Definition, classification and diagnosis of pulmonary hypertension

Gabor Kovacs[1,2], Sonja Bartolome[3], Christopher P. Denton [4], Michael A. Gatzoulis[5,6], Sue Gu[7], Dinesh Khanna[8], David Badesch[7] and David Montani [9,10,11]

[1]Division of Pulmonology, Department of Internal Medicine, Medical University of Graz, Graz, Austria. [2]Ludwig Boltzmann Institute for Lung Vascular Research Graz, Graz, Austria. [3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA. [4]Division of Medicine, University College London, London, UK. [5]Adult Congenital Heart Centre and National Centre for Pulmonary Hypertension, Royal Brompton Hospital, Guy's and St Thomas's NHS Foundation Trust, London, UK. [6]National Heart and Lung Institute, Imperial College, London, UK. [7]Division of Pulmonary Sciences and Critical Care Medicine University of Colorado Anschutz Medical Campus Aurora, Aurora, CO, USA. [8]Scleroderma Program, Division of Rheumatology, Department of Medicine, University of Michigan, Ann Arbor, MI, USA. [9]Université Paris-Saclay, Faculté de Médecine, Le Kremlin-Bicêtre, France. [10]Assistance Publique - Hôpitaux de Paris (AP-HP), Service de Pneumologie et Soins Intensifs Respiratoires, Hôpital Bicêtre, Le Kremlin-Bicêtre, France. [11]INSERM UMR_S999 "Pulmonary Hypertension: Pathophysiology and Novel Therapies", Hôpital Marie Lannelongue, Le Plessis-Robinson, France.

Corresponding author: Gabor Kovacs (gabor.kovacs@uniklinikum.kages.at)

Shareable abstract (@ERSpublications)
In this article, we provide the definitions, the current clinical classification and the diagnostic algorithm for pulmonary hypertension, based on the 7th World Symposium on Pulmonary Hypertension. https://bit.ly/3W442cD

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Abstract

Pulmonary hypertension (PH) is a haemodynamic condition characterised by elevation of mean pulmonary arterial pressure (mPAP) >20 mmHg, assessed by right heart catheterisation. Pulmonary arterial wedge pressure (PAWP) and pulmonary vascular resistance (PVR) distinguish pre-capillary PH (PAWP ⩽15 mmHg, PVR >2 Wood Units (WU)), isolated post-capillary PH (PAWP >15 mmHg, PVR ⩽2 WU) and combined post- and pre-capillary PH (PAWP >15 mmHg, PVR >2 WU). Exercise PH is a haemodynamic condition describing a normal mPAP at rest with an abnormal increase of mPAP during exercise, defined as a mPAP/cardiac output slope >3 mmHg/L/min between rest and exercise. The core structure of the clinical classification of PH has been retained, including the five major groups. However, some changes are presented herewith, such as the re-introduction of "long-term responders to calcium channel blockers" as a subgroup of idiopathic pulmonary arterial hypertension, the addition of subgroups in group 2 PH and the differentiation of group 3 PH subgroups based on pulmonary diseases instead of functional abnormalities. Mitomycin-C and carfilzomib have been added to the list of drugs with "definite association" with PAH. For diagnosis of PH, we propose a stepwise approach with the main aim of discerning those patients who need to be referred to a PH centre and who should undergo invasive haemodynamic assessment. In case of high probability of severe pulmonary vascular disease, especially if there are signs of right heart failure, a fast-track referral to a PH centre is recommended at any point during the clinical workup.

Haemodynamic criteria of pulmonary hypertension

Pulmonary hypertension (PH) is a haemodynamic condition that is characterised by the elevation of mean pulmonary arterial pressure (mPAP) above the upper limit of normal. Based on a large number of invasive haemodynamic measurements in healthy subjects in the supine position, the upper limit of normal mPAP is 20 mmHg [1–4].

Pre-capillary PH is defined by mPAP >20 mmHg and the elevation of pulmonary vascular resistance (PVR) above the upper limit of normal that is considered to be 2 Wood Units (WU) [1–3, 5] and by a pulmonary arterial wedge pressure (PAWP) ⩽15 mmHg. This form of PH is characteristic of

haemodynamic conditions and diseases with pulmonary arterial involvement and no significant left heart disease.

Post-capillary PH is defined by mPAP >20 mmHg and PAWP >15 mmHg and is strongly suggestive of left heart disease. The value of the PVR further distinguishes between isolated post-capillary PH (ipcPH, PVR ⩽2 WU) and combined post- and pre-capillary PH (cpcPH, PVR >2 WU).

Exercise PH is a haemodynamic condition describing a normal mPAP at rest with an abnormal increase of mPAP during exercise and is defined as a mPAP/cardiac output (CO) slope >3 mmHg/L/min between rest and exercise.

These haemodynamic criteria (table 1) adhere to the recommendations of the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH [1, 2]. In this section, we provide specific comments on these criteria, address related topics and identify gaps in the evidence in order to make proposals for future collaborative research efforts.

Invasive assessment of pulmonary haemodynamics

Invasive haemodynamic measurements by right heart catheterisation (RHC) are required to assess mPAP, PAWP and cardiac output and to calculate PVR with sufficient accuracy for the diagnosis and haemodynamic stratification of PH (table 1). Noninvasive methods such as echocardiography or cardiac MRI lack precision or are not sufficiently validated to accurately assess pulmonary haemodynamics.

Incorporating haemodynamics into the clinical context

Although the above haemodynamic criteria represent the cornerstone of the diagnosis of different forms of PH and highlight the importance of invasive haemodynamic assessment, they should always be interpreted within the clinical context. The final diagnosis and classification should reflect the results of all investigations. Some haemodynamic parameters may be strongly influenced by acute conditions (*e.g.* cardiac decompensation) or general treatment measures (*e.g.* diuretic treatment), which may strongly influence the haemodynamic stratification of patients.

Definition of early PH

It has been previously shown that elevated mPAP and PVR values above the upper limits of normal are associated with poor survival [6–8]. A large recent nationwide study from the United Kingdom revealed that in patients with mildly elevated mPAP (21–24 mmHg) or PVR (2–3 WU), independent of comorbid lung and heart disease, survival was worse than among those with normal pressures (mPAP <21 mmHg) and normal PVR (PVR ⩽2 WU) [9]. In addition, patients with liver cirrhosis and PVR 2–3 WU frequently develop PVR >3 WU during follow-up, suggesting the presence of an early stage of progressive pulmonary vascular disease in these patients [10]. Similarly, patients with systemic sclerosis presenting with mPAP 21–24 mmHg and PVR 2–3 WU frequently develop mPAP ⩾25 mmHg during follow-up [11]. These observations suggest that the current haemodynamic criteria of PH and pre-capillary PH are clinically relevant and that patients with a risk condition for PH and mPAP 21–24 mmHg and/or PVR 2–3 WU may be at risk of haemodynamic progression. Therefore, this haemodynamic condition may be

TABLE 1 Haemodynamic criteria of pulmonary hypertension (PH)

	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU
Isolated post-capillary PH (ipcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU
Combined post- and pre-capillary PH (cpcPH)	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope >3 mmHg/L/min between rest and exercise

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units; CO: cardiac output.

referred to as "early PH". Conversely, many patients with mildly elevated mPAP and/or PVR may be haemodynamically and clinically stable. Further studies are needed to understand the long-term sequelae of this condition and to identify the patients at risk of progression.

Impact of recent changes in the haemodynamic definition of PH on the number of patients with post-capillary PH

The 2022 ESC/ERS PH guidelines lowered the threshold of PVR to distinguish cpcPH and ipcPH compared to previous recommendations, leading to a shift of patients from the ipcPH to the cpcPH subgroup [12]. However, the current haemodynamic criteria for these forms of post-capillary PH are based on the upper limit of normal PVR and little is known about their clinical relevance. Further studies may reveal alternative haemodynamic thresholds among patients with post-capillary PH with prognostic and potentially therapeutic relevance.

