

PULMONARY ARTERIAL HYPERTENSION

Definition

Pulmonary arterial hypertension (PAH) is a clinical condition characterized by the presence of pre-capillary pulmonary hypertension, and pulmonary vascular resistance >3 Wood units (or >2 according to 2022 ESC GL on PH), in the absence of other causes of pre-capillary pulmonary hypertension, such as due to lung diseases, chronic thromboembolic pulmonary hypertension, or other rare diseases. PAH is caused by restricted flow through the pulmonary arterial circulation resulting in increased pulmonary vascular resistance and ultimately in right heart failure.¹

Epidemiology

The prevalence of PAH is estimated to 15-25 per million.^{1,2} It is estimated that 1% of the world population and up to 10% of persons older than 65 years of age have pulmonary hypertension.¹

Aetiology

Idiopathic PAH is the most common subtype (50–60% of all cases), followed by PAH associated with **connective tissue disease**, **congenital heart disease**, and portal hypertension (**porto-pulmonary hypertension**).³ Idiopathic pulmonary arterial hypertension, the most common type of PAH, is more prevalent in women. Approximately 25-30% of patients diagnosed with idiopathic PAH have an underlying Mendelian genetic cause for their condition and should be classified as **heritable PAH**.⁴⁻⁶ Phenotypic features associated with pulmonary arterial hypertension mutations are presented in Table 1. Several **drugs** and **toxins** may cause PAH or PAH associated pulmonary venous capillary abnormalities but it represents a rare complication (see below). **Schistosomiasis** is one of the most common chronic infectious diseases worldwide, affecting around 200 million people. Schistosomiasis-associated PAH is present in 5% of patients with the hepatosplenic form of the disease.³ It is a leading cause of PAH, especially in some regions of South America, Africa, and Asia. **Chronic haemolytic anaemia** such as sickle cell disease, thalassaemia, hereditary spherocytosis, stomatocytosis, and microangiopathic haemolytic anaemia may result in PAH (Table 2). The prevalence of PAH in β -thalassemia is 2.1%, and the β -thalassemia intermedia phenotype, splenectomy, and advanced age are risk factors.⁷ The mechanism of PAH in chronic haemolysis is related to a high rate of nitric oxide (NO) consumption leading to a state of resistance to NO bioactivity. **POEMS syndrome** (polyneuropathy, organomegaly,

endocrinopathy, monoclonal gammopathy, and skin changes) is a rare cause of precapillary pulmonary hypertension and acute heart failure.⁸ **Swimming-induced pulmonary edema** occurs during swimming or scuba diving, often in young individuals with no predisposing conditions, and its pathophysiology is poorly understood. It usually resolves spontaneously within 24 hours, or with β_2 -adrenergic agonist or diuretic therapy, but it can rarely be fatal.⁹

Pathophysiology

PAH is a panvasculopathy predominantly affecting small pulmonary arteries ($<500\mu\text{m}$) that regulate regional blood flow in the lung (resistance arteries), whereas pulmonary veins are unaffected. Intimal hyperplasia, medial hypertrophy, adventitial proliferation, thrombosis in situ, varying degrees of inflammation and plexiform arteriopathy are histologic characteristics (Figure 1).^{10,11} Multiple pathogenic pathways have been implicated in the development of PAH, including those at the molecular and genetic levels and in the smooth muscle and endothelial cells and adventitia. Excessive cell proliferation and reduced rates of apoptosis, as well as excessive vasoconstriction in 20% of patients, induce vascular remodeling with loss of vascular luminal cross section. Nicotinamide phosphoribosyl transferase, a pleiotropic protein with extracellular proinflammatory cytokine-like activity and intracellular enzymatic activity as a phosphoribosyltransferase, is upregulated in human and experimental pulmonary hypertension and promotes pulmonary vascular remodeling in vivo and in vitro.¹² Eventually, pathological increases in PVR cause right heart failure characterized by reduced RV ejection fraction and increased RV diastolic stiffness.¹³ Fibrosis develops in the RV free wall, the ventricular insertion points, and the septum in these patients.¹⁴ RV maladaptation may include reactivation of fetal gene expression, autonomic nervous system dysregulation, abnormal mitochondrial metabolism with inefficient adenosine triphosphate production, and reduced coronary artery perfusion with optional myocardial and microvascular injury.¹⁰ Left ventricular atrophy with resultant reduced LV contractility also occurs.¹⁵

Presentation

Patients initially present with dyspnea and fatigue. Peripheral edema and other signs of RV failure follow. Syncope in PAH is associated with worsening right heart function and is an independent predictor of a poor prognosis.¹⁶ Angina may be due to extrinsic compression of the left main stem by a dilated pulmonary artery.

