Diagnosis and management of pulmonary arterial hypertension

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Shareable abstract (@ERSpublications)
The preceding decades have witnessed significant improvements in our understanding of PAH and an expansion in treatment options. The haemodynamic definition of PAH has been refined and a number of risk assessment tools have been developed. https://bit.ly/3CKYNpV

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Abstract

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature that is characterised by elevated pressures within the pulmonary vascular tree. Recent decades have witnessed a dramatic expansion in our understanding of the pathobiology and the epidemiology of PAH, and improvements in treatment options and outcomes. The prevalence of PAH is estimated to be between 48 and 55 cases per million adults. The definition was recently amended and a diagnosis of PAH now requires evidence of a mean pulmonary artery pressure >20 mmHg, a pulmonary vascular resistance >2 Wood units and a pulmonary artery wedge pressure ⩽15 mmHg at right heart catheterisation. Detailed clinical assessment and a number of additional diagnostic tests are required to assign a clinical group. Biochemistry, echocardiography, lung imaging and pulmonary function tests provide valuable information to assist in the assignment of a clinical group. Risk assessment tools have been refined, and these greatly facilitate risk stratification and enhance treatment decisions and prognostication. Current therapies target three therapeutic pathways: the nitric oxide, prostacyclin and endothelin pathways. While lung transplantation remains the only curative intervention for PAH, there are a number of promising therapies under investigation which may further reduce morbidity and improve outcomes.
This review describes the epidemiology, pathology and pathobiology of PAH and introduces important concepts regarding the diagnosis and risk stratification of PAH. The management of PAH is also discussed, with a special focus on PAH specific therapy and key supportive measures.

Educational aims

- To provide an introduction to the epidemiology, pathology and pathobiology of pulmonary arterial hypertension.
- To describe important diagnostic tests and risk assessment tools.
- To outline the therapeutic pathways and important supportive measures in pulmonary arterial hypertension.

Introduction

Pulmonary hypertension (PH) is a prevalent disease that is characterised by elevated pressures within the pulmonary circulation. The haemodynamic definition of PH requires right heart catheterisation (RHC) and demonstration of a mean pulmonary artery pressure (mPAP) >20 mmHg [1, 2]. Detailed clinical assessment and a variety of additional investigations are required to assign a clinical group. Clinically, PH is classified into one of five distinct groups based on shared clinical, haemodynamic and treatment characteristics [1, 3]. These include group 1 pulmonary arterial hypertension (PAH), group 2 PH associated with left heart disease (PH-LHD), group 3 PH associated with lung disease and/or hypoxia, group 4 PH associated with pulmonary artery obstructions, and group 5 PH with unclear and/or multifactorial mechanisms [1–3]. This review focuses on group 1 PAH and outlines important concepts surrounding the diagnosis, risk assessment and treatment of these cases.

Epidemiology

PAH is a progressive disease of the pulmonary vasculature that is characterised by premature morbidity and mortality. The pathology of PAH was first published in 1891 by von Romberg, but it wasn't until 1951 that the first detailed clinical description of primary PH, now referred to as idiopathic PAH (IPAH), was published by Dresdale and co-workers [4]. The disease soon attracted international attention, due to the epidemic of anorexigen-associated PAH in the 1960s associated with the appetite suppressant aminorex [5]. This crisis inspired the first World Symposium on PH (WSPH), in 1973, and generated the first cohesive PH classification system. The classification has been further refined at subsequent WSPH and PAH is now assigned to Group 1 in the current classification system. Group 1 PAH is further divided into subgroups as outlined in table 1. These include subgroups such as IPAH, heritable PAH (HPAH), drug-associated PAH (DPAH) and PAH associated with connective tissue disease (CTD-PAH).

The true global incidence and prevalence of PAH are unknown. Analysis of contemporary registries indicate that PAH has an incidence and prevalence of approximately six and 48–55 cases per million adults, respectively [2]. The age at diagnosis varies, and often ranges from individuals in their forties to late sixties [9]. Specific PAH subgroups, such as HPAH, typically demonstrate a female predominance and may present at a younger age. However, the demographics of PAH are evolving and an equal sex distribution is often observed in older subjects. Furthermore, older individuals with PAH may have confounding comorbidities and present with more advanced and symptomatic disease. Therefore, a high index of suspicion is required to avoid delayed or missed diagnoses [10].

Pathology

The pulmonary circulation is a high flow, low pressure circuit, which receives the entire cardiac output from the right heart. The pulmonary arteries transport deoxygenated blood from the right ventricle to the pulmonary capillaries for gas exchange. In PAH, there is pulmonary artery remodelling due to proliferation, inflammation and thrombosis *in situ*. This results in progressive luminal narrowing and leads to increased pulmonary vascular resistance (PVR) and right ventricular afterload, which culminates in right heart failure if left untreated. The histopathological changes in PAH involve all three layers of the pulmonary artery wall, including the intima, media, and adventitia.

Endothelial cells are the predominant cell type in the intima. In PAH, endothelial cells may adopt contractile and motility properties that are typical of cells of mesenchymal origin such as smooth muscle cells, a process that is termed endothelial-to-mesenchymal transition [11]. Concentric intimal fibrosis (onion-skin lesions) is also frequently noted, in association with plexiform lesions. Plexiform lesions are often considered the histological hallmark of PAH and they consist of organised vascular channels formed by the monoclonal proliferation of endothelial cells [12]. Their biological significance remains unclear, and it has been proposed that they may represent anastomosing bronchial and pulmonary circulations [13]. Thrombosis *in situ*, organised thrombotic lesions (termed "colander-like-lesions") and atypical fibrovascular lesions (called singular millimetric fibrovascular lesions (SiMFis)) have also been described [14].

The media of pulmonary arteries are rich in smooth muscle cells, and these are often hyperplastic in PAH [15]. The surrounding adventitia is a diverse compartment, which is full of fibroblasts, inflammatory cells and pericytes [16, 17]. Altered fibroblasts characteristics, perivascular inflammation and ectopic lymphoid tissues are also commonly observed in PAH. Histopathological changes in capillaries, post-capillary venules and veins, bronchial vessels and the right ventricle have also been shown [14, 15].

