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Detecting and managing pulmonary hypertension

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SPECIAL REPORT

Detecting and managing pulmonary hypertension

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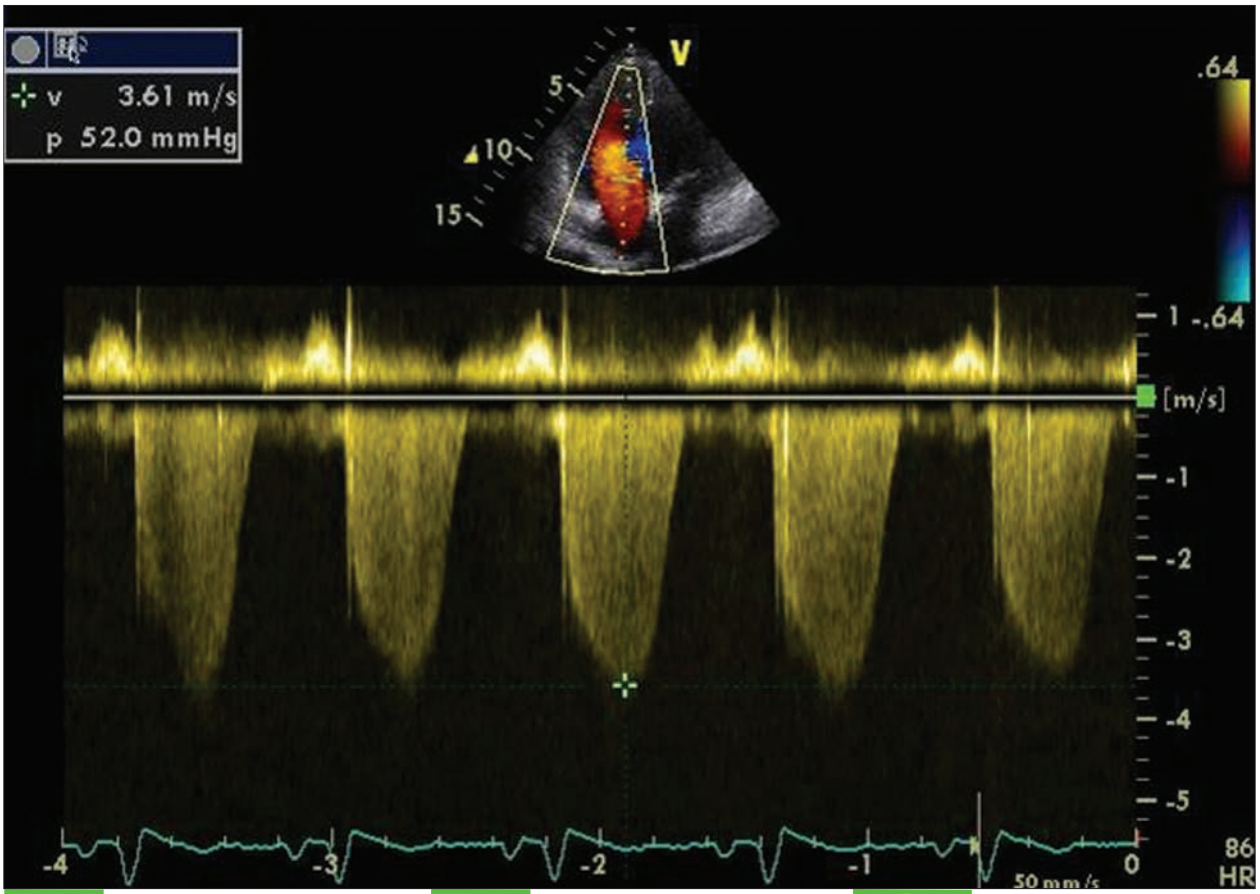


FIGURE 1
Doppler echocardiogram recording of peak tricuspid regurgitation velocity measured in a four chamber view

How is pulmonary hypertension classified?

