An overview of the 6th World Symposium on Pulmonary Hypertension

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Since 1973 the World Symposia on Pulmonary Hypertension (WSPH) proceedings have summarised the scientific advances and future needs in this field through the efforts of multiple task forces, each focusing on a different aspect of pulmonary hypertension (PH) [1]. The 6th WSPH comprised 124 experts, divided into 13 task forces, that began their work in January 2017 and presented their consensus opinions to an audience of 1376 participant attendees between February 27 and March 1, 2018 in Nice, France. A newly created task force dedicated to patients’ perspectives, including representatives of patients’ associations worldwide, was added for the 6th WSPH.

The task forces continued their work after the 6th WSPH to incorporate participants’ input during the plenary session discussions into the 13 manuscripts published in the current issue of the European Respiratory Journal. The publication process, which in the past had been performed after each world symposium and included editors and blinded peer-review and revisions, has been modified with these proceedings in order to improve the quality and the timeliness of these state-of-the-art articles. The key points included in each task force’s manuscript, representing both current achievements and starting points for future research in the field of the pulmonary vascular science, are summarised below.

The task force on pathology and pathobiology summarised the most advanced achievements in the cellular and molecular basis and pathology of pulmonary vascular remodelling associated with various forms of PH [2]. The manuscript reports new insights on specific pulmonary vascular lesions, including plexiform lesions, complex lesions and venous and venular lesions. Recent advances in cellular abnormalities are discussed, such as dysfunction of the pulmonary vascular endothelium, accumulation of pulmonary artery smooth muscle cells and adventitial fibroblasts, and dysregulation of the innate and adaptive immune system. Finally, multiple molecular mechanisms are explored and considered as emerging therapeutic targets that may constitute the rationale for future clinical studies.

The genetics and genomics task force estimated that about 25–30% of patients diagnosed with idiopathic pulmonary arterial hypertension have an underlying Mendelian genetic cause for their condition and
should be classified as heritable pulmonary arterial hypertension [3]. The article reports links between mutations and disease, and factors affecting disease penetrance. Genetic counselling and testing, management of healthy mutation carriers and psychosocial considerations and reproductive options are also discussed. Advances in DNA sequencing technology may facilitate genomic studies in large cohorts and potentially lead to a molecular classification of the disease. This may help identify novel targets for new drugs, expanding our therapeutic options.

The task force on the pathophysiology of the right ventricle and of the pulmonary circulation has revisited the pathophysiological description of the cardio-pulmonary unit (consisting of both the right ventricle and the pulmonary vascular system) in order to improve clinical data interpretation [4]. A better understanding of right heart haemodynamic data as well as imaging data of the right ventricle obtained by echocardiography or magnetic resonance imaging is also provided. Provocative tests such as exercise and fluid loading are addressed, and the need for additional outcome studies to clarify the clinical relevance of an “abnormal” response is outlined. Finally, an update is provided on the latest insights in the pathobiology of right ventricular failure, including key pathways of molecular adaptation of the pressure-overloaded right ventricle.

One of the most significant (and controversial) recommendations from the 6th WSPH has been the proposal by the task force on haemodynamic definitions and clinical classification, to reconsider the haemodynamic definition of PH [5]. Based on data from normal subjects, the normal mean pulmonary arterial pressure (mPAP) at rest is approximately 14±3.3 mmHg [6]. Two standard deviations above this mean value would indicate that a mPAP >20 mmHg is the threshold for abnormal pulmonary arterial pressure (above the 97.5th percentile). However, this level of mPAP is not sufficient to define pulmonary vascular disease, since it could be due to increases in cardiac output or pulmonary artery wedge pressure (PAWP). The task force has therefore proposed including a pulmonary vascular resistance (PVR) ≥3 WU into the definition of pre-capillary PH associated with mPAP >20 mmHg, irrespective of aetiology. Future trials should assess the efficacy of pulmonary arterial hypertension (PAH) medications (currently approved based on a mPAP ≥25 mmHg) in patients with mPAP from 21 to 24 mmHg and PVR ≥3 WU. Due to limited data, the task force declined to identify a clinically useful definition of exercise PH, encouraging additional outcome studies instead. The clinical classification of PH was simplified, maintaining the traditional five-group structure. A new entity entitled “PAH long-term responders to calcium channel blockers” was introduced to the group 1.