Pathobiology

The pathobiology of PAH is complex and cannot be isolated to a single pathway or defect. The following section focuses on key molecular pathways and genetic factors that have been implicated in the pathobiology of PAH. However, a comprehensive overview of the pathobiology is beyond the scope of this review.

PAH is characterised by an imbalance of vasoactive mediators, with a relative deficiency of nitric oxide and prostacyclin, and an excess of endothelin and thromboxane [14]. In the pulmonary circulation, nitric oxide and prostacyclin are important vasodilators and replacement is an important therapeutic strategy [18]. Conversely, endothelin-1 is increased in PAH and attenuation of this pathway is another key therapeutic strategy in PAH [19, 20].

Transforming growth factor-β (TGF-β) and bone morphogenetic protein (BMP) signalling is imbalanced in PAH, with reduced signalling *via* the BMP pathway and increased signalling *via* the TGF-β pathway [21]. This results in a pro-proliferative environment and contributes to pulmonary vascular remodelling (figure 1).

TABLE 1 An overview of the clinical classification of pulmonary hypertension (PH), with associated conditions and important investigations to consider

Group 1 Pulmonary arterial hypertension (PAH)	
1.1 Idiopathic PAH	
1.1.1 Non-responders at vasoreactivity testing	Important to exclude alternative causes of PAH before assigning this diagnosis
1.1.2 Acute responders at vasoreactivity testing	Diagnosed during vasoreactivity testing at RHC: • mPAP reduction of ⩾10 mmHg (to <40 mmHg) • Cardiac output is increased/maintained
1.2 Heritable PAH	Enquire regarding family history of PAH • Offer genetic counselling and consider gene panel • *e.g.* gene mutations in BMPR2, EIF2AK4, TBX4, ACVRL1, ENG [6]
1.3 Associated with drugs and toxins	Enquire regarding specific drug and toxin exposure at home and at work (*e.g.* aminorex, fenfluramine, methamphetamines)
1.4 Associated with:	
1.4.1 Connective tissue disease (CTD)	CTDs associated with PAH include SSc-PAH, SLE, mixed CTD, rheumatoid arthritis, dermatomyositis, Sjögren syndrome [3] Considerations for subjects with SSc and suspected PAH: • Ask regarding symptoms of Raynaud's, GORD, *etc*. • Examine for features such as digital ulcers, sclerodactyly, calcinosis, telangiectasia, microstomia; consider nailfold capillaroscopy • Request serum ANA and CTD panel • Exclude comorbid LHD, and ILD in suspected SSc-PAH
1.4.2 HIV infection	Assess for infection with HIV
1.4.3 Portal hypertension	Portal hypertension with or without cirrhosis is associated with PAH Investigate with: • Liver screen including autoimmune serology, viral hepatitis screen and HIV • Doppler ultrasound of liver and portal system • A hepatic venous pressure gradient >5 mmHg during invasive catheterisation (may be normal in subjects with extrahepatic portal hypertension)
1.4.4 Congenital heart disease	Eisenmenger syndrome; PAH associated with prevalent systemic-to-pulmonary shunts, PAH-with small/coincidental defects, PAH after defect correction [3, 7] Consider investigation with: • Doppler and contrast echocardiography • Cardiac MRI • Stepwise assessment of oxygen saturations at RHC if left-to-right shunt suspected
1.4.5 Schistosomiasis	Present in 5% of patients with hepatosplenic schistosomiasis infection Consider investigation with: • Confirm infection, *e.g.* through the detection of parasite eggs in the stool or urine • Doppler ultrasound of liver and portal system to assess for portal hypertension
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement	Consider family history, medical history (*e.g.* prior chemotherapy), occupational exposures (*e.g.* organic solvents) Consider genetic screening for EIF2AK4 Suspect if: • Often accompanied by severe hypoxia and marked reductions in D_{LCO} (<50%) • Treatment with PAH specific therapy may be complicated by pulmonary oedema • CT thorax: septal lines, centrilobular ground-glass opacities, mediastinal adenopathy
1.6 Persistent PH of the newborn	Failed circulatory adaptation at birth with sustained elevation in PVR; diagnosed in neonates and often resolves
Group 2 PH associated with left heart disease	
Consider the pre-test probability of LHD and ensure adequate imaging of left heart, such as echocardiography, cardiac MRI. If suspected, consider fluid challenge at RHC [2, 8].	
2.1 Heart failure:	
2.1.1 With preserved ejection fraction	
2.1.2 With reduced or mildly reduced ejection fraction	
2.2 Valvular heart disease	
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH	
Group 3 PH associated with lung diseases and/or hypoxia	
Investigate with ABG, PFTs, chest imaging such as high-resolution CT thorax, polysomnography.	
3.1 Obstructive lung disease or emphysema	
3.2 Restrictive lung disease	
3.3 Lung disease with mixed restrictive/obstructive pattern	
3.4 Hypoventilation syndromes	

Continued

TABLE 1 Continued

3.5 Hypoxia without lung disease (*e.g.* high altitude)
3.6 Developmental lung disorders
Group 4 PH associated with pulmonary artery obstructions
CTPA and *V′*/*Q′* imaging are important investigations. Consider invasive pulmonary angiogram if Group 4 PH suspected.
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
Group 5 PH with unclear and/or multifactorial mechanisms
Guided by individual history and assessment.
5.1 Haematological disorders
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis

RHC: right heart catheterisation; mPAP: mean pulmonary artery pressure; BMPR2: bone morphogenetic protein receptor type 2; EIF2AK4: eukaryotic translation initiation factor 2 alpha kinase 4; TBX4: T-box 4; ACVRL1: activin receptor-like kinase 1 (ALK1); ENG: endoglin; SSc: systemic sclerosis; SLE: systemic lupus erythematosus; GORD: gastro-oesophageal reflux disease; ANA: antinuclear antibody; LHD: left heart disease; ILD: interstitial lung disease; MRI: magnetic resonance imaging; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; D_{LCO}: diffusion capacity of the lung for carbon monoxide; CT: computed tomography; PVR: pulmonary vascular resistance; ABG: arterial blood gas; PFTs: pulmonary function tests; CTPA: computed tomography pulmonary angiogram; *V′*/*Q′*: ventilation/perfusion. Reproduced and modified from [2], with permission.

