Management of primary pulmonary hypertension

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Abstract

The onset of symptoms in primary pulmonary hypertension (PPH) is usually insidious with several years elapsing before the diagnosis is actually made. It is important that general physicians should be made aware of this fact and that they should have a high rate of suspicion of the subtle nature of the clinical presentation in this group of patients. Patients with a suspected diagnosis of PPH should be referred to specialised centres where early diagnosis and treatment can be initiated. We review the salient features of PPH and provide an insight into the various therapeutic options that are now available for this disease.

Key words: primary pulmonary hypertension, investigations, cardiac catheterisation, vasodilators, surgical treatment.

Clinical presentation

Patients usually present with dyspnoea. A common and troublesome complaint is syncope, which may occur on exertion but can also occur spontaneously. Patients with PPH have right ventricular ischaemia, and angina is not an infrequent symptom. They may also present with sudden death (in the majority of cases the cause is unknown).

Pulmonary hypertension is usually advanced by the time the patient presents and hence the physical examination findings tend to be rather striking. The patient may be centrally and peripherally cyanosed and may have signs of elevated pulmonary artery pressure and right ventricular failure. A pansystolic murmur of tricuspid regurgitation is commonly heard at the left sternal edge.

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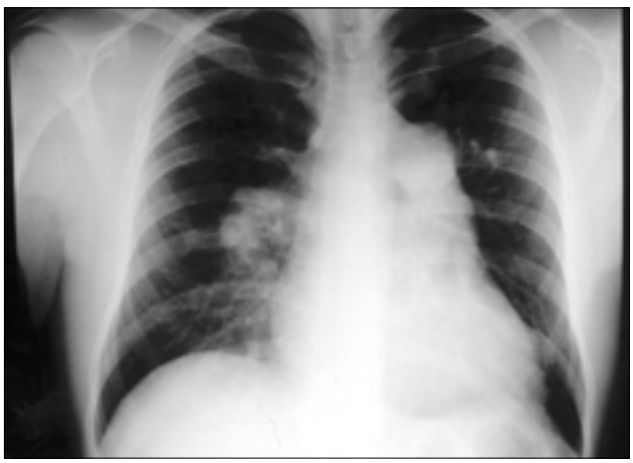
Figure 1. A chest X-ray of a patient with primary pulmonary hypertension. There is significant enlargement of the main pulmonary artery and of the hilar pulmonary vessels bilaterally. The peripheral parenchymal vascularity appears diminished



Screening for pulmonary hypertension

Screening appropriate patients with suspected pulmonary hypertension is important for the early diagnosis so that the initiation of treatment can be made when it is most likely to be successful.

Thorough history taking and clinical examination are required in order to elicit any relevant symptoms and physical signs. Initial investigations should include an electrocardiogram, chest radiograph (figure 1) and respiratory function tests. If PPH is suspected, a transthoracic echocardiogram with Doppler studies to measure tricuspid regurgitant velocity is the investigation of choice. If baseline investigations reveal any evidence of pulmonary hypertension, there should be no delay in referring such a patient to a specialised centre for further investigations and for the initiation of appropriate treatment regimes.

Cardiac catheterisation remains the gold standard for establishing the diagnosis of PPH. Pulmonary hypertension is defined as an increase in mean pulmonary artery pressure > 25 mmHg at rest or > 30 mmHg with exercise. At cardiac catheterisation, full haemodynamic measurements are carried out and acute vasodilator response is tested. Cardiac catheterisation carries a low but definite risk. No deaths, however, were reported in the NIH registry.[1]

Table 1. Investigations for the diagnosis and assessment of PPH

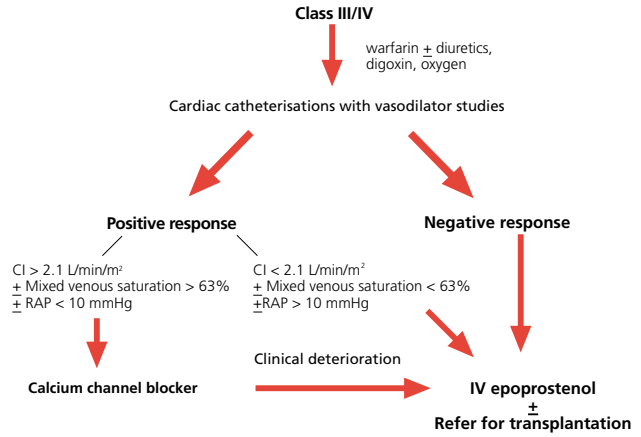
Electrocardiogram
Chest radiograph
Respiratory function tests
Echocardiogram
Ventilation perfusion scan
High resolution CT scan
Helical CT with pulmonary angiography
Six minute walk or incremental shuttle test
Nocturnal oxygen saturation

