Pulmonary Hypertension

Pulmonary hypertension (PH) is an increase in mean pulmonary arterial pressure (PAP), which can be caused by or associated with a wide variety of conditions.

Idiopathic pulmonary arterial hypertension (PAH) is a rare disorder that can be defined as a sustained elevation in PAP and pulmonary vascular resistance, with normal pulmonary artery wedge pressure, in the absence of a known cause. It is a diagnosis of exclusion after other possible causes of PH have been excluded. It is a severe and often rapidly progressive illness in many cases.

The injury to the pulmonary endothelium causes a tendency to in situ thrombosis in the pulmonary arterial tree, the so-called thrombotic pulmonary arteriopathy. The disease process continues through vascular scarring, endothelial dysfunction and proliferation of smooth muscle cells within the intima and media of the pulmonary arterial tree, causing progressive pulmonary arterial hypertension. This leads to progressive right heart strain due to obliteration of small pulmonary arterial vessels, and eventually right heart failure.

Definitions[1]

PH is a haemodynamic and pathophysiological condition defined as an increase in mean PAP ≥25 mm Hg at rest as assessed by right heart catheterisation.

PAH is a clinical condition characterised by the presence of precapillary PH in the absence of other causes of precapillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases (see 'Classification', below). PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation.

Classification of pulmonary hypertension[1]

Classification is crucial in determining the treatment and prognosis.[2]

- **PAH:**
  - Idiopathic.
  - Heritable:
    - There is a small subset (~6%) of cases that are inherited in an autosomal dominant fashion due to mutations in the BMPR2 gene (receptor in TGF-beta family).[3]
    - Other mutations.
  - Drug- and toxin-induced.
  - Associated with:
    - HIV infection, portal hypertension, congenital heart disease, schistosomiasis, chronic haemolytic anaemia.
    - A relatively high rate in certain connective tissue disorders such as the CREST syndrome (Calcinosis, Raynaud's phenomenon, [O]Esophageal dysmotility, Sclerodactyly and [T]elangiectasia), progressive systemic sclerosis, Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus (SLE), mixed connective tissue disorder and polymyositis/dermatomyositis.[4]

- Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis.
- Persistent PH of the newborn.
- PH due to left heart disease: systolic dysfunction, diastolic dysfunction, valvular disease, left heart inflow or outflow tract obstruction, congenital cardiomyopathies, pulmonary vein stenosis.
- PH due to lung diseases and/or hypoxia:
  - Chronic obstructive pulmonary disease.
  - Interstitial lung disease.
  - Other pulmonary diseases with mixed restrictive and obstructive pattern.
  - Sleep-disordered breathing.
  - Alveolar hypoventilation disorders.
  - Chronic exposure to high altitude.
  - Developmental abnormalities.

- Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions.
- PH with unclear and/or multifactorial mechanisms:
  - Haematological disorders: myeloproliferative disorders, splenectomy.
  - Systemic disorders: sarcoidosis, pulmonary Langerhans’ cell histiocyteosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis.
  - Metabolic disorders: glycogen storage disease, Gaucher’s disease, thyroid disorders.
  - Others: tumour obstruction, fibrosing mediastinitis, chronic kidney disease, segmental pulmonary hypertension.
Epidemiology\cite{2}

Idiopathic PAH is rare. However, the prevalence of PAH is higher in certain patient groups, such as those with systemic sclerosis, portal hypertension, congenital heart disease and HIV infection.

The prevalence of PAH is estimated at 15-52 per million. The incidences are estimated to be 1-3.3 per million per year for idiopathic PAH and 1.75-3.7 per million per year for chronic thromboembolic PH.

PH is more common in severe respiratory and cardiac disease, occurring in 18-50\% of patients assessed for transplantation or lung volume reduction surgery, and in 7-83\% of those with diastolic heart failure.

Between 0.5\% and 4\% of patients develop chronic thromboembolic PH after acute pulmonary embolism. There is an increased risk for patients presenting with large, recurrent or unprovoked clots.

Presentation\cite{2}

Most commonly presents with progressive breathlessness, weakness and tiredness. Exertional dizziness and syncope may also develop. Oedema and ascites tend to occur late in the disease. Angina and tachyarrhythmias, particularly atrial flutter, may also occur. Haemoptysis is uncommon but may occur in Eisenmenger's syndrome and chronic thromboembolic PH.

Clinical signs include right ventricular (parasternal) heave, a loud pulmonary second heart sound, murmur of pulmonary regurgitation, systolic murmur of tricuspid regurgitation, raised jugular venous pressure, peripheral oedema and ascites. These signs may be subtle or absent in early disease.

There may also be signs of associated conditions, such as connective tissue disease or liver disease.