The task force on PH diagnosis has revised the diagnostic algorithm, providing a methodical approach for diagnosis of patients with suspected PH both prior to and following referral to expert centres [7]. In addition, expedited referral has been recommended for high-risk or complex patients, as well as patients with confounding comorbidities. Updated screening procedures in asymptomatic patients with conditions associated with a high PH prevalence have been proposed, together with a review of current diagnostic tools and emerging diagnostic technologies.

The task force on clinical risk stratification and medical therapy in PAH patients has provided an update of all data available on these topics [8]. The strong relationship between risk stratification, initial treatment strategy and follow-up treatment escalations has been emphasised and serves as the rationale for a treatment strategy that is based on disease severity as assessed by a multi-parametric risk stratification approach. Clinical, exercise, right ventricular function and haemodynamic parameters and biomarkers are combined to define a low-, intermediate- or high-risk status based on the expected 1-year mortality. The comprehensive treatment algorithm provides an overview of initial strategies, including monotherapy (in a minority of patients), and double or triple combination therapy. Further treatment escalation is required in case low-risk status (considered as treatment goal) is not achieved in structured follow-up assessments.

The task force on right ventricular assistance and lung transplantation has presented a comprehensive intensive care approach for patients with PH and right-sided heart failure, including treatment of factors causing or contributing to heart failure, careful fluid management and strategies to reduce right ventricular afterload and improve cardiac function [9]. Extracorporeal membrane oxygenation should be considered in candidates for lung transplantation (bridge to transplant) or, occasionally, in patients with a reversible cause of right-sided heart failure (bridge to recovery). For patients with advanced disease, lung transplantation remains an important treatment option. Patients should be referred to a transplant centre when they remain in an intermediate- or high-risk category despite receiving maximal PAH therapy. In experienced centres, the 1-year survival rates after lung transplantation for PH now exceeds 90%.

The task force on clinical trial design and new therapies for PAH has reviewed the progress in clinical trial design and end-points achieved over the past two decades, highlighting the crucial collaboration between international experts, industry and regulatory agencies [10]. New drug targets have been proposed and are summarised, including genetics, epigenetics, DNA damage, growth factors, metabolism, inflammation and immune modulation, oestrogen signalling, oxidative and hypoxic stress, serotonin and humoral...
modulation. Additional strategies such as pulmonary artery denervation and stem cell therapies are also discussed. The task force also addressed the challenges facing future PAH clinical trials and has outlined the characteristics for phase 1, 2 and 3 registration studies.

New defining criteria for the different haemodynamic types of PH that occur with left heart disease (LHD) has been proposed by the task force on PAH due to left heart disease [11]. After consideration of the changes in the general definition of PH [5], the proposed haemodynamic definition of PH in LHD was: 1) isolated post-capillary PH: PAWP >15 mmHg and mPAP >20 mmHg and PVR <3 WU; 2) combined post- and precapillary PH: PAWP >15 mmHg and mPAP >20 mmHg and PVR >3 WU. The importance of the differential diagnosis between idiopathic PAH and PH due to heart failure with preserved left ventricular ejection fraction has been emphasised. A pre-test probability score for PH-LHD may help in the differential diagnosis. The nomenclature of PAH with cardiovascular risk factors should be preferred over any other, to account for their co-existence without suggesting that these risk factors are de facto the cause of the pulmonary vascular disease. The diagnostic relevance of provocative tests such as fluid loading and exercise were also discussed, together with the uncertainties over their clinical meaning. Finally, since multicentre randomised trials using PAH therapies in PH-LHD have not demonstrated benefit and have raised safety concerns, their use is still not recommended by the task force in PH-LHD.

