

Pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a rare condition characterized by elevated pulmonary arterial resistance leading to right heart failure. PAH can be sporadic (idiopathic PAH, or primary pulmonary hypertension), familial (caused by germline BMPR2 mutations, a type II member of the TGF beta receptor superfamily), or related to other conditions including connective tissue disease, congenital heart disease, human immunodeficiency virus infection, portal hypertension, appetite suppressant exposure. Prevalence of PAH is 15 per million in France. The lack of specificity of PAH symptoms (mostly dyspnea) presumably leads to underdiagnosis of this condition. Echocardiography is the investigation of choice for non-invasive screening. Measurement of hemodynamic parameters during right-heart catheterizing is mandatory to establish the diagnosis (mean pulmonary artery pressure > 25 mmHg and pulmonary artery wedge pressure < 12 mmHg). Acute pulmonary vasodilator testing should be performed with nitric oxide or prostacyclin during right-heart catheterization. Recent advances in the management of PAH including continuous intravenous prostacyclin infusion and endothelin receptor antagonists have improved markedly the patients' prognosis. Novel treatments such as inhaled iloprost and type 5 phosphodiesterase inhibitors have to be further evaluated in this setting. Lung transplantation is the last option for patients deteriorating despite medical treatment.

Keywords

Bone morphogenetic protein receptor; Echocardiography; Endothelin; Pulmonary arterial hypertension; Prostacyclin; Right-heart catheterism; Transforming growth factor beta.

Disease name

Pulmonary arterial hypertension

Definition/diagnostic criteria

(For references see Humbert 2004, Montani 2004, Simonneau 2004)

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries, characterized by vascular proliferation and remodeling. It results in a progressive increase in pulmonary vascular resistance and, ultimately, right ventricular failure and death. PAH is defined by right-heart catheterization showing a precapillary pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg at rest or > 30 mmHg with exercise, with a normal pulmonary artery wedge pressure <15 mmHg).

Current clinical classification of PAH comprises apparently heterogeneous conditions, which share comparable clinical and hemodynamic pictures and virtually identical pathologic changes of the lung microcirculation. PAH includes the idiopathic (IPAH, formerly termed primary pulmonary hypertension) and familial forms (FPAH) and PAH associated with various conditions, such as scleroderma and other connective tissue diseases (CTD), congenital heart defects with systemic-to-pulmonary shunts, portal hypertension, human immunodeficiency virus infection, exposure to drugs and toxins and other more rare settings: thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies (Sickle disease especially), myelo-proliferative disorders, splenectomy. PAH is a rare condition even if appropriate prospective epidemiological data are lacking.

The diagnostic process of PAH requires a series of investigations that are intended to make the diagnosis, to clarify the clinical class of pulmonary hypertension and the type of PAH and to evaluate the functional and hemodynamic impairment.

The clinical suspicion of pulmonary hypertension should arise in case symptoms such as breathlessness without overt signs of specific heart or lung disease, in cases of screening in predisposing conditions or in cases of incidental findings. The detection of pulmonary hypertension requires investigations such as clinical examination, ECG, chest radiograph and transthoracic echocardiogram. Other conditions than PAH which can induce pulmonary hypertension will be identified by tests such as pulmonary function tests, arterial blood gases, ventilation and perfusion lung scan, high resolution computed tomography of the chest with contrast medium injection, and pulmonary angiography. Additional investigations are required for the exact identification of the type of PAH, and for the

assessment of exercise capacity and hemodynamics (see Diagnostic methods).

Clinical description

Symptoms and signs of pulmonary hypertension (Montani 2004)

The symptoms of PAH include of breathlessness, fatigue, weakness, angina, syncope, and abdominal distension. Symptoms at rest are reported only in very advanced cases. The physical signs of pulmonary hypertension include left parasternal lift, accentuated pulmonary component of S2, pansystolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency. Jugular vein distension, hepatomegaly, peripheral edema, ascites and cool extremities characterize patients in a more advanced state. Lung sounds are usually normal. Finally, PAH can be suspected when abnormal electrocardiographic, chest radiograph 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 pulmonary hypertension 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 significant pulmonary hypertension. In 90% of IPAH patients the chest radiograph is abnormal at the time of diagnosis. 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. The chest radiograph allows associated moderate-to-severe lung disease or pulmonary venous hypertension due to left heart abnormalities to be sometimes identified.

