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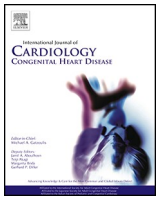

The latest definition and classification of pulmonary hypertension

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A B S T R A C T

Pulmonary hypertension (PH) is a serious potential complication of some congenital heart diseases (CHDs). PH encompasses a range of diseases which may be idiopathic or inherited, or secondary to cardiac, respiratory, systemic or thromboembolic conditions, amongst others. Our increasing understanding of the normal ranges of pulmonary haemodynamics, as well as evidence supporting the benefits of early treatment, has resulted in a number of recent revisions to the haemodynamic definition of PH. In this Review Article, we report on the recent updates to haemodynamic definitions and classification of PH, as reflected in the 2022 Pulmonary Hypertension Guidelines and particularly focus on the CHD related sub-type of PH, where the aetiology is often multi-factorial.

1. Introduction

Pulmonary hypertension (PH) is a serious potential complication of some congenital heart diseases (CHDs) and may result in (or accelerate the onset of) right heart failure [1]. Whilst previously considered a disease which primarily affected young women, there is now a greater understanding that PH encompasses a range of diseases which may be idiopathic or inherited, or secondary to cardiac, respiratory, systemic or thromboembolic conditions, amongst others [1].

In recent classification systems, pulmonary *arterial* hypertension (PAH) (Group 1) is that subset with pulmonary arteriopathy causing elevated pulmonary vascular resistance. PAH encompasses several different sub-groups, including idiopathic and heritable PAH as well as congenital heart disease (CHD) related PH [1]. Group 1 PH was traditionally defined by the haemodynamic definition: mean pulmonary arterial pressure (mPAP) $\geqslant$25 mmHg, pulmonary arterial wedge pressure (PAWP) $\leqslant$15 mmHg and pulmonary vascular resistance (PVR) $>$ 3 Wood units (WU) [2]. Our increasing understanding of the normal ranges of pulmonary haemodynamics, as well as evidence supporting the benefits of early treatment, has resulted in a number of recent revisions to this definition, over the last five years [1,3–6].

The demographics and characteristics of patients diagnosed with PH have also changed in the modern era [7]. With more patients diagnosed with PH (and even PAH) above the age of 60-years-old, this cohort is increasingly comorbid [7–10]. The presence of cardiopulmonary co-morbidities can mean that individual patients can have multiple causes of raised pulmonary pressures, making it increasingly difficult to differentiate Group 1 from Group 2 and 3 PH [1]. Accurate diagnosis and classification is imperative to guide appropriate management using PAH-specific medications, as the effectiveness and tolerability of PAH-specific medications is dictated by the underlying aetiology.

Thus, in this Review Article, we report on the recent updates to haemodynamic definitions and classification of PH, as reflected in the 2022 Pulmonary Hypertension Guidelines [1]. We particularly focus on the CHD related sub-type of PH, where the aetiology is often multi-factorial and the right ventricular (RV) phenotype often differs from other types of PH.

1.1. Haemodynamic definition – recent updates

The three key haemodynamic values needed for a diagnosis of the subtype of PH are the mPAP, PAWP and PVR with right heart catheterisation being the ‘gold standard’ diagnostic technique to determine these values [1]. To clarify the nomenclature used in this area, PH is any condition where the mPAP is elevated. PAH (Group 1) is the subset of PH with a normal left atrial (LA) pressure. This is also referred to as “pre-capillary” PHT [1]. Post-capillary PH (Group 2) is thought to be due to the backward transmission of elevated LA pressure into the pulmonary vasculature [11]. The PVR is derived as the ratio of the transpulmonary gradient to the cardiac output [12]. Patients with PAH are haemodynamically characterised by as Group 1, if they have neither lung disease (Group 3 PH) or CTEPH (Group 4 PH) [1,12]. Haemodynamic confirmation of diagnosis is imperative to determining suitability and response to treatment with PAH-specific medications, as well as to guide prognosis [12]. It is now widely accepted that early treatment of PAH is associated with improved outcomes [4–6].

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Table 1
Haemodynamic definitions of pulmonary hypertension.