The task force on PH due to chronic lung disease points out that PH frequently complicates the course of patients with various forms of chronic lung disease (CLD-PH) [12]. CLD-PH is invariably associated with reduced functional ability, impaired quality of life, greater oxygen requirements and an increased risk of mortality. The different aetiologies are discussed and the haemodynamic profile is compared with the combination of physiological and imaging assessment. An updated definition and severity grading of CLD-PH is also provided. The risk-to-benefit ratio of PAH approved drugs in CLD-PH patients has been revisited in depth. Although such therapy cannot be endorsed given the current lack of efficacy evidence and in the face of serious safety concerns, future studies in this area are strongly encouraged.

The task force on chronic thromboembolic pulmonary hypertension (CTEPH) has provided an overview of the state-of-the-art diagnostic and treatment modalities in this rapidly evolving field [13]. The new entity of chronic thromboembolic disease (CTED) has been characterised by similar symptoms and perfusion defects to CTEPH, but without PH at rest. CTEPH treatment recommendations should not yet be applied to CTED, since additional prospective studies are needed. Digital subtraction pulmonary angiography had been considered the gold standard for characterising vessel morphology in CTEPH, but is being challenged by advances in noninvasive modalities. Computed tomography pulmonary angiography is currently widely used for assessment of operability. Pulmonary endarterectomy (PEA) is the treatment of choice, and patient operability should be evaluated by an expert multidisciplinary CTEPH team including a PEA surgeon, PH expert, balloon pulmonary angioplasty (BPA) interventionist and radiologist. BPA, an emerging procedure in non-operative patients, requires specific training of dedicated interventionists. The level of expertise of the CTEPH team should be evaluated based on the centre’s number of procedures performed and the outcome results. Medical therapy has a supporting role to improve symptoms and haemodynamics.

The task force on paediatric PH has revised a number of aspects of this specific field [14]. The definition of PH is consistent with the newly proposed definition in adults [5]. The use of cardiac catheterisation as a diagnostic modality and haemodynamic assessment of PAH, including acute vasoreactivity testing, are addressed. The common clinical classification for both adults and children has been integrated with modifications in order to highlight aspects of paediatric disorders and better address specific features of paediatric PH within the core of the existing classification. Several features of paediatric PH, including the prominence of neonatal PAH, especially in preterm infants and those with developmental lung diseases and novel genetic causes of paediatric PAH, are highlighted. Although a lack of clinical trial data for the use of PAH-targeted therapy in this population persists, emerging data are improving the identification of appropriate targets for goal-oriented therapy in children. Such data will likely improve future clinical trial design to enhance outcomes in paediatric PAH. Specific paediatric interventional management of PAH, including the Potts shunt, were also discussed.

The importance of the patients’ perspective has been outlined by a newly created task force [15]. Despite recent progress in patients’ involvement in the PH field, patient surveys indicate that more can be done to improve this aspect. The relevance of health-related quality of life has been outlined, and specific questionnaire use may improve direct clinical care. Patients should be provided with access to accredited specialist centres that provide a multidisciplinary approach including narrative medicine, shared decision making, palliative care and participation in education. The role of patients’ associations in supporting patients and carers, lobbying for access to best care and treatments, providing input in to the development of clinical trials and registries, and focusing on the patient perspective have also been highlighted.
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Clinical and translational research has played a major role in advancing our understanding of pulmonary hypertension (PH), including pulmonary arterial hypertension and other forms of PH with severe vascular remodelling (e.g. chronic thromboembolic PH and pulmonary veno-occlusive disease). However, PH remains an incurable condition with a high mortality rate, underscoring the need for a better transfer of novel scientific knowledge into healthcare interventions. Herein, we review recent findings in pathology (with the questioning of the strict morphological categorisation of various forms of PH into pre- or post-capillary involvement of pulmonary vessels) and cellular mechanisms contributing to the onset and progression of pulmonary vascular remodelling associated with various forms of PH. We also discuss ways to improve management and to support and optimise drug development in this research field.
Introduction
Pulmonary hypertension (PH) encompasses a group of severe clinical entities, such as pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH), in which loss and obstructive remodelling of the pulmonary vascular bed is responsible for the rise in pulmonary arterial pressure and pulmonary vascular resistance (PVR), resulting in progressive right heart failure and functional decline. Pulmonary vascular remodelling in PAH is not only characterised by an accumulation of different vascular cells in the pulmonary arterial wall (pulmonary artery smooth muscle cells (PA-SMCs), endothelial cells, fibroblasts, myofibroblasts and pericytes), but also by loss of pre-capillary arteries and by an exaggerated perivascular infiltration of inflammatory cells (B- and T-lymphocytes, mast cells, dendritic cells, macrophages, etc.). Because current PAH treatments do not specifically target pulmonary vascular remodelling and inflammation, there is an urgent need to better identify the pathobiological mechanisms underlying the progressive narrowing of the pulmonary arterial lumen and perivascular inflammation and the loss of vessels in order to support therapeutic innovation aimed at reversing these features and regenerating normal pulmonary vessels.