Cardiac catheterisation with vasodilator study

Blood tests
- **Haematology**
  - Full blood count
  - ESR
  - Clotting screen
  - Thrombophilia screen
    - Protein C
    - Protein S
    - Lupus anticoagulant
    - Antithrombin III
    - Leiden factor V
  - Abnormal haemoglobin
  - Blood group
- **Biochemistry**
  - Urea and electrolytes
  - Liver function tests
  - CRP
  - Serum ACE
  - Thyroid function
  - Arterial blood gases
- **Autoimmune screen**
  - Anti-nuclear factor
  - Anti-smooth muscle
  - Anti-centromere
  - Anti-SCL70
  - Anti-RNP
  - Anti-phospholipid
  - Anti-mitochondria
  - Anti-parietal
- **Microbiology**
  - Hepatitis B status
  - Hepatitis C status
  - VDRL/TPHA
  - HIV
- **Viral titres**
  - CMV, EBV
  - H simplex
  - Toxoplasma, Pneumocystis
  - Aspergillus screen

Other investigations include blood tests (table 1), ventilation perfusion scans, high resolution CT scans, pulmonary angiography and helical CT angiography for the diagnosis of thromboembolic lung disease. The six minute walk test[2] or incremental shuttle test[3] are used for assessing functional capacity.

Figure 2. Treatment of primary pulmonary hypertension



Key: CI = cardiac index, RAP = right atrial pressure; IV = intravenous

Medical treatment

Established therapies

Although the pathophysiology of PPH has not been fully defined, therapeutic options continue to develop for this group of patients. Vasodilator therapy is used in an attempt to reduce pulmonary artery pressure and thus right ventricular afterload. Vasodilator therapy, although beneficial, can be associated with an increased risk to the patient. Pulmonary haemodynamics should be measured if such drug therapy is used. Thus all patients with PPH should have an initial trial with short-acting vasodilator therapy (such as inhaled nitric oxide, nebulised prostacyclin or intravenous adenosine) during right heart catheterisation before chronic therapy is started. A positive response is defined as > 20% reduction in mean pulmonary artery pressure or pulmonary vascular resistance without a decrease in cardiac output.[4] Patients who respond to acute pharmacological testing and who have a cardiac index > 2.1 L/min/m^2, and/or mixed venous oxygen saturation > 63%, and/or right atrial pressure < 10 mmHg, should be commenced on calcium channel blockers (figure 2).[5] High-dose calcium channel blockers (nifedipine up to 240 mg/day and diltiazem up to 700 mg/day) for PPH have been shown to cause long-term reductions in pulmonary arterial pressure and regression of right ventricular hypertrophy.[6,7] Calcium channel blockers have a negative inotropic effect, however, and may have an adverse effect on an already impaired right ventricle. In such cases, amlodipine may be considered.

Various studies have shown that patients who are 'non-responders' and who have an adverse haemodynamic response to vasodilator testing, demonstrate improved exercise tolerance, haemodynamics and survival if treated with continuous intravenous epoprostenol.[8-11] The use of long-term (over one year) intravenous epoprostenol in patients with PPH has shown not only that the effect of this therapy may be associated with

vasodilation but that epoprostenol may have a role in reversing vascular remodelling and the raised pulmonary artery pressure in patients with pulmonary hypertension.[12]

Patients on long-term intravenous epoprostenol therapy tend to require an increase in dosage over time to prevent recurrence of symptoms. The long-term effects of intravenous epoprostenol have been so promising that some patients who have been administered epoprostenol as a bridge to transplantation have shown clinical improvement to such an extent that they are being treated long term with intravenous epoprostenol rather than being transplanted.[10,12]

It is, therefore, recommended that patients in New York Heart Association class III and IV with a cardiac index < 2.1 L/min/m^2 and/or mixed venous oxygen saturation < 63% and/or right atrial pressure >10 mmHg should be commenced on long-term intravenous epoprostenol regardless of whether they demonstrate any response to acute vasodilator administration during cardiac catheterisation.[5] Epoprostenol therapy should also be considered in patients who do not respond to conventional medical therapy or who continue to deteriorate despite its use (figure 2).

The major drawback of intravenous epoprostenol is with the drug delivery system, including pump failure and, in particular, catheter infection. Nebulised epoprostenol, which acts as a selective pulmonary vasodilator, has been shown to reduce the pulmonary vascular resistance in patients with adult respiratory distress syndrome and with pulmonary hypertension with little effect on systemic arterial pressure.[13,14] Currently, delivery systems for the use of nebulised epoprostenol are being developed and they could have an important impact on the treatment of the disease.

Inhaled nitric oxide is a selective pulmonary vasodilator which is normally used in the hospital setting for the acute reduction of pulmonary artery pressure in patients with PPH. Its administration, however, requires close observation as it is spontaneously oxidised to form the toxic by-product nitrite and, to a lesser extent, nitrate.[15]

Anticoagulation has been used in the treatment of PPH because there is a predisposition to thrombosis (due to right ventricular failure, oedema and inactivity) in this condition. Furthermore, thrombotic lesions are commonly demonstrated in small pulmonary arteries in a large number of patients with PPH.[16] Various studies have also shown the presence of a hypercoagulable state in some patients with pulmonary hypertension.[17-19] In keeping with this, the use of warfarin has been shown to prolong survival in patients with PPH.[20]

Patients with PPH are hypoxaemic because of the presence of ventilation perfusion mismatches in the lung and patients often have a fall in arterial oxygen saturation at night. The use of oxygen therapy helps in reducing the hypoxaemia and improving symptoms but its long-term use has little effect on the natural history of the disease. This is also the case with diuretic therapy, which is mainly used for the treatment of the right-sided cardiac failure. Digoxin has also been shown to improve right ventricular function and cardiac output in patients with PPH.[21] Its long-term effects, however, are unknown.