Definition	Haemodynamic Characteristics
Pulmonary Hypertension	mPAP >20 mmHg
Pre-Capillary Pulmonary Hypertension	mPAP >20 mmHg, PAWP ≤15 mmHg, PVR >2WU
Post-Capillary Pulmonary Hypertension	mPAP >20 mmHg, PAWP >15 mmHg
• Ipc-PH	• DPG <7 mmHg and/or PVR<2WU
• Cpc-PH	• DPG >7 mmHg and PVR>2WU

mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; pulmonary vascular resistance; Ipc-PH = isolated post-capillary pulmonary hypertension; Cpc-PH = combined pre- and post-capillary pulmonary hypertension; DPG = diastolic pulmonary gradient.

At the 6th World Symposium on Pulmonary Hypertension (2018, Nice, France), it was recognised that the original haemodynamic definition of PAH was somewhat arbitrary and did not reflect the evidence base for "normal" pulmonary haemodynamics [3]. Invasive RHC studies have demonstrated that in healthy subjects, normal mPAP averages 14 mmHg with an upper limit of approximately 20 mmHg[13]. Prior studies also showed that patients with mildly elevated mPAP, between 21 mmHg and 24 mmHg, experience functional limitation and poorer outcomes, compared to those with strictly normal mean PAP ⩽20 mmHg [13–15]. These findings have been further confirmed in data from large cohorts based on RHC or estimates from transthoracic echocardiography [16,17]. Thus, the mPAP threshold for "upper limit of normal" was lowered to 20 mmHg (from 25 mmHg), whilst the cut-off values of PAWP ⩽15 mmHg and PVR >3 WU remained unchanged [3].

In the recently published 2022 Pulmonary Hypertension guidelines these definitions were endorsed and expanded upon [1]. A meta-analysis of all published data on healthy controls showed that the upper normal PVR was 2 Wood units [18]. The normal threshold in the elderly remains unclear, however, given PVR is dependent on both body surface area and age, higher values are likely to be noted in healthy elderly patients [1]. Several recent studies have also demonstrated that the lowest prognostically relevant threshold for PVR, and the threshold where medication is potentially beneficial, is approximately 2WU [19–21]. To reflect these findings, the threshold for abnormally elevated PVR was reduced to <2WU (from 3WU) in the most recent PH guidelines [1].

PAWP remains a key haemodynamic parameter to discriminate between pre- and post-capillary PH. Despite the fact the upper limit of normal PAWP is considered 12 mmHg, the threshold for pre-capillary PH remains ≤15 mmHg [22]. This is in part because almost all PAH therapeutic studies have used the PAWP ≤15 mmHg threshold, and, also, the consensus recommendations that suggested the threshold for invasive diagnosis of heart failure with preserved ejection fraction (HFpEF) also used this threshold [23]. Thus, the haemodynamic definition for post-capillary PH remains mPAP >20 mmHg and PAWP >15 mmHg [1]. The recent PH guidelines do however acknowledge the arbitrary nature of this PAWP cut-off and encourage clinicians to consider the patient's phenotype, left-heart disease risk factors and echocardiographic findings in conjunction with haemodynamic data, when distinguishing between pre and post-capillary PH [1].

Approximately 15 % of cases of post-capillary PH have an increase in mPAP that is "disproportionate" to raised LA pressure and is likely due to super-imposed pre-capillary pulmonary vascular disease [24]. To delineate these patients from those with isolated post-capillary PH, additional haemodynamic criteria have been proposed: (1) isolated post-capillary PHT (Ipc-PH) (diastolic pulmonary vascular pressure gradient DPG <7 mmHg and/or PVR<2WU, (2) combined post- and pre-capillary PHT (Cpc-PH) (DPG >7 mmHg and PVR>2WU) [1,24]. Patients with Cpc-PH tend to have poorer prognosis and may respond favourably to PH therapy and are thus important to identify [24].

The 2022 guidelines highlight that there are patients with an elevated mPAP (>20 mmHg) but low PVR and (<2WU) and PAWP<15 mmHg. These patients have PH, but do not meet the criteria for either pre- or post-capillary PH. This haemodynamic condition is now described as 'unclassified PH' and the elevated pulmonary blood flow may be secondary to CHD, liver disease, airway or ling disease or hyperthyroidism [1]. When this haemodynamic profile is identified, further investigation for the underlying aetiology is recommended, as is ongoing follow up [1].