PULMONARY HYPERTENSION (PH) IS A HAEMODYNAMIC STATE WHERE THE MEAN PULMONARY ARTERY pressure measured at cardiac catheterisation is ≥ 25 mmHg.[1]

Precapillary PH arises from increased resistance to blood flow in the pulmonary arterioles and postcapillary PH from elevated left atrial pressure. In postcapillary PH the cause is left heart disease whereas precapillary PH may be caused by any other form of PH.

The causes of PH are wide ranging (see table 1, p22). Once identified the cause will guide treatment. Left heart disease and parenchymal lung disease are the main causes of PH worldwide. The prevalence of PH is approximately 1 in 10 in those aged 65 and over.[2] In patients with heart and lung disease the presence of PH shortens life expectancy.

Rare forms of PH, including pulmonary arterial hypertension (PAH), chronic thromboembolic pulmonary hypertension (CTEPH), and miscellaneous causes are important to identify because they may be rapidly lethal if unrecognised and untreated. Treatments for PAH slow disease progression but are not curative.

The median survival of patients with different forms of PH referred to PH centres in the UK is shown in table 2, p22.[3]

How should diagnosis be confirmed?

PRESENTATION

Patients develop symptoms only when the disease is advanced. The symptoms of PH at clinical presentation are non specific. Adults almost universally present with breathlessness in addition to which they may also complain of exercise-induced dizziness or syncope (an ominous sign) and angina pectoris. When heart failure supervenes, patients may complain of abdominal distension and dependent oedema.

Rarely exercise-induced nausea and even vomiting are induced via the Bezold-Jarisch reflex.

Clinical examination usually reveals an abnormal right ventricular pulsation »

What are the management options?

Table 1

Clinical classification of pulmonary hypertension[5]

Group 1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH including aminorex, cocaine, fenfluramine, dexfenfluramine, benfluorex, methamphetamines, dasatinib, and toxic rapeseed oil; some possible toxins include cocaine and St John's wort (for a full list see original reference)
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis) involvement
1.7 Persistent pulmonary hypertension of the newborn syndrome

Group 2. Pulmonary hypertension due to left heart disease
2.1 Heart failure with preserved left ventricular ejection fraction (LVEF)
2.2 Heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to postcapillary PH

Group 3. PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders

Group 4. PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension (CTEPH)
4.2 Other pulmonary artery obstructions including tumours, arteritis without connective tissue disease, congenital pulmonary artery stenosis, and parasites

Group 5. PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders including chronic haemolytic anaemia, and myeloproliferative disorders
5.2 Systemic and metabolic disorders including pulmonary Langerhan's cell histiocytosis, Gaucher's disease, glycogen storage disease, neurofibromatosis, and sarcoidosis
5.3 Others including chronic renal failure with or without haemodialysis, and fibrosing mediastinitis
5.4 Complex congenital heart disease

Table 2

Current real world survival of pulmonary hypertension patients referred to designated pulmonary hypertension centres in the UK[3]

Cause of pulmonary hypertension	Median age at diagnosis (years)	Median survival from diagnosis (years)
Idiopathic, heritable and drug-induced pulmonary arterial hypertension	60	5.8
Congenital heart disease	45	> 8*
Connective tissue disease associated pulmonary arterial hypertension with scleroderma	67	3.5
Connective tissue disease associated pulmonary arterial hypertension without scleroderma	61	4.1
Operated chronic thromboembolic pulmonary hypertension	61	> 9*
Unoperated chronic thromboembolic pulmonary hypertension	69	5.7
Pulmonary hypertension due to left heart disease	74	4.5
Pulmonary hypertension due to lung disease and/or hypoxia	68	1.8