Mutations in the BMP receptor 2 (BMPR2) gene represent the main PAH susceptibility gene and carriers have a 20% lifetime risk of developing PAH [2, 4]. BMPR2 gene mutations are inherited in an autosomal dominant pattern, with incomplete penetrance and a female preponderance [22, 23]. The difference in penetrance between female and male carriers (*i.e.* females with BMPR2 gene mutations are more likely to develop HPAH than males) indicates that additional factors are necessary for disease manifestation. This underscores the complex interplay of genetic and environmental factors in the pathobiology of PAH. Several additional gene mutations have been identified and some of these are displayed in table 2.

Assessment and investigations in PAH

Clinical history and examination

Comprehensive clinical assessment is essential to identify suspected cases of PH and to accurately assign a clinical group. Clinical symptoms of PAH are often nonspecific and may be difficult to differentiate from other cardiorespiratory conditions by history alone. Symptoms often include dyspnoea, fatigue, signs of right heart failure and syncope. Past medical history, prior diet pill and drug exposures, and family history of PAH should be explored in detail. Clinical examination may reveal signs of the underlying aetiology. For example, sclerodactyly, digital ulceration, telangiectasia and microstomia would be indicative of systemic sclerosis as the cause of PAH, while the presence of digital clubbing would guide the examiner to consider cyanotic congenital heart disease, interstitial lung disease (ILD) or liver disease as potential aetiologies [3]. Furthermore, clinical assessment of volume status is important to guide decisions regarding right heart function, risk stratification and diuretic therapies.

Investigations

Routine full blood count, liver and renal profiles, thyroid function tests, and N-terminal pro-brain natriuretic peptide (NT-proBNP) should be requested in all patients. A number of additional blood tests should be requested at baseline for specific conditions that are associated with PAH, as highlighted in table 1. These include HIV and hepatitis screens and CTD panels including serum antinuclear antibody, anti-centromere antibodies and dsDNA antibodies [3]. Genetic counselling, consent and testing should be considered in specific PAH subgroups such as IPAH, suspected HPAH and pulmonary veno-occlusive disease (PVOD) (table 2) [3, 6].

Pulmonary function tests

Pulmonary function tests (PFTs) provide very helpful information in PH [3]. Spirometry can assess for underlying obstructive or restrictive lung disease and the diffusion capacity of the lung for carbon monoxide (D_{LCO}) can provide prognostic information [28]. Additionally, the D_{LCO} might suggest specific diagnoses, as marked reductions (*e.g.* <45%) are often associated with PVOD, systemic sclerosis associated PAH and ILD (group 3 PH). Cardiopulmonary exercise testing (CPET) has a typical pattern in subjects

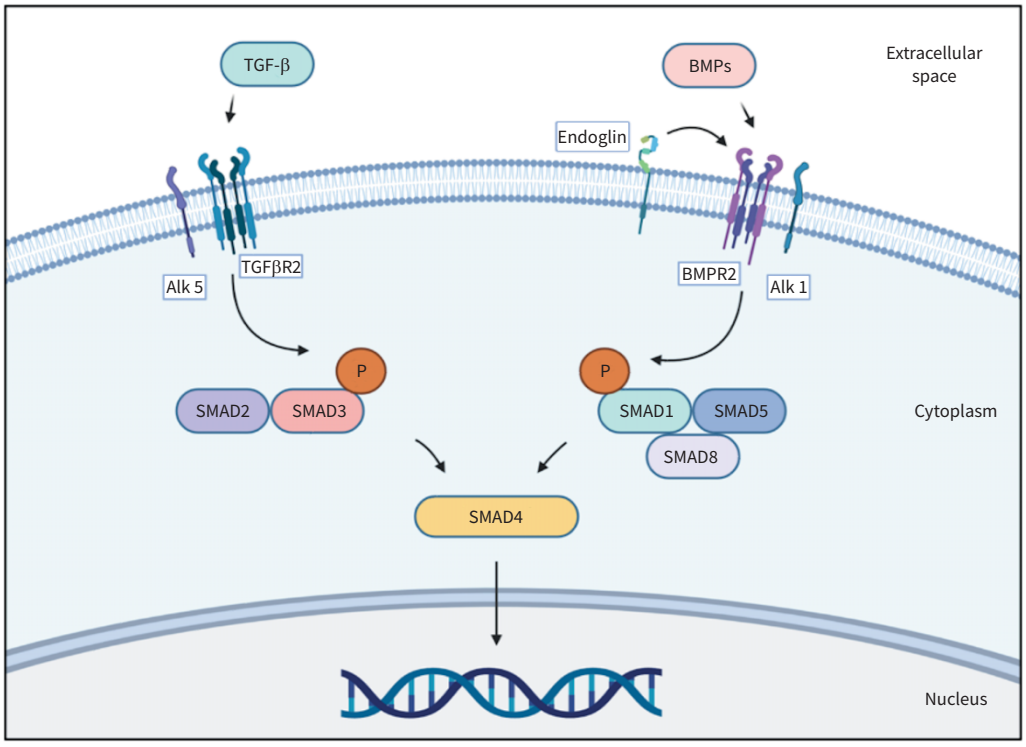

FIGURE 1 Transforming growth factor-β (TGF-β) and bone morphogenetic protein (BMP) signalling pathways in pulmonary arterial hypertension (PAH). In the extracellular space, ligands such as such as BMP9 or BMP10 bind to BMP receptor 2 (BMPR2). This forms a heteromeric complex with ALK1 (activin receptor-like kinase 1 or ACVRL1) and associates with the co-receptor endoglin, to trigger a cascade of intracellular events, including the phosphorylation of receptor-regulated SMADs (small mothers against decapentaplegic), SMADs 1, 5 and 8 proteins. These proteins form a complex with the common mediator SMAD, named SMAD4, and translocate to the nucleus to modulate gene transcription. This pathway is disrupted in PAH, with resultant increased signalling *via* the TGFβR2/ALK-5/SMAD2 and SMAD3 pathway, and subsequent pro-proliferative signalling. This figure was created with BioRender.com.

with pulmonary vascular disease, demonstrating a low end-tidal partial pressure of carbon dioxide, high ventilatory equivalent for carbon dioxide (minute ventilation/carbon dioxide production), low oxygen pulse (oxygen uptake/heart rate), and low peak oxygen uptake (V'_{O_2}) [2]. This can be useful to phenotype and risk stratify patients with PAH.

