Key points

- ▶ PAH is defined by RHC showing a pre-capillary PH.
- ▶ Clinical suspicion of PH should arise in the case of symptoms such as dyspnoea without overt signs of specific heart or lung disease.
- ▶ RHC is required to confirm the diagnosis of PAH, to assess the severity of the haemodynamic impairment and to test the vasoreactivity of the pulmonary circulation.
- ▶ Variables that have been shown to predict prognosis in IPAH include baseline NYHA functional classification, history of right heart failure, baseline 6-minute walk distance, and baseline haemodynamics.
- ▶ FPAH segregates as an autosomal dominant trait, but with markedly reduced penetrance. Germline *BMPR2* mutations have been detected in at least 60% of the families studied to date, as well as in cases of so-called IPAH.
- ▶ Basic PAH therapy includes oxygen, diuretics and warfarin.
- ▶ Chronic treatment with oral CCBs should be considered for PAH patients who respond to acute vasodilator challenge.
- ▶ Cohort analysis of IPAH patients receiving continuous intravenous epoprostenol, as compared to historical control groups, clearly demonstrated clinical benefits in NYHA functional class III and IV patients.
- ▶ Two double-blind, randomised, placebo-controlled trials have supported the efficacy of oral bosentan in patients with PAH class III.
- ▶ One double-blind, randomised placebo-controlled trial has supported the efficacy of oral sildenafil in patients with symptomatic PAH.
- ▶ Lung transplantation is the ultimate alternative for severe PAH cases who cannot be managed medically.

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Pulmonary arterial hypertension

Educational aims

- ▶ To improve awareness of PAH.
- ▶ To describe the novel classification of PH.
- ▶ To provide information regarding the therapeutic approach of PAH.

Summary

Pulmonary arterial hypertension (PAH) is a rare condition characterised by elevated pulmonary arterial resistance, leading to right heart failure. PAH can be sporadic (idiopathic PAH), familial or related to other conditions. Echocardiography is the investigation of choice for non-invasive screening. Measurement of haemodynamic parameters during right heart catheterisation (RHC) is mandatory to establish the diagnosis. Recent advances in the management of PAH include prostaglandins, endothelin receptor antagonists and PDE5 inhibitors. Lung transplantation is the last option for patients who deteriorate despite medical treatment. This review aims to update the reader on all these aspects of PAH.

▶ PAH is a disease of the small pulmonary arteries, characterised by vascular proliferation and remodelling [1, 2]. It results in a progressive increase in pulmonary vascular resistance (PVR) and, ultimately, right ventricular failure and death. PAH is defined by RHC showing a pre-capillary pulmonary hypertension (PH) (mean pulmonary arterial pressure (PAP) >25 mmHg at rest or >30 mmHg during exercise, with a normal pulmonary artery wedge pressure (PWP) <15 mmHg) [1].

The current clinical classification of PAH comprises apparently heterogeneous conditions that share comparable clinical and

haemodynamic features and virtually identical pathological changes of the lung microcirculation (table 1) [3, 4]. PAH includes the idiopathic (IPAH; formerly termed "primary pulmonary hypertension") and familial forms (FPAH), and is associated with various conditions, such as scleroderma and other connective tissue diseases, congenital heart defects with systemic-to-pulmonary shunts, portal hypertension, HIV infection, exposure to drugs and toxins, and other more rare settings (e.g. thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative

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Glossary

▶ 6-minute walk test

Commonly used to assess exercise capacity in patients with PAH and to track functional change resulting from disease progression or therapeutic intervention.

▶ Pulmonary vascular resistance

Vascular resistance of the pulmonary circulation, equal to the difference between the mean pulmonary arterial pressure and the left atrial filling pressure divided by the cardiac output.

disorders, splenectomy) [3, 4]. PAH is a rare condition, even if the appropriate prospective epidemiological data to show this are lacking [5].

The diagnostic process of PAH requires a series of investigations that are intended to make the diagnosis, to clarify the clinical class of PH and the type of PAH, and to evaluate functional and haemodynamic impairment [6].

The clinical suspicion of PH should arise in case of symptoms such as breathlessness without overt signs of specific heart or lung disease, in cases of screening in predisposing conditions or of incidental findings. The detection of PH requires investigations such as a clinical examination, ECG, chest radiography and transthoracic echocardiography. Conditions other than PAH that can induce PH can be identified by tests such as pulmonary function tests, arterial blood gases, ventilation and perfusion lung scans, high-resolution computed tomography of the chest, and pulmonary angiography. Additional investigations are required for the exact identification of the type of PAH, and for the assessment of exercise capacity and haemodynamics.

