is short. PAH, arising secondary to other disorders, contributes to exercise intolerance and reduces survival.

3: Medical therapies for pulmonary arterial hypertension

Drug class: trial results	Drug	References	Level of evidence*	Administration and dosage	Limitations in Australia
Anticoagulants: Associated with improved survival in primary pulmonary hypertension in responders and nonresponders to calcium-channel blockers	Warfarin	16	II	To keep international normalised ratio (INR) in the range 2.5–4.0	
Calcium-channel blockers: Improved survival and reduced symptoms in 10% of primary pulmonary hypertension patients	Diltiazem, amlodipine, nifedipine	16	II	Oral; high dose, eg, diltiazem 900 mg daily	Restricted to patients with preserved right ventricular function
Prostacyclin analogues: Increased survival, reduced symptoms, improved functional class, haemodynamics and walk distance, reduced pulmonary vascular resistance	Prostacyclin	17–19	III-1	Continuous intravenous infusion (because of very short half-life); 22–45 ng/kg per minute	Not reimbursed
	Iloprost	14	II	Inhaled; 20 μg 5–12 times per day	Not reimbursed
	Beraprost	13	II	Oral; ⩾40 μg four times per day	Not available
	Treprostinil	12	II	Subcutaneous infusion; >10 ng/kg per minute	Injection site pain, not reimbursed
Endothelin receptor antagonists: Improved walk distance and haemodynamics, delayed clinical worsening, improved echo parameters	Bosentan	10,11	I	Oral; initial, 62.5 mg twice daily; target, 125 mg twice daily	Currently available in an open label study Elevated serum transaminase levels in 3%–5% of patients
Phosphodiesterase 5 inhibitors: Improved functional class and walk distance, reduced pulmonary arterial pressure	Sildenafil	20, 21	III-3	Oral; uncertain dose, 25–100 mg three times per day	Currently in trial, possible retinal toxicity
Medical foods: Acute reduction in pulmonary vascular resistance	l-Arginine	22	IV	Oral (powder, capsules); 6 g per day	Gastrointestinal side effects

*Level of evidence according to National Health and Medical Research Council grades.[23]

Referral

With the increasing availability of effective treatment for severe pulmonary hypertension, it is important that patients are referred to centres offering the range of diagnostic and therapeutic interventions. Assessing dose response, monitoring clinical outcomes, switching agents and applying combination therapy (including different modalities) requires considerable experience to ensure optimal outcomes. Complex decisions are required in delineating patients with chronic thromboembolic pulmonary hypertension suitable for pulmonary thromboendarterectomy and the timing of listing for lung transplantation. These issues have been recently addressed in the United Kingdom where the National Health Service has designated national centres for the assessment and management of severe pulmonary hypertension.[15] In addition, one centre only has been nominated to perform pulmonary thromboendarterectomy surgery, so as to ensure concentration of experience and expertise.

Conclusion

Historically, Australia has been unable to offer patients with PAH adequate treatment, largely because of the high cost of therapy. The performance of pulmonary thromboendarterectomy in Australia was recently shown to achieve success rates similar to international practice. Transplantation continues to be limited by donor availability.

Now, with the availability of new and effective oral agents, we can abandon the therapeutic nihilism of past decades, and offer patients effective therapies. Some of these agents allow reverse remodelling of the right ventricle within very short periods. Reverse remodelling of the pulmonary artery and the potential to reverse the entire disease process are realistic targets.

This new era of effective agents gives clinicians a sound reason to diagnose PAH, to tease out all contributing elements and to detect cases early. Trials to date have been performed in moderately to severely affected patients, but are now in progress in less ill patients. As with most cardiovascular diseases, earlier detection and intervention is likely to be rewarded with better outcomes.

Competing interests

All the authors are members of the Australian Advisory Board, Actelion Pharmaceuticals, Australia (manufacturer of bosentan).
The authors are involved in clinical trials with the following companies: AMK: Actelion, AstraZeneca, Aventis, Myogen, Novartis, Pfizer, Roche, Schering AG, United Therapeutics, Wyeth; KDM: Actelion; TW: Actelion, Pfizer; EG: Actelion; LGC: Actelion, Goodman Fielder.

References

1. Rich S. Primary pulmonary hypertension. *Prog Cardiovasc Dis* 1988; 31: 205-238.
2. 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: 343-349.

3. Rich S (ed). World Health Organization: Primary Pulmonary Hypertension — Executive Summary, World Symposium, Primary Pulmonary Hypertension 1998. Available at: http://www.who.int/ncd/cvd/pph.html (accessed Apr 2003).
4. Recommendations on the management of pulmonary hypertension in clinical practice. *Heart* 2001; 86 Suppl 1: i1-i13.
5. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six minute walk test in patients with primary pulmonary hypertension. *Am J Resp Crit Care Med* 2000; 161: 487-492.
6. Thomson JR, Machado RD, Pauciulio MW, et al. Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPRII, a receptor of the TGF-beta family. *J Med Genet* 2000; 37: 741-745.
7. Jamieson S, Auger W, Fedullo P, et al. Experience and results with 150 pulmonary thromboendarterectomy operations over a 29 month period. *J Thorac Cardiovasc Surg* 1993; 106: 116-127.
8. Sajkov D, Wang T, Saunders N, et al. Continuous positive pressure airway treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2002; 165: 152-158.
9. Steen VD. Clinical manifestations of systemic sclerosis. *Semin Cutan Med Surg* 1998; 17: 48-54.
10. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346: 896-903.
11. Galiè N, Hinderliter AL, Torbicki A, et al. Effects of the oral endothelin receptor antagonist bosentan on echocardiographic and Doppler measures in patients with pulmonary arterial hypertension. American Congress of Cardiology, Atlanta, USA; 17–20 March 2002. Abstract #2179.
12. Simmoneau G, Barst R, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension. *Am J Respit Crit Care Med* 2002; 165: 800-804.
13. Galié N, Humbert M, Wachiery JL, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002; 39: 1496-1502.
14. Olchewski H, Ghofrani H, Schmehl T, et al. Inhaled iloprost to treat severe pulmonary hypertension: an uncontrolled trial. *Ann Intern Med* 2000; 132: 435-443.
15. Evans TW, Gatzoulis MA, Gibbs JSR. A national pulmonary hypertension service for England and Wales: an orphan disease is adopted? *Thorax* 2002; 57: 471-472.
16. 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: 76-81.
17. Barst R, Rubin L, Long W, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996; 334: 296-301.
18. Barst RJ, Rubin LJ, McGoon MD, et al. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med* 1994; 121: 409-415.
19. McLaughlin V, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; 106: 1477-1482.
20. Wilkens H, Guth A, Konig J, et al. Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. *Circulation* 2001; 104: 1218-1222.
21. Sastry B, Narasimhan C, Reddy N, et al. A study of clinical efficacy of sildenafil inpatients with primary pulmonary hypertension. *Indian Heart J* 2002; 54: 410-414.
22. Mehta S, Stewart DJ, Langleben D, et al. Short-term pulmonary vasodilation with L-arginine in pulmonary hypertension. *Circulation* 1995; 92: 1539-1545.
23. Rychetnik L, Frommer M. A schema for evaluating evidence on public health interventions; version 4. Melbourne: National Public Health Partnership, 2002; Appendix 1. Available at: http://www.nphp.gov.au/ppi/evidence/schema/appendix1.htm (accessed Apr 2003).
24. Rich S, Dodin E, McLaughlin V, et al. Usefulness of atrial septostomy as a treatment for primary pulmonary hypertension and guidelines for its application. *Am J Cardiol* 1997; 80: 369-371.

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