Table 1 summarises the current haemodynamic definitions for the different PH Groups.

Table 2
Clinical classification of pulmonary hypertension.

	Group 1 PAH	Group 2 PH associated with left heart disease	Group 3 PH associated with lung disease	Group 4 PH associated with pulmonary artery obstructions	Group 5 PH with unclear and/or multifactorial mechanisms
Types	• Idiopathic - Non-responders at vasoreactivity testing - Acute responders at vasoreactivity testing • Heritable • Associated with drugs and toxins • Associated with -Connective tissue disease - HIV infection - Portal hypertension - Congenital heart disease - Schistomiasis • PAH with feature of venous/capillary involvement	• HFrEF • HFpEF • Valvular pathology • Congenital/acquired cardiac condition leading to post-capillary PH	• Obstructive lung diseases or hypoxia • Restrictive lung disease • Lung disease with mixed restrictive/obstructive pattern • Hypoventilation syndromes • Hypoxia without lung disease • Developmental lung disorders	• Chronic thromboembolic PH • Other pulmonary artery obstruction	• Haematological disorders • Systemic disorders • Metabolic disorders • Chronic renal failure with or without haemodialysis • Pulmonary tumour thrombotic microangiopathy • Fibrosing mediastinitis
Prevalence	Rare	Very common	Common	Rare	Rare
Haemodynamics	mPAP >20 mmHg, PAWP ≤15 mmHg, PVR >2WU	mPAP >20 mmHg, PAWP 15 mmHg	mPAP >20 mmHg, PAWP ≤15 mmHg, PVR >2WU	mPAP >20 mmHg, PAWP ≤15 mmHg, PVR >2WU	mPAP >20 mmHg, PAWP ≤15 mmHg, PVR >2WU

PAH = pulmonary arterial hypertension; PH = pulmonary hypertension, HFrEF = heart failure reduced ejection fraction; HFpEF = heart failure preserved ejection fraction; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; pulmonary vascular resistance.

Table 3
Clinical Classification of Pulmonary Hypertension associated with Congenital Heart Disease.

Left-to-Right Shunts
Atrial septal defects (secundum, primum, sinus venosus type) Ventricular septal defect (perimembranous more than muscular, more than doubly-committed sub arterial) Ventricular septal defect with TGA Persistent ductus arteriosus Truncus arteriosus Aortopulmonary window Aortopulmonary collaterals
Left heart diseases
Supramitral stenosis Congenital mitral stenosis at valvular level Severe aortic stenosis Severe coarctation of the aorta Shone's syndrome (multi-level left heart obstructive disease)
Eisenmenger's Syndrome
Large intra-cardiac lesions which begin as systemic-to-pulmonary shunts → severely ↑ PVR → shunt reversal → pulmonary-to-systemic or bidirectional shunt. Large extra-cardiac shunts e.g. patent ductus arteriosus.
Post-Operative
Systemic to pulmonary artery shunts – such as Blalock, Waterston, Potts PAH which persists or recurs after correction despite the absence of significant residual haemodynamic lesions
Combination of Above

TGA = transposition of the great arteries; PVR = pulmonary vascular resistance.

1.2. Classification

The clinical classification for PH categorises the clinical conditions associated with PH according to their pathophysiology, clinical presentation, haemodynamics and management into 5 major groups [1]. This classification is summarised in Table 2. As outlined briefly above these groups are.

- Group 1: pulmonary arterial hypertension (PAH)
- Group 2: pulmonary hypertension due to left heart disease
- Group 3: pulmonary hypertension due to lung diseases and/or hypoxia
- Group 4: pulmonary hypertension due to chronic thromboembolic disease
- Group 5: pulmonary hypertension with unclear, multifactorial mechanisms

This classification system has been largely unchanged from the 2015 to the 2022 clinical guidelines [1]. The major changes which were made include.