Table 1	Diagnostic classification of PH
PAH	
IPAH	
FPAH	
	Associated with collagen vascular disease, congenital left-to-right shunt, portal hypertension, HIV infection, drugs and toxins, other conditions*, substantial venous or capillary involvement, pulmonary veno-occlusive disease, pulmonary capillary haemangiomatosis and persistent pulmonary hypertension of the newborn
PH with left heart disease	
	Left-sided atrial or ventricular heart disease
	Left-sided valvular heart disease
PH associated with lung disease, hypoxaemia or both	
	Chronic obstructive pulmonary disease
	Interstitial lung disease
	Sleep-disordered breathing
	Alveolar hypoventilation disorders
	Chronic exposure to high altitude
	Developmental abnormalities
PH due to chronic thrombotic, embolic disease or both	
	Thrombo-embolic obstruction of proximal pulmonary arteries
	Thrombo-embolic obstruction of distal pulmonary arteries
	Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)
Miscellaneous	
	Sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangiomatosis and compression of pulmonary vessels (adenopathy, tumour and fibrosing mediastinitis)
Table modified from [4]. *: including thyroid disorders, type-1 glycogen storage disease, Gaucher's disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders and splenectomy.	

Clinical description

The symptoms of PAH include dyspnoea, fatigue, weakness, angina, and syncope. Symptoms at rest are reported only in very advanced cases. The physical signs of PH include left parasternal lift, accentuated pulmonary component of S2, pansystolic murmur of tricuspid regurgitation and diastolic murmur of pulmonary insufficiency. Jugular vein distension, hepatomegaly, peripheral oedema, ascites and cool extremities characterise patients in a more advanced state. Lung sounds are usually normal. Finally, PAH can be suspected when abnormal ECG, chest radiography or echocardiographic findings are detected in the course of procedures performed for other clinical reasons.

Diagnostic methods

ECG

The ECG may provide suggestive or supportive evidence of PH by demonstrating right ventricular hypertrophy and strain, and right atrial dilation. Right ventricular hypertrophy on ECG is present in 87% and right axis deviation in 79% of patients with IPAH. The ECG has inadequate sensitivity (55%) and specificity (70%) to be a screening tool for detecting PH.

Chest radiography

In 90% of IPAH patients, chest radiography is abnormal at the time of diagnosis (figure 1). Findings include central pulmonary arterial dilatation, which contrasts with "pruning" (loss) of the peripheral blood vessels. Right atrial and ventricular enlargement may be seen and it progresses in more advanced cases. Chest radiography allows associated moderate-to-severe lung disease or pulmonary venous hypertension, due to left heart abnormalities, to be sometimes identified [6, 7].

Transthoracic Doppler echocardiography

Transthoracic Doppler echocardiography (TTE) is an excellent non-invasive screening test for a patient with suspected PH. TTE estimates pulmonary artery systolic pressure and can provide additional information about the cause and consequences of PH. According to data obtained in normal subjects, mild PH can be defined as a pulmonary artery systolic pressure of ~36–50 mmHg. Additional echocardiographic and

Figure 1
Chest radiography in PAH showing central pulmonary arterial dilatation and right heart enlargement.

Doppler parameters are important for diagnosis confirmation and assessment of severity of PH, including right ventricular dimensions and function, and left ventricular dimensions, tricuspid, pulmonary and mitral valve abnormalities, right ventricular ejection and left ventricular filling characteristics, inferior vena cava dimensions and pericardial effusion size.

Besides the identification of PH, TTE also allows a differential diagnosis of possible causes. In fact, TTE can recognise left heart valvular and myocardial diseases responsible for post-capillary PH, and easily identify congenital heart diseases with systemic-to-pulmonary shunts. The venous injection of agitated saline as a contrast medium can assist the identification of patent foramen ovale or small sinus venosus-type atrial septal defects that can be overlooked on the standard TTE examination. Transoesophageal echocardiography is rarely required.

