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Why are they breathless: could it be pulmonary arterial hypertension?

Keep in mind the possibility of pulmonary arterial hypertension when evaluating patients with unexplained breathlessness. The availability of new therapies now means that early diagnosis and referral of patients with this rare group of disorders can make a substantial difference to patient outcome.

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What is pulmonary arterial hypertension?

Pulmonary hypertension is the term used to describe increased pulmonary artery pressure (PAP), defined as a mean of greater than 25 mmHg at rest or 30 mmHg with exertion on right heart catheterisation. This equates to a pulmonary arterial systolic pressure estimated on transthoracic echocardiography (TTE) of above 40 mmHg. Pulmonary hypertension often occurs as a complication of cardiac and respiratory disorders – for example, left ventricular failure or severe chronic obstructive pulmonary disease (COPD).

Pulmonary arterial hypertension (PAH) describes a rare (incidence 2 to 10 per million population per year) group of diseases characterised by a narrowing of the pulmonary arteries (especially the arterioles), increasing the afterload on the right ventricle. Compensatory right ventricular hypertrophy develops with time and pulmonary hypertension results. As shown in Table 1, PAH is classified separately to other causes of pulmonary hypertension, such as cardiac or respiratory disorders.

PAH can occur in association with a systemic disorder such as a connective tissue disease (particularly limited cutaneous scleroderma, previously called CREST), portal hypertension or HIV infection. It can also occur as a result of exposure to drugs and toxins. Familial PAH accounts for 5 to 10% of cases of PAH. PAH can also occur in the absence of an identifiable cause. This is now called idiopathic PAH, but was previously referred to as primary pulmonary hypertension. Before the availability of specific therapies, prognosis of patients with PAH was poor (for example, patients with

IN SUMMARY

- **Pulmonary arterial hypertension (PAH) comprises a group of rare diseases presenting as unexplained dyspnoea.**
- **Diagnosis of PAH is often delayed by more than 18 months.**
- **Consider the possibility of PAH in patients presenting with breathlessness.**
- **Detailed evaluation, including a right heart catheterisation, is needed for patients with PAH.**
- **Pulmonary hypertension is a common finding on transthoracic echocardiography, but it is rarely PAH.**
- **New treatments for PAH are available that can improve quality of life, exercise capacity and survival.**

Table 1. Revised clinical classification of pulmonary hypertension (Venice 2003)[1]

1. Pulmonary arterial hypertension (PAH)
- Idiopathic (IPAH)
- Familial (FPAH)
- Associated with (APAH):
  - Collagen vascular disease
  - Congenital systemic-to-pulmonary shunts
  - Portal hypertension
  - HIV infection
  - Drugs and toxins
  - Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
- Associated with significant venous or capillary involvement
  - Pulmonary veno-occlusive disease (PVOD)
  - Pulmonary capillary haemangiomatosis (PCH)
- Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension with left heart disease
- Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung diseases and/or hypoxaemia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Development abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Nonthrombotic pulmonary embolism (tumour, parasites, foreign material)

5. Miscellaneous
- Sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangiomatosis, compression of pulmonary vessels by adenopathy, tumour, fibrosing mediastinitis, or other process

idiopathic PAH had a median survival of 30 months from diagnosis).

The key pathological features of PAH are obstruction of small pulmonary arteries (especially arterioles) due to intimal, medial (smooth muscle hypertrophy and constriction) and adventitial proliferation and *in situ* thrombosis. Vessel rupture and extravasation lead to plexiform lesions in severe disease.

When to suspect PAH?

PAH has a predilection for young women; however, it can occur in both genders at all ages. It most commonly presents as unexplained breathlessness. Reduced oxygen delivery can lead to fatigue, weakness, syncope and exercise intolerance. The increased right ventricular pressure can reduce blood flow through the right coronary artery, leading to 'right ventricular' angina. Peripheral oedema and ascites tend to be late symptoms due to chamber dilatation (with tricuspid regurgitation) and right heart dysfunction.