Echocardiography

Echocardiography is one of the most important diagnostic tests to consider in subjects with suspected PH. Measurement of the peak tricuspid regurgitation velocity (TRV) and additional echocardiographic variables in symptomatic subjects can estimate the probability of PH [3]. This can be stratified as low, intermediate or high probability and can guide decisions regarding which patients would benefit from additional RHC. A peak TRV >3.4 $m \cdot s^{-1}$ suggests a high probability of PH in a symptomatic patient. Conversely, a peak TRV $\leqslant$2.8 $m \cdot s^{-1}$ in the absence of other PH echocardiography signs indicates a low probability of PH [2].

Echocardiographic parameters also facilitate comprehensive risk assessment in subjects with established PAH [2]. The right atrial area, the presence of a pericardial effusion and the ratio of tricuspid annular plane systolic excursion (TAPSE) to pulmonary arterial systolic pressure (PASP) are meaningful prognostic parameters in PAH. The TAPSE/PASP ratio is a valuable, noninvasive indication of right ventricle and pulmonary artery coupling, which is typically impaired in severe PAH [2].

Radiology

A number of radiological investigations are valuable in the assessment of subjects with PAH. These include chest radiography, computed tomography (CT) and ventilation–perfusion (V'/Q') imaging. CT pulmonary angiogram can assess for parenchymal lung disease and for features of chronic thromboembolic

TABLE 2 Important pulmonary arterial hypertension (PAH) susceptibility genes

Genes	Overview	References
BMPR2	Member of the TGF-β receptor superfamily Ubiquitously expressed, important for vascular homeostasis Autosomal dominant inheritance, with incomplete penetrance (estimated 14% penetrance in male carriers and 42% in female carriers) Mutations associated with paediatric and adult PAH	[22]
ALK1/ACVRL1	Member of the TGF-β receptor superfamily Forms a heteromeric complex with BMPR2 Causes PAH associated with HHT Mutations are associated with paediatric and adult PAH	[24, 25]
Endoglin	Member of the TGF-β receptor superfamily Co-receptor to BMPR2/ALK1 receptors Causes PAH associated with HHT	[25]
SMAD9	Important protein in the BMP signalling pathway Encodes the transcription factor Smad8	[25]
BMP9/GDF2	Mediator in the BMP signalling pathway Encodes the BMP9 ligand	[22]
TBX4	Associated with small patella/coxopodopatellar syndrome Mutations are associated with paediatric and adult PAH Its precise role in the development of PAH is unclear	[25, 26]
CAV1	Encodes the protein caveolin-1, which is responsible for the integrity of caveolae; these are specialised invaginations in endothelial plasma membranes that are rich in cell surface receptors, including BMPR2 and endothelial nitric oxide synthase This is important for vascular homeostasis and is implicated in proliferative, apoptotic signalling Mutations in this gene are a rare cause of HPAH	[22, 25]
KCNK3	Also called TASK-1 (TWIK-related acid-sensitive K^+ channel 1) This was the first identified channelopathy in PAH Encodes a pH-sensitive potassium channel, which is important for the regulation of plasma membrane resting potential Reduced function of KCNK3 in PAH may affect vascular tone	[25]
EIF2AK4	Encodes GCN2 (general control nonderepressible 2) which is a serine-threonine kinase with a role in cellular adaptation to stress and amino acid deprivation Mutations are associated with paediatric and adult PAH Autosomal recessive inheritance, with near complete penetrance Results in pulmonary veno-occlusive disease/PCH The exact mechanism by which this leads to pulmonary vascular disease is unclear	[27]

An overview of gene mutations in heritable PAH (HPAH). These mutations are inherited in an autosomal dominant fashion, with reduced penetrance, apart from EIF2AK4 (eukaryotic translation initiation factor 2α kinase 4), which is inherited in an autosomal recessive pattern, with suspected near complete penetrance. BMPR2: bone morphogenetic protein receptor 2; TGF-β: transforming growth factor-β; ALK1/ACVRL1: activin A receptor-like type 1; HHT: hereditary haemorrhagic telangiectasia; SMAD: small mothers against decapentaplegic; BMP: bone morphogenetic protein; GDF2: growth and differentiation factor 2; TBX4: T-box 4; CAV1: caveolin-1; KCNK3: potassium channel two-pore domain subfamily K member 3; PCH: pulmonary capillary haemangiomatosis.

pulmonary hypertension (CTEPH). *V′/Q′* imaging of the lungs is important to exclude distal CTEPH, which might otherwise be missed. Doppler ultrasound of the liver and portal system should be performed to exclude underlying portal hypertension and cirrhosis. The role of cardiac magnetic resonance imaging (cMRI) in the assessment of subjects with PAH has evolved and the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH incorporate cMRI into the updated risk stratification table [2]. These parameters include cMRI right ventricular end-systolic volume index, right ventricular ejection fraction and stroke volume index.

Invasive diagnostics

Right heart catheterisation

RHC is an invasive test that provides direct access to pulmonary haemodynamics. The first human RHC was performed in 1929 by the newly qualified Dr Werner Forssmann on himself [29]. This was subsequently refined by Cournand and Richards in the 1940s and their collective work received the Nobel Prize in 1956 [4]. RHC is a technically demanding and nuanced procedure and there are specific recommendations regarding the execution of these procedures [3]. Ideally, RHC and vasoreactivity testing should be performed in expert centres, where they are typically associated with low morbidity and mortality [30].