Haemodynamics

RHC is required to confirm the diagnosis of PAH, to assess the severity of the haemodynamic impairment and to test the vasoreactivity of the pulmonary circulation. PAH is defined by a mean PAP >25 mmHg at rest or >30 mmHg with exercise, by an occluded PWP ≤ 15 mmHg (pre-capillary PH) and by a PVR >3 mmHg per L per min (Wood units). Left-heart catheterisation is required in the rare circumstances in which a reliable PWP cannot be measured. The assessment of

PWP may allow a distinction between arterial and venous PH in patients with concomitant left heart diseases.

RHC is also important in patients with definite moderate-to-severe PAH, because the haemodynamic variables have prognostic relevance. Elevated mean right atrial pressure, PVR, and reduced cardiac output and central venous oxygen saturation identify IPAH patients with the worst prognosis. An acute vasodilator challenge performed during RHC can identify patients who may benefit from long-term calcium channel blocker (CCB) treatment.

Acute vasodilator testing should only be carried out using short-acting pulmonary vasodilators at the time of the initial RHC in experienced centres to minimise the potential risks. Currently, the agents used in acute testing are intravenous prostacyclin or adenosine and inhaled nitric oxide (NO). A positive acute vaso-reactive response (positive acute responders) is defined as a reduction in mean PAP of ≥ 10 mmHg to reach an absolute value of mean PAP ≤ 40 mmHg with an increased or unchanged cardiac output. Generally, only $\sim 10\%$ of IPAH will meet these criteria [6–8].

Assessment of severity

The variables that have been shown to predict prognosis in IPAH when assessed at baseline or after targeted treatments include clinical parameters (baseline New York Heart Association (NYHA) functional classification, NYHA functional class on chronic epoprostenol treatment, history of right heart failure), exercise capacity (baseline 6-minute walk distance, 6-minute walk distance on chronic epoprostenol treatment, baseline peak oxygen uptake), echocardiographic parameters (pericardial effusion, right atrial size, *etc.*), haemodynamics (right atrial pressure, cardiac output, mixed venous saturation, PVR, positive acute response to vasoreactivity test, fall in PVR after 3 months of intravenous epoprostenol, *etc.*) and blood tests (hyperuricaemia, baseline brain natriuretic peptide, troponin, *etc.*). Very little information is available for other conditions, such as PAH associated with connective tissue disease (CTD), congenital systemic-to-pulmonary shunts, HIV infection or portal hypertension. In these circumstances, additional factors may contribute to the overall outcome. In fact, PAH associated with CTDs has a worse prognosis than IPAH patients, whereas patients with PAH associated with congenital systemic-to-pulmonary shunts have a more slowly

progressive course than IPAH patients. In clinical practice, the prognostic value of a single variable in the individual patient may be less than the value of multiple concordant variables [6, 8, 9].

Epidemiology

In France, the prevalence of PAH is 15 cases per million adult individuals, with higher values in the Paris area (30 cases per million). The prevalence of IPAH is 6 cases per million. In the 1990s, the International Primary Pulmonary Hypertension Study (IPPHS) results demonstrated that the incidence of IPAH was 1.7 cases per million in Belgium [6].

Genetics

PAH can be either sporadic or clustered in families. The first detailed description of FPAH by Dresdale in 1954 included a description of related subjects with severe pulmonary vascular disease of unknown aetiology. Later, it became apparent that this familial condition was less rare than initially believed, in part because of patient and physician unawareness of the familial occurrence of the disease, but also because of the markedly reduced penetrance of the genetic defects. A pioneering report by Loyd and colleagues in 1984 clearly supported the concept that a proportion of cases of so-called sporadic PAH were in fact mislabelled as non-familial when family histories were incomplete, suggesting that the incidence of FPAH is higher than previously reported. Due to the lack of data, the true incidence of FPAH is unknown. The National Institutes of Health Registry has provided the best estimate for this condition. This prospective analysis of 187 patients from 32 North American medical centres identified 12 cases with familial history affecting a first-blood relative. As a consequence, it has been widely accepted that at least 6% of individuals diagnosed with PAH have a family history of the disorder, thereby identifying relatives as being at an additional risk of developing the disorder.