Although physical examination may reveal typical features such as right ventricular lift and a broadly split second heart sound with an accentuated pulmonary component (P2), examination findings are usually normal. Delayed diagnosis (greater than 18 months) is common as symptoms are often vague and patients tend to struggle to articulate them.

Screening should be undertaken in patients with additional risk factors, such as a family history of PAH or an underlying connective tissue disorder, and PAH should be suspected if such patients present with breathlessness.

Which investigations are necessary?

Initial evaluation of unexplained breathlessness

Following history, examination and screening investigations, most patients with unexplained breathlessness are found to have asthma, COPD, interstitial lung disease, left heart disease or anaemia (Table 2). Therefore, initial evaluation should include full blood examination, electrocardiography, chest radiography (Figure) and spirometry (including diffusion capacity [DLCO]). Bronchial provocation testing and TTE are the next steps if initial testing is unhelpful (Table 3).

Electrocardiography

The electrocardiogram in PAH is often normal but may show right axis deviation, right ventricular hypertrophy and strain pattern, as well as features of other cardiac disease or arrhythmias.

Table 2. Causes of unexplained breathlessness*

- Undiagnosed asthma
- Cardiovascular disease
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Anaemia
- Obesity
- Multifactorial/deconditioning
- Miscellaneous: metabolic acidosis/psychogenic

* Modified from reference 2.

Chest radiography

The chest radiograph may show pulmonary artery dilatation, peripheral vessel pruning and right atrial and right ventricular enlargement, but it can be normal. Alternative causes of dyspnoea, such as COPD, pulmonary fibrosis or pulmonary venous congestion, may be evident.

Spirometry

Spirometry, including DLCO, allows the determination of coexistent or causative parenchymal or airway disease contributing to pulmonary hypertension. Spirometry is usually normal in PAH, and a reduced DLCO with normal spirometry is highly suggestive of PAH.

Transthoracic echocardiography

TTE is a key screening investigation if pulmonary hypertension is suspected. It allows the estimation of pulmonary arterial systolic pressure (sPAP) by measuring tricuspid regurgitant flow and right atrial pressures. It generally correlates well with sPAP measured on right heart catheterisation; however, false-positives and false-negatives can occur. Echocardiography also allows evaluation of valvular heart disease, left ventricular myocardial disease (systolic and diastolic) and congenital heart disease with intracardiac shunts.

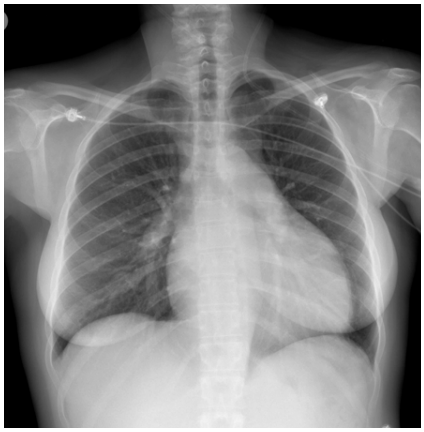

Figure. Chest x-ray of a 38-year-old woman with severe PAH showing cardiomegaly, prominent pulmonary arteries and clear lung fields.

If pulmonary hypertension is considered as a differential diagnosis, this should be carefully noted on the echocardiogram request slip so that the most appropriate TTE study is obtained.

Specialist evaluation of pulmonary hypertension

If initial evaluation for PAH does not identify an alternative diagnosis, specialist referral of the patient is generally recommended (Table 4). This would usually be to a respiratory medicine physician, cardiologist or, in the setting of a rheumatological disease, a rheumatologist. Most Australian capital cities now have specialist pulmonary hypertension clinics that facilitate the multidisciplinary approach usually required. Further investigations are described below.

Screening for connective tissue diseases

Diagnosis of a connective tissue disease is based on clinical and serological criteria. An autoimmune screen, including antinuclear antibodies, anticentromere antibodies, anti-Scl70 and RNP (ribonucleoprotein) antibodies, should be completed. Patients with clinical symptoms and significantly elevated autoantibodies should be further investigated and referred to a rheumatologist.