Transthoracic Doppler-echocardiography (TTE)

TTE is an excellent non-invasive screening test for the patient with suspected pulmonary hypertension. TTE estimates pulmonary artery systolic pressure and can provide additional information about the cause and consequences of pulmonary hypertension. According to data obtained in normal subjects, mild pulmonary hypertension can be defined as a pulmonary artery systolic pressure of approximately 36-50 mmHg. Additional echocardiographic and Doppler parameters are important for diagnosis confirmation and assessment of severity of

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

Hemodynamics

Right heart catheterization (RHC) is required to confirm the diagnosis of PAH, to assess the severity of the hemodynamic 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 a pulmonary wedge (occluded) pressure (PWP) \leq 15 mmHg (demonstrating pre-capillary pulmonary hypertension) and by PVR > 3 mmHg/l/min (Wood units). Left heart catheterization is required in the rare circumstances in which a reliable pulmonary wedge pressure cannot be measured. The assessment of pulmonary wedge pressure may allow the distinction between arterial and venous pulmonary hypertension in patients with concomitant left heart diseases. RHC is important also in patients with definite moderate-to-severe PAH because the hemodynamic variables have prognostic relevance. Elevated mean right atrial pressure, mean pulmonary artery pressure and reduced cardiac output and central venous O₂ 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 treatment (CCB) (see below). Acute vasodilator testing should only be done using short-acting pulmonary vasodilators at the time of the initial RHC in experienced centers to minimize the potential risks. Currently the agents used in acute testing are intravenous prostacyclin or adenosine and inhaled nitric oxide. A positive acute vasoreactive response (*positive acute responders*) is defined as a reduction of mean pulmonary artery pressure \geq 10 mmHg to reach an absolute value of mean pulmonary artery pressure \leq 40 mmHg with an increase or unchanged cardiac output. Generally, only about 10% of IPAH will meet these criteria.

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 NYHA functional classification, NYHA functional class on chronic epoprostenol treatment, history of right heart failure), exercise capacity (baseline six-minute walk distance, six-minute walk distance on chronic epoprostenol treatment, baseline peak VO₂), echocardiographic parameter (pericardial effusion, right atrial size), hemodynamics (right atrial pressure, cardiac output, mixed venous saturation, pulmonary vascular resistance, positive acute response to vasoreactivity test, fall in pulmonary vascular resistance after 3 months of intravenous epoprostenol), and blood tests (hyperuricemia, baseline brain natriuretic peptide, troponin). Very little information is available in other conditions such as PAH associated with 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 CTD tissue disorders 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.

Epidemiology

The prevalence of PAH is 15 per million in adult individuals in France with higher values in the Paris area (30 per million). The prevalence of IPAH is of 6 per million. In the 1990's, the IPPHS results demonstrated that the incidence of IPAH is 1.7 per million in Belgium (Abenheim 1996).

Genetics

(For reference see Humbert 2002)

PAH can be either sporadic or clustered in families. The first detailed description of familial PAH by Dresdale in 1954 included a description of related subjects with severe pulmonary vascular disease of unknown etiology. 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 pioneer 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 the family histories were incomplete, suggesting that the incidence of familial PAH is higher than previously reported. Because of the lack of data, the true incidence of familial PAH is unknown. The

NIH Registry has provided the best estimate of this condition. This prospective analysis of 187 patients from 32 North American medical centers identified 12 cases with familial history affecting a first-blood relative. In consequence, it has been widely accepted that at least 6% of individuals diagnosed with PAH have a family history of the disorder, and thereby identifying relatives as being at additional risk of developing the disorder.

Familial PAH segregates as an autosomal dominant trait but with markedly reduced penetrance. Defects within bone morphogenetic protein receptor type II gene (*BMP2*), coding for a type II receptor member of the transforming growth factor beta (TGF- β) family, have been shown to underlie familial PPH. Germline *BMP2* mutations have been detected in at least 60% of the families studied to date. Disease-associated mutations are predicted to interrupt the BMP 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 idiopathic PAH as well as appetite-suppressant-associated PAH turn out to have an inherited basis, as demonstrated by detection of germline *BMP2* mutations.

Analysis of other genes encoding TGF- β receptor proteins, led to the demonstration that PAH in association with hereditary hemorrhagic telangiectasia, an autosomal dominant vascular dysplasia, can involve *ALK-1* mutations, a type I TGF- β receptor. The relevance of the TGF- β superfamily in the etiology of PAH is further supported by a recent report of endoglin germline mutation in a patient who had hereditary hemorrhagic telangiectasia and dexfenfluramine-associated PAH. These observations support the hypothesis that mutations in the TGF- β superfamily may be a trigger for pulmonary vascular remodeling. While this achievement has generated extreme interest, the pathobiology of severe PAH remains unclear and genomic approaches to pulmonary hypertension 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.

Management

(For references see Humbert 2004, Klepetko 2004, Montani 2004, Sandoval 2002)

Basic therapy

Patients with PAH have a restricted pulmonary circulation. Increased oxygen demand may worsen pulmonary hypertension 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, lightheadness, or severe dyspnea because of a risk of life-threatening syncope. Chronic hypoxemia due to impaired cardiac output, right-to-left shunting through a patent foramen ovale or a congenital heart defect results in desaturation of mixed venous blood. When chronic hypoxemia develops, supplemental oxygen including ambulatory oxygen therapy is indicated.

The value of cardiac glycosides in treating isolated right heart dysfunction is controversial. These agents are most useful in cor pulmonale, when left ventricular failure is also present. However, since neurohormonal activation has been demonstrated in pulmonary hypertension, digoxin might be considered because of its sympatholytic properties. Digoxin may be most beneficial in PAH with concomitant intermittent or chronic atrial fibrillation. No prospective, randomized, 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 including anti-aldosterone diuretics, which reduces the right ventricular preload.

As pregnancy and labor increase the demand on the heart-pulmonary system, they should be contraindicated in patients with pulmonary hypertension. Consequently, safe and effective contraception is always recommended in women of childbearing age. Intrauterine devices or surgical sterilization have been proposed but since these procedures can promote bleeding, it may be impossible to perform in severely compromised patients. Many centers treating patients with PAH recommend oral contraception with progesterone derivatives or low dose estrogens, when there is no history of thromboembolic disease or thrombophilia.

The rationale for anticoagulant therapy in PAH is based on the presence of well-recognized risk factors for venous thromboembolism such as heart failure, sedentary lifestyle, and thrombophilic predisposition. Indeed, the identification of thrombosis in post-mortem examinations of patients with IPAH further supports this strategy. However, no data exist to support anticoagulants use specifically in PAH. Warfarin has been evaluated in only two studies with small numbers of patients (one retrospective and one prospective but non-randomized). On the basis of these limited studies, aiming for an International

Normalized Ratio between 1.5 and 2.5 is recommended.

Calcium channel blockers (CCB)

Pulmonary artery vasoconstriction may contribute to the pathogenesis of PAH. Uncontrolled studies suggest that long-term administration of high-dose CCB prolong survival in responsive patients (approximately 10 percent of all patients referred to pulmonary vascular units). Patients who may benefit from long-term CCB are identified by performing an acute vasodilator challenge during right-heart catheterization (see above). The occurrence of severe life-threatening hemodynamic compromise during acute vasodilator challenge with CCB 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 nitric oxide should be employed. Chronic treatment with oral CCB should then be considered for those who respond to one of these three drugs.

Prostacyclin therapy

Intravenous Prostacyclin (Epoprostenol)

Prostaglandin I₂ (prostacyclin), the main product of arachidonic acid metabolism in the vascular endothelium, induces vascular smooth muscle relaxation by stimulating cyclic adenosine monophosphate production and inhibiting smooth muscle cell growth. In addition, it is a powerful inhibitor of platelet aggregation. Intravenous prostacyclin (epoprostenol) was first used to treat primary pulmonary hypertension (IPAH) in the early 1980s giving substantial long-term hemodynamic and symptomatic improvement. A prospective, randomized open trial in 81 patients with severe IPAH has demonstrated significant efficacy on survival, exercise capacity, hemodynamics and survival. There is no long-term randomized trial with epoprostenol in PAH. Nevertheless, 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. Despite these improvements approximately one-third of primary pulmonary hypertension patients succumb within three years of diagnosis. Common side-effects attributable to epoprostenol include jaw pain, headache, diarrhea, flushing, leg pain, and nausea, though generally mild and dose-related. More serious complications are usually related to the delivery system. The incidence of catheter-related sepsis ranges from 0.1 to 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 pulmonary hypertension with prominent pulmonary vein involvement such as pulmonary

veno-occlusive disease and pulmonary capillary hemangiomatosis, severe pulmonary edema and death may occur, presumably because of increased pulmonary perfusion in the presence of downstream vascular obstruction.