FPAH segregates as an autosomal dominant trait, but with markedly reduced penetrance. Defects within the bone morphogenetic protein receptor type-II (*BMPR2*) gene, coding for a type-II receptor member of the transforming growth factor (TGF)- β family, have been shown to underlie familial PAH. Germline *BMPR2* mutations have been detected in at least 60% of the families studied to date. Disease-associated

mutations are predicted to interrupt the bone morphogenetic protein-mediated signalling pathway, predisposing to proliferation rather than apoptosis of cells within small pulmonary arteries. Several lines of evidence point to the potential requirement of additional factors, either environmental or genetic, in the pathogenesis of the disease. In addition, a proportion of so-called IPAH, as well as appetite suppressant-associated PAH, are eventually shown to have an inherited basis, as demonstrated by detection of germline *BMPR2* mutations.

Analysis of other genes encoding TGF- β receptor proteins has led to the demonstration that PAH in association with hereditary haemorrhagic telangiectasia, an autosomal dominant vascular dysplasia, can involve activin receptor-like kinase-1 mutations, a type-I TGF- β receptor. The relevance of the TGF- β superfamily in the aetiology of PAH is further supported by a recent report of an endoglin germline mutation in a patient who had hereditary haemorrhagic telangiectasia and dexfenfluramine-associated PAH. These observations support the hypothesis that mutations in the TGF- β superfamily may be a trigger for pulmonary vascular remodelling. While this achievement has generated extreme interest, the pathobiology of severe PAH remains unclear and genomic approaches to PH research may identify additional molecular determinants for this disorder. Finally, there is an urgent need to develop guidelines for genetic counselling to assist patients, their relatives and pulmonary vascular specialists. Such guidelines do not exist yet [10–17].

Management

Basic therapy

Patients with PAH have a restricted pulmonary circulation. Increased oxygen demand may worsen PH and right heart failure. However, a diagnosis of PAH does not preclude an active and fulfilling lifestyle, and patients are usually advised to engage in activities appropriate to their physical capabilities in order to prevent deconditioning and attendant worsening of overall function. Extreme caution concerning physical activity is advised for those patients with advanced PAH and symptoms of dizziness, lightheadedness or severe dyspnoea, due to a risk of life-threatening syncope. Chronic hypoxaemia is the result of impaired cardiac output resulting in mixed venous desaturation and/or right-to-left shunting through a patent foramen ovale or a

congenital heart defect as a consequence of advanced pulmonary vascular disease. When chronic hypoxaemia develops, supplemental oxygen with ambulatory oxygen therapy is indicated.

The value of cardiac glycosides in treating isolated right heart dysfunction is controversial. These agents are most useful in PH when left ventricular failure is also present. However, as neurohormonal activation has been demonstrated in PH, digoxin also has the potential to be of value due to its sympatholytic properties. Digoxin may be most beneficial in PAH with concomitant intermittent or chronic atrial fibrillation. No prospective, randomised, double-blind, placebo-controlled trials are available to provide clear treatment guidelines. Dramatic clinical improvements in patients with right heart failure can be achieved by instituting diuretic therapy, which reduces right ventricular pre-load.

As pregnancy and labour increase the demand on the heart–pulmonary system, they should be contraindicated in patients with PH. Consequently, safe and effective contraception is always recommended for females of childbearing age. Intra-uterine devices or surgical sterilisation have been proposed, but these procedures can promote bleeding and may be impossible to perform in severely compromised patients. Many centres treating patients with PAH recommend oral contraception with progesterone derivatives or low-dose oestrogens, provided there is no history of thromboembolic disease or thrombophilia.

The rationale for anticoagulant therapy in PAH is based on the presence of well-recognised risk factors for venous thromboembolism, such as heart failure, sedentary lifestyle and thrombophilic predisposition. Indeed, the identification of thrombosis in *post mortem* examinations of primary PH patients further supports this strategy. However, no data exist that actually support anticoagulant use specifically for PAH. Warfarin has been evaluated in only two studies with small numbers of patients (one retrospective and one prospective, but non-randomised). On the basis of these limited studies, aiming for an international normalised ratio (INR) between 1.5 and 2.5 is recommended [18, 19].

Calcium channel blockers

Pulmonary artery vasoconstriction may contribute to the pathogenesis of PAH. Uncontrolled studies suggest that long-term administration of high-dose CCBs prolong survival in responsive patients (*i.e.* ~10% of all patients referred to pulmonary vascular units). Patients who may benefit

from long-term CCBs are identified by performing an acute vasodilator challenge during RHC. The occurrence of severe life-threatening haemodynamic compromise during acute vasodilator challenge with CCBs is well documented, and these agents should not be used as first-line vasodilators for acute testing. Rather, short-acting agents such as intravenous prostacyclin, adenosine or inhaled NO, should be employed. Chronic treatment with oral CCBs should then be considered for those who respond to one of these three drugs.