Table 3. Evaluating patients with unexplained dyspnoea

- Undertake a clinical history and examination
- Organise the following investigations:
  - Full blood examination to evaluate for anaemia
  - ECG to evaluate for rhythm or cardiac abnormalities
  - Chest x-ray to identify parenchymal disease
  - Spirometry, including diffusing capacity, with or without provocation test, to identify asthma, chronic obstructive pulmonary disease, restrictive lung disease
- If there is still no explanation for dyspnoea, organise a transthoracic echocardiography (TTE)
- If pulmonary hypertension is diagnosed on TEE or still no cause for dyspnoea is found, refer the patient to a specialist centre

Table 4. Patients with PAH: indications for referral

- Unexplained dyspnoea on exertion with evidence of PAH on transthoracic echocardiography (TTE)
- Evidence of moderate to severe PAH
  - Estimated pulmonary arterial systolic pressure >45 mmHg on TTE
  - WHO/NYHA class II – IV symptoms
  - Near syncope or syncope
- Absence of substantial left-sided heart disease or parenchymal lung disease
- Evidence of right heart failure – clinically or on TTE
  - Peripheral oedema
  - Ascites
  - Right ventricular enlargement or systolic dysfunction

continued

Table 5. WHO/NYHA functional classification for pulmonary hypertension

Class I	No limitation of usual physical activity (normal)
Class II	Mild limitation of physical activity No discomfort at rest but normal physical activity causes increased dyspnoea, fatigue, angina or presyncope
Class III	Marked limitation of physical activity No discomfort at rest but less than ordinary activity causes increased dyspnoea, fatigue, angina or presyncope
Class IV	Unable to perform any physical activity without breathlessness and may have signs of right heart failure Dyspnoea and fatigue may be present at rest

Nuclear medicine ventilation and perfusion lung scanning

Nuclear medicine ventilation and perfusion lung scanning are the best screening tests for chronic thromboembolic pulmonary hypertension (CTEPH), which has a potentially curative surgical treatment option – pulmonary thromboendarterectomy. CT pulmonary angiography usually shows potentially diagnostic features in CTEPH (for example, pulmonary arterial obstruction with webs, band or thrombus, mosaic perfusion and/or old pulmonary infarcts) but is sometimes reported as negative. In patients in whom CTEPH is identified, pulmonary angiography is required to identify those who may benefit from pulmonary thromboendarterectomy.

Right heart catheterisation

Right heart catheterisation remains the gold standard to confirm the diagnosis, cause and severity of pulmonary hypertension. It should include measurements of pressure (right atrial, right ventricular, pulmonary arterial and pulmonary capillary wedge pressures) and cardiac output to allow the derivation of pulmonary vascular resistance. A measurement of mixed venous saturation also provides helpful prognostic information. Acute vasodilator challenge to assess haemodynamic response may also be necessary. Repeat right heart catheterisation may be required as the final arbiter of therapeutic response and to reset the baseline for further therapeutic intervention.

Evaluation of functional capacity

Evaluation of functional capacity is essential in patients with PAH as it provides prognostic information, allows for the assessment of the patient for suitability for specific drug therapies and allows assessment of treatment response. The WHO functional

classification for pulmonary hypertension is an adaptation of the New York Heart Association scale for cardiac disease and is used to determine a patient's functional class (Table 5). Patients also undergo assessment via a six-minute walk test, which is a simple and objective test giving a useful metric for therapeutic decision-making and prognosis.

How is PAH managed?

Patients with PAH are usually carefully monitored at specialist centres in conjunction with their GPs. Treatments have potential benefits, but almost all have important risks. In the modern era of therapy, survival has substantially improved, with yearly mortality more than halved (now less than 10% per year for idiopathic PAH).

Patient advice

Physical activity

There are few data on which to base recommendations regarding physical activity. A gradual increase in activity as tolerated should be encouraged; however, heavy physical activity that leads to exertional syncope or chest pain should be avoided.