The information obtained from RHC should be combined with clinical characteristics to assign patients to one of five clinical groups. This information can be used to facilitate risk stratification and prognostication. A resting mPAP >20 mmHg at RHC is diagnostic of PH [1]. This threshold was reduced from a mPAP of ⩾25 mmHg at the sixth WSPH, reflecting that 20 mmHg is the upper limit of normal, and that a normal mPAP is 14±3 mmHg [3, 31]. Once PH is confirmed, the haemodynamic pattern can be described using the mPAP, pulmonary artery wedge pressure (PAWP) and PVR [2].

Haemodynamic patterns at RHC:

- Pre-capillary:
  mPAP >20 mmHg, PVR >2 Wood units (WU), PAWP ⩽15 mmHg
- Post-capillary:
  mPAP >20 mmHg, PVR ⩽2 WU, PAWP >15 mmHg
- Combined pre- and post-capillary:
  mPAP >20 mmHg, PVR >2 WU, PAWP >15 mmHg

Consideration of the PAWP is necessary to accurately interpret RHC results and differentiate pre-capillary from post-capillary disease. The PAWP is obtained by inflating a balloon at the tip of the catheter and wedging it into a distal pulmonary artery, in order to occlude it. This creates a static column of blood from the occluded pulmonary artery to the left heart, that is used to estimate left atrial pressure. A normal PAWP ranges from 6 to 12 mmHg and values higher than this are indicative of underlying left heart disease. However, the measurement is affected by intrathoracic swings in pressure during the respiratory cycle, which can be particularly pronounced in subjects with underlying lung disease. Therefore, if there is any uncertainty regarding the accuracy of this measurement, then left heart catheterisation (LHC) *via* arterial access and measurement of the left ventricular end-diastolic pressure (LVEDP) should be considered [3, 32].

Another key measurement at RHC is the PVR. The PVR describes the resistance to blood flow through the pulmonary vasculature, which is elevated in PAH. The updated haemodynamic definition of PAH uses a PVR threshold of >2 WU to diagnose PAH. This is reduced from the former threshold of >3 WU [2]. The PVR is calculated as a ratio of the transpulmonary gradient to cardiac output using the following equation [33]:

$$\mathrm{PVR}=\frac{\mathrm{mPAP}\ -\ \mathrm{PAWP}}{\mathrm{CO}}$$

Additional important RHC parameters include the cardiac output (CO), cardiac index (CI), mean right atrial pressure (mRAP), stroke volume index (SVI) and mixed venous oxygen saturation (S_{vO_2}) [2].

Vasoreactivity testing

All patients with IPAH, HPAH and DPAH should undergo acute vasoreactivity testing. This involves the administration of a vasoactive agent such as inhaled nitric oxide or inhaled iloprost during RHC [2]. Less than 10% of these patients will have an acute response during vasoreactivity testing and even less will maintain long-term responsiveness. However, those that do can be treated with long-term calcium channel blockers and typically have a favourable prognosis [34]. Vasoreactivity testing is not routinely performed in other PAH subgroups or PH groups as the diagnostic yield is low and the test may result in unwanted side-effects, such as pulmonary oedema [3]. The definitions of an acute and a long-term responder are as follows [34].

Acute responder:

- mPAP reduction of ⩾10 mmHg (to a value ⩽40 mmHg)
- Cardiac output increased/maintained (*i.e.* does not drop with testing)

Long-term responder:

- Sustained clinical (*i.e.* functional class I/II), biochemical (B-type natriuretic peptide <50 $ng \cdot L^{-1}$ or NT-proBNP <300 $ng \cdot L^{-1}$) and haemodynamic response to calcium channel blocker monotherapy for greater than 12 months

Screening in specific populations

Screening high-risk populations for PAH is important, as early diagnosis and treatment may lead to better long-term outcomes [3]. Current screening strategies focus on specific populations with a high prevalence of PAH; namely, first-degree relatives of individuals with HPAH, patients with portal hypertension undergoing assessment for liver transplantation and individuals with systemic sclerosis [35].

The DETECT algorithm is a two-step screening tool that was designed to identify PAH in asymptomatic individuals with systemic sclerosis, due to the high prevalence of the disease in this group. Step 1 of the algorithm determines which patients will require echocardiography and step 2 suggests who would benefit from additional RHC. Step 1 examines six variables: forced vital capacity % predicted/D_{LCO} % predicted, current/past telangiectasias, anti-centromere antibodies, NT-proBNP, serum urate and right axis deviation on ECG. Step 2 incorporates right atrial area and TRV at echocardiography to determine whether RHC is required [36]. Screening tools such as these are invaluable to augment clinical decision making and to identify PAH at an earlier stage. It should be noted, that if subjects with systemic sclerosis require RHC, caution is advised in those with severe Raynaud phenomenon or digital ulceration, as the radial approach can result in digital ischaemia.

Risk assessment in PAH

Comprehensive risk assessment in PAH is multifaceted, dynamic and an important component of individualised patient care. A number of scores, tables and equations have been developed to facilitate this. The National Institutes of Health equation was the first prognostic equation dedicated to risk assessment in PAH [37]. This used three RHC parameters: mPAP, mRAP and cardiac index. Since then, risk assessment has evolved and typically incorporates various clinical, laboratory, imaging and haemodynamic parameters, as outlined in table 3.

Decisions regarding which assessment tool to use in day-to-day clinical practice are often guided by individual physician preference. Popular risk stratification tools include the ESC/ERS risk stratification table and the REVEAL (Registry to Evaluate Early And Long-term PAH Disease Management) registry risk equations and scores [2, 3, 41, 49–52]. The ESC/ERS risk stratification table was recently updated in the revised 2022 guidelines [2]. Multiparametric risk assessment is used to estimate the 1-year mortality risk and divides patients into low (<5%), intermediate (5–20%) and high risk (>20%) strata [2]. At follow-up visits, a noninvasive four-strata model is now recommended, using World Health Organization functional class, 6-min walking distance and NT-proBNP. Patients are divided into low, intermediate-low, intermediate-high and high-risk groups [2].

