

## What is Pulmonary Hypertension?

### Introduction

PH is defined as a mean pulmonary artery pressure (mPAP), measured at right heart catheterisation, of  $\geq 25$  mmHg. Although there are many causes of PH (Fig 1) there are currently recognised therapies for group 1 (pulmonary arterial hypertension) and group 4 (chronic thromboembolic pulmonary hypertension) and generally only patients with these forms of PH will be treated and followed in the PVDU.

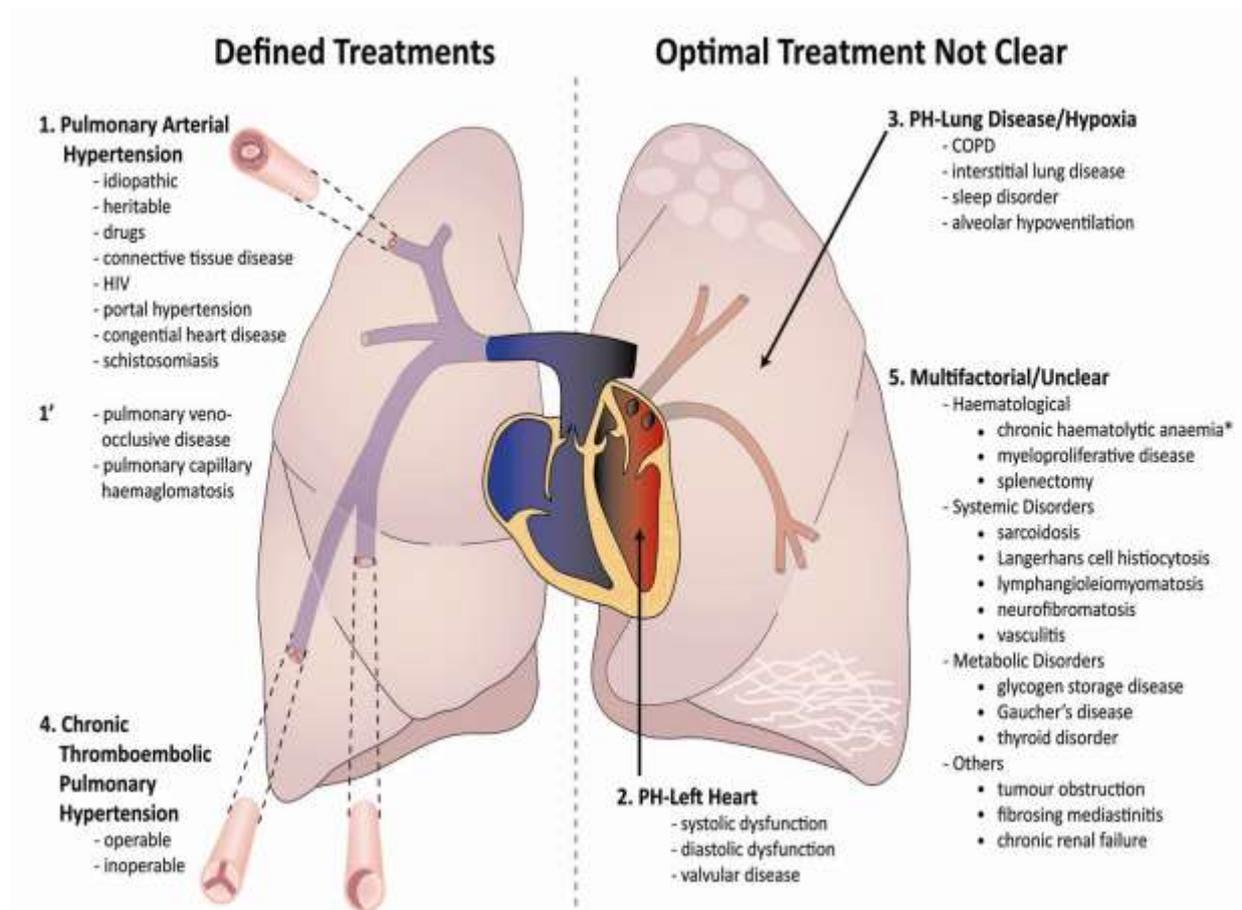


Fig 1: PH Classification

**Group 1: Pulmonary arterial hypertension (PAH)**

Idiopathic PAH is a rare condition with an incidence of  $\approx 2$ /million/yr. PAH is more common in several associated medical conditions including systemic sclerosis ( $\approx 10\%$ ), cirrhosis ( $\approx 2-6\%$ ), HIV ( $\approx 0.5\%$ ) and congenital heart disease (5-10%).

**Group 4: Chronic Thromboembolic Pulmonary Hypertension (CTEPH)**

CTEPH occurs following acute Pulmonary Embolism in  $\approx 2\%$  of cases and can also occur in patients with previous splenectomy and myeloproliferative disease. Two-thirds of patients are candidates for potentially curable surgery (pulmonary endarterectomy, currently only performed in the UK at Papworth Hospital) while the remaining patients with inoperable disease are often treated with medications used for the treatment of PAH.

**Group 2: Pulmonary Hypertension associated with Left Heart Disease (PH-LHD)**

PH is not uncommon in the context of significant left heart disease. PH-LHD associated with diastolic dysfunction is commonly misdiagnosed as IPAH. Clues towards a diagnosis of PH-LHD in this circumstance include a history of systemic hypertension, atrial fibrillation, diabetes and ischaemic heart disease, a dilated left atrium, LVH and  $E/e' > 15$ . There is currently no proven role of PAH-specific therapy in PH-LHD.

**Group 3: Pulmonary Hypertension associated with Lung Disease (PH-Lung)**

Again, PH is not uncommon in the context of underlying lung disease and is generally mild-moderate. Patients with severe (or "out-of proportion") PH in association with lung disease are not infrequently referred. Currently there is no proven role for PAH-specific therapy in this group of patients. Chronic thromboembolic should be excluded in patients in group 2 and group 3 who have severe pulmonary hypertension and significant RV dilatation and dysfunction.

## Signs and Symptoms

Symptoms in PAH and CTEPH originate from narrowing of the pulmonary arterial bed resulting in an increased preload to the right ventricle. Exertional dyspnoea is the earliest symptom but as the right ventricle begins to fail patients develop peripheral oedema and eventually exertional presyncope or syncope. Patients may have a loud P2, a systolic murmur of tricuspid regurgitation and a right ventricular heave in the presence of significant right ventricular pressure loading.

## Therapies

- 5% of patients with idiopathic PAH respond to long-term therapy with high dose calcium channel blockade (typically long-acting diltiazem up to 480-720 mg/day). In the majority of PH patients high-dose calcium channel blockade is likely to be harmful due to negative inotropic and chronotropic effects and so this therapy is reserved for a minority of idiopathic PAH patients who respond to inhaled nitric oxide at diagnostic right heart catheterisation.
- PH-specific therapies are used in the majority of PAH patients. There are 3 groups of therapies in current use (Table 1):
  - Phosphodiesterase-5 Inhibitors (PDE5-I, oral)
  - Endothelin Receptor Antagonists (ERA, oral)
  - Prostacyclin analogues - nebulised or intravenous. A sub-cutaneous formulation of treprostinil is only rarely commenced now due to funding issues.

**Table 1: Currently Used PH-Specific Therapy in Sheffield PVDU**

| <b>Drug</b>                   | <b>Usual Dose</b>  | <b>Administration</b> | <b>Important or Common Side Effects</b>  | <b>Important Complications</b>                   |
|-------------------------------|--|-----------------------|--|--|
| <b>Prostanoid</b><br>Iloprost | 400-1000 mcg made up to 19 ml Normal Saline infused at 2mm/hr via Graseby Pump | iv                    | Nausea, headache, leg pain, jaw pain, flushing, diarrhoea                      | Line infection                                   |
| Iloprost                      | 5 mcg 6-7/day  | neb (i-neb)           | As per iv but less severe  |  |
| <b>ERA</b><br>Bosentan        | 62.5-125mg bd  | oral                  |  | 5-10% abnormal LFT<br>Teratogenicity             |
| Ambrisentan                   | 5-10mg bd  | oral                  | Peripheral oedema  |  |
| <b>PDE5-I</b><br>Sildenafil   | 25-100mg tds   | oral                  | Headache, indigestion, nasal stuffiness, Blurred vision, visual colour change. | Non-arteritic ischaemic optic neuropathy (NAION) |
| Tadalafil                     | 20-40mg od   | oral                  | As per sildenafil  | As per sildenafil                                |

## Treatment Approach

Patients in World Health Organisation (WHO) functional classes II or III are generally commenced on PDE5-I as first line unless there is a significant contraindication (e.g. current nitrate use). A second oral agent (i.e. Endothelin Receptor Antagonist) may be subsequently added if suboptimal response. Patients presenting in WHO functional class IV or those not responding to oral therapy may commence iloprost (nebulised or continuous intravenous).

### Box 2 WHO functional classes

Class I: Patients with pulmonary hypertension but in whom ordinary physical activity does not cause undue symptoms

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest but ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope

Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest but less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope

Class IV: Patients with pulmonary hypertension who cannot carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea or fatigue may be present at rest. Discomfort is increased by any physical activity

## Practical Issues of PH Therapy

- All PH-Specific therapy (excluding calcium channel blockade) is prescribed from Sheffield and delivered monthly via Healthcare at Home.
- Patients treated with ERAs (Bosentan or Ambrisentan) require monthly LFTs and 3-monthly FBCs. Blood tubes, lab request forms and a pre-paid box are delivered via the homecare delivery service with their medication. We would be grateful if blood samples could be taken monthly and sent back to us in the pre-paid box.

## Other Therapies

- Warfarin (target INR 2-3) likely improves survival in idiopathic PAH and anticoagulation is mandatory in CTEPH. Its benefit in other forms of PAH is less clear although will often be used in systemic sclerosis-associated PAH. If there is a clear contraindication then anticoagulation may be stopped in PAH.
- Diuretics are often required to treat peripheral oedema secondary to right heart failure (see below)
- Contraception is mandatory as PH is associated with 20-30% maternal mortality. Due to its prothrombotic effect, oestrogen containing contraception is not recommended.
  - Cerazette 1 tab od (if Bosentan is used then 2 tab od due to increased metabolism of progestogen)
  - Nexplanon (if Bosentan is used then additional cerazette required, as above)
  - Depo-Provera (no clinically relevant interaction with Bosentan)
  - Mirena-Coil (needs to be inserted in a hospital setting due to the risk of syncope)

- Oxygen is only required if significant hypoxaemia is present. Indications for long term oxygen therapy (LTOT) are the same as for COPD while the majority of patients with Eisenmenger's syndrome do not require LTOT.
- There is no current indication for ACE-I and beta-blockers and indeed the negative chronotropic and inotropic effects of beta-blockers may lead to clinical worsening.
- Referral for transplantation (most commonly double-lung) may be considered in appropriate patients with severe progressive disease.

### **Prognosis**

PH is often associated with poor survival, similar to many cancers. Historically, median survival in idiopathic PAH was 2.8 years but this has improved with 5 year survival in patients <50yrs of ≈75%. Survival in more elderly patients and in patients with systemic sclerosis associated PAH continues to be poorer with median survival of 3-4 years. Survival in patients who respond to high-dose calcium channel blockade is significantly superior. Survival in other forms of PAH including Eisenmenger's syndrome and HIV-associated PAH also appears to be superior to IPAH. CTEPH is potentially curable via pulmonary endarterectomy.

### **Contacting Medical Staff**

A member of medical staff is always available to discuss patients; ring the Royal Hallamshire Hospital switchboard (0114 271 1900) and ask for:

- PH SPR on bleep 2387 (9am-5pm)
- On-Call PH Consultant (5pm-9am)

Or contact secretaries for Drs Condliffe, Elliot & Kiely on (0114) 271 2132 or 271 2187

- For pharmacy issues (0114) 271 3259
- Clinical Nurse Specialists 07920 150 099

### **Referrals**

Patients in whom PAH or CTEPH is suspected on the basis of history and echocardiography should be referred promptly for further assessment. We would suggest excluding thromboembolic disease but would not generally recommend extensive investigations locally as this can delay diagnosis and treatment. We are happy to review patients with pulmonary hypertension where there is diagnostic doubt regarding the form of PH. We may in some circumstances initially review imaging before deciding whether or not to review the patient physically.