

Pulmonary hypertension

— the condition and specialist assessment

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Pulmonary hypertension is a vascular disease that can be difficult to diagnose accurately, but early recognition and treatment can greatly improve patient outcome. This article describes the causes of pulmonary hypertension and the techniques used to diagnose and classify the disease



A pulmonary angiogram is sometimes used to investigate the cause of pulmonary hypertension

Pulmonary hypertension is a condition characterised by increased pressure in the pulmonary arteries. It is defined as a mean pulmonary artery pressure ≥ 25 mmHg at rest or 30mmHg on exercise¹. This elevation of pressure can be due to a number of causes.

Diseases that affect the pulmonary vasculature directly can increase pulmonary pressures but so can those of the left side of the heart, by passive congestion. Pulmonary arterial hypertension (PAH) is therefore defined as a mean pulmonary artery pressure ≥ 25 mmHg at rest or 30mmHg on exercise with an increased pulmonary vascular resistance and a normal pulmonary capillary wedge pressure or left ventricular end diastolic pressure.

PAH is a rare condition that, until the last two decades, was associated with a poor outcome and ineffective treatment. This has now changed. PAH has now become increasingly recognised in association with

other medical conditions and more effective therapies have been developed.

It is of critical importance to establish the cause of pulmonary hypertension as this will determine its subsequent management. This was recognised at the third World Symposium on Pulmonary Hypertension in 2003 where clinical classification was established to identify five major groups and causes of pulmonary hypertension² (see Panel 1). This classification groups together the causes of pulmonary hypertension that share pathological features and may have similar treatment responses. It highlights the need for accurate diagnosis and assessment as the treatments for one group would not necessarily benefit others.

Classically, in those with underlying lung or heart diseases, the mainstay of treatment should be aimed at the underlying cause of the pulmonary hypertension.

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) can potentially be cured by surgery (pulmonary endarterectomy, see p13) and a number of pharmacological treatments are now available for those with PAH (see p10). The classification of PAH is outlined in Panel 2 (p8).

PAH is a challenging disease to diagnose accurately and to treat. There is often a delay of up to three years from the first appearance of symptoms to the diagnosis^{1,3} and the diagnostic process requires invasive investigations.

Before heart and lung transplantation, no specific treatment for PAH existed, but the past two decades have seen significant advances in this field. Therapies have been

Panel 1: WHO classification of pulmonary hypertension

- Pulmonary arterial hypertension
- Pulmonary hypertension with left heart disease*
- Pulmonary hypertension associated with lung diseases and/or hypoxaemia*
- Pulmonary hypertension due to thrombotic and/or embolic disease
- Miscellaneous group

*In these instances treatment is best aimed at the underlying disease and these patients do not usually require specialist assessment

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Panel 2: Classification of PAH

- Idiopathic pulmonary arterial hypertension (IPAH)
 - Sporadic
 - Familial
- Related to
 - Collagen vascular disease
 - Portal hypertension
 - Congenital heart disease
 - HIV infection
 - Drugs or toxins
- Persistent pulmonary hypertension of the newborn
- PAH with significant venous or capillary involvement

developed which improve both the symptoms and the survival of patients with PAH.

With supportive treatment, those with severe disease previously had a five-year survival of 27 per cent. This has been increased to 54 per cent with certain targeted therapies.¹ These treatments are often complicated and their use requires significant expertise. Thus the investigation and treatment of certain forms of PAH are currently focused at nationally designated specialist centres. There are five specialist centres in the UK, located in Glasgow, Newcastle, Sheffield, Cambridge and London. There is also a specialist centre in Dublin, Republic of Ireland.

— Epidemiology

PAH has an estimated prevalence of 30–50 cases per million.⁴ Idiopathic pulmonary arterial hypertension (IPAH), a form of PAH previously known as primary pulmonary hypertension, has an incidence of 1–2 cases per million per year and is three times more common in women.³ However, the difficulties in detection and providing a definitive diagnosis of PAH make it difficult to assess its prevalence accurately in the general population.