Fluid balance

Although there is no authoritative recommendation of fluid restriction, close monitoring of a patient's fluid intake and weight with careful titration of diuretics to maintain euvolaemia are appropriate.

Immunisation

It is recommended that all patients with PAH receive annual influenza vaccination and five-yearly pneumococcal vaccination unless otherwise contraindicated.

Pregnancy

The mortality rate in pregnant women with PAH is 30 to 50%. Furthermore, some new therapies are teratogenic. Thus it is recommended that all women with PAH who are of childbearing age use a reliable method of contraception.

Contraception

Although oestrogen-containing contraceptives increase the risk of venous thromboembolism, the absolute risk may be low with low-dose oestrogen products combined with oral anticoagulation. This risk, therefore, needs to be assessed in the context of the high maternal mortality in pregnancy. Furthermore, some of the new agents, such as the endothelin receptor antagonist bosentan, can decrease the efficacy of hormonal contraception.

Given the complexities of contraception and mortality associated with pregnancy and PAH, women of childbearing age with PAH should be referred for specialist advice on appropriate contraceptive techniques.

Over-the-counter medications

Although there are some reports that L-arginine, a precursor of nitric oxide, can augment endothelin-dependent vasodilation, there is no evidence that other natural medications are useful in the treatment of PAH. Care should be taken to educate patients about the potential interactions that can occur between over-the-counter medications and prescribed medications, in particular oral anticoagulants.

Surgery

Patients with PAH are at increased risk in the perioperative and operative periods. If surgery is proposed, it is recommended that it be undertaken in consultation with staff from specialist centres and with ICU and anaesthetic support.

General therapies for PAH

Patients with hypoxaemia (resting or exercise PaO_2 less than 60 mmHg) should be treated with supplemental oxygen to minimise pulmonary vasoconstriction.

Diuretics are used to manage symptoms of right ventricular overload such as peripheral oedema and ascites, with an aim to maintain euvolaemia.

Anticoagulation, with a target INR of 2 to 3, is recommended in all patients with idiopathic PAH as retrospective studies have reported improved survival with this treatment. The risk-to-benefit balance for anticoagulation in patients with other types of PAH is unclear.

A small proportion (fewer than 10%) of patients with PAH have sustained haemodynamic and symptomatic response to high doses of nonselective vasodilators, such as calcium channel blockers, and have a conspicuously better prognosis with this treatment (greater than 90% five-year survival). These patients can be identified during right heart catheterisation by their showing improved haemodynamic measures in response to short-acting vasodilators (for example, epoprostenol). In such cases, a trial of a calcium channel blocker is indicated with ongoing monitoring of clinical response. Verapamil should not be used as it is a negative inotrope. More than 90% of patients with PAH show no worthwhile response (and may even be worse symptomatically). Nonselective vasodilators should, therefore, only be used in those showing acute vasodilator responsiveness.

Specific therapies for PAH

Several new therapies have become available to treat PAH and are supported by randomised control trial data. The three main classes of drugs available in Australia are the prostaglandin analogues, the endothelin receptor antagonists and the phosphodiesterase inhibitors/nitric oxide antagonists. These classes of drugs exploit the three main identified pathogenic pathways. They are only available through designated prescribing centres. They can be prescribed through the PBS, but in view of their considerable cost, detailed and specific criteria must be met both for drug initiation and every six months for continuation.

Prostanoids

Prostacyclin I_2 (epoprostenol [Flolan]) is an arachidonic acid metabolite. It is a potent vasodilator with antiproliferative and antithrombotic effects and is

administered as a continuous intravenous infusion. Although marketed for almost two decades, it has been used little in Australia until its recent PBS listing. It remains the most effective single agent for PAH, improving haemodynamics, exercise capacity and survival. Adverse effects include jaw pain, headache and diarrhoea. Administration is via a tunnelled central line, which can be complicated by line thrombosis, sepsis and pump failure. Sudden interruption of the infusion must be avoided as this can lead to severe rebound pulmonary hypertension.