Distinguishing pre- and post-capillary PH

The optimal threshold of PAWP for distinguishing pre- and post-capillary PH has been a topic of longstanding discussion. Importantly, PAWP should always be considered within the clinical context for appropriate classification of PH and for optimal decision-making regarding the management of patients. In addition, the value of PAWP may be influenced by the applied methodology and there are sources of potential imprecision [13]. Based on the largest currently available systematic literature review, the upper limit of normal PAWP is 13 mmHg [14]. However, based on the definition of pre-capillary PH, almost all therapeutic studies for pulmonary arterial hypertension (PAH) have included patients with PAWP up to 15 mmHg [1, 2] and demonstrated clinical efficacy of treatment, including patients with PAWP 13–15 mmHg [15]. Notably, in patients with elevated mPAP, PAWP values <12 mmHg and >15 mmHg were associated with increased mortality [16]. In those with PAWP <12 mmHg, increased mortality was mainly driven by elevated PVR, whereas in patients with PAWP >15 mmHg, this was mainly due to left heart disease. Taking into account all of these considerations, we propose maintaining the definition of post-capillary PH as PAWP >15 mmHg. However, when presented with an individual patient, especially when PAWP is 12–18 mmHg, we suggest that instead of focusing on a single haemodynamic parameter, the entire presentation of the patient including clinical history, cardiovascular risk factors, the history of episodes of pulmonary oedema, echocardiographic findings and perhaps PAWP response to provocation should be taken into consideration for the appropriate classification of patients [13].

Different haemodynamic criteria for diagnosis and treatment of pre-capillary PH

All currently available drugs for the treatment of PAH, chronic thromboembolic PH (CTEPH) or PH associated with lung diseases were approved based on clinical trials using previous haemodynamic definitions of PH and pre-capillary PH, characterised by mPAP ⩾25 mmHg, PAWP ⩽15 mmHg and PVR >3 WU. Therefore, these drugs should be administered exclusively to patients meeting these definitions. We are aware of the disparity between the current criteria for PH (and pre-capillary PH) and for the indication for targeted therapy. Presently, the treatment of patients with early PH, or mPAP 21–24 mmHg and PVR 2–3 WU, using PH drugs lacks justification due to the absence of sufficient data from clinical trials. We strongly advocate for more clinical trials to investigate the effects of PH drugs in patients with mildly elevated mPAP and/or PVR.

Unclassified PH

Patients exhibiting elevated mPAP but normal PVR (⩽2 WU) and PAWP ⩽15 mmHg do not meet the criteria for either pre-capillary or post-capillary PH and are considered to have "unclassified PH" [1, 2]. Many of these subjects are characterised by elevated pulmonary blood flow. While PH therapy is not indicated for these patients, the exploration of potential underlying conditions (congenital heart disease, liver disease, hyperthyroidism, alcoholism, *etc*.) is recommended.

Exercise PH

It has been shown in retrospective single-centre studies that the mPAP/CO slope is a robust predictor of prognosis in patients with exercise dyspnoea or at risk for PH [17]. The normal value of the mPAP/CO slope is strongly age-dependent, but a slope >3 mmHg/L/min is abnormal even among the most elderly subjects and is independently associated with poor survival [18].

A recent large multicentre study confirmed the mPAP/CO slope as an independent predictor of prognosis beyond the predictive value of resting haemodynamics alone [19]. Patients with a mPAP/CO slope >3 mmHg/L/min had a significantly worse prognosis than those with a mPAP/CO slope ⩽3 mmHg/L/min. These results support the current haemodynamic criteria of exercise PH. Of note, mPAP increase during exercise was also associated with survival, but in a time-dependent manner. Initially, a smaller mPAP

increase during exercise was associated with worse survival, while later a larger mPAP increase was associated with poor prognosis. This time-dependency and the dependency of mPAP on the level of exercise make this parameter less attractive when defining exercise PH. The mPAP at peak exercise was not an independent predictor of prognosis.

Both the PAWP/CO slope with a threshold >2 mmHg/L/min and a PAWP threshold (*e.g.* 25 mmHg) during exercise have been suggested to distinguish between pre- and post-capillary causes of exercise PH. Further studies are needed to decide which of them is more helpful for this clinical question [18, 20–22].

Clinical classification of PH

The general purpose of the clinical classification of PH is to categorise clinical conditions associated with PH according to similar pathophysiological mechanisms, clinical presentation, haemodynamic characteristics and therapeutic management [1, 2, 4]. The 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018 and the 2022 ESC/ERS guidelines [1, 2, 4] offered a comprehensive, simplified version of the classification for both children and adults, divided into five subgroups (table 2). We suggest retaining the core structure of the clinical classification of PH; however, some clarifications and adjustments might be needed. Here, we provide specific comments and underline potentially relevant areas of ambiguity and gaps in the evidence that warrant further research.

Common and rare forms of PH

The term "PH" defines a haemodynamic state rather than a disease entity. In aggregate, PH is a relatively common condition, with a global prevalence of ∼1% [1, 2]. The current classification of PH classifies the rare pulmonary vascular diseases into groups 1 and 4 (PAH and CTEPH), and PH as a complication of more common conditions such as left heart disease and lung disease and/or hypoxia into groups 2 and 3.

A recent systematic review of the global disease burden found the mean reported prevalence of PAH confirmed by RHC to be 3.7 cases per 100 000 [23]. Group 2 and 3 PH are the most prevalent forms of PH, accounting for 90–95% of PH cases worldwide [24]. Within groups 2 and 3 PH, most patients suffer from mild to moderate PH with limited pulmonary vascular involvement.

An alternative classification might focus solely on pulmonary vascular diseases. Nevertheless, severe PH and significant pulmonary vascular involvement disproportionate to the severity of the underlying condition are occasionally observed, affecting ∼1–10% of patients with left heart or lung diseases. Thus, it seems challenging to exclude these conditions from pulmonary vascular diseases completely. The situation is even more complex in group 5 PH, which includes PH with unclear and/or multifactorial mechanisms, with sometimes severe and specific vascular involvement, such as sarcoidosis. Therefore, we propose to keep the architecture of the current clinical classification.

In addition, the currently proposed clinical classification aims to disseminate information to nonspecialists, thereby highlighting the importance of listing all possible causes that should be considered in evaluating PH.

Notably, in the 2022 ESC/ERS guidelines, the term "PH due to" for PH groups 2, 3 and 4 has been changed to "PH associated with". We support this change in that it underscores the fact that the presence of an associated condition (such as left heart disease, chronic respiratory disease, or chronic thromboembolic disease) may not be sufficient to cause PH, but instead constitutes a risk factor associated with complex pathophysiological mechanisms.

PAH with comorbidities

In current clinical registries, the number of PAH patients with cardiopulmonary comorbidities may be as high as 60–85%, and even in pivotal PAH trials, ∼50% of subjects had cardiopulmonary comorbidities [25–27]. Registry data reveal that the age at PAH diagnosis is often >60 years, increasing the likelihood of concurrent cardiopulmonary comorbidities that are common in the general population at this age [28]. We acknowledge that patients with PAH may suffer from cardiopulmonary comorbidities. At the same time, the presence of severe cardiac and pulmonary comorbidities is a strong indicator for classification as PH associated with left heart or lung diseases (groups 2 and 3 PH). However, when there is severe pre-capillary involvement and only mild or moderate cardiopulmonary comorbidity, distinguishing between PAH with comorbidities and group 2/3 PH is sometimes difficult and represents a gap in current knowledge.