Without targeted pulmonary vascular therapy, there is a median survival of 2.8 years from diagnosis.⁶ The non-specific and subtle nature of the signs and symptoms of pulmonary vascular disease often delay diagnosis but awareness of pulmonary hypertension and early referral to one of the specialist centres will expedite the process.

PAH is now increasingly recognised in association with other conditions such as collagen vascular disease (10–20 per cent),⁷ sickle cell disease (20 per cent),⁵ HIV infection (0.5–2 per cent), portal hypertension (1–2 per cent), and congenital heart disease (15 per cent).⁸ A recent study suggested that the cumulative incidence of CTEPH after pulmonary embolism was as high as 3.8 per cent after two years.⁹

— Pathophysiology

The pathophysiology of PAH is complex. Central to the disease process is an elevation in the pulmonary vascular resistance (PVR) to blood flow through normally distensible, low resistance vessels. This usually occurs as a consequence of vasoconstriction, remodelling of the pulmonary vessel wall and also thrombosis.

Pulmonary vasoconstriction is thought to be an early factor in the development of PAH, and may be due to abnormal function of the pulmonary vascular endothelium. Endothelial dysfunction results in impaired release of vasodilators, such as nitric oxide and prostacyclin, or over-expression of vasoconstrictors, such as endothelin.

Vascular remodelling affects all layers of the pulmonary vessel wall, the adventitia, media and intima. In PAH medial smooth muscle hypertrophy is seen in the small arteries with thickening and fibrosis of the vessel intima. In situ thrombosis can occur and in some cases other obstructive lesions can also form. In CTEPH the normal response to thrombosis is incomplete. Instead of being broken down and removed from the pulmonary circulation, thrombotic material persists and becomes "organised" or incorporated into the wall of the vessel. This causes obstruction of the vascular bed and a subsequent rise in the PVR. Interestingly, in some cases there are also changes similar to those seen in PAH in non-obstructed vessels.

The elevated PVR in what is usually a low resistance system increases pressure in the pulmonary vessels and thus the workload of the right side of the heart. This consequently causes the patient to experience symptoms, although these symptoms

are often only recognised once haemodynamic and pathological changes are well established.

As the disease progresses, the PVR increases, and so does the load on the right heart. Cardiac output is then compromised, causing right ventricular failure.

— Clinical features

The principal symptom of pulmonary hypertension is breathlessness, which may be mild initially and is often mistaken for other more common conditions such as asthma. Another common yet non-specific problem experienced by patients with pulmonary hypertension is fatigue. Symptoms are progressive and can later be accompanied by chest pains and syncope, often on exercise. This chest pain can be very similar to, and is often mistaken for, angina. Syncope usually reflects a low cardiac output and indicates severe disease.

As the right heart fails, patients may suffer from abdominal distension (from ascites). Ankle swelling also occurs, often late in the progression of the disease, although this can be absent in advanced PAH, even in the presence of ascites. Many symptoms of PAH may not become evident until the disease has significantly progressed and there is some degree of right heart failure. Furthermore, clinical features of PAH may be masked by associated medical conditions, especially when they impact on exercise capacity or breathing.

In advanced PAH there is little cardiac reserve to compensate for additional stresses such as sepsis and the adverse haemodynamic effects of some drugs. Hence, these patients are often more susceptible to the adverse effects of negatively inotropic drugs and poorly tolerate intercurrent illness.

Panel 3: Investigations into the cause of pulmonary hypertension

- Imaging
 - Chest x-ray
 - Ventilation/perfusion scanning
 - High resolution computed tomograph of the lungs
 - Contrast helical computed tomograph of the pulmonary arteries
 - Magnetic resonance angiography
 - Pulmonary angiogram (in selected cases)
- Pulmonary
 - Arterial blood gases
 - Lung function
 - Nocturnal oxygen saturation monitoring
 - Exercise test (six minute walk/shuttle)
- Cardiology
 - Electrocardiogram
 - Echocardiography
 - Cardiac catheterisation
- Blood
 - Routine hematology and biochemistry
 - Thrombophilia screening
 - Autoimmune screening
 - HIV testing

— Investigations

Patients with significant dyspnoea usually seek medical advice and undergo basic investigations that can alert the clinician to the presence of pulmonary hypertension. These include:

- Electrocardiogram and/or chest x-ray. These are said to be abnormal in 80 per cent of patients with established disease.
- Trans-thoracic echocardiogram (TTE). This is the most common non-invasive investigation suggesting pulmonary hypertension. With TTE the systolic pulmonary artery pressure and the right atrial (RA) pressure can be estimated from the velocity of the tricuspid regurgitation jet by Doppler echocardiography. In addition, other features may suggest pulmonary hypertension (dilated right sided chambers, right ventricular hypertrophy) and its causes can be diagnosed (valvular heart disease, left ventricular dysfunction, intra-cardiac shunts).