Iloprost (Ventavis) is a PBS-listed, chemically stable analogue of prostacyclin suitable for inhalation. Due to its short duration of action it must be inhaled six to nine times per day.

Subcutaneous administration of treprostinil (Remodulin), a long-acting prostanoid, shows efficacy but site pain is problematic. Although it is TGA approved, it is not currently PBS listed.

Trials assessing the effectiveness of oral prostanoids are ongoing.

Endothelin receptor antagonists

Endothelin 1 is a potent vasoconstrictor and causes vascular proliferation. It exerts its actions via endothelin A and B receptors. Bosentan (Tracleer) is an orally administered dual receptor antagonist that has been shown to improve haemodynamics, exercise capacity and, more recently, survival in patients with PAH. It was the first PAH-specific therapy available through the PBS. Its most common serious adverse effect is hepatotoxicity.

Sitaxentan (Thelin) is a selective type A endothelin-1 receptor antagonist, also recently available through the PBS. Although it is associated with less hepatotoxicity, it interacts substantially with warfarin.

Liver function should be monitored monthly in patients prescribed endothelin receptor antagonists.

Phosphodiesterase type 5 (PDE5) inhibitors

Sildenafil (Revatio) is an orally administered PDE5 inhibitor that acts to prolong the vasodilatory effects of nitric oxide. It was used quite extensively off label for several years prior to approval by any regulatory body, including Australia's TGA. One recently published randomised control trial has shown short-term improvement in haemodynamics and six-minute walk distance.[3] Long-term effects on prognosis are unclear at the PBS-listed (20 mg three times daily) dose.

Other options for PAH

Lung transplantation (usually bilateral or heart–lung) is reserved for those patients

Table 6. Patients with PAH: role of the GP

- Think of PAH in patients with unexplained exertional dyspnoea
- Initiate appropriate screening
- Refer patient to appropriate specialist centre
- Provide regular follow up
- Assess volume status
- Monitor pathology
- Manage anticoagulation

who are deteriorating despite maximal therapy. Pulmonary thromboembolectomy should be considered for patients with CTEPH. Patients with severe heart failure may be suitable for the decompressing procedure of atrial septostomy.

Role of the GP

The role of the GP is pivotal in recognising the possibility of pulmonary arterial hypertension as the cause for unexplained dyspnoea, arranging appropriate screening and referring patients to specialists (Table 6). The GP also has an important role in monitoring the patient's fluid balance, electrolytes and renal and liver functions; managing anticoagulation; and generally supporting the patient and family. GPs in country areas will need to refer patients to major cities for detailed assessment. To expedite efficient follow-up, blood tests and even echocardiograms may need to be organised locally before review at a pulmonary hypertension centre.

Role of the specialist referral centre

The staff at the specialist referral centre will ensure that the diagnostic evaluation is complete, including referral of the patient to other specialists, if appropriate. They will discuss treatment options, initiate therapy and arrange follow up (Table 7), and continue to update the GP and other involved specialists.

Table 7. Patients with PAH: role of the referral centre

- Complete the diagnostic evaluation, including right heart catheterisation
- Liaise with relevant specialists – cardiologists, respiratory physicians and rheumatologists
- Discuss treatment options
- Initiate therapy
- Provide ongoing management and review
- Monitor progress
  - stable patients: three-to six-monthly
  - unstable patients: more frequently
- Refer patient for pulmonary thromboembolectomy or lung transplantation when appropriate

Conclusion

PAH comprises a rare group of diseases; affected patients present with unexplained breathlessness. Diagnosis is often delayed for more than 18 months so it is important to consider this diagnosis when investigating patients with shortness of breath. New therapies have provided significant improvements in patient quality of life and survival, thus any patient with suspected PAH or breathlessness that can otherwise not be explained should be referred for further evaluation. MT

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Further reading

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COMPETING INTERESTS. Dr Paraskeva: None. Professor Williams is a pulmonary hypertension scientific advisory board member for Actelion, CSL and GlaxoSmithKline.