In cases involving cardiac comorbidities, the differentiation between pre- and post-capillary PH (*i.e.* PAWP ⩽15 mmHg *versus* >15 mmHg) is often used to determine whether a patient falls into group 1 or group 2 PH. Notably, a PAWP <15 mmHg does not exclude the presence of left heart disease, and patients may be

TABLE 2 Updated clinical classification of pulmonary hypertension (PH)

Group 1: PAH
1.1 Idiopathic
1.1.1 Long-term responders to calcium channel blockers
1.2 Heritable[#]
1.3 Associated with drugs and toxins[#]
1.4 Associated with:
1.4.1 connective tissue disease
1.4.2 HIV infection
1.4.3 portal hypertension
1.4.4 congenital heart disease
1.4.5 schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn
Group 2: PH associated with left heart disease
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction
2.1.3 cardiomyopathies with specific aetiologies[¶]
2.2 Valvular heart disease:
2.2.1 aortic valve disease
2.2.2 mitral valve disease
2.2.3 mixed valvular disease
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
Group 3: PH associated with lung diseases and/or hypoxia
3.1 COPD and/or emphysema
3.2 Interstitial lung disease
3.3 Combined pulmonary fibrosis and emphysema
3.4 Other parenchymal lung diseases[+]
3.5 Nonparenchymal restrictive diseases:
3.5.1 hypoventilation syndromes
3.5.2 pneumonectomy
3.6 Hypoxia without lung disease (*e.g.* high altitude)
3.7 Developmental lung diseases
Group 4: PH associated with pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions[§]
Group 5: PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders[*f*]
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1
5.3 Metabolic disorders[##]
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis
5.7 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis. [#]: patients with heritable PAH or PAH associated with drugs and toxins might be long-term responders to calcium channel blockers; [¶]: hypertrophic, amyloid, Fabry disease and Chagas disease; [+]: parenchymal lung diseases not included in group 5; [§]: other causes of pulmonary artery obstructions include sarcomas (high- or intermediate-grade or angiosarcoma), other malignant tumours (*e.g.* renal carcinoma, uterine carcinoma, germ-cell tumours of the testis), nonmalignant tumours (*e.g.* uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses and hydatidosis; [*f*]: including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders; [##]: including glycogen storage diseases and Gaucher disease.

classified as PH associated with left heart disease based on the clinical presentation. In patients with PAWP toward the upper end of the range, a more comprehensive evaluation might uncover latent left heart disease [18, 29, 30].

In patients with PH and chronic respiratory diseases, defining thresholds for classification is challenging. We suggest multimodal assessment of these subjects, including pulmonary function tests (PFTs), diffusion capacity of the lung for carbon monoxide (D_{LCO}) and high-resolution computed tomography (HRCT). HRCT should be performed especially in former or current smokers with strongly reduced D_{LCO} (<45%

predicted). For patients with significant abnormalities in pulmonary function or relevant parenchymal involvement in HRCT, particularly pulmonary fibrosis and/or emphysema, classification into group 3 PH should be favoured [31].

In general, we advocate for the utilisation of multimodal clinical investigations, including detailed history, echocardiography, magnetic resonance imaging (MRI), PFTs and HRCT for appropriate classification in patients with cardiac and/or pulmonary comorbidities. We caution against reliance solely on haemodynamic measurements or any clinical parameter in isolation. We do not suggest the introduction of a subgroup of PAH for patients with comorbidities.

Classification of patients with multiple mechanisms for PH

Patients may present with several conditions predisposing them to PH. Examples are numerous, including COPD patients who frequently develop significant left heart disease and chronic thromboembolic disease or patients with systemic sclerosis who not only develop PAH, but also frequently present with interstitial lung disease or pulmonary veno-occlusive disease (PVOD). The primary classification of these complex patients should be based on the presumed predominant cause of PH.

Connective tissue disease (CTD)-associated pulmonary hypertension exemplifies the challenge of classification of PH that may arise from several overlapping or distinct mechanisms and occur in the context of CTD-related comorbidity [32]. This is not only important for terminology and classification, but also has an impact on the management of PH. The most frequently associated CTDs are systemic sclerosis (SSc), mixed/overlap CTD (MCTD) and systemic lupus erythematosus (SLE). The best-studied CTD is SSc, where the majority of patients suffers from pre-capillary PH due either to group 1 PAH or interstitial lung disease-associated group 3 PH [33]. However, cardiac involvement, especially diastolic dysfunction (heart failure with preserved ejection fraction), is an important contributor to SSc-PH [34]. Other relevant mechanisms in some SSc patients include PVOD and group 4 thromboembolic PH. Defining the predominant PH mechanism in a patient presents a significant challenge, requiring expert PH assessment and multidisciplinary management, along with appropriate classification, to allow optimal treatment decisions. In cases of SLE and MCTD, it is essential to optimise therapy for the underlying disease, because this may cause substantial improvement of PH [35]. An additional consideration is that PAH therapies, especially phosphodiesterase-5 inhibitors and bosentan, are routinely prescribed for the treatment of digital vasculopathy in SSc. Further research is needed to understand how this may influence the screening and detection as well as the development and natural history of PH in this context [36].

Long-term responders to calcium channel blockers

A positive acute response to vasoreactivity testing is observed in ∼12% of patients with idiopathic PAH or PAH associated with drugs and toxins, and in a smaller proportion (<5%) in heritable PAH [37–39]. A positive acute response to vasoreactivity testing predicts a potential long-term response to high-dose calcium channel blockers (CCBs) in these cases. However, in all other forms of PAH and other PH groups, the results of this acute testing can be misleading, and true long-term responders are rare. Fewer than two-thirds of patients with an acute response demonstrate sustained clinical and haemodynamic improvement after ⩾1 year on CCBs alone [37–40]. Indeed, some patients with long-term response to CCBs gradually lose this response, sometimes after years, and eventually progress similarly to those with idiopathic PAH. Of note, a recently published multicentre study revealed that in addition to established vasodilator responder criteria, pulmonary artery compliance at acute vasoreactivity testing, as well as low risk status, and normal N-terminal pro-brain natriuretic peptide (NT-proBNP) levels at early follow-up correlated with long-term response and predicted survival [40].

At the 6th WSPH in 2018, a subgroup of “long-term responders to CCBs” was individualised within PAH (group 1.5) [4]. The rationale for distinguishing these patients lies in their specific entity with a significantly better prognosis, unique management and different pathophysiology, driven primarily by vasoconstriction rather than pulmonary arterial remodelling. Nevertheless, this proposal raised questions about classification changes over time, at least in two situations: 1) patients could only be included in this subgroup after 1 year of follow-up, and 2) patients losing their response to CCBs have a progression similar to those with idiopathic PAH.

In the 2022 ESC/ERS PH guidelines [1, 2], the “long-term responders to CCBs” subgroup was removed from the clinical classification. This was replaced by a distinction between “acute responders at vasoreactivity testing” and “nonresponders at vasoreactivity testing” within idiopathic PAH (subgroups 1.1.1 and 1.1.2). Nevertheless, this does not resolve all gaps and misunderstandings. The aim of clinical classification is to group PH with common pathophysiological mechanisms. However, acute responders are

a mix of long-term responders to CCBs and those who will require management with PAH-targeted drugs. Additionally, this is the only subgroup defined solely by the initial therapeutic strategy (CCBs) rather than pathophysiology.

We advocate for re-introducing of the term "long-term responders to CCBs" as a subgroup of idiopathic PAH. We acknowledge the challenge of achieving a consistently uniform classification of this important group of patients. The re-introduction of this subgroup stresses the importance of vasoreactivity testing in idiopathic PAH, heritable PAH and drug-associated PAH (table 2) and emphasises the importance of long-term haemodynamic and clinical follow-up in these patients [41].

Challenges in the classification of PH associated with pathogenic variants in developmental genes

A recent international consensus statement on genetic counselling and testing in PAH proposed an update on predisposing PAH genes [42]. The recent discovery of the involvement of PAH predisposing genes (*TBX4*, *SOX17*, *KDR*), which play a role in the development of pulmonary vessels, lung parenchyma or bronchi, and heart, has led to the recognition of complex phenotypes. These sometimes include congenital heart disease and severe pulmonary developmental abnormalities.

Among children and adults initially classified as having congenital heart disease (CHD)-associated PAH, a significant number have heritable PAH, especially in cases of pathogenic *SOX17* variants.

In the presence of a pathogenic *TBX4* variant (small patella syndrome) [43], there is considerable phenotypic variability, even within the same family. PH may be associated with significant pulmonary developmental anomalies, particularly in children, or resemble idiopathic PAH in adults, with no or minimal pulmonary developmental anomalies. Depending on the patient, this could be classified into two distinct groups: heritable PAH (group 1 PH) or PH associated with developmental disorders (group 3 PH).