Prostacyclin therapy

1. Intravenous prostacyclin (epoprostenol)

Prostaglandin I₂ (Pgl₂; prostacyclin), the main product of arachidonic acid in the vascular endothelium, induces vascular smooth muscle relaxation by stimulating cyclic adenosine monophosphate production and inhibiting smooth muscle cell growth (figure 2). In addition, it is a powerful inhibitor of platelet aggregation. Intravenous prostacyclin (epoprostenol) was first used to treat primary PH in the early 1980s. It was apparent early on that the absence of an acute haemodynamic response to intravenous epoprostenol did not preclude improvement with long-term therapy. A prospective, randomised open trial in 81 patients with severe IPAH has demonstrated significant efficacy on survival, exercise capacity, haemodynamics and survival.

There is no long-term randomised trial with epoprostenol in PAH. Nevertheless, cohort analysis

Figure 2

Targets for current or emerging therapies in PAH. Dysfunctional pulmonary artery endothelial cells (blue) have a decreased production of prostacyclin and NO with an increased production of endothelin-1, promoting vasoconstriction and proliferation of pulmonary artery smooth muscle cells (orange). Current or emerging therapies interfere with specific targets in pulmonary artery smooth muscle cells. ET: endothelin; ET_A: endothelin receptor A; ET_B: endothelin receptor B.

of IPAH patients receiving continuous intravenous epoprostenol, as compared to historical control groups, clearly demonstrated clinical benefits in NYHA functional class III and IV patients. Despite these improvements, approximately one-third of primary PH patients succumb within 3 years of diagnosis. Common side-effects that are attributable to epoprostenol include jaw pain, headache, diarrhoea, flushing, leg pain and nausea, although these are generally mild and dose related. More serious complications are usually related to the delivery system (figure 3). Epoprostenol can only be administered by continuous intravenous infusion owing to its short half-life in the circulation (3 minutes) and its inactivation at low pH. In the long term, epoprostenol is infused *via* a portable continuous infusion pump connected to a permanent tunnelled subclavian vein catheter. The incidence of catheter-related sepsis ranges 0.1–0.6 per patient-year. Pump failure or dislocation of the central venous catheter leading to interruption in drug infusion may be life threatening. In patients with PH, with prominent pulmonary vein involvement such as pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, severe pulmonary oedema and death may occur, presumably because of increased pulmonary perfusion in the presence of downstream vascular obstruction.

Figure 3
An epoprostenol-treated patient.

2. Subcutaneous treprostinil

The potential complications related to the central venous catheter required for intravenous prostacyclin have led to the development of treprostinil, a stable prostacyclin analogue amenable to continuous subcutaneous infusion. Local pain at

the infusion site was a significant side-effect, occurring in 85% of subjects. Infusion site pain precluded dose increase in a significant proportion of patients and led to discontinuation in 8%. Despite these limitations, patients with PAH who developed life-threatening complications with intravenous epoprostenol have been safely transitioned to subcutaneous treprostinil. Recent developments of treprostinil include intravenous and nebulised forms of the drug.

3. Oral beraprost

Beraprost sodium, the first biologically stable and orally active prostacyclin analogue, is absorbed rapidly in fasting conditions, reaches a peak concentration after 30 minutes and has an elimination half-life of 35–40 minutes. Present clinical results with this therapy are disappointing.

4. Inhaled iloprost

Iloprost is a chemically stable prostacyclin analogue that may be delivered *via* inhalation in patients with PAH. The delivery system produces aerosol particles of an appropriate size to ensure alveolar deposition, thus improving pulmonary selectivity. Iloprost has a disadvantageous relatively short duration of action, requiring up to 6–12 inhalations per day. Side-effects include cough and symptoms linked to systemic vasodilatation. In addition, syncope is more frequent with iloprost. Although uncontrolled data are encouraging, the long-term efficacy of inhaled iloprost remains to be established. Recent data indicate that add-on iloprost may improve patients who remain in NYHA functional class III, despite bosentan therapy.