Physical Examination

Initial findings are **S₃** (right ventricular), accentuated **P₂**, early **systolic click from PV**, **pansystolic murmur of TR**, **diastolic murmur of PR**, and **left parasternal lift**.

Jugular vein distension, hepatomegaly, peripheral oedema, ascites, and cool extremities characterize patients in a more advanced state.¹⁷

Lung sounds are usually normal. Signs of associated disorders may be also seen.

Investigations

NT-proBNP levels carry prognostic value. Post hoc analyses from the GRIPHON study also suggest that they can be used to predict response to selexipag treatment.¹⁸

Echocardiography shows right atrial and right ventricular enlargement, abnormal contour, flattening, or reverse curvature of the interventricular septum, TR, and underfilled left heart chambers. The Doppler echocardiographic index (Tei index or myocardial performance index), an index of combined RV systolic and diastolic function obtained by dividing the sum of both isovolumetric contraction and relaxation intervals by the ejection time, appears to be predictive of an adverse outcome.¹ In addition, stress Doppler echocardiography is useful for the assessment of RV contractile reserve (increase of systolic PA pressure >30 mm Hg) that carries a better prognosis.¹⁹ Doppler measurements of the PA pressure, however, may be significantly inaccurate (by as much as 38 mm Hg).²⁰

Chest X-ray is abnormal in 90% of patients and typically displays decreased peripheral lung vascular markings (pruning), hilar pulmonary artery prominence due to central pulmonary arterial dilatation. Right atrium and RV enlargement may be seen in more advanced cases.

ECG may reveal right atrial enlargement, right ventricular hypertrophy and strain, and right axis deviation of the QRS complex. A normal ECG does not exclude PAH.

Cardiac Catheterization It is necessary to establish the diagnosis and allow vasodilator testing. Associated mortality of the procedure is 0.05%.

Coronary angiography Computed tomography or invasive coronary angiography is indicated in patients with angina-like symptoms. A PA main trunk diameter ≥ 40 mm predicts left main stem coronary significant stenosis.²¹

Vasoreactivity testing is useful both for diagnostic and therapeutic purposes. However, there is heterogeneity within the distinct group of acute vasoresponders, and use of pulmonary artery compliance, defined as (stroke volume/[systolic–diastolic pulmonary artery pressure]), in addition to current measures may better identify patients likely to have a good long-term response to calcium channel blockers.²²

Lung function tests There is decreased lung diffusion capacity for carbon monoxide (typically in the range of 40–80% predicted) and mild to moderate reduction of lung volumes. Mild peripheral airway obstruction can also be detected. PO₂ is usually normal and PCO₂ low due to hyperventilation.

High resolution CT is important to exclude interstitial lung disease and emphysema. The

presence of interstitial markings similar to those seen with advanced left ventricular failure such as diffuse central ground-glass opacification and thickening of interlobular septa suggest pulmonary veno-occlusive disease. Diffuse bilateral thickening of the interlobular septae and the presence of small, centrilobular, poorly circumscribed nodular opacities suggest pulmonary capillary haemangiomas.

CMR is the image modality of choice for assessment of RV function. Poor RV function, including stroke volume ≥ 25 mL/m², RV end-diastolic volume ≥ 84 mL/m², and LV end-diastolic volume ≤ 40 mL/m², are independent predictors of mortality and treatment failure.²³

Lung biopsy is not generally indicated.

Genetic screening is recommended to patients with an a priori diagnosis of PAH and not 'at-risk' populations being screened for PAH.³

Diagnosis of pulmonary arterial hypertension is by excluding other possibilities. Differential diagnosis of pulmonary hypertension in general is discussed in the Chapter on Classification.