Therefore, the classification of these patients largely depends upon the availability and systematic implementation of genetic testing. The impact is minimal for CHD-PAH because the management is similar to that of heritable PAH. For PH associated with pulmonary developmental abnormalities, the classification into either group 1 or 3 PH could lead to different management approaches. Studies are needed in these situations to determine which group the pathophysiology of these pulmonary vascular conditions most closely aligns with.

Update on drugs with a risk for development of PAH

The current classification of drugs definitively or possibly associated with the development of PAH is regularly updated during the WSPH and in the ERS/ESC guidelines. It has evolved from three classes (definite, likely and possible) to two classes (definite and possible) since the 6th WSPH (2018). The following definitions are used: "definite association" includes drugs with data based on outbreaks, epidemiological case–control studies or large multicentre series; "possible association" is suggested by multiple case series or cases with drugs having similar mechanisms of action. However, these criteria do not take into account the diversity of evidence and criteria that have been explored to assess a causal link between a drug and PAH. Among the specificities of drug-associated PAH, we may note that 1) the duration of exposure before PAH diagnosis varies from a few weeks to several years depending on the drug; 2) regression of the disease after drug withdrawal has been observed for some, but not all drugs; 3) PAH has been reproduced for only a few drugs in pre-clinical models; and 4) pharmacoepidemiological and pharmacovigilance studies have generated various estimates of associations between drugs and PAH.

During the 7th WSPH, we proposed an updated classification of drug-associated PAH based on the same criteria as earlier. Additionally, we have considered that other factors should be taken into account, particularly for drugs with a possible association with PAH. These factors include reversibility of PH after withdrawal of the drug, the existence of pre-clinical experimental data, histopathological findings typical of PAH, and common mechanisms with drugs that have a definite association with PAH. The task force emphasises the importance of developing multimodal and comprehensive criteria to assess the level of evidence of the aetiology of drug-associated PAH (*i.e.* to judge the plausibility of a drug–PAH association). These criteria may then be used to calculate a causality score that could be the basis of a new classification.

Based on recent data, we suggest minor changes compared to the list of drugs and toxins associated with PAH that was provided in the 2022 ESC/ERS PH guidelines [1, 2]. Mitomycin-C and carfilzomib have been added to the "definite association" group. Mitocycin-C, a bioreductive alkylating agent, has been reported to be associated with PAH with features of venous/capillary (PVOD/pulmonary capillary haemangiomatosis) involvement in case series and epidemiological data [44–46]. This association has been

reinforced by human histopathological assessments [47–49] and experimental data reproducing the characteristics of the disease in animal models [47, 50]. Due to limited data, other alkylating agents have been maintained in the "possible association" group [45]. In individual case reports, carfilzomib, a proteasome inhibitor, has been reported to be associated with PAH. Recently, a study using multiple approaches, including analysis of a national PH registry, a pharmacovigilance disproportionality analysis using the World Health Organization global database (VigiBase), and a meta-analysis of randomised controlled trials, showed a significant association between carfilzomib and PAH [51].

We suggest the inclusion of bevacizumab as possibly being associated with PAH [46], along with bortezomib, which has been reported to be associated with PAH to a lesser extent than carfilzomib, but shares potential common pathophysiological mechanisms [46, 51]. In addition, we suggest replacing "indirubin (Chinese herb Qing-Dai)" with "indigo naturalis (Chinese herb Qing-Dai)", as possibly being associated with PAH, because the available case reports on this herb and its association with PAH resulted from the use and purchase of indigo naturalis (Qing dai) and not indirubin, which is one of the pharmacodynamic components of indigo naturalis. The causative ingredient of indigo naturalis for PAH has not been identified (table 3) [52, 53].

Update on PAH associated with HIV, portopulmonary hypertension and group 5 PH

In recent years, several studies have confirmed previous findings in large databases of patients with less-studied forms of PAH. Accordingly, the increased risk of incident PH was confirmed among veterans with HIV as compared to veterans without HIV. A low number of CD4-positive cells and high viral load were predictors of PH in patients with HIV [54]. In addition, a recent population-based cohort study revealed that patients with concomitant HIV and PH have a high burden of comorbidities, and the presence of PH is associated with increased mortality [55]. The incidence of HIV-associated PAH has decreased in the past decade in well-resourced countries, probably due to a better management of HIV and its associated comorbidities. In the French PH registry, HIV-associated PAH represented ∼7% of newly diagnosed PAH cases in 2008 and <3% in 2021. The epidemiology of HIV-associated PAH in less-resourced countries is largely unknown.

In patients with portopulmonary PH (PoPH), according to a large, national cohort of patients in the USA, cardiac index emerged as the critical haemodynamic variable for risk stratification [56]. In another recent analysis, the survival of patients with PoPH was found to be strongly associated with the severity of liver disease [57]. Patients who underwent liver transplantation had the best long-term outcomes, while patients with PoPH not undergoing liver transplantation had a poor prognosis [58].

Based on a large international registry, new cut-offs for decreased transplant-free survival have been identified for patients with PH associated with sarcoidosis. Accordingly, mPAP ⩾40 mmHg and PVR ⩾5 WU have been associated with poor prognosis [59]. Lung transplantation remains an option for eligible

TABLE 3 Drugs and toxins associated with pulmonary arterial hypertension (PAH)

Definite association	Possible association
Aminorex	Alkylating agents
Benfluorex	Amphetamines
Carfilzomib	Bevacizumab
Dasatinib	Bortezomib
Dexfenfluramine	Bosutinib
Fenfluramine	Cocaine
Methamphetamines	Diazoxide
Mitomycin C[#]	Direct-acting antiviral agents against hepatitis C virus (sofosbuvir)
Toxic rapeseed oil	Indigo naturalis (Chinese herb Qing-Dai)
	Interferon-α and -β
	Leflunomide
	L-tryptophan
	Phenylpropanolamine
	Ponatinib
	Solvents (trichloroethylene)[#]
	St John's wort

[#]: PAH with features of venous (pulmonary veno-occlusive disease)/capillary (pulmonary capillary haemangiomatosis) involvement.

patients. Post-transplant survival in patients with pulmonary sarcoidosis appears to be similar to that in patients with other indications for lung transplantation. The main factors associated with worse survival are older age and extensive pre-operative lung fibrosis [60].

A recent prospective cohort study reported on the long-term outcomes of adult pulmonary Langerhans cell histiocytosis and suggested that with a 93% estimated survival rate at 10 years, the prognosis of this disease may be more favourable than previously considered, provided that complications are recognised and treated early. The cumulative incidence of PH in this cohort study was <5% at 5 and 10 years of follow-up [61].

Recently, PH has also been described as a possible complication of common variable immunodeficiency (CVID). CVID-associated PH mainly presents as pre-capillary PH with multiple possible causes including portal hypertension, pulmonary vascular remodelling, sometimes pulmonary parenchymal involvement, and occasionally an extrinsic compression of the pulmonary vessels by mediastinal lymphadenopathy [62].

Patients with neurofibromatosis type 1 may also develop PH. Mechanisms of PH may be multifactorial, including interstitial lung disease and specific pulmonary vascular involvement [63]. Neurofibromatosis type 1 associated PH is characterised by a female predominance, a low D_{LCO} and severe functional and haemodynamic impairment [63].

Regarding complex CHD, we suggest that this entity remain a subgroup of group 5 PH, as these patients have pulmonary vascular disease, but not PAH according to current criteria [64].

Suggested new subgroups of group 2 and 3 PH

Previous PH guidelines utilised classifications based on pulmonary function measurements, “obstructive lung diseases”, “restrictive lung diseases” and “lung diseases with mixed restrictive/obstructive pattern”, as subgroups of group 3 PH (PH associated with lung diseases and/or hypoxia). Instead of these classifications, we suggest using clinical diagnoses such as COPD, interstitial lung disease and combined pulmonary fibrosis and emphysema to identify these groups of patients with PH associated with lung diseases and/or hypoxia (table 2). This emphasises the importance of the clinical presentation of patients and the role of imaging (mainly chest computed tomography) in addition to pulmonary function tests for the characterisation of the pulmonary condition associated with PH. Furthermore, we suggest introducing the term “nonparenchymal restrictive disease” for patients with PH associated with respiratory insufficiency and restriction that is not directly related to parenchymal lung pathology [31]. Patients with musculoskeletal disorders may develop PH as a consequence of hypoventilation and can be classified in this subgroup.