Recent advances in pathology and laboratory medicine

General considerations
In addition to stiffening of large elastic main, lobar and segmental pulmonary arteries, PH can be attributed to lesions mainly occurring in distal muscular-type arteries, ranging in diameter from 500 µm down to 70 µm in humans (medial hypertrophy/hyperplasia, intimal and adventitial fibrosis, and (in situ) thrombotic lesions, plexiform lesions) (figure 1). They can be clearly differentiated from pulmonary veins due to their topography within the lung, since they are always neighboured by an airway (bronchiole), as well as through their microscopic anatomy, which includes a neatly defined tunica media that is delimited by the internal and the external elastic lamina. Small pre-capillary pulmonary arteries ranging in diameter from 70 µm down to 20 µm in humans (arterioles) are also involved in all groups of human and experimental PH, through processes of loss and obliteration, abnormal muscularisation, and perivascular inflammation (figure 2). In contrast to the muscular-type arteries, they can only be indirectly distinguished from small post-capillary venules of the same size, through serial section tracing, or, if feasible, injection techniques with dye or beads. The capillary compartment that arises from the arteriolar microvasculature and that represents the largest vascular surface within the lung is also frequently involved. There is also accumulating evidence supporting the involvement of the post-capillary pulmonary venous vasculature in all PH groups with varying degrees of intensity. In PH due to left heart disease and chronic respiratory disease, post-capillary involvement is likely to be explained at least in part by parenchymal destruction and inflammation in patients with lung fibrosis and emphysema, and by chronic elevation in post-capillary pressure in left heart failure where PH is associated with global pulmonary vascular remodelling. Interestingly, the severity of PH in heart failure correlates with venous and small indeterminate vessel intimal thickening, resembling the pattern observed in pulmonary veno-occlusive disease (PVOD) [1]; larger pulmonary veins running within the interlobular septa may appear

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arteriolised’, mimicking the exact microscopic anatomy of muscular-type pulmonary arteries. In apparently pure pre-capillary forms of PH, such as PAH and CTEPH, the mechanisms of post-capillary involvement are not obvious, since the post-capillary vessels, in theory, should be shielded from increased pre-capillary pressure by the arterial and capillary compartment [2].

New interpretation of specific pulmonary vascular lesions

Plexiform lesions/complex lesions

Complex pulmonary arterial lesions comprise different elements, such as onion-skin lesions, plexiform core lesions and dilation lesions, which are commonly observed in close topographic association (figure 1a–c). However, the pathophysiological significance of these typical vascular changes in PAH has yet to be elucidated. In this regard, recent reports suggest that systemic vessels, such as the vasa vasorum and bronchial arteries running within the adventitia of pulmonary arteries or within the peribronchial connective tissue, respectively, could be involved in the plexiform vasculopathy (figure 1c). Analysis of serial sections from PAH patients with digital three-dimensional reconstruction supports a shunting hypothesis, where plexiform lesions appear to represent anastomosing structures between bronchial microvessels and pulmonary arteries and veins [3]. Shunting between the bronchial and pulmonary vasculature has been described by means of morphometric analysis of explanted lung tissue sections from PAH patients, including idiopathic PAH (IPAH) and heritable PAH (HPAH) due to a BMPR2 (bone morphogenetic protein receptor type 2) mutation [4]. Hypertrophy and dilatation of bronchial arteries and increase in bronchial microvessel density in BMPR2 mutation carriers correlated with pulmonary venous remodelling [4]. Moreover, large fibrous vascular structures (“SiMFis” (singular millimetric fibrovascular lesions)) appear to connect the systemic vasculature to pulmonary arteries and veins (figure 1d). A
functional role for the hypertrophic systemic vasculature in PAH that would allow short-circuiting a primary pulmonary arterial obstruction (figure 3) has yet to be confirmed.