Risk Stratification

The prognosis of PAH is poor, with mortality within 1 year depending on the severity of the disease (Tables 3-5). Right ventricular function is the major determinant of clinical outcomes and survival among patients with pulmonary hypertension.¹ Exercise-induced pulmonary artery systolic pressure (>30 mm Hg) indicates RV contractile reserve and a better prognosis.¹⁹ Table 6 presents recommendations for assessment and follow-up of patients with pulmonary arterial hypertension.

Therapy

Treatment of PAH is cumbersome.^{24,25} According to the revised haemodynamic definition by the ESC, PAH may be diagnosed in patients with mPAP >20 mmHg and PVR >2 WU.

However, the efficacy of drugs approved for PAH has only been demonstrated in patients with mPAP ≥ 25 mmHg and PVR >3 WU. Acute vasodilator testing to test the presence of pulmonary vasoreactivity has prognostic value and should be performed in all patients with idiopathic PAH for the choice of appropriate therapy. Those with overt right heart failure or hemodynamic instability should not undergo acute vasodilator testing.

General measures such as exercise, appropriate vaccinations, long-term oxygen therapy, and correction of iron deficiency should be considered (Tables 7 and 8). Exercise training is beneficial.²⁶ In-flight O₂ administration (2 L/min) should be considered for patients in WHO-FC III and IV and those with arterial blood O₂ pressure consistently <8 kPa (60 mmHg). Patients should avoid going to altitudes above 1500–2000 m without supplemental O₂. If AF

intervenes, rhythm control is recommended.¹⁷

Oxygen is recommended to maintain oxygen saturation greater than 90%.

Anticoagulation may be considered on an individual basis. Data from the COMPERA European registry indicate that the use of anticoagulants is associated with a survival benefit in patients with idiopathic, but not other forms of PAH such as due to connective tissue disease (mainly scleroderma), congenital heart disease, and portopulmonary hypertension.²⁷

Diuretics are used for symptomatic management of RV volume overload.

Calcium channel blockers, (but not the more potent negative inotropic verapamil) are indicated only for patients who have a positive acute vasodilator response (Tables 9 and 10, and Figure 2). Patients treated with calcium channel blockers as with other vasodilators, should be followed closely for both the safety and the efficacy of this therapy.

Nebivolol, has also been found to attenuate experimental pulmonary hypertension by correcting endothelial dysfunction.²⁸

Endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase activators, prostacyclin analogues, and prostacyclin receptor agonists are also approved for PAH. These drugs (encompassing 15 different compounds or routes of administration) target three main signaling pathways. **Endothelin receptor antagonists** block endothelin-1, which is a potent pulmonary vasoconstrictor. **Phosphodiesterase type 5 inhibitors** and **soluble guanylate cyclase activators** target the nitric oxide pathway and increase cyclic guanosine monophosphate, which is vasodilatory and anti-proliferative.

Prostacyclin analogues and **prostacyclin receptor agonists (prostanoids)** increase cyclic adenosine monophosphate, which is anti-proliferative, vasodilatory, and anti-thrombotic. Endothelin receptor antagonists are oral therapies that improve exercise capacity in PAH (Figure 3, and Tables 10-14). **Bosentan**,²⁹ and more selective antagonists such as **ambrisentan**³⁰ have been successfully tried in various forms of PAH. Another antagonist, sitaxentan, was withdrawn in 2010 due to reported cases of hepatic toxicity. Aminotransferase rise (3–10%) is less with ambrisentan, but liver function tests must be monitored indefinitely on a monthly basis. **Macitentan**, a relatively new dual endothelin-receptor antagonist, significantly reduced morbidity and mortality without aminotransferase rise but with increased incidence of headache, nasopharyngitis, and anemia (SERAPHIN trial).³¹