Similarly, within the classification group of PH associated with left heart diseases, specific forms of heart failure and valvular heart disease have been distinguished [30].

Potential future PH classifications

The current clinical classification of PH is based on epidemiological and clinical considerations to categorise clinical conditions associated with PH according to their presentation, haemodynamic characteristics, and therapeutic management. As in other fields of contemporary medicine, future scientific advances may lead to more personalised PH classifications based on characteristics of pathophysiology, genetic background and therapy responses at an individual level. This may allow for a more customised approach in diagnosing and managing patients with PH and help to overcome current limitations that are derived from the relatively rigid structure of the clinical classification.

Diagnosis of PH

The ultimate diagnosis of PH is established through RHC, which should be performed at a PH centre by an experienced team. The main aim of the diagnostic algorithm (figure 1) is to discern those patients who need to be referred to a PH centre and who should undergo invasive haemodynamic assessment. The time between diagnostic steps should be minimised. At each step, patients with a low likelihood of PH and a more plausible alternative cause (*e.g.* significant left heart disease) for their symptoms may be identified and managed with an alternative diagnostic approach. Nevertheless, patients with interstitial lung disease and suspected PH, and patients with pulmonary conditions or left heart disease and suspected severe PH should be referred to a PH expert centre. In case of a high probability of PAH or CTEPH, especially if there are signs of right heart failure, a fast-track referral to a PH centre is recommended at any point during the clinical workup.

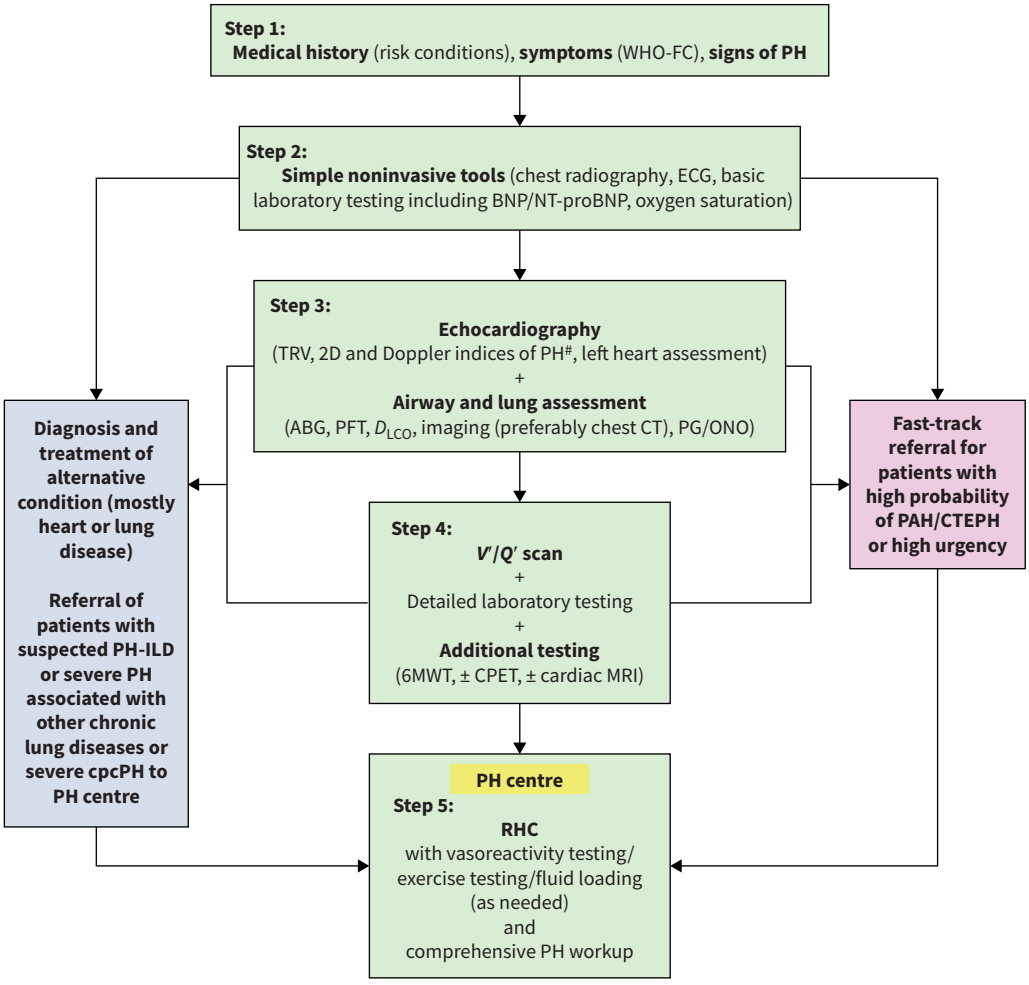

FIGURE 1 Suggested diagnostic approach to pulmonary hypertension (PH). Steps 1–5 represent the most important diagnostic steps of PH from the first presentation of the patient with symptoms or an existing risk condition towards final diagnosis with invasive assessment. WHO-FC: World Health Organization functional class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; TRV: tricuspid regurgitation velocity; 2D: two-dimensional; ABG: arterial blood gases; PFT: pulmonary function testing; D_{LCO}: diffusion capacity of the lung for carbon monoxide; CT: computed tomography; PG: polygraphy; ONO: overnight oximetry; *V′/Q′* scan: ventilation/perfusion scan of the lung; 6MWT: 6-min walk test; CPET: cardiopulmonary exercise testing; MRI: magnetic resonance imaging; RHC: right heart catheterisation; PH-ILD: pulmonary hypertension associated with interstitial lung disease; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; cpcPH: combined post- and pre-capillary PH. #: refer to figure 2.

In this section, we provide specific comments on the suggested diagnostic algorithm for PH.

Diagnostic algorithm

Most patients who undergo diagnostic evaluation for PH present with symptoms of dyspnoea, exercise intolerance and/or clinical signs of right heart failure. We suggest a stepwise diagnostic approach for these patients, starting with simple, noninvasive tools and followed by more complex diagnostic methods, including the assessment for common cardiac and pulmonary conditions (figure 1).

In step 1, a thorough clinical history of the patient, as well as their symptoms and physical examination signs should be assessed. The most frequent symptoms in patients with PH are dyspnoea on exertion, fatigue and rapid exhaustion. Bendopnoea (dyspnoea when bending forward), weight gain due to fluid retention or syncope during physical exertion may occur. Particular attention should be paid to risk factors in the patient's history that are associated with PH (*e.g.* connective tissue disease, portal hypertension,