Venous and venular lesions
A substantial proportion of PH patients display pulmonary venous and venular remodelling (figure 2e) [4]: lungs from PAH patients with scleroderma often exhibit PVOD-like pathology [5], and CTEPH lungs commonly show pulmonary veins and venules abnormalities [2]. CTEPH is of particular interest in this context. Although the primary insult, i.e. chronic thromboembolic occlusion of elastic and muscular arteries, occurs on the pre-capillary side of the pulmonary vasculature and contributes to increased PVR, remodelling of microvessels is also present, affecting pre-capillary arterioles and post-capillary venules [2, 6]. Importantly, bronchial arterial hypertrophy is associated with pulmonary venous remodelling in CTEPH, supporting the concept that systemic lung vessels associated with bronchopulmonary anastomoses could contribute to these changes [2].

In PVOD, pulmonary vascular lesions are thought to predominate on the post-capillary side, but arteries are also involved [7]. Post-capillary lesions affecting septal veins and pre-septal venules frequently consist of loose, fibrous remodelling of the intima that may totally occlude the lumen. The walls of septal veins and pre-septal venules may show smooth muscle cell hyperplasia and can be difficult to distinguish from abnormally muscularised arterioles <70 µm in diameter in PVOD lungs [7]. Post-capillary remodelling is frequently associated with pulmonary capillary angioectasia and capillary angioproliferation with doubling and tripling of the alveolar septal capillary layers that may be focally distributed (pulmonary capillary haemangiomatosis). See figure 2b–d and f.

Recent advances in cellular abnormalities and emerging therapeutic targets

Dysfunction of pulmonary vascular endothelium
In PAH, the term pulmonary endothelial dysfunction has been used to denote impairment of endothelial-dependent vasodilation in favour of vasoconstriction, but it also refers to reduced anticoagulant properties, active metabolic changes, reactive oxygen species production, increased expression of adhesion molecules (E-selectin, intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1)), and a local unadapted release of different chemokines, cytokines and growth factors (figure 4). These latter changes result in impairments in angiogenesis and repair mechanisms that play primary roles in pulmonary vascular remodelling [8]. It is now well established that cultured pulmonary endothelial cells from patients with PAH maintain in vitro several abnormal phenotypic features more or less pronounced, perhaps reflecting different subpopulations. Among them,
decreased capacity for vascular tube formation in vitro, heightened aerobic glycolysis, and loss of some endothelial cell markers and acquisition of several mesenchymal cell markers have been described [9–11].

In PAH, a pro-inflammatory phenotype of pulmonary endothelial cells characterised by an increase in surface expression of E-selectin, ICAM1 and VCAM1 together with an excessive release of various key cytokines and chemokines has been reported [12]. Some features can be reproduced in endothelial cells grown from induced pluripotent stem cells (iPSCs) derived from the skin of the same patients [13, 14]. Various stimuli, such as high glucose, insulin resistance, disturbed blood flow and oxidative stress, can lead to endothelial dysfunction. However, the cause and the underlying mechanisms responsible for dysfunction of the pulmonary endothelium in PAH are still incompletely understood.