*50% mortality of the cohort has not been reached in 2019

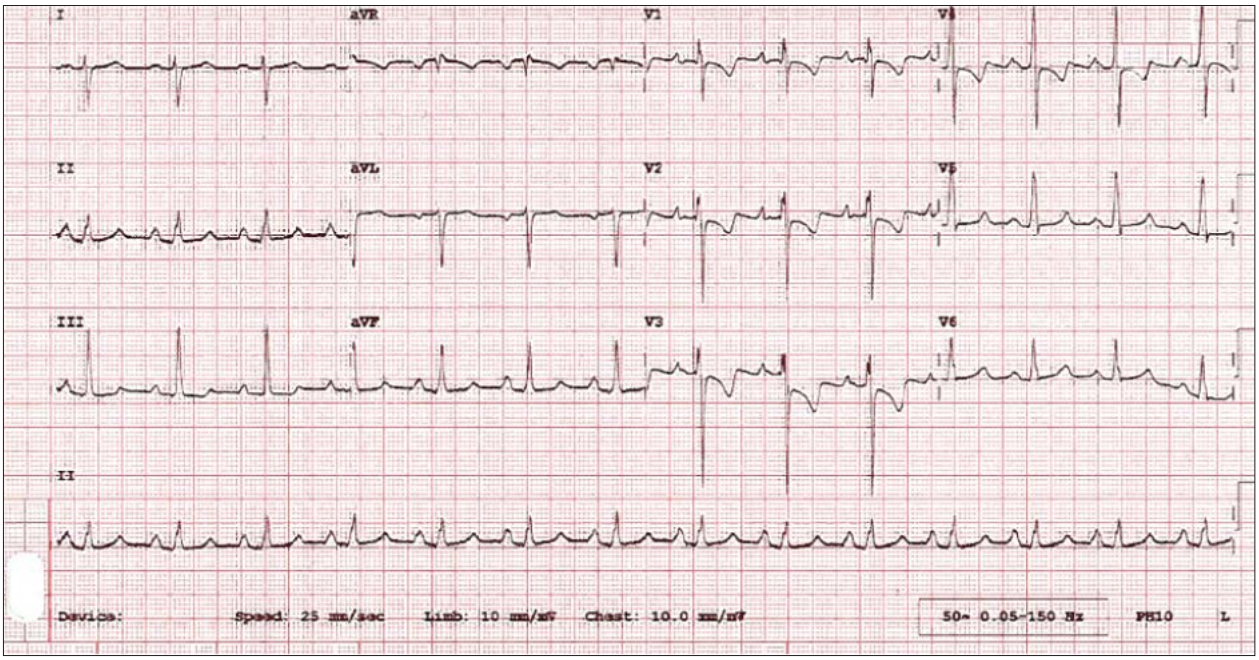


FIGURE 2
Typical ECG in a patient with severe pulmonary hypertension showing right axis deviation with right ventricular hypertrophy

on palpation of the precordium and a loud pulmonary second sound, but these findings are easily missed.

Jugular venous pressure may be elevated but may not necessarily be obvious without mild exertion to stress an abnormal right ventricle.

Adventitial lung sounds suggest pulmonary disease. Some patients may have reduced oxygen saturation, cyanosis and exhibit finger clubbing. Facial or hand telangiectasia, and/or Raynaud's may suggest scleroderma.

Deep vein thrombosis should be sought. Signs of fluid retention may be present including hepatic enlargement, ascites and lower extremity oedema.

The differential diagnosis of breathlessness is wide. A stepwise history of sudden worsening may suggest recurrent pulmonary embolism. Orthopnoea and paroxysmal nocturnal dyspnoea are unusual in PAH and CTEPH. Risk factors for PAH, left heart disease, parenchymal lung disease and/or hypoxia, and CTEPH may provide a clue to the diagnosis. Overall, 75% of CTEPH cases have a history of pulmonary embolism.[4] PAH may be suggested by any of its associated diseases (see table 1, p22).[5]

DIAGNOSIS

An echocardiogram is the best investigation to ascertain the probability of PH.[1] This is estimated from the peak velocity of the tricuspid regurgitation (TRV) jet using continuous wave Doppler (see figure 1, p21) and integrated with other echo signs of PH. Based on the probability of PH, appropriate referral can be made for further investigation.

Echo may also identify a cardiac cause for PH. Note that the echocardiographic estimation of systolic pulmonary artery pressure based on TRV correlates but does not translate directly into an invasive measurement of mean pulmonary artery pressure, at least in part because echo may underestimate or overestimate pressure in half of patients.[6]

Additional echocardiographic signs of PH include right ventricular enlargement, right atrial enlargement and an enlarged pulmonary artery.