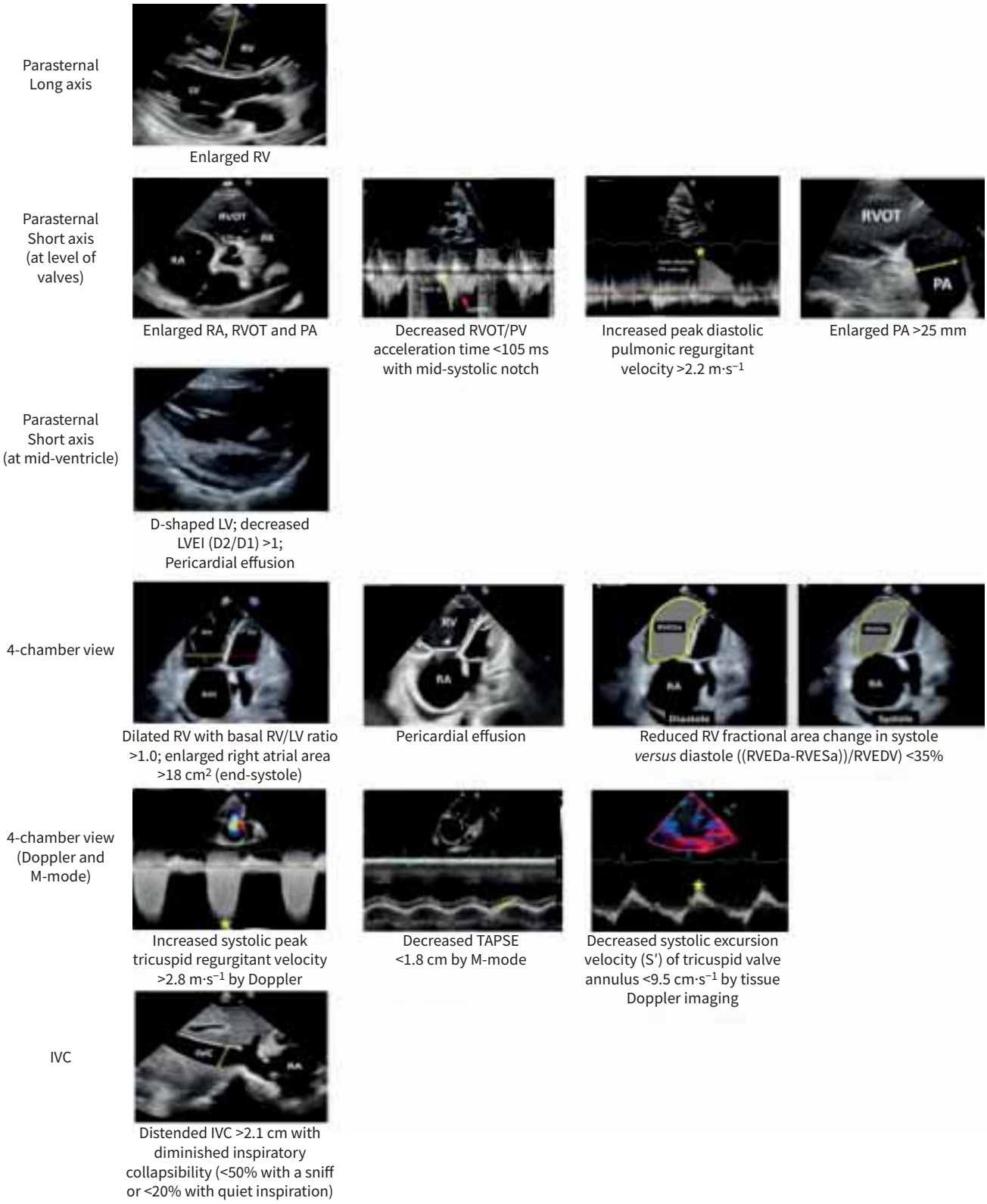

FIGURE 2 Most important two-dimensional and Doppler indices of pulmonary hypertension (PH) in transthoracic echocardiography. RV: right ventricle; RA: right atrium; RVOT: right ventricular outflow tract; PA: pulmonary artery; PV: pulmonary valve; LV: left ventricle; LVEI: left ventricle eccentricity index; RVEDa: right ventricular end-diastolic area; RVESa: right ventricular end-systolic area; RVEDV: right ventricular end-diastolic volume; TAPSE: tricuspid annular plane systolic excursion; IVC: inferior vena cava. Images courtesy of E. Ashley Hardin (University of Texas Southwestern Medical Center, Dallas, TX, USA).

HIV, congenital cardiac disorders, thromboembolic disease, left heart diseases, lung diseases and illicit drug use). A thorough physical examination of the patient may reveal an accentuated second heart sound and, in more advanced cases, a systolic murmur due to tricuspid regurgitation, or a diastolic murmur due to pulmonary valve insufficiency (Graham Steell murmur). Signs of right heart failure such as peripheral oedema, distended and pulsating jugular veins, hepatic heave or ascites are suggestive of severe right heart failure.

In step 2, basic investigations should be performed using simple, noninvasive tools. Although these tools do not allow for the confirmation or exclusion of PH, they are very helpful for an initial clinical assessment of patients and for generating differential diagnostic considerations. This basic assessment should at least include a chest radiograph, an ECG, the measurement of oxygen saturation and the evaluation of basic laboratory parameters, including blood counts, serum electrolytes, kidney function, liver parameters and BNP or NT-proBNP. Right axis deviation in ECG in adult patients with dyspnoea has a high positive predictive value for PH [65]. ECG may also detect arrhythmias and signs of left heart disease. In the absence of severe dyspnoea, a normal ECG in combination with normal BNP or NT-proBNP and normal gas exchange is associated with a low likelihood of PH [65, 66].

A more detailed assessment of the heart and the lung is suggested in step 3. Echocardiography is the most important noninvasive tool to provide comprehensive information on left and right ventricular anatomy and function, valvular abnormalities and on the pulmonary circulation [67, 68]. The estimation of systolic pulmonary arterial pressure based on the peak tricuspid regurgitation velocity (TRV) (after excluding pulmonary stenosis) and the assessment of additional signs suggestive of PH (figure 2, table 4) allow the estimation of the probability of PH. It is worth noting that recent changes in the haemodynamic definition of PH did not lead to changes in the echocardiographic thresholds for estimating the probability of PH [69]. Accordingly, TRV >3.4 $m \cdot s^{-1}$ suggests a high probability of PH, independent of additional signs of PH in echocardiography. TRV values between 2.9 and 3.4 $m \cdot s^{-1}$ are associated with an intermediate probability of PH, but the additional presence of further echocardiographic signs of PH result in high PH probability. TRV $\leqslant$2.8 $m \cdot s^{-1}$ is associated with low PH probability, but further echocardiographic signs of PH may increase PH probability to intermediate [1, 2].

While echocardiographic probability plays a significant role in the decision to pursue diagnostic RHC, potential overestimation and underestimation of pulmonary pressures is quite common [70]. Therefore, the final decision regarding RHC in an individual patient should be made after carefully considering of all available clinical information. Generally, RHC should be performed if clinically meaningful information and/or a therapeutic consequence is expected. This is most frequently the case when PH probability is high, or intermediate in patients presenting with risk factors or associated conditions for PAH or CTEPH. However, in some cases, RHC may not be expected to lead to further clinically significant information or to a change in therapeutic planning, thus resulting in the decision not to perform RHC even if the echocardiographic probability is high (*e.g.* in patients with severe comorbidities). In case of diagnostic uncertainty based on noninvasive investigations and unexplained symptoms, a diagnostic RHC may be justified, even if the echocardiographic probability of PH is intermediate or low.

The assessment of left ventricular function by echocardiography allows the identification of patients with heart failure with reduced or preserved ejection fraction and those with valvular heart disease, or cardiomyopathies. These patients may present with similar symptoms and signs as patients with PAH or CTEPH, but further exploration of PH is only suggested if severe cpcPH is suspected.

TABLE 4 Additional echocardiographic signs suggestive of pulmonary hypertension (PH) (modified after [1, 2])

Ventricles	RV/LV basal diameter/area ratio >1.0
	Flattening of interventricular septum (LVEI >1.1 in systole and/or diastole)
	TAPSE/sPAP ratio <0.55 $mm \cdot mmHg^{-1}$
PA	RVOT AT <105 ms and/or mid-systolic notching
	Early diastolic pulmonary regurgitation velocity >2.2 $m \cdot s^{-1}$
	PA diameter>AR diameter; PA diameter >25 mm
IVC and RA	IVC diameter >21 mm with decreased inspiratory collapse
	RA area (end-systole) >18 cm^2

PA: pulmonary artery; IVC: inferior vena cava; RA: right atrium; RV: right ventricle; LV: left ventricle; LVEI: left ventricular eccentricity index; TAPSE: tricuspid annular plane systolic excursion; sPAP: systolic pulmonary arterial pressure; RVOT AT: right ventricular outflow tract acceleration time; AR: aortic root.