Recent studies have focused on two key modulators of endothelial structure and function that initiate and perpetuate pulmonary vascular remodelling associated with PH/PAH, i.e. fluid flow-induced high shear stress as well as low oxygen tension (chronic hypoxia). Normally, vascular endothelial cells respond to high shear stress by losing their cobblestone appearance and elongating in the direction of flow. Failure to adapt these morphological changes is associated with an increased tendency toward vascular remodelling. Interestingly, pressure off-loading by pulmonary artery banding has been reported to prevent and even reverse occlusive vascular remodelling in the Sugen hypoxia rat model [15]. This observation is consistent with findings from more recent studies showing that microvascular pulmonary endothelial cells, but not proximal pulmonary artery endothelial cells, isolated from PAH patients exhibit delayed morphological adaptation to high shear stress in vitro [16]. Chronic hypoxia also gives rise to structural remodelling of the pulmonary vasculature in experimental and human PH. Recent studies have supported this notion by showing that pulmonary vascular endothelial cells from plexiform lesions in patients with PAH have
decreased expression of prolyl-4 hydroxylase 2 (PHD2), an enzyme that facilitates the degradation of the hypoxic-inducible factor HIF1 and HIF2 hypoxia sensors. Furthermore, mice with endothelial cell-targeted disruption of the gene for PHD2 (EGLN1) develop obliterative pulmonary vascular remodelling and complex lesions as found in human PAH [17]. A combination of amphetamine and hypoxia can increase endothelial propensity to apoptosis and cause DNA damage by interfering with the normal metabolic function of HIF1α in switching to a glycolytic state [18]. Dasatinib can induce PAH and has also emerged as a modulator of pulmonary endothelial function: dasatinib at high doses induces pulmonary endothelial cell dysfunction via increased production of reactive oxygen species, thereby increasing the susceptibility to pleural effusions and PH in rodents [19–21]. A better understanding of the molecular mechanisms underlying endothelial adaptation to high shear stress and chronic hypoxia will greatly enhance our understanding of the pathogenesis of PH/PAH, and may aid in identifying new therapeutic strategies.

Additional insights into the altered pulmonary endothelial communication with both resident vascular cells (PA-SMCs, myofibroblasts, pericytes) and circulating cells (immune cells) are also a prerequisite for a better understanding of PH/PAH pathogenesis.

The endothelium is also critical for the development of a functional vascular network that is dependent upon signals exchanged between the different cell types responsible for coordinating this process. In experimental and human PH/PAH, angiogenesis is disturbed with loss and progressive obliteration of pre-capillary arteries leading to a pattern of pulmonary vascular rarefaction (“dead-trec” picture), even if several pro-angiogenic factors are overabundant and/or overactive and an overexpression of Notch3 signalling in PA-SMCs has been reported. Therefore, further studies are needed to identify how the endothelial microenvironment, at the cell–cell and cell–matrix interfaces, impairs pulmonary endothelial integrity and its regenerative angiogenic capacity in PH/PAH. In this context, a better knowledge of the contribution of circulating cells and resident vascular progenitors should be determined [22–28]. Indeed, pericytes are important not only for vessel maturation and stabilisation, but also for the prevention of endothelial sprout formation and endothelial proliferation required for the production of a new functional vasculature. In experimental and human PH/PAH, the total number of pulmonary pericytes in distal pulmonary arteries increases substantially during disease progression [26] and defects in pericycle function have been demonstrated [28]. Isolated pericytes from PAH patients exhibit reduced levels of genes crucial for the Wnt/planar cell polarity pathway and fail to associate with endothelial cells during tube formation as assessed in Matrigel tube formation assays [28].

It is now clearly established that abnormal BMPR2 signalling can adversely impact endothelial barrier function, DNA lesion persistence related to impaired DNA repair [29], metabolism, mitochondrial fission and fusion [30, 31], and also inflammation and its resolution [32–34]. Therefore, much effort should be
made to better understand the interplay between the BMPR2 signalling system and the process of pulmonary vascular remodelling.