Differential diagnosis

- Cor pulmonale causing secondary PH.
- Cardiomyopathies.
- Primary right ventricular failure - eg, following myocardial infarction.
- Congestive cardiac failure.
- Recurrent pulmonary emboli.
- Mitral or tricuspid stenosis.
- Tricuspid regurgitation.
- Pulmonary stenosis.
- Portal hypertension.
- Obstructive sleep apnoea.
- Hypothyroidism.
- Sickle cell disease.\cite{5}

Investigations\cite{2}

- Routine biochemistry screen including LFTs (portal hypertension), TFTs and autoimmune screening - particularly antinuclear antibody to detect possible SLE/scleroderma-like syndrome.
- CXR to exclude other lung diseases but this is not useful for diagnosing PH.
- ECG - can show right ventricular hypertrophy and strain patterns but may be normal.
- Pulmonary function tests.
- Lung biopsy may be needed to exclude interstitial lung disease.
- Polysomnography may be used to exclude obstructive sleep apnoea.
- Echocardiography to assess right ventricular function and estimate pulmonary arterial pressures.
- High-resolution CT of the thorax to investigate other possible causes of PH.
- Isotope perfusion lung scanning has high sensitivity for chronic thromboembolic PH.
- MRI:
  - MRI to assess cardiac structure and function, prognosis and response to treatment.
  - Magnetic resonance pulmonary angiography in the assessment of chronic thromboembolic PH operability.
  - Magnetic resonance perfusion imaging is as sensitive as isotope perfusion lung scanning.

- Right heart catheterisation is needed to confirm the diagnosis by directly measuring pulmonary pressure.

Management

Specific treatments exist for PAH and chronic thromboembolic PH. In PAH due to left heart disease, lung disease or hypoxia, treatment is best directed at the underlying condition.\cite{2} Patients are best managed through regional specialist units that have the expertise to manage their severe illness, relevant complex investigations, expensive medication and clinical trial administration.

- Management of any underlying cause.
- Although some drugs seem to have significant effects on symptoms and exercise tolerance in the short term, there is little useful information on their effect on long-term survival in this devastating illness, an issue that future trial designs will have to address.\cite{6}
Atrial septostomy is a palliative procedure that may provide some benefit to patients whose condition is deteriorating.

**Cardiosupportive therapy**
- Supplemental oxygen can help symptomatically with exercise tolerance. Diuretics are used to treat right heart failure and remove peripheral oedema, along with digoxin as a positive inotrope.
- There are no convincing trial data to support their use but consensus is that they are helpful.
- High-dose calcium-channel blockade (eg, diltiazem titrated to 480-720 mg/day or nifedipine titrated to 60-120 mg/day) may be used for idiopathic PAH. Because of the potential negative inotropic effect, treatment should not be started without a positive acute vasoreactive test.^[2^]

**Prostacyclin analogues**
- Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation. Various prostacyclin analogues may be used to treat the condition. Most need to be given by continuous intravenous infusion, usually through a long-term indwelling central venous catheter.
- A Cochrane review of intravenous prostacyclin analogues found evidence of short-term benefit (up to 12 weeks of treatment) in exercise capacity, NYHA functional class and cardiopulmonary haemodynamics. There was also some evidence that patients with more severe disease showed a greater response to treatment.^[7^]

**Endothelin-A receptor antagonists^[2^]**
- Endothelin is a potent vasoconstrictor of vascular smooth muscle. Bosentan and ambrisentan have been shown to improve exercise capacity and time to clinical worsening.
- Bosentan may cause reversible abnormalities in LFTs so regular monitoring of LFTs is needed.
Phosphodiesterase-5 inhibitors
- These drugs modulate the effects of nitric acid on vascular tone via their effect on cyclic GMP and appear to be relatively selective pulmonary arterial vasodilators.
- They are traditionally used to treat erectile dysfunction and sildenafil has been shown to have beneficial effects in primary PH, being licensed in the USA for its treatment. [8]

Drugs under clinical investigation [9]
Other drugs under current clinical investigation include serotonin antagonists, vasoactive intestinal peptide, stimulators of soluble guanylate cyclase and tyrosine kinase inhibitors.

Transplantation
Single/double-lung or cardiopulmonary transplantation may be considered in some severe cases. With pulmonary protection and immunosuppression, the long-term prognosis after lung and heart-lung transplant is good. [10]

Complications
- Deteriorating right heart function and right-sided cardiac failure.
- Gross peripheral oedema.
- Hepatic congestion and cardiac cirrhosis.
- Pleural effusions.
- Gross exertional dyspnoea.
- Exertional syncope.
- Sudden cardiac death.
- Problems during childbirth, including sudden death. [11, 12]

Prognosis [2]
- Median survival in untreated idiopathic PAH is 2.8 years; however, more recent registries have observed overall median survival of at least five years.
- In the past, the mean age at diagnosis in idiopathic PAH was 35 years; current five-year survival in this age group is now about 75%.
- PAH associated with systemic sclerosis carries a worse prognosis than idiopathic PAH. However, PAH associated with congenital heart disease has a better prognosis than idiopathic PAH.
- The development of PH in cardiac and respiratory disease adversely affects prognosis, which depends on the underlying cause and severity of PH.
- Patients who do not respond to medical therapy tend to develop progressive right-sided heart failure if transplantation cannot be carried out.

Further reading & references
- Pulmonary Hypertension Association UK
- PHA - Pulmonary Hypertension Association (international)

1. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension; European Society of Cardiology (Aug 2015)
3. Pulmonary Hypertension, Primary. 1, PPH1; Online Mendelian Inheritance in Man (OMIM)

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