In step 3, respiratory investigations are suggested as well. This includes arterial blood gas analysis, PFT with D_{LCO}, imaging (preferably chest computed tomography (CT)), and polygraphy or overnight oximetry if there is suspicion of hypoventilation syndromes. Patients with PAH usually have normal or slightly reduced partial pressure of oxygen. More severe reductions should raise suspicion for significant airflow obstruction, parenchymal lung disease, right-to-left shunt, PVOD or hepatic disease. Partial pressure of arterial carbon dioxide is typically normal or decreased in PAH due to alveolar hyperventilation, and PFT is usually normal or shows only mild abnormalities [71, 72]. More severe abnormalities suggest the presence of significant airway or parenchymal lung disease. A low D_{LCO} (<40% predicted) in patients with PH is frequently associated with parenchymal lung disease or PVOD; therefore, chest HRCT should be performed in these patients [27].

Chest CT is the preferred imaging modality in patients with PH as compared to chest radiography. Even conventional chest radiography may present abnormal findings in PH patients, including a characteristic configuration of the cardiac silhouette in the lateral view and the enlargement of the pulmonary arch and arteries. However, chest CT delivers more information on PH and potentially underlying lung diseases or specific conditions [73]. Signs of PH in chest CT include an enlarged pulmonary artery diameter and its ratio to the aorta, and enlarged right heart chambers [73]. At the same time, parenchymal changes such as centrilobular ground-glass opacities, septal lines and lymphadenopathy raise suspicion of PVOD [74]. Of note, chest CT may reveal significant pulmonary parenchymal diseases (*e.g.* combined pulmonary fibrosis and emphysema) that remain undetected or may be underestimated by PFT. CT pulmonary angiography is mainly used to detect direct and indirect signs of chronic thromboembolic pulmonary disease, including filling defects, webs or bands in the pulmonary arteries. In recent years, novel automated algorithms have significantly contributed to the increased clinical utility of chest CT. Artificial intelligence has already been successfully implemented in pilot studies and is likely to increase the diagnostic accuracy of PH in the following years [75, 76].

If pulmonary assessment reveals significant lung disease, including relevant airflow obstruction or emphysema, further assessment of PH in an expert centre is suggested if severe PH is suspected and its diagnosis affects management. Patients with interstitial lung disease and suspected PH should also be referred to a PH expert centre.

In step 4, ventilation/perfusion (V'/Q') imaging should be performed. A negative V'/Q' scan excludes significant thromboembolic disease, while missing perfusion in the presence of normal ventilation is highly suggestive of thromboembolic disease [77]. Nevertheless, patchy abnormalities may be present even in patients with PAH and matched V'/Q' defects are frequently found in patients with parenchymal lung diseases. Detailed laboratory testing should include testing for iron status, thyroid-stimulating hormone, hepatitis viruses, HIV and basic immunology laboratory workup incorporating screening tests for antinuclear antibodies, anticentromere antibodies, and anti-Ro. Screening for biological markers of antiphospholipid syndrome is recommended in patients with suspected CTEPH. Urine drug screening is recommended for all patients with idiopathic PAH or a history of substance use disorder, as methamphetamine use has been found to be a contributor when screening in cases formerly classified as idiopathic PAH [78]. A 6-min walk test should be performed to evaluate the patient's exercise tolerance and functional capacity. Abdominal ultrasound should be performed to identify the presence and underlying cause of portal hypertension such as cirrhosis, vascular malformations and portal vein thrombosis or obstruction. Additional investigations including cardiopulmonary exercise testing and cardiac MRI may improve diagnostic accuracy.

In step 5, if PH is suspected based on noninvasive investigations, the patient should be referred to a PH expert centre to evaluate all available clinical information and perform RHC. Depending on the haemodynamic phenotype, vasoreactivity testing, exercise testing or fluid loading may be indicated as part of the diagnostic RHC.

Diagnosis of patients with lung or left heart diseases and PH

The 2022 ESC/ERS PH guidelines recommend the referral of patients with suspected severe PH associated with lung disease to a PH centre and an individualised approach to treatment, if severe PH is confirmed. In addition, inhaled treprostinil may be considered for the treatment of patients with PH associated with interstitial lung disease [1, 2]. In accordance with the guidelines, we suggest comprehensive workup for PH in patients with chronic lung diseases, if diagnostic assessment may impact management. This includes patients with suspected PH associated with interstitial lung disease, patients with suspected severe PH associated with other chronic lung diseases and special patient populations (*e.g.* patients evaluated for lung transplantation, as haemodynamics may influence allocation). Importantly, comprehensive workup of these

patients, including RHC, should be performed in PH centres with additional experience in managing pulmonary diseases. Although accurate criteria are not available, patients with severe PH associated with lung disease are frequently characterised by symptoms/signs that are not explained by the underlying lung disease alone. They often present with an intermediate to high echocardiographic probability of PH, and signs of PH in other noninvasive examinations (*e.g.* elevated BNP or NT-proBNP or an increased pulmonary artery/aorta diameter ratio in chest CT) [79].

Although currently no PH drugs have been approved for patients with PH associated with left heart diseases, patients with suspected severe cpcPH should be referred to PH expert centres so that individualised management decisions can be made.

Role of cardiopulmonary exercise testing and MRI in the diagnosis of PH

Cardiopulmonary exercise testing belongs to clinical examinations that explore the causes of exercise dyspnoea. Several parameters, including a decreased peak oxygen uptake, an increased carbon dioxide (CO_2) equivalent and end-tidal CO_2 tension may be suggestive of PH [80, 81] and may support the indication of RHC. In addition, cardiopulmonary exercise testing is helpful in the diagnosis of CTEPH even in patients with low echocardiographic probability of PH [82], and the method has been suggested for screening for PH in patients with SSc [83]. The disadvantages of this method include its limited availability and specificity. In diagnosing PH, we suggest its use in selected cases, when no clear decision on whether to perform RHC can be made based on echocardiography and other noninvasive tools.

Cardiac MRI accurately and reproducibly visualises the cardiac chambers and represents the gold standard for the noninvasive assessment of right ventricular function. In addition, single-centre studies showed high correlations between MRI- and RHC-derived pulmonary pressures, making cardiac MRI a promising candidate for noninvasive haemodynamic and functional characterisation of the right ventricle and the pulmonary circulation [84, 85]. However, currently extended validation of the method is lacking, and cost and availability represent further limitations.

Methodological aspects of RHC, vasoreactivity testing, assessment of exercise haemodynamics and fluid loading

RHC makes the final diagnosis of PH, which allows haemodynamic stratification and aids clinical classification of patients. Haemodynamics provide prognostic information and contribute to risk stratification in PAH patients. Invasive assessment should be performed in PH expert centres, and several methodological issues need to be considered in order to obtain reliable results.

In the past, various zero reference levels have been established for haemodynamic measurements, leading to significant differences in intrathoracic pressures, including mPAP and PAWP between centres. Since the recommendations of the 5th WSPH, there is broad consensus that the mid-thoracic level corresponding to the level of the left atrium should be used as zero reference level in the supine position [86, 87]. In all other positions (including the semi-upright and upright positions, which are frequently used for exercise testing), a zero reference point should be determined as the intersection of the frontal plane at the mid-thoracic level, the transverse plane at the level of the fourth anterior intercostal space, and the midsagittal plane, and the corresponding horizontal level should be used as zero reference level [88].

Respiratory swings may also influence the value of assessed intrathoracic pressures. In most clinical studies, pressure measurements have been either performed at end-expiration or averaged over several respiratory cycles. The main argument for end-expiratory measurements is that at this time point the physiologically slightly negative intrathoracic pressure is closest to zero. Of note, the measurement should be performed without a breath-holding manoeuvre to avoid the rise of intrathoracic pressure. However, in subjects with large respiratory swings, including patients with obesity and especially COPD patients, who may even have positive intrathoracic pressures at end-expiration, the assessment of pulmonary vascular pressures averaged over several (in practice, three to four) respiratory cycles is more reliable, and avoids significant overestimation [88, 89]. In addition, during exercise, respiratory swings increase even in healthy subjects, and the end-expiratory assessment of pressures becomes unreliable. Therefore, during exercise testing, averaging of pulmonary vascular pressure values over three to four respiratory cycles is suggested. To compare resting to exercise pressures and to determine pressure/CO slopes, the same method of pressure assessment should be used both at rest and during exercise [90]. Taken together, both end-expiratory and averaged pressure measurements over several respiratory cycles are acceptable, but limitations and considerations for specific situations need to be taken into account. Methodological details regarding the zero reference level and the assessment of pressures should be reported in all clinical studies.