The REVEAL registry risk equation and scores were derived using statistical methods and consist of 12–14 weighted, modifiable and non-modifiable variables. Risk is divided into five strata in order to provide an estimation of the likelihood of survival in the next 12 months [41, 49–52]. Several additional risk stratification tools have been developed using the REVEAL registry, including the REVEAL 1.0 risk score calculator [49], simplified noninvasive REVEAL model [53], REVEAL 2.0 risk calculator [51], REVEAL Lite 2 [54] and PHORA risk prediction model [55].

Accurate risk assessment guides treatment decisions and prognostication. When used appropriately and at regular intervals, these tools augment clinical judgement. The acquisition and maintenance of a low-risk profile is the goal of care and is consistently associated with a favourable prognosis [41, 50, 52]. Failure to do so should prompt further interventions, including escalation of PAH therapy and consideration of referral for lung transplant assessment. Some of the risk stratification tools are outlined in table 3.

Management and treatment

Individuals with PAH should be managed by multidisciplinary teams in expert centres. As it is a rare and progressive disease, a dynamic and person-centred approach is required. Typically, there is no “one-size-fits-all” and individual patient characteristics and needs may change over time. This section provides a brief introduction to PAH specific therapy and important supportive measures.

PAH specific therapy

The first approved drug for PAH was parenteral epoprostenol in 1995 [56]. Epoprostenol is a synthetic prostacyclin analogue that is administered by continuous intravenous infusion *via* a permanent central venous catheter. It is a potent, short-acting vasodilator and inhibitor of platelet aggregation. Monotherapy with epoprostenol was revolutionary for a disease that had a median survival of 2.8 years from the time of diagnosis. It led to improvements in exercise capacity, haemodynamic profiles and a reduction in mortality in individuals with IPAH [57]. More therapies subsequently became available and in modern practice, there are three central treatment pathways: the prostacyclin, nitric oxide and endothelin pathways [3].

Endothelial dysfunction in the pulmonary vasculature in PAH is associated with reduced levels of endogenous nitric oxide and prostacyclin, and increased levels of endothelin-1. This results in an imbalance of vasoactive mediators, leading to vasoconstriction and remodelling in the pulmonary circulation. The aim of therapy is to restore this balance, by augmenting nitric oxide and prostacyclin pathways, and attenuating endothelin

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TABLE 3 Overview of some of the risk assessment tools for pulmonary arterial hypertension (PAH)

Risk assessment tool	Year of publication	Patients included	PAH subgroup	Variables included					Survival estimation
				Clinical	Exercise	Laboratory	Imaging	Haemodynamic	
NIH equation [37]	1991	Incident	IPAH	#	#	#	#	1. mPAP 2. mRAP 3. CI	1-, 3-, 5-year
PH connection registry [38]	2010	Incident and prevalent	IPAH HPAH APAH	#	#	#	#	1. mPAP 2. mRAP 3. CI	1-, 3-, 5-year
FPHN registry risk equation [39, 40]	2010	Incident and prevalent	IPAH HPAH APAH	1. Sex	2. 6MWD	#	#	3. CO	1-, 2-, 3-year
REVEAL registry [41]	2010	Incident and prevalent	Group 1 PAH	1. Age 2. Sex 3. PAH subgroup 4. Renal insufficiency 5. FC 6. SBP 7. HR	8. 6MWD	9. BNP	10. Pericardial effusion 11. D_{LCO}	12. PVR 13. mRAP	1-year
Scottish composite score [42]	2012	Incident	Group 1 PAH (CHD-PAH and CCB-R excluded)	1. Age 2. Sex 3. PAH subgroup	4. 6MWD	#	#	5. mRAP 6. CO	1-, 2-, 3-year
Nickel *et al*. [43]	2012	Incident	IPAH	# *FC, NT-proBNP, CI, S_{vO_2} at follow-up*	1. 6MWD	2. NT-proBNP	#	3. CI 4. S_{vO_2}	1-, 3-, 5-year
ESC/ERS 2015 Guidelines [3]	2015	#	Group 1 PAH	1. Progression of symptoms 2. Syncope 3. FC 4. Clinical signs RHF	5. 6MWD 6. Peak V'_{O_2} (CPET) 7. V'_E/V'_{CO_2} slope (CPET)	8. BNP/ NT-proBNP	9. RA area 10. Pericardial effusion	11. RAP 12. CI 13. S_{vO_2}	1-year
FPHN registry [44]	2017	Incident	IPAH HPAH DPAH	1. FC *FC, 6MWD, BNP/ NT-proBNP at first follow-up*	2. 6MWD	#	#	3. mRAP 4. CI	1–5 years
COMPERA registry [45]	2017	Incident	Group 1 PAH	1. FC	2. 6MWD	3. BNP/ NT-proBNP	#	4. mRAP 5. CI	1–5 years
SAPHR registry [46]	2018	Incident	Group 1 PAH	1. FC	2. 6MWD	3. NT-proBNP	4. RA area 5. Pericardial effusion	6. mRAP 7. CI 8. S_{vO_2}	1-, 3-, 5-years

Continued

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TABLE 3 Continued

Risk assessment tool	Year of publication	Patients included	PAH subgroup	Variables included					Survival estimation
				Clinical	Exercise	Laboratory	Imaging	Haemodynamic	
Modified Risk Assessment Score of PAH [47]	2018	Incident and prevalent	Group 1 PAH	1. FC	2. 6MWD	3. BNP	4. RA area	#	1-year
COMPERA 2.0 [48]	2021	Incident	Group 1 PAH	1. FC	2. 6MWD	3. BNP/ NT-proBNP	#	#	1-, 3-, 5-years
ESC/ERS 2022 Guidelines [2]	2022	#	Group 1 PAH	1. Progression of symptoms 2. Syncope 3. FC 4. Clinical signs RHF	5. 6MWD 6. Peak V'_{O_2} (CPET) 7. V'_E/ V'_{CO_2} slope (CPET)	8. BNP/ NT-proBNP	9. Echocardiography: RA area Pericardial effusion TAPSE/PASP 10. cMRI: RVEF SVI RVESVI	11. RAP 12. CI 13. S_{vO_2} 14. SVI	1-year