Subcutaneous Treprostinil

The potential complications related to the central venous catheter required for intravenous prostacyclin administration 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.

Oral Beraprost

Beraprost sodium, the first biologically stable and orally active prostacyclin analogue, is absorbed rapidly in fasting conditions. It 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.

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 appropriate size to ensure alveolar deposition, improving pulmonary selectivity. Iloprost has a disadvantageous relatively short duration of action requiring up to 6 to 12 inhalations a day. Side-effects included cough and symptoms linked to systemic vasodilatation. In addition, syncope was more frequent in the iloprost-treated group. Although uncontrolled data are encouraging, long-term efficacy of inhaled iloprost remains to be established.

Endothelin receptor antagonists

Bosentan (dual endothelin receptor antagonist)

In addition to its direct vasoconstrictor effect, endothelin-1 (ET-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 ET-1 are mediated through ET_A and ET_B receptors. Activation of ET_A receptors causes sustained vasoconstriction and proliferation of vascular smooth muscular cells, while ET_B receptors mediate pulmonary endothelin clearance and induce endothelial cell production of nitric oxide and prostacyclin. Bosentan is an orally active dual (ET_A and ET_B) endothelin receptor antagonist. Two double-blind, randomized, placebo-controlled trials have supported the efficacy of oral bosentan

in patients with PAH (primary or associated with scleroderma). No dose response for efficacy could be ascertained. Bosentan is metabolized by the liver and may increase 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 dose-dependent, providing a rationale for the approved dose of 125mg bid. Elevations to more than eight times the upper limit of normal occurred in 3% and 7% of patients receiving 125 mg and 250 mg bosentan bid, respectively. The drug is contraindicated during pregnancy due to its teratogenic potential.

Selective ET_A blockers

Sitaxsentan and ambrisentan are currently being investigated for efficacy in PAH.

Potential future therapies

Nitric oxide

Nitric oxide 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 (cGMP). Chronic inhaled nitric oxide, while showing benefit in small series and case reports, is very cumbersome to use, and because of this, unlikely to be given to a large number of patients. It can cause hemodynamic deterioration when the inhalation is interrupted.

Sildenafil

Another strategy for increasing the activity of endogenous nitric oxide in PAH would be to enhance the nitric oxide-dependent, cGMP-mediated pulmonary vasodilatation by inhibition of phosphodiesterase type 5, responsible for cGMP-breakdown. Phosphodiesterase type 5 inhibitors such as sildenafil have an acute pulmonary vasodilator effect. In patients with PAH, short-term intravenous application of sildenafil during right-heart catheterization reduced pulmonary vascular resistance in a dose-dependent manner. In combination with inhaled iloprost, augmentation of the pulmonary vasodilator effect of each single agent was noted. In patients deteriorating despite ongoing iloprost therapy, long-term adjunctive oral sildenafil improved exercise capacity and pulmonary hemodynamics. Although promising, there are few data on long-term sildenafil treatment in PAH apart from case reports and short series. The experience with sildenafil is thus preliminary and controlled studies are ongoing to determine efficacy, side effects and safety.

Combination therapy

Combination therapy using drugs with different mechanisms of action to maximize the 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 have produced favorable outcomes in some patients already receiving oral, inhaled or intravenous prostacyclin analogues. Conversely, recent report on thirteen patients already receiving vasodilators for PAH (including calcium channel blockers, epoprostenol, or bosentan) indicated that adding long-term sildenafil had unsubstantial results on functional status and right-heart function. Further adequately powered, prospective, randomized, 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 have already a low arterial oxygen saturation or evidence of right ventricular failure. Atrial septostomy may be an interesting 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 that cannot be managed medically. Many patients with PAH have had a single lung transplant with good long-term results. However, nearly all transplant centers currently prefer to transplant both lungs (double-lung transplant), in part because there are generally less postoperative 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 about 75% and 50%, respectively. Long-term survival and quality of life is limited by the high prevalence of chronic allograft rejection. The optimal timing to make the initial referral to a transplant center is the crucial initial 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 (epoprostenol, treprostinil, bosentan) and Europe (epoprostenol, iloprost, bosentan). 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.

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

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