- Response to vasoreactivity testing has been added as a sub-category to Group 1 to delineate the sub-group of patients with PAH, heritable PAH or drug induced PAH who may respond to calcium channel blocker therapy.
- New sub-groups have been added to Group 1:
  1. PAH with features of venous/capillary (pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis
  2. Persistent PH of the newborn
- 'Hypoventilation syndromes' is the term used to describe the conditions within Group 3 where PH is frequently associated and can cause daytime hypercapnia.

1.3. Cardiopulmonary Co-Morbidities

All PH groups can have pre- and post-capillary components contributing to elevation of PA pressures. The classification for each patient is dependent on the dominant cause of this elevation. This has become particularly relevant in recent years as the demographics of patients with PAH have changed. Whilst previously considered a disease affecting young women, several modern PH registries have reported that the average age of diagnosis for PAH is now 60 years, or greater [7–10]. These patients often have concomitant cardiopulmonary comorbidities, making the distinction between PH groups 1, 2 or 3 more difficult.

It is important for treating clinicians to identify such patients as they have a poorer response and tolerability to PAH-specific medication, are less likely to achieve low-risk status and have increased long-term mortality. Thus, the updated 2022 PH guidelines describe two phenotypes to further classify such patients.

1. **Left-Heart Phenotype:** older patient, female predominance with left-heart risk factors which may include hypertension, obesity, diabetes coronary artery disease or atrial fibrillation [8,25,26]. This sub-group has similar age-adjusted mortality to the 'classic' PAH group.
2. **Cardiopulmonary Phenotype:** older patient, male predominance, DLCO <45 % predicted, often hypoxemic, significant smoking history and other risk factors for left heart disease [7,27–29]. Patients have a significantly higher mortality risk compared to the 'classic' PAH group.

There is no standardised definition to classify patients into one of the above phenotypes. The COMPERA registry report that the presence of 1 risk factor may change a patients phenotype and report in a breakdown of newly diagnosed idiopathic PAH patients (n = 841) 12.6 % had a 'classic phenotype', 35.8 % had a left-heart phenotype and 51.6 % had a cardiopulmonary phenotype [8]. The AMBITION study on the other hand, used the threshold of ≥3 left heart disease risk factors to exclude patients from the primary analysis [25].

Patients with these phenotypes are generally underrepresented in clinical trials, thus an evidenced-based algorithm or recommendations cannot be made for these patients [1]. However, initial monotherapy has been suggested, with PDE-5 inhibitors being the most common first-line therapy, according to registry data. There is a higher rate of discontinuation of combination therapy (ERA + PDE5 inhibitor) compared to patients with 'classic' PAH. This may be because ERA therapy is associated with an increased risk of fluid retention in patients with a left-heart phenotype and PAH medication may lead to a decrease in

peripheral oxygen saturations in patients with a cardiopulmonary phenotype [25,30]. Furthermore, there is little published data on the of prostacyclin analogues or prostacyclin receptor agonists in this group [31]. Thus, clinicians are encouraged to adapt treatment plans for individual patients with the support of an "expert" PH centre [1].

1.4. Causes and classification of congenital heart disease related pulmonary hypertension

PH in adults with CHD has a negative impact on symptoms and long-term outcomes [32]. As shown in Table 3, there are 5 major circumstances in which congenital heart disease can lead to PH [1,33,34]. These are.

1 Left to right shunts, with volume and/or pressure overload on the right ventricle (for example, atrial or ventricular septal defects).
2 Left heart diseases, which lead to pulmonary hypertension via increased left atrial pressure.
3 Eisenmenger's Syndrome, large intra-cardiac, or extra-cardiac, lesions which begin as systemic-to-pulmonary shunts but progress to severely elevated PVR and eventually the shunt reverses to become a pulmonary-to-systemic or bidirectional shunt.
4 The post operative situation, where pulmonary blood flow has been augmented surgically and this has been "excessive". Or, PAH which persists, or recurs, following correction despite the absence of significant residual haemodynamic lesions.
5. Some combination of the 4 factors above.