Pulmonary function tests are often normal in patients with pulmonary hypertension, although a reduced gas transfer of carbon monoxide may be present.

If PAH is suspected, the patient should be referred to a specialist centre for further assessment.

— Specialist assessment

Once a patient is referred to a specialist centre, the aim is to confirm or exclude a diagnosis of pulmonary hypertension and, if present, assess disease severity and establish its cause. A management plan can then be instituted with ongoing support and assessment. It is particularly important to recognise patients with CTEPH as a proportion of these patients can resume a normal quality of life by undergoing pulmonary endarterectomy.

Patients referred to the specialist centre at the Royal Hallamshire Hospital in Sheffield undergo a “one stop” or “two stop” assessment. The first stop allows patients to meet the team and undergo several non-invasive tests before admission for the invasive investigations that form the second stop. For most individuals the two stop process is appropriate but some require in-patient transfer for assessment or direct admission meaning the two visits are combined in one. At the first stop, patients will also receive verbal and written information about pulmonary hypertension, so they should be well informed and able to understand the potential implications of a positive diagnosis of the condition.

As part of the admission process patients undergo cardiothoracic imaging, an assessment of exercise capacity and cardiac

catheterisation to establish the diagnosis and provide important prognostic information.

Imaging tests performed include chest x-rays, ventilation/perfusion lung scans, high-resolution computed tomographs (CT) of the thorax, CT pulmonary angiograms, cardiac magnetic resonance imaging and magnetic resonance angiograms, and, in selected cases, formal pulmonary angiograms.

Exercise testing in patients with pulmonary hypertension is carried out in order to establish exercise capacity and a baseline against which future measures can be compared. This enables monitoring for clinical worsening or a treatment response. The most established exercise test in PAH is the six-minute walk test. In IPAH, studies have demonstrated a prognostic significance of both distance walked¹⁰ and oxygen desaturation during the walk test.¹¹

Right heart catheterisation is required to confirm the diagnosis of pulmonary hypertension. As well as mean pulmonary artery pressure this allows the measurement of RA pressure, cardiac output, and can establish the presence of an intra-cardiac shunt.

Parameters indicating a poor prognosis include a RA of >10mmHg, a cardiac index (cardiac output corrected for body surface area) of <2.1 and mixed venous oxygen saturation of <63 per cent.¹

A vasodilator challenge is also an integral part of the assessment. This involves the administration of a short-acting vasodilator (eg, intravenous epoprostenol, intravenous adenosine, or inhaled nitric oxide) while monitoring haemodynamics. Those with IPAH who have a significant drop in mean pulmonary artery pressure (approximately 10 per cent of patients) fall into a better prognostic group and may be suitable for treatment with high dose calcium channel blockers. It should be noted that this test can be hazardous, and patients with a “down stream” obstruction, ie, pulmonary venous hypertension, can develop life-threatening pulmonary oedema. Chronic vasodilator treatment is therefore contraindicated in this group of patients. A summary of the investigations used to clarify the cause of the pulmonary hypertension is shown in Panel 3 (p8).

The results of these investigations are reviewed and discussed by a multidisciplinary team usually allowing a clear pulmonary vascular diagnosis. With this comes the establishment of a management plan in conjunction with each individual patient.

Although pulmonary hypertension is a rare condition the importance of making a positive diagnosis is clear. This can be a complex process involving many investigations.

It is a condition with various causes and underlying disease processes for which the treatments can be very different. These will be discussed further in a second article, where the treatment of this rare condition is looked at in more detail (p10).

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