Prostanoids improve exercise capacity, hemodynamics, and is the preferred treatment option for the most critically ill patients. Intravenous **epoprostenol** is a therapy for PAH that has been shown to prolong survival, but its use may be prohibited by its high cost. Treatment is initiated at a dose of 2–4 ng/kg/min, with doses increasing at a rate limited by side effects (flushing, headache, diarrhoea, leg pain). The optimal dose varies between individual patients, ranging in the majority between 20 and 40 ng/kg/min. Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and

sepsis. Abrupt interruption of the epoprostenol infusion should be avoided as, in some patients, this may lead to death.¹⁷ **Treprostinil**, a prostanoid, may be delivered via either continuous intravenous or subcutaneous infusion. Initial dose is 1–2 ng/kg/min, with doses increasing at a rate limited by side effects (local site pain, flushing, headache), up to 20 and 80 ng/kg/min. Oral and inhaled formulations that avoid gram-negative infections induced by IV administration are promising. Oral treprostinil monotherapy has been shown to improve exercise capacity in PAH patients not receiving other treatment (FREEDOM-M trial).³² Therapy is generally well tolerated; the most common adverse events were headache (69%), nausea (39%), diarrhea (37%), and pain in jaw (25%). Inhaled treprostinil has also led to a smaller decline in FVC and fewer clinical-worsening events than placebo over the course of 52 weeks (TETON-1 and TETON-2 RCTs).³³ **Iloprost** is a prostanoid delivered by an adaptive aerosolized device 6 times daily (2.5–5 mg/inhalation). Inhaled iloprost is well tolerated, with flushing and jaw pain being the most frequent side effects.³⁴ **Selexipag**, an oral selective prostacyclin receptor antagonist, has been shown to reduce a composite of death and PAH-related complications compared to placebo.³⁵

Phosphodiesterase (PDE)-5 inhibitors (sildenafil and tadalafil) also improve exercise capacity and hemodynamics in PAH.^{36,37} Side effects are mild to moderate and mainly related to vasodilation (headache, flushing, epistaxis). A combination of ambrisentan with tadalafil has also been found useful (AMBITION trial).³⁸ Sildenafil has also been found useful for prophylaxis of swimming-induced pulmonary oedema.⁹

Riociguat is a soluble guanylate cyclase activator, acting in synergy with endogenous nitric oxide and also directly stimulating guanylate cyclase independently of nitric oxide availability. It increases the level of cGMP, with resultant vasorelaxation and antiproliferative and antifibrotic effects. In the PATENT-1 trial, riociguat significantly improved exercise capacity, and secondary efficacy end-points such as PVR, NTpro-BNP and functional class in patients with pulmonary arterial hypertension.³⁹ The drug received FDA approval in 2013. Treatment response is assessed by improvement in exercise capacity (6 minutes walk test, cardiopulmonary exercise test, treadmill test), and hemodynamics.

Imatinib is a specific inhibitor of the Bcr-Abl protein tyrosine kinase that has activity against platelet-derived growth factor (PDGF)-driven pathways. Among patients with advanced PAH who remained symptomatic on at least two PAH-specific drugs, treatment with imatinib compared with placebo was associated with significant improvements in echocardiographic measures of RV function, in addition to LV size and LV early diastolic relaxation (IMPRES trial).⁴⁰

Sotatercept is a novel fusion protein, member of the transforming growth factor β (TGF- β) superfamily, binds activins and growth differentiation factors in the attempt to restore balance between growth-promoting and growth-inhibiting signaling pathways. It has resulted in a

reduction in pulmonary vascular resistance in patients receiving background therapy for pulmonary arterial hypertension (PULSAR and STELLAR Trial)s.^{41,42} In the ZENITH RCT, among patients receiving the maximum tolerated dose of background therapy, sotatercept resulted in a lower risk of a composite of death from any cause, lung transplantation, or hospitalization (≥ 24 hours) for worsening pulmonary arterial hypertension than placebo.⁴³ In the HYPERION RCT, the addition of sotatercept to standard background therapy within the first year after the diagnosis of pulmonary arterial hypertension resulted in a lower risk of clinical worsening events than placebo among patients at an intermediate or high risk of death.⁴⁴

In patients with pre-capillary pulmonary hypertension (mainly PAH and chronic thromboembolic PH) and sleep-disturbed breathing on optimized pharmacological therapy, **nocturnal oxygen** (3 L/min), and **acetazolamide** (250 mg bd) may improve exercise capacity, and functional class.⁴⁵ New therapies are also being tested.¹

PCI with stenting is effective both for symptom relief and for long-term outcome in patients with extrinsic compression of the left main stem by a dilated pulmonary artery.²¹

Considerations for patients in need for **intensive care** are presented in Table 15.