It is estimated that 3–7% of patients with adult CHD will develop PAH, however, this is a heterogenous group and the risk of PH developing depends on the underlying lesion and the age of defect closure [35]. Whilst it is estimated that the prevalence of PAH after correcting a 'simple' defect is 3 % there is variation even within specific defects [36]. For example, an uncorrected secundum ASD with lead to PH in approximately 10 % of cases whereas a sinus venosus ASD is thought to lead to PH in 25 % of cases [37].

Defects where both pulmonary pressures and blood flow are elevated often lead to pulmonary vascular disease from a younger age. A non-restrictive ventricular septal defect (VSD) is a classic example of this. Interestingly, it has also been noted that a VSD with transposition of the great arteries leads to irreversible PH earlier than infants who have a VSD and normally related great vessels [38]. Truncus arteriosus and aortopulmonary window are also associated with severe pulmonary vascular disease at a very early age (<12 months). Thus, the combination of high pulmonary blood flow and pressures are key factors in the early development of PH, and this is further compounded when the great vessels are transposed.

In CHD, the phenotype of the RV is dependent on whether that ventricle is predominantly volume or pressure loaded, and the duration of these changes [33]. If the RV is mainly volume loaded, as with an ASD, the RV dilates and may develop eccentric hypertrophy from the volume load, before eventually developing a pressure load. In a VSD or partial anomalous pulmonary venous return, on the other hand, the RV volume and pressure are both elevated from birth, there is simultaneous chamber dilatation and concentric hypertrophy [33,39]. Thus, the RV phenotype depends exquisitely on the haemodynamic loading conditions of the RV, which varies depending on the size and location of the underlying CHD.

Post-capillary PH can also occur in adult CHD in the form of systolic or diastolic systemic ventricular dysfunction, left-sided valvular regurgitation or stenosis and may occur in combination with shunt lesions or complex CHD [1,40]. In this sub-type, the RV phenotype resembles that in adult-onset Group 2 PH. Similar, to adults without CHD, the treatment of this a combination of treating the left-heart disease and diuretics, rather than PAH specific therapy [33]. Examples include severe congenital supra-mitral, mitral or aortic valve stenosis [40].

Eisenmenger's syndrome occurs when large intra-cardiac shunt lesions, or extra-cardiac shunts (e.g. Eisenmenger patent ductus arteriosus, which are initially systemic-pulmonary lesions (left-to-right), lead to progressive pulmonary vascular disease resulting in the PVR elevating above the systemic vascular resistance, causing the shunt to reverse and become pulmonic-to-systemic (right-to-left) [1,33,40]. These RV's become increasingly hypertrophied but rarely 'fail'. Associated complications include cyanosis, erythrocytosis and polycythaemia. Surgical correction of these lesions is contraindicated [40].

Post-operative PH falls into two broad categories. The first is where the pulmonary blood flow has been augmented surgically and has been excessive. This was more common when older surgical techniques such as Waterston and Potts shunts were used, but these patients are now experiencing the complications related to their corrective surgery in adulthood [1,33,40]. The second relates to PAH which persists after correction or recurs months-years following correction despite the absence of significant residual haemodynamic lesions [1]. Post-operative PH is generally associated with LV dilatation as well as high RV afterload. The severity is dependent on the underlying CHD as well as the size and location of surgical shunt [33].

Mixed aetiology PH is also common in the setting of CHD; for example, AVSD in Down syndrome with co-existing sleep apnoea; or in patients ASD and obstructive left heart lesions. Each case needs to be considered on its individual merits, in these often complex situations.

Advances in the diagnosis and management of CHD in childhood are likely to lead to a change in the epidemiology of PAH associated with CHD. There are likely to be fewer adult patients with simple CHD and more with complex lesions/prior surgery who develop PAH in adulthood [41].

2. Conclusions

The definitions of PH and PAH have been revised in recent years to better reflect deviations from normal pulmonary haemodynamics and to allow patients earlier access to treatment. PH is a relatively common and important complication of many congenital heart diseases and the mechanisms for this are often complex. Accurate diagnosis, classification and consideration of coincident cardiopulmonary risk factors are important in treating CHD patients with PH, effectively.

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Seshika Ratwatte: Writing – review & editing, Writing – original draft, Conceptualization. **David S. Celermajer:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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