Baseline haemodynamic measurements at RHC should include the assessment of mean, systolic and diastolic pulmonary arterial pressure, PAWP, right atrial pressure, heart rate, cardiac output and the calculation of PVR. In addition, blood gases should be measured at least in a systemic artery, the pulmonary artery, and a large vein (*e.g.* superior or inferior vena cava) to assess arterio-venous oxygen difference and to reveal systemic to pulmonary shunts. The gold standard method to assess cardiac output is the direct Fick method, while thermodilution represents a reliable alternative in patients without shunt. The indirect Fick method uses estimated and not measured oxygen uptake values and is therefore not suggested [91]. In patients with PAH, heritable PAH (HPAH) and drug-associated PAH, vasoreactivity testing should be performed to identify patients who show an acute response and may be candidates for long-term CCB treatment. Nitric oxide is recommended for acute vasoreactivity testing, while inhaled iloprost or intravenous epoprostenol might be considered as alternatives [1, 2]. A positive response to nitric oxide is defined as decrease of mPAP by $\geqslant$10 mmHg to a value <40 mmHg with an unchanged or increased cardiac output [38].

Exercise haemodynamics may provide differential diagnostic and prognostic information in addition to resting haemodynamics. Invasive exercise testing should be performed in experienced centres as part of the diagnostic RHC in selected cases [90]. Primarily, patients with normal or moderately increased mPAP and/or PAWP 13–15 mmHg should undergo exercise testing to identify early forms of pulmonary vascular or left heart disease. Exercise haemodynamics have also been described to be of prognostic relevance and therefore clinically valuable for patients with more severe PH [92, 93]. The performance of invasive haemodynamic assessment during exercise has yet to be fully standardised. We suggest cycle ergometry as the preferred exercise method, because it is safe, reliable and used most frequently in clinical studies [90]. We recommend increasing the workload until peak individual exercise or a predefined maximal exercise level. Both step and ramp protocols are acceptable. Of note, at each exercise level, all pressures and corresponding cardiac output should be assessed at very close time points to each other and at the same workload. If at least four or five haemodynamic measurements have been performed at increasing exercise levels, it may be possible to calculate the distensibility coefficient α, which is an important parameter reflecting even moderate changes of the pulmonary vasculature and potentially predicts the development of more severe pulmonary vascular disease. Exercise may be performed in the supine, semi-upright or upright position. Notably, haemodynamic assessment during exercise should also be performed in the same position as at rest, to assess haemodynamic changes accurately. In interpreting data, the effect of posture on haemodynamics needs to be considered [94].

The mPAP/CO slope defines exercise PH. For assessment, linear regression based on multipoint measurements is possible but cumbersome, and a more practical method is assessing the mPAP/CO relationship based on measurements at rest and peak exercise [95]. Exercise PH is defined as mPAP/CO slope >3 mmHg/L/min [1, 2, 18]. From the differential-diagnostic point of view, recognising post-capillary causes of exercise PH is of significant relevance. The PAWP/CO slope >2 mmHg/L/min between rest and exercise [20] and an increase of the absolute value of PAWP>25 mmHg are considered markers of post-capillary exercise PH [21].

Besides exercise, volume challenge represents a method that may uncover left heart disease in patients with pre-capillary PH and PAWP 13–15 mmHg. In these subjects, rapid infusion of 500 mL saline may lead to a significant increase of PAWP, and values >18 mmHg may be suggestive of left heart disease [29]. Based on the available data, fluid loading appears clinically safe; however, all studies were conducted in highly experienced centres. Further studies should provide information on the optimal management of patients with pre-capillary PH and a positive fluid loading test.

Screening for PH in patients at risk

Early detection and diagnosis of PH is an important goal and can be facilitated through appropriate screening of asymptomatic "high-risk" groups that have a high probability developing PH. These include bone morphogenetic protein receptor type 2 (*BMPR2*) mutation carriers, first-degree relatives of patients with HPAH, patients undergoing assessment for liver transplantation or transjugular portosystemic shunt and patients with SSc spectrum disorders [1, 2]. In general, annual echocardiography, ECG and NT-proBNP (or BNP) are considered valuable tools for screening in these patients. The DETECT screening tool can be applied to appropriate patients with SSc spectrum disorders who meet the key inclusion and exclusion criteria [33, 96–98]. Patients with other CTDs, portal hypertension or HIV infection have lower risk for the development of PH, thus screening of asymptomatic patients is not recommended, and triggered investigation is more appropriate, although frequency of PH may vary across different ethnic and geographic regions [99]. If these patients develop signs or symptoms suggestive of PAH, the diagnostic algorithm for PH should be implemented (figure 1).

Patients with PAH and suspected or confirmed associated CHD should be cared for in conjunction with a CHD centre. The updated classification of PAH-CHD is included elsewhere [64].

Role of genetic testing in the diagnosis of PAH

Although a possible genetic origin of PAH was described in the 1950s [100], a new era was opened when pathogenic germline mutations in the *BMPR2* gene were found to be responsible for familial PAH cases in the late 1990s [101, 102]. Since then, several additional genes have been associated with PAH [103]. An international expert panel recently classified 12 genes (*BMPR2*, *ACVRL1*, *ATP13A3*, *CAV1*, *EIF2AK4*, *ENG*, *GDF2*, *KCNK3*, *KDR*, *SMAD9*, *SOX17* and *TBX4*) as having definitive evidence, while three further genes were classified as having moderate evidence (*ABCC8*, *GGCX* and *TET2*) and six genes as having limited evidence supporting a PAH gene–disease relationship [104].

Based on the evidence on the potential genetic background of PAH, HPAH was introduced as a distinct subcategory of group 1 PH in the ERS/ESC PH guidelines in 2009 [105], comprising ∼3% of all PAH patients [42]. According to the most recent ESC/ERS PH guidelines, all patients with idiopathic PAH, a family history of PAH (suspected HPAH), anorexigen-associated PAH and PAH associated with CHD should be informed about the possibility of a genetic condition [1, 2]. We suggest that genetic counselling and testing be offered to these patients [42, 104]. Genetic testing may reveal potential misclassifications, facilitating appropriate management. In addition, considering that HPAH patients frequently present with a more compromised haemodynamic profile and increased risk of clinical worsening, genetic testing may significantly influence therapeutic strategies.

Genetic counselling and testing should also be offered for patients with suspected PVOD/pulmonary capillary haemangiomatosis. Biallelic pathogenic variants in the eukaryotic translation initiation factor 2α kinase 4 gene (*EIF2AK4*) support this diagnosis, allowing appropriate management and early referral for lung transplantation for eligible patients [1, 2, 42].

If a pathogenic variant is identified in a patient, genetic counselling for family members should be encouraged. There is insufficient evidence to recommend genetic testing for pulmonary hypertension patients in groups 2–5 [42].

Conclusion

In conclusion, PH is characterised by the elevation of mPAP >20 mmHg. From the haemodynamic point of view, pre- and post-capillary forms of PH may be distinguished. Patients with exercise PH are characterised by a normal mPAP at rest, but an abnormal increase of mPAP during exercise. The clinical relevance of current haemodynamic criteria of PH has been supported by recent studies. They represent the cornerstone for diagnosis of different forms of PH, but they should always be interpreted within the individual patient's clinical context.

The core structure of the clinical classification of PH has been retained, including the five major groups. However, some changes have been implemented based on current developments. These include the re-introduction of "long-term responders to CCBs" as a subgroup of idiopathic PAH, the update of subgroups within group 2 and 3 PH and the addition of mitomycin-C and carfilzomib to the list of drugs with "definite association" with PAH.

For diagnosis of PH, we propose a stepwise approach, starting with simple, noninvasive tools, and with the main aim of discerning those patients who need to be referred to a PH centre and should undergo invasive haemodynamic assessment.

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