Endothelin receptor antagonists

1. Bosentan (dual endothelin receptor antagonist)

In addition to exerting a direct vasoconstrictor effect, endothelin-1 stimulates vascular smooth muscle cell proliferation, acts as a co-mitogen, induces fibrosis, and is a pro-inflammatory mediator *via* stimulation of leukocytes and adhesion molecules. The effects of endothelin-1 are mediated through ET_A and ET_B receptors (figure 2). Activation of ET receptors causes sustained vasoconstriction and proliferation of vascular smooth muscular cells, whereas ET_B receptors mediate pulmonary endothelin clearance and induce endothelial cell production of NO and prostacyclin. Bosentan is an orally active dual (ET_A and ET_B) endothelin receptor antagonist. Two double-blind, randomised, placebo-controlled trials have

supported the efficacy of oral bosentan in patients with PAH class III (idiopathic or associated with scleroderma). No dose response for efficacy could be ascertained. Bosentan is metabolised by the liver and may induce an increase in hepatic aminotransferase levels. This also applies to other endothelin receptor antagonists, such as ambrisentan and sitaxsentan. In the bosentan trial, development of abnormal hepatic function appeared to be dose dependent, providing a rationale for the approved dose of 125 mg *b.i.d.* Elevations to more than eight times the upper limit of normal occurred in 3 and 7% of patients receiving 125 and 250 mg bosentan *b.i.d.*, respectively. The drug is contraindicated during pregnancy due to its teratogenic potential.

2. Selective ET_A blockers

Sitaxsentan and ambrisentan are currently being investigated for efficacy in PAH. A large, randomised, placebo-controlled trial, including an open-label bosentan arm, has recently been completed showing similar improvements in 6-minute walk distance with sitaxsentan 100 mg per day and bosentan 125 mg *b.i.d.*, as compared to placebo (STRIDE-2 trial). Particular attention should be given to patients treated with antivitamin K and sitaxsentan, which can lead to a risk of raised INR.

Potential future therapies

1. Nitric oxide

NO is a potent, endogenous, endothelium-derived vasodilator that directly relaxes vascular smooth muscle through stimulation of soluble guanylate cyclase and increased intracellular cyclic guanosine monophosphate (figure 2). Chronic inhaled NO, while showing benefit in small series and case reports, is very cumbersome to use and, as a result, is unlikely to be given to a large number of patients, and can cause haemodynamic deterioration when the inhalation is interrupted.

2. Sildenafil

Another strategy for increasing the activity of endogenous NO in PAH would be to enhance NO-dependent, cyclic guanosine monophosphate (cGMP)-mediated pulmonary vasodilatation by inhibition of the breakdown of cGMP by phosphodiesterase type 5 (PDE5). PDE5 inhibitors, such as sildenafil, have an acute pulmonary vasodilator effect. In patients with PAH, short-term intravenous application of sildenafil during RHC reduced PVR in a dose-dependent manner.

In combination with inhaled iloprost, augmentation of the pulmonary vasodilator effect of each single agent was noted. In patients who deteriorate despite ongoing iloprost therapy, long-term adjunctive oral sildenafil improved exercise capacity and pulmonary haemodynamics. The experience with sildenafil is still preliminary. A large pivotal placebo-controlled trial has been completed, indicating that 20, 40 or 80 mg *t.i.d.* of sildenafil similarly improve the 6-minute walk distance at 4, 8 and 12 weeks, respectively, as compared with placebo, whereas more side-effects were observed on 40 and 80 mg *t.i.d.* as compared with 20 mg *t.i.d.* Based on these findings, a dose of 20 mg *t.i.d.* sildenafil has been recently approved for the treatment of PAH class III in Europe.

3. Combination therapy

Combination therapy, using drugs with different mechanisms of action to maximise clinical benefit, is an emerging therapeutic option in PAH. Long-term combination therapies have been recently evaluated in patients with severe disease. Adjunctive sildenafil or bosentan therapy has produced favourable outcomes in some patients already receiving oral, inhaled or intravenous prostacyclin analogues. Conversely, a recent report on 13 patients already receiving vasodilators for PAH (including CCBs, epoprostenol or bosentan) indicated that adding long-term sildenafil had unsubstantial results on functional status and right heart function. Further adequately powered, prospective, randomised, double-blind, placebo-controlled studies are needed to conclusively determine the effect of combination therapy in PAH.

Atrioseptostomy

The prognosis of patients with severe PAH is heavily dependent on the function of the right ventricle. Early experimental trials have shown that performing an atrial septal defect is associated with decreased right ventricular pressure and increased systemic blood flow. In addition, patients with a right-to-left cardiac shunt due to congenital heart defect or patent foramen ovale have a better prognosis than those without intracardiac shunting. Blade balloon atrial septostomy in refractory PAH has been successfully applied in several studies. Unfortunately, the procedure-related mortality remains high, especially if patients already have a low arterial oxygen saturation or evidence of right ventricular failure. Atrial septostomy may be an interesting

Educational questions

- Which of the following does a definite diagnosis of PAH require?
 - A mean PAP >15 mmHg.
 - A mean PAP >25 mmHg.
 - A mean PAP >35 mmHg.
 - A mean PAP >45 mmHg.
 - A systolic PAP >25 mmHg.
- The most common symptom of PAH is:
 - Dyspnoea.
 - Syncope.
 - Chest pain.
 - Haemoptysis.
 - Dysphonia.
- Acute vasodilator challenge allows identification of patients who may benefit from:
 - Calcium channel antagonists.
 - Epoprostenol.
 - Bosentan.
 - Sildenafil.
 - Treprostinil.
- FPAH and IPAHA may be associated with germline mutations of the gene coding for:
 - TGF- β 1.
 - PDGF A.
 - Serotonin.
 - ALK2.
 - BMPR2.
- Treatment of PAH class III may include:
 - β -blockers.
 - Warfarin.
 - Diuretics.
 - Epoprostenol.
 - Bosentan.

alternative for selected patients with severe disease, particularly if a transplantation candidate deteriorates despite maximal medical therapy.

Lung transplantation

Lung transplantation is the ultimate alternative for severe PAH cases who cannot be managed medically. Many patients with PAH have had a single lung transplant with good long-term results. However, nearly all transplant centres currently prefer to transplant both lungs (double lung transplant), in part because there are generally less post-operative complications. Heart–lung transplantation may be needed in some patients with end-stage heart failure or complex congenital heart disease. Patients with severe PAH who have undergone lung transplantation show an overall 1- and 5-year survival of ~75 and 50%, respectively. Long-term survival and quality of life are limited by the high prevalence of chronic allograft rejection. Optimal timing of the initial referral to a transplant centre is the first crucial step in the transplantation process, and the long waiting time before transplantation due to the shortage of organ donors must be integrated into this decision.

Treatment algorithms

Several treatments for PAH are now approved in North America and Europe (*i.e.* epoprostenol,

treprostinil, iloprost, bosentan and sildenafil). With the exception of recent data from patients receiving prolonged epoprostenol therapy, the long-term effects of novel treatments are still unknown. There is a substantial need for long-term observational studies evaluating the different treatments in terms of survival, side-effects, quality of life and costs. As head-to-head comparisons of currently approved therapies are not available, the choice of optimal treatment will be dictated by clinical experience and drug availability, as well as patient preference. A recent treatment algorithm for PAH is proposed in figure 4. The different treatments presented have been evaluated mainly in idiopathic (primary) PAH, and in cases associated with systemic sclerosis or with anorexigens. The drugs of choice for testing of acute vasoreactivity are short-acting agents (intravenous prostacyclin, intravenous adenosine or inhaled NO). Patients with a sustained response from CCBs are defined as being in NYHA functional class I or II with near-normal haemodynamics after at least 1 year of follow-up. It is recommended that NYHA functional class IV patients should receive continuous intravenous epoprostenol. The experience with sildenafil is preliminary and controlled studies are ongoing to determine efficacy and safety. Combination therapy of drugs with different mechanisms of action warrants further investigation. Lung

Figure 4
Algorithm for the treatment of PAH, specific for patients in NYHA functional class III or IV, since few data exist for those with functional class I or II.

transplantation is considered an option for all eligible patients who remain in NYHA functional class IV after 3 months of epoprostenol. Atriostomy is proposed for selected patients with severe disease.

The treatment of PAH has historically been restricted due to limited therapeutic options. Recent advances in the understanding of the

pathophysiological and molecular mechanisms that may underlie PAH, with the subsequent availability of novel pharmacological therapies, provide renewed hope for both patients and their physicians. Advancing knowledge of this devastating disease may ultimately lead to the development of therapies that ensure a better prognosis.

Useful web links

The Pulmonary Hypertension Association (PHA)
www.phassociation.org
PHA Europe
www.phaeurope.org

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Suggested answers

- b
- a
- a
- e
- b, c, d, e