Mechanical support of a failing right ventricle is an option as a bridge to transplantation or recovery.⁴⁶

Heart-lung or **bilateral lung transplantation** are options for selected patients who progress despite optimal medical management (Tables 16 and 17). Percutaneous interventional therapies such as atrial septostomy and transcatheter Pott's shunt are specialized procedures under assessment.⁴⁷

Non-cardiac Surgery

Patients with severe PAH, who are undergoing elective surgery, should be managed in a centre with appropriate and by the multidisciplinary pulmonary hypertension team (Table 18).

Pregnancy

Maternal and foetal risk are considerably increased in patients with PAH.⁴⁸ Recommendations are provided in Table 19.

Specific Subsets of Pulmonary Hypertension

Pulmonary Hypertension Associated with Drugs and Toxins

Several **drugs** and **toxins** may cause PAH or PAH associated pulmonary venous capillary abnormalities (Table 20) but it represents a rare complication, and many of these drugs have also been linked to other pulmonary complications such as parenchymal lung disease or pleural effusions.

Pulmonary arterial hypertension associated with connective tissue disease

Pulmonary arterial hypertension is a well-known pulmonary vascular complication of systemic lupus erythematosus, mixed CTD, and, rarely, dermatomyositis, and Sjögren's syndrome.³ The relationship between rheumatoid arthritis and PAH is not established. Recommendations are presented in Table 21.

Pulmonary arterial hypertension associated with HIV infection

Clinical and histopathological findings in PAH associated with HIV infection share many similarities with idiopathic PAH.³ Prognosis have improved with the availability of highly active antiretroviral therapy. Recommendations are provided in Table 22.

Pulmonary arterial hypertension associated with portal hypertension

Pulmonary arterial hypertension associated with **portal hypertension** develops in 2–6% of patients with portal hypertension, with or without liver disease. In PAH registries, portal pulmonary hypertension represents 5–15% of the patients.³ Recommendations are provided in Table 23.

Pulmonary arterial hypertension associated with congenital heart disease

The clinical classification of pulmonary arterial hypertension associated with congenital heart disease is presented in Table 24. Pulmonary hypertension in the context of congenital heart disorders may lead to Eisenmenger's syndrome (Table 25, see also ACHD).⁴⁹

Recommendations are provided in Tables 26 and 27.

Pulmonary hypertension associated with pulmonary venous capillary abnormalities

The typical histological findings of PAH are associated with an occlusive venopathy (pulmonary venoocclusive disease-PVOD) or a microvasculopathy (pulmonary capillary hemangiomatosis-PCH). In addition to the histology of PAH, these entities also exhibit the findings of pulmonary venous hypertension, including pulmonary hemosiderosis, interstitial edema, and lymphatic dilation.⁵⁰

The proportion of patients with IPAH that fulfil the criteria for PVOD/PCH is approximately 10%.³ Familial PVOD/PCH typically occurs in the young siblings of one generation, with unaffected and sometimes consanguineous parents, indicating that the disease segregates as a recessive trait. Biallelic mutations in the EIF2AK4 gene cause heritable PVOD/PCH.^{51,52} Rarely, PVOD/PCH may be seen in patients with systemic sclerosis or be associated with exposure to environmental triggers, such as alkylating agents (cyclophosphamide, mitomycin C), and solvents (trichloroethylene).⁵³

Patients with PVOD are more severely hypoxaemic and have a much lower diffusion capacity of carbon monoxide than in other forms of PAH. High-resolution CT scanning is the investigation of choice. Typical findings suggestive of PVOD are the presence of subpleural thickened septal lines, centrilobular ground-glass opacities (contrasting with a panlobular

distribution found in idiopathic PAH), and mediastinal lymphadenopathy. Changes consistent with pulmonary edema may also be seen on CT imaging in patients with PVOD. Wedge pressure is normal in veno-occlusive disease. Pulmonary capillary hemangiomatosis is difficult to differentiate from PVOD, and the diagnostic and therapeutic aspects are very similar. Medical therapy is unsatisfactory and lung transplantation is the only curative option. Therapy is undertaken in specializing centers (Table 28).

Pulmonary hypertension during anticancer treatment

The management of pulmonary hypertension during anticancer treatment is presented in Table 29.

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