An ECG and chest radiograph will be normal in about 10% of patients at presentation.[7] When abnormal, the ECG may show right axis deviation (see figure 2, above), right bundle branch block, right atrial enlargement and right ventricular hypertrophy.

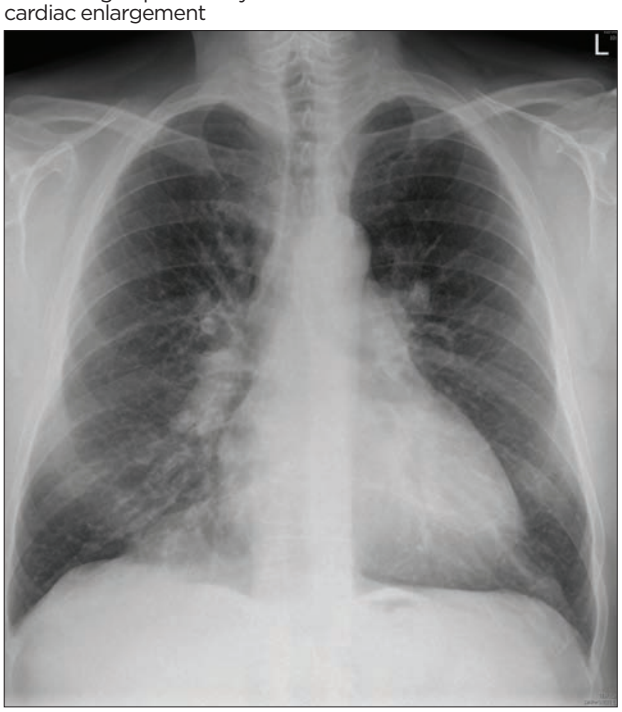
The chest radiograph may show pulmonary artery and cardiac enlargement (see figure 3, right). Pleural effusions may suggest left heart failure or a pulmonary cause. Pulmonary oedema usually indicates that left heart disease is causing PH although this can also be documented in pulmonary veno-occlusive disease, a rare type of PAH.

Pulmonary function tests are important to look for airways disease and parenchymal lung disease. Blood tests including a full blood count, renal, liver, thyroid function, autoantibodies and HIV may reveal a cause for PH and its differential diagnosis.

Further detailed imaging and invasive haemodynamic investigations in hospital are mandatory to confirm the diagnosis.

Many PH patients describe being treated with an asthma inhaler in the first instance. In any patient it is critical to investigate unexplained or worsening breathlessness.

FIGURE 3
Typical chest radiograph in a patient with pulmonary arterial hypertension with enlarged pulmonary arteries and cardiac enlargement



ASSESSMENT

Patients who are suspected of having PH and who have already had an echo showing an intermediate or high probability of PH should be referred directly to the UK National Pulmonary Hypertension Service at one of seven designated adult centres: Hammersmith Hospital, London, Royal Brompton Hospital, London, Royal Free Hospital, London, Royal Papworth Hospital, Cambridge, Royal Hallamshire Hospital, Sheffield, Freeman Hospital, Newcastle upon Tyne, Golden Jubilee Hospital, Glasgow.

Patients who have not had an echocardiogram should be referred to cardiology or respiratory medicine.

Recent evidence in the UK demonstrates significant delays in patients with PH reaching a designated centre while their disease is progressing.[8] These delays occur at patient, general practice and secondary care levels. No studies have shown improvement in delayed diagnosis internationally over the past two decades.

POTENTIAL COMPLICATIONS

Atrial arrhythmias reduce cardiac output with loss of atrial contraction and are poorly tolerated in patients with severe PH. Atrial flutter is the most common of these arrhythmias in PAH and requires prompt cardioversion to sinus rhythm.

Haemoptysis may occur as a result of rupture of small bronchial collateral vessels and may also occur with pneumonia. Haemoptysis typically occurs with a hypertrophied bronchial circulation, in particular in CTEPH.

Infections to which some PH patients may be prone may precipitate worsening PH by stressing the cardiovascular system in the face of low cardiac output.

Dissection or rupture of aneurysmal pulmonary arteries and/or compression of the left main stem causing angina occurs rarely.