NIH: National Institutes of Health; PH: pulmonary hypertension; FPHN: French PH Network; REVEAL: US Registry to Evaluate Early and Long-term PAH Disease Management; ESC/ERS: European Society of Cardiology/European Respiratory Society; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; SAPHR: Swedish PAH register; IPAH: idiopathic PAH; HPAH: hereditary PAH; APAH: anorexigen-associated PAH; CHD: congenital heart disease; CCB-R: long-term responder to calcium channel blockers; DPAH: drug-associated PAH; FC: functional class; SBP: systolic blood pressure; HR: heart rate; RHF: right heart failure; 6MWD: 6-min walk distance; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro-brain natriuretic peptide; D_{LCO}: diffusion capacity of the lung for carbon monoxide; RA area: right atrium area; mPAP: mean pulmonary artery pressure; mRAP: mean right atrial pressure; CI: cardiac index; CO: cardiac output; PVR: pulmonary vascular resistance; S_{vO_2}: mixed venous oxygen saturation; TAPSE/PASP: tricuspid annular plane systolic excursion/pulmonary arterial systolic pressure; RVEF: right ventricular ejection fraction; SVI: stroke volume index; RVESVI: right ventricular end-systolic volume index; V'_{O_2}: oxygen uptake; CPET: cardiopulmonary exercise testing; V'_E: minute ventilation. #: absent data.

signalling. It is common practice to prescribe a combination of PAH specific therapies, using one drug from each of these pathways (table 4). Initial double combination therapy is recommended for most patients, with a view to achieving a low-risk profile. The first clinic visit following the initiation of PAH specific therapy is an important time for risk assessment and stratification, as additional PAH specific therapies should be considered for individuals who do not achieve low risk on double combination therapy [3].

The vasodilatory properties of these drugs may result in systemic side-effects, particularly during drug initiation and dose titration [4]. These commonly include hypotension, flushing, light-headedness and gastrointestinal symptoms, as outlined in table 4 [4]. Specific side-effects also include anaemia (macitentan), ocular changes (*e.g.* conjunctival injection, changes in colour vision and photosensitivity with phosphodiesterase type-5 inhibitors such as sildenafil), elevated aminotransferases (bosentan) and thrombocytopenia (parenteral prostacyclin). Patients prescribed parenteral prostacyclin *via* central venous catheters require special consideration, as they are at risk of line infections. Furthermore, infusion pump malfunction may interrupt drug delivery and result in acute deteriorations. Therefore, vigilance regarding sterile drug preparation and pump maintenance are essential.

Monotherapy with high-dose calcium channel blockers (CCBs) are prescribed for subjects with PAH that are long-term responders to CCBs only. It is important to be aware that CCBs may be prescribed in other PAH subgroups for alternative indications, such as Raynaud phenomenon in systemic sclerosis associated PAH.

PAH therapy is a dynamic and evolving field and there are numerous clinical trials underway. There has been a concerted drive by the global PH community to discover new drugs and therapeutic pathways. Sotatercept is a first-in-class fusion protein that modulates TGF-β and BMPR2 signalling, and it is currently undergoing phase 3 studies. This may provide a much needed additional fourth therapeutic pathway [58]. Additional therapies and routes of administration are under investigation, such as the inhaled tyrosine kinase inhibitor imatinib (ClinicalTrials.gov identifier: NCT04903730).

Supportive measures

General supportive measures are a central and constant component of comprehensive PAH care. Supplemental oxygen and diuretic therapies should be considered in individuals with evidence of hypoxia or volume

TABLE 4 An overview of the three major therapeutic pathways in pulmonary arterial hypertension

Therapeutic pathways	Nitric oxide (NO)	Prostacyclin (PGI_2)	Endothelin 1 (ET_1)
Levels in PAH	Reduced	Reduced	Increased
Aim of therapy	To increase NO	To increase PGI_2	To reduce ET_1
Current available drugs	Sildenafil Tadalafil Riociguat	Epoprostenol Treprostinil Iloprost Selexipag	Macitentan Ambrisentan Bosentan
Routes of administration	Oral	Oral, parenteral, inhaled	Oral
Method of action	To increase cGMP *via* the inhibition of PD5 or by direct stimulation of sGC	To increase the conversion of ATP to cAMP	To inhibit ET_A receptors ± ET_B receptors
Side-effects			
Common side-effects	Systemic vasodilation resulting in hypotension, flushing, light-headedness, gastrointestinal side-effects (*e.g.* nausea, diarrhoea)		
Specific drug side-effects	Sildenafil and tadalafil: ocular side-effects	Parenteral prostacyclin: thrombocytopenia, bone marrow suppression Rash	Macitentan: anaemia Bosentan: deranged transaminases

The aim of therapy is to promote vasodilation in the pulmonary circulation. Within the nitric oxide pathway, sildenafil and tadalafil are phosphodiesterase type-5 (PD5) inhibitors and riociguat is a soluble guanylate cyclase (sGC) stimulator. In the endothelin (ET) pathway, bosentan and macitentan are dual ET receptor antagonists (*i.e.* they block both ET_A and ET_B receptors) and ambrisentan is a selective ET_A receptor antagonist. Modern therapy typically consists of double or triple combination therapy, using one drug from each therapeutic pathway. Monotherapy is uncommon and should only be considered in patients with low-risk profiles. cGMP: cyclic guanosine monophosphate.

overload. Vaccinations, psychological support, nutritional advice and specialised exercise programmes should be offered to all patients. Exercise training and rehabilitation are safe and efficacious add-ons to medical therapy in stable patients with PH [59]. Evidence suggests that these programmes can improve exercise capacity, haemodynamic profiles, muscle strength, quality of life and wellbeing in individuals with PAH [59]. In light of the high maternal mortality in PAH, reliable contraception is imperative for women of reproductive age. Empiric anticoagulation for IPAH, APAH and HPAH is no longer routinely prescribed, due to the paucity of high-quality evidence surrounding this practice. Decisions regarding empiric anticoagulation in these subgroups should be made on a case-by-case basis and in expert centres [3].

Timely referral for lung transplant assessment should be considered in eligible patients, as it remains the only cure for this progressive disease. Palliative care is a valuable and underused resource in PAH management, and can alleviate chronic symptom burden and support end-of-life care. Finally, atrial septostomy can be considered in select individuals with advanced PAH, as a bridge to transplant or as a palliative procedure [60, 61]. This procedure creates a shunt from the right to the left atrium, and can improve symptoms and haemodynamic parameters in advanced PAH by offloading the failing right ventricle. However, as oxygen saturations will deteriorate due to the creation of a shunt, some individuals will not be suitable for this procedure.

Conclusion

The preceding decades have witnessed significant improvements in our understanding of PAH. The fourth edition of the ESC/ERS guidelines (2022) provides a comprehensive overview of the diagnosis and treatment of individuals with PH. The haemodynamic definition of PH has been revised and a diagnostic threshold of a mPAP >20 mmHg has been chosen to define PH. The therapeutic consequences of this new definition are of immense clinical interest and relevance [2]. Furthermore, new diagnostic, risk stratification and treatment algorithms have been developed and appropriate standards for PH centres have been proposed. There is a greater appreciation for the role of the TGF-β superfamily in the pathobiology of the disease and a number of novel therapies are under investigation. It is an exciting time to work in this evolving field and witness the expansion in treatment options.

Key points

- A mPAP >20 mmHg at RHC is required to confirm PH. However, the mPAP provides little prognostic information and is not a core component of risk stratification.
- Vasoreactivity testing should be performed during initial RHC in subjects with IPAH, HPAH and DPAH.
- A radial approach to RHC should be avoided in subjects with systemic sclerosis associated PAH and severe Raynaud phenomenon or digital ulceration, due to the risk of distal ischaemia.
- Marked reductions in D_{LCO} in individuals with PH may be suggestive of PVOD, systemic sclerosis associated PAH and ILD.

Self-evaluation questions

1. A 25-year-old woman presents to her general practitioner with syncope on exertion and is referred to the local emergency department for further investigations. A CT pulmonary angiogram reveals pulmonary artery dilatation and an enlarged right heart, and the study is negative for a pulmonary embolism. RHC and vasoreactivity testing are requested to investigate for PH. The results of the vasoreactivity test with inhaled nitric oxide are shown below.

RHC	Pre nitric oxide	Post nitric oxide
mRAP (mmHg)	2	2
mPAP (mmHg)	38	21
PAWP (mmHg)	8	7
Cardiac output (L·min^{-1})	4.33	5.33
PVR (Wood units)	6.92	2.6

Which of the following statements regarding these results is/are correct?

a) This is a positive vasoreactivity test and this patient is a long-term responder to calcium channel blockers.
b) Therapeutic anticoagulation should be prescribed in this case.
c) Pulmonary hypertension has been excluded in this case.
d) This patient should be referred for lung transplant assessment.
e) This patient has a positive vasoreactivity test and is an acute responder to nitric oxide.

2. True or false: exercise training and rehabilitation are absolutely contraindicated in subjects with PAH due to the risk of increasing pulmonary artery pressures and precipitating right heart failure.
3. True or false: treatment with endothelin receptor antagonists such as bosentan may cause abnormal liver function tests.
4. A 23-year-old man presents to a respiratory clinic with progressive dyspnoea, limb oedema and one episode of syncope. He has no medical history and is a never-smoker. On examination, he is hypoxic (saturations 84% on room air at rest) and has evidence of right heart failure. CT thorax revealed septal lines, centrilobular ground-glass opacities and there is mediastinal adenopathy. Pulmonary function tests reveal a D_{LCO} of 36%, with normal spirometry, and echocardiography shows a normal left atrium and left ventricle and an enlarged right heart. Subsequent RHC confirms PH, and shows a mPAP of 58 mmHg, PAWP of 8 mmHg and a PVR of 12 Wood units. The initiation of PAH specific therapy is complicated by pulmonary oedema. Which one of the following is the most likely diagnosis?
    a) Group 3 PH due to chronic obstructive lung disease
    b) PAH long-term responder to calcium channel blockers
    c) PVOD
    d) Group 2 PH, due to heart failure preserved ejection fraction
    e) Portopulmonary hypertension

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Suggested answers

1. Correct answer: e. This patient has a positive vasoreactivity test and is an acute responder to nitric oxide. Following the administration of inhaled nitric oxide, the mPAP reduced by ⩾10 mmHg from baseline values, and the cardiac output increased. This is a positive vasoreactivity test and she is a candidate for trial of treatment with calcium channel blockers.
   Incorrect answers:
   a. While this is a positive vasoreactivity test, we do not have enough information to define this patient as a "long-term responder" to calcium channel blockers. This would require evidence of a sustained clinical, biochemical and haemodynamic response to calcium channel blocker monotherapy, typically for more than a year.
   b. There is no indication for therapeutic anticoagulation in this case.
   c. This is incorrect. PH has been diagnosed in this case, as the mPAP was 38 mmHg at baseline (*i.e.* >20 mmHg).
   d. There is not enough information to indicate that this patient requires referral for lung transplant assessment.
2. False. This statement is incorrect. Exercise training and rehabilitation are encouraged in subjects with stable, chronic PAH, and are considered safe and efficacious.
3. True. Bosentan is associated with deranged transaminases, which may even require drug cessation.
4. Correct answer: c. PVOD is the most likely diagnosis given the clinical findings, CT results and markedly reduced D_{LCO}.
   Incorrect answers:
   a. This patient is a never-smoker and there is no history of lung disease, so Group 3 PH due to COPD is less likely.
   b. Information regarding vasoreactivity testing was not provided in this case and therefore it is not possible to diagnose a PAH long-term responder to calcium channel blockers.
   d. The patient's young age, lack of comorbidities, normal left heart size on imaging and precapillary haemodynamic pattern at RHC make Group 2 PH less likely.
   e. There is no history of liver disease and liver/portal imaging is not provided in this case. Therefore, portopulmonary hypertension was not the diagnosis in this case.