**Accumulation of PA-SMCs and adventitial fibroblasts**

In PAH, the pulmonary arterial microenvironment and the presence of several inherent intrinsic abnormalities and dysregulated signals are known to partly explain the progressive accumulation of resident PA-SMCs and adventitial fibroblasts. In recent years, preclinical and early-stage clinical efforts have highlighted emerging targets in PAH pathophysiology. As in endothelial cells, DNA damage response pathways are critically implicated in PA-SMC and fibroblast survival in PAH. In both human and experimental PH/PAH the decrease in BRCA1 (breast cancer 1) protein following BMPR2 downregulation is associated with the upregulation of poly(ADP ribose) polymerase 1 (PARP1) in response to the increase in DNA damage insults [35]. The upregulation of PARP1 in PAH PA-SMCs allows them to cope with the environmental stresses by damping DNA damage consequences, adapting their mitochondrial functions into a survival mode [36, 37]. Inhibition of PARP1 in experimental PH models has shown greater efficacy than the combination of current standard of care, and thus the US Food and Drug Administration-approved PARP1 inhibitor olaparib is under clinical investigation in PAH (ClinicalTrials.gov identifier NCT03251872). Another advance derives from observations of a downregulation of miRNA-124 leading to an upregulation of the RNA splicing factor polypyrimidine tract binding protein 1 (PTBP1) in both fibroblasts and endothelial cells in the PH vasculature [38, 39]. PTBP1, along with other members of the heterogeneous nuclear ribonucleoprotein family of splicing factors, has been demonstrated to regulate splicing of pyruvate kinase muscle (PKM) isoforms. Increases in PTBP1 lead to increased accumulation of the PKM2 isoform, which in its dimeric (unactivated state) promotes glycolysis, proliferation and apoptosis resistance even in aerobic environments. Restoration of a normal PKM2/PKM1 ratio using pharmacological inhibitors attenuated fibroblast and endothelial cell proliferation in vitro and in vivo. In addition, it has been found that tumour necrosis factor-α (TNF-α) inhibits BMPR2 expression and promotes post-translational cleavage via the “a disintegrin and metalloproteinase” ADAM10 and ADAM17 in PA-SMCs, favouring BMP-mediated proliferation via alternative activin receptors [40]. Furthermore, exposure of PA-SMCs to high glucose increases expression of SMURF1, an E3 ubiquitin-protein ligase that dampens BMP signalling, and decreases phospho-Smad1/5/8, mimicking signalling patterns in mutation-negative PAH-derived PA-SMCs, which are normalised by blocking glucose uptake [41]. Similarly, Smad3 depletion in PA-SMCs and in pulmonary endothelial cells was found to contribute to the heightened proliferation and migration, which was attenuated by inhibition of myocardin-related transcriptional factor [42].

Other promising targets have also been recently identified in this context and include, among others: leukotriene B4 (LTB4), interleukin-6 (IL-6) and leptin receptors, as well as the transcriptional co-repressor C-terminal binding protein 1 (CtBP1), transforming growth factor-β, peroxisome proliferator-activated receptor-γ (PPAR-γ), mammalian target of rapamycin complex 1 (mTORC1) and Forkhead box O1 (FoxO1) pathways [43–47]. In PAH, it is also established that the dynamic and unadapted remodelling of the extracellular matrix forms a permissive milieu that not only favours cell motility, proliferation, apoptosis, and differentiation of resident vascular cells and recruitment of inflammatory cells, but can also have a considerable effect on vessel stiffness [48–51]. Owing to their close locations, and because there are several lines of evidence that indicate the existence of a complex interrelationship between pulmonary arterial cells and perivascular monocytes and macrophages [52, 53], a more complete understanding of these complex interrelationships is needed.

**Dysregulation of the innate and adaptive immune system**

In experimental PH, perivascular inflammatory infiltrates of mixed inflammatory cells often precede the structural pulmonary vascular remodelling, supporting the notion that maladaptation of the inflammatory and immune systems exists and contributes to remodelling. Consistent with this notion, small lymphoid aggregates to large accumulations of lymphocytes resembling highly organised lymphoid follicles can be observed in lungs of patients with PAH. Similarly, it is now established that circulating levels of inflammatory mediators correlate with a worse clinical outcome in PAH and that alterations of circulating cell subsets can be observed [54–56]. As a result, therapies that directly modulate inflammatory processes have become a recent focus of clinical studies in PAH.