MANAGEMENT

Pulmonary arterial hypertension

For patients with idiopathic, heritable or drug-induced PAH, a vasoreactivity study carried out at cardiac catheterisation determines their suitability for high-dose calcium channel blocker treatment.[1]

For patients with a negative vasoreactivity study or another cause of PAH, specialist PH drug therapies have been developed with the first randomised clinical trial reported in 1996. There are now 11 licensed vasodilator drugs and these interact with three biochemical pathways affecting the nitric oxide system, endothelin receptors and prostacyclin receptors.

The choice of therapy depends on a risk assessment based on a full assessment of clinical, exercise, imaging and haemodynamic data[1] or a limited assessment based on breathlessness severity, brain natriuretic peptide, six-minute walk distance ± invasive haemodynamics.[9]

For most patients, initial dual combination therapy is recommended. For those at high risk this includes intravenous epoprostenol by continuous infusion given indefinitely by microinfusion pump in addition to an oral therapy, and for low- and intermediate-risk patients this includes two oral drug therapies.

Failure to achieve low-risk status indicates the need for a third drug and if triple therapy is inadequate then bilateral sequential lung transplantation should be considered in eligible patients. A small number of patients who present severely ill may require mechanical circulatory support as a bridge to transplantation.

General treatment measures in these patients include avoiding pregnancy which carries a high maternal mortality, vaccination against influenza and pneumococcal pneumonia, diuretic management of fluid retention, and psychological and social support.[1]

Patients should exercise at a level that is moderate enough for them to be able to carry on a normal conversation while exercising. Lifting heavy weights may cause syncope. Iron deficiency is common in PAH patients and the correction of anaemia and iron replacement may be considered while trial data is awaited.[1]

With the exception of CTEPH patients, where lifelong anticoagulation is essential, the evidence of benefit for anticoagulation in other PH patients has been contradictory so far.

Continuous long-term oxygen therapy is recommended in PAH patients when arterial blood oxygen pressure is consistently < 8 kPa (60 mmHg). Patients with PH and no lung parenchymal disease are not infrequently normoxaemic at rest, but they can desaturate significantly on exertion.

Supplemental oxygen for air travel should be considered for patients in WHO functional class III and IV and also if PaO_2 is consistently < 8 kPa. PAH patients should avoid spending time at high altitude.

Note that general anaesthesia is high risk and for elective procedures should be carried out in close liaison with a PH expert centre or at the PH centre itself. Regional anaesthesia is preferred if possible but is also not without risk.

Left heart disease

The aim of treatment is to lower left atrial pressure by managing the underlying left heart disease effectively. Specialist PH drug therapies as used in PAH are contraindicated as they either have no beneficial effect or increase morbidity and mortality.[1]

Lung disease ± hypoxia

The aim of treatment is to manage the underlying diffuse parenchymal lung disease. Specialist PH drug therapies as used in PAH are contraindicated as they either have no beneficial effect or increase morbidity and mortality.[1] Obstructive sleep apnoea syndrome should be considered as a potential cause of PH particularly in obese patients with suspicious symptoms, as treatment with non-invasive ventilation can significantly reduce pulmonary pressure.

Chronic thromboembolic pulmonary hypertension

The mainstay of treatment for CTEPH is lifelong anticoagulation.[1] On completion of the investigations for CTEPH at a designated PH centre, the patient data and imaging should be reviewed by a CTEPH multidisciplinary team (MDT) comprising a pulmonary endarterectomy surgeon, specialist radiologist and pulmonary hypertension physician.

In the UK, this is conducted at Royal Papworth Hospital. An MDT decision is made about suitability for pulmonary endarterectomy based on the surgical accessibility of the vascular disease. This is the treatment of choice when patients are technically operable. The next step for these patients is to meet the surgeon and discuss their individual surgical risk and then proceed to surgery.

Patients who are not operable (surgically inaccessible disease) are managed with specialist PH drug therapies of which two have demonstrated efficacy in clinical trials: riociguat, a soluble guanylate cyclase stimulator, and macitentan, an oral endothelin antagonist.

Another option in selected patients with inoperable CTEPH or persistent PH post pulmonary endarterectomy is balloon pulmonary angioplasty. This normally requires multiple angioplasty procedures.

key points

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Pulmonary hypertension (PH) is a haemodynamic state where the mean pulmonary artery pressure measured at cardiac catheterisation is ≥ 25 mmHg. Precapillary PH arises from increased resistance to blood flow in the pulmonary arterioles and postcapillary PH from elevated left atrial pressure. In postcapillary PH the cause is left heart disease whereas precapillary PH may be caused by any other form of PH. Patients develop symptoms only when the disease is advanced. The symptoms at clinical presentation are non specific. Adults almost universally present with breathlessness and they may also complain of exercise-induced dizziness or syncope (an ominous sign) and angina pectoris.

An echocardiogram is the best investigation to ascertain the probability of PH. This is estimated from the peak velocity of the tricuspid regurgitation jet using continuous wave Doppler and integrated with other echo signs of PH. Based on the probability of PH, appropriate referral can be made for further investigation. Echo may also identify a cardiac cause for PH.

An ECG and chest radiograph will be normal in 10% of patients at presentation. When abnormal, the ECG may show right axis deviation, right bundle branch block, right atrial enlargement and right ventricular hypertrophy. The chest radiograph may show pulmonary artery and cardiac enlargement. Pulmonary function tests are important to look for airways disease and parenchymal lung disease. Blood tests including a full blood count, renal, liver, thyroid function, autoantibodies and HIV may reveal a cause for PH and its differential diagnosis. Further imaging and invasive haemodynamic investigations in hospital are mandatory to confirm diagnosis.

Patients who are suspected of having PH and who have already had an echo showing an intermediate or high probability of PH should be referred directly to the UK National Pulmonary Hypertension Service at one of seven designated adult centres. Patients who have not had an echo should be referred to cardiology or respiratory medicine.

For patients with idiopathic, heritable or drug-induced PAH, a vasoreactivity study carried out at cardiac catheterisation determines their suitability for high-dose calcium channel blocker treatment. For patients with a negative vasoreactivity study or another cause of PAH, specialist PH drug therapies have been developed. There are now 11 licensed vasodilator drugs. For most patients, initial dual combination therapy is recommended. Failure to achieve low-risk status indicates the need for a third drug. If triple therapy is inadequate then bilateral sequential lung transplantation should be considered in eligible patients. General measures include avoiding pregnancy which carries a high maternal mortality, vaccination against influenza and pneumococcal pneumonia, diuretic management of fluid retention, and psychological and social support.

Miscellaneous causes

The management of PH in this group of conditions has limited evidence and should be on a case by case basis directed by a PH expert centre.

REHABILITATION

In patients who are clinically stable on treatment, monitored exercise rehabilitation has been shown to be effective at improving symptoms, exercise capacity, haemodynamics and quality of life.[10] This requires specialist supervision given the risk of adverse events including syncope.

MONITORING AND FOLLOW-UP

Patients with PAH, CTEPH and miscellaneous causes of PH should be followed up regularly at their PH expert centre. Follow-up includes regular investigations to assess risk and adjust drug therapies. Patients with CTEPH who have normal or near normal haemodynamics post pulmonary endarterectomy will normally only require annual follow-up for five years since the risk of recurrence after this time is low.

Specialist follow-up also creates the opportunity for patients to enter clinical trials in an effort to find new treatments.

Patients with PH caused by left heart disease and lung disease are normally followed up by their cardiologist or pulmonologist.

Competing interests

Dr J Simon Gibbs has received honoraria for consultancy and/or speakers' bureau from Acceleron, Actelion, Arena, Bayer, Bellophoron, Complexa, MSD, and Pfizer. Dr Athanasios Charalampopoulos has received honoraria and financial support to attend medical conferences from Actelion, GSK and Novartis

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Useful information

PHA UK
www.phauk.org/

National Audit of Pulmonary Hypertension
digital.nhs.uk/data-and-information/clinical-audits-and-registries/national-pulmonary-hypertension-audit

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