Evolving therapies

Therapeutic options for PPH continue to evolve and a number of research studies are being conducted on newer therapies for this disease.

Iloprost is a stable analogue of prostacyclin with a longer half-life.[22] Iloprost appears to be more potent than epoprostenol: only half the dose is required to produce the same effects. The number of patients studied with iloprost is small, however, and its use for PPH has not yet been licensed in the UK. Using inhaled iloprost, Hoeper *et al.* showed that, over a one-year period, patients with PPH had improved exercise capacity and pulmonary haemodynamics.[23] It has also been shown to be beneficial in severely ill patients.[24] Randomised trial data are still awaited.

A study investigating the effects of subcutaneous administration of a heat-stable form of prostacyclin (treprostinil) has recently been completed. This demonstrated that patients with PPH who received treprostinil over a 12-week period had improved exercise capacity and improved pulmonary haemodynamics.[25] There are problems, however, with injection site pain which may limit its use.

Beraprost (Toray Industries Inc, Tokyo, Japan) is an oral prostacyclin analogue which has been shown to have a vasodilator and antiplatelet activity similar to that of prostacyclin,[26] and which is effective by oral administration.[27]

Bosentan is an oral endothelin-1 antagonist which has also been shown to be of benefit in PPH. Recent trials have shown improvements in pulmonary haemodynamics, exercise capacity and functional class in patients with PPH who were given bosentan.[28,29]

More recently, sildenafil, an inhibitor of cGMP-specific phosphodiesterase (PDE5), has been shown to improve exercise capacity and pulmonary haemodynamics in a patient with PPH.[30] Zaprinast (an inhibitor of guanosine-3, 5-cyclic monophosphate-specific phosphodiesterase), when given both as an injection[31] and in an inhaled form,[32] can also lead to pulmonary vasodilation.

Surgical treatment

Atrial septostomy has been shown to be of benefit in patients with recurrent syncope.[33] By creating a right to left shunt at the atrial level, it is possible to decompress the right ventricle and to improve left ventricular filling pressure, thus maintaining cardiac output. However, there is a risk of severe oxygen desaturation with this procedure. Adults who have received atrial septostomy have shown a one-year and two-year survival of 87% and 76%, respectively.[33]

Patients with chronic thromboembolic pulmonary hypertension have an overall poor prognosis. Surgical removal of the organised thrombotic material can be carried out using thromboendarterectomy. Operative mortality is usually less than 10%.[34] Good long-term results are observed, with a fall in pulmonary vascular resistance and improvement in right ventricular function.[34-36]

In some pulmonary hypertensive patients, there is a progressive deterioration despite medical therapy. In such patients,

Key messages

- Patients with suspected PPH should be referred to a specialised centre where diagnosis and treatment can be initiated
- Cardiac catheterisation with acute vasodilator testing is performed in order to establish the diagnosis
- Responders with a cardiac index of >2.1 L/min/m^2 should be commenced on calcium channel blockers
- Non-responders or those who do not improve on conventional medical therapy should be commenced on a prostacyclin analogue
- Patients who deteriorate despite medical therapy should be considered for lung transplantation

transplantation remains the only option. With the continuing improvement in surgical technique and the rapid advances in immunosuppressive therapy, the survival for heart and lung transplantation in this group of patients has reached approximately 65%–70% at one year. Obliterative bronchiolitis remains the major complication of long-term survival in lung transplant recipients.

Natural history and prognosis

PPH is a relentlessly progressive disease that ultimately leads to right ventricular failure and death. The mean survival from the time of diagnosis is two to three years.[37]

The clinical course of the disease, however, is extremely variable. Some patients may present early and can then progress to death over a period of six months, while others who present at the same stage of the disease may survive for a period of six years. There have even been reports of spontaneous regression of the disease.[38] This emphasises the point that patients who are suspected of having PPH should, without delay, be referred to specialised centres for investigation and treatment.

Conclusions and future directions

Patients with PPH constitute a small but consistently neglected group who require a highly specialised and integrated system of investigation and treatment. The diagnosis of PPH is usually made at the end stages of the disease, when many irreversible changes exist. The prognosis has been thought to be so poor that thorough investigation has in the past been denied to all but a minority of patients. A rational approach to combating and treating this condition depends on early diagnosis and on defining its exact aetiology and pathophysiology. During the last few years, there has been considerable progress in all these areas. These have been outlined in this review. It is hoped that this will help to stimulate further research and to optimise the treatment of patients with this condition.

Editors' note

Part one of this article on 'The pathophysiology of primary pulmonary hypertension' was published in last month's issue (*Br J Cardiol* 2002;**9**:265–72).

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