The fact that steroid or aspirin treatment is not effective in IPAH and HPAH, and that prostacyclin, which has anti-inflammatory properties [57], does not reverse the pulmonary vascular remodelling underscores the fact that additional insights into the roles played by the immune cells and key cytokines/chemokines are a prerequisite for developing novel therapeutic strategies. Recent investigations provide evidence that pulmonary vascular cells are important local sources of soluble signals in PAH that contribute to pulmonary vascular remodelling. Indeed, PA-SMCs, endothelial cells, fibroblasts and myofibroblasts from
patients with PAH exhibit a marked pro-inflammatory signature characterised by heightened expression of various cytokines and chemokines, and of key inflammatory cell adhesion molecules, such as ICAM1. The excessive local secretion of IL-1, IL-6, LTB4, macrophage migration inhibitory factor, leptin and TNF-α, and the inactivation of FoxO1, play an integral role in mediating the structural and functional changes in the pulmonary vasculature in PAH [12, 40, 43–46, 58].

Impaired T-regulatory cell function, T-helper 17 cell immune polarisation [59] and dendritic cell recruitment in pulmonary vascular lesions have been demonstrated in tissues from PAH patients, supporting maladaptation of the immune response. Accordingly, circulating autoantibodies are commonly detected in PAH patients without evidence of an associated autoimmune condition. Furthermore, lymphoid neogenesis in PH/PAH lungs has been reported. Moving forward, a better understanding of the mechanisms leading to alteration in the balance between immunity and tolerance in PAH may allow the identification of immunopathological approaches to PAH management.

Additional contributing factors to the dysregulation of the innate and adaptive immune system in PAH include, among others: shear stress, chronic exposure to hypoxia, dysregulation in BMPR2 signalling, ageing of the pulmonary circulation, metabolic derangements, dysfunctional or distressed mitochondria, circulating autoantibodies and immune complexes. Indeed, environmental or genotoxic stresses favour pulmonary vascular remodelling through the activation of vascular, inflammatory and immune cells. Recently, perivascular immune complexes containing the antiviral protein SAMHD1 (SAM domain and HD domain-containing protein 1) has been found to be an innate immune response to an unexplained elevation in sequences and protein products of the human endogenous retrovirus K observed in PAH perivascular macrophages and circulating monocytes [60]. These abnormalities, in addition to others, may perpetuate a dysregulated immune and inflammatory response (figure 5). Unadapted immunity and inflammation appear to play an active role in pulmonary endothelial dysfunction and vascular remodelling in PH/PAH, and are also likely to have a detrimental effect on cardiac function. However, there are subtleties and complexities that require further investigation to determine whether and which anti-inflammatory strategies will be best suited to treat PAH.

The prominent roles of autoimmunity and inflammation in the pathogenesis of PAH warrant future clinical studies of newer biological agents that can target specific inflammatory pathways. Several clinical trials are currently exploring the efficacy and safety of different anti-inflammatory agents in PAH; these include, among others: rituximab, a chimeric anti-human CD20 (ClinicalTrials.gov identifier NCT01086540) in patients with systemic sclerosis-associated PAH; tocilizumab, a humanised anti-IL-6...
receptor antibody (ClinicalTrials.gov identifier NCT02676947) in PAH patients; FK506, an inhibitor of calcineurin and a binding partner of FKBP12 (12-kDa FK506-binding protein) that has also been shown to upregulate BMPR2 expression; and the elastase inhibitor produced as a recombinant protein.

Recent advances in molecular mechanisms and emerging therapeutic targets
Although much remains to be understood, decades of extensive studies have related PAH pathobiology to genetic, epigenetic and environmental factors (viruses, drugs, toxins, hypoxia and inflammation) that can cause or accelerate irreversible remodelling of the pulmonary vascular bed. We propose that the genetic, epigenetic and environmental factors lead to deregulation of growth factors, ion channels, hormones and cytokines that subsequently activate a complex cascade of signalling pathways causing abnormalities in vascular cell phenotype, including proliferation, differentiation/de-differentiation and inflammation. This suggests that transcriptional dysregulation in the pulmonary vasculature can be an early event that shapes the pulmonary vascular transcriptome, causing both depletion and ectopic activation of gene products that eventually lead to aberrant cellular processes and consequently adverse vascular remodelling [61]. How cells sense and respond to environmental triggers that lead to transcriptional dysregulation remains a central question of pulmonary vascular research. Recent studies are providing new insights that include: the role of non-receptor kinases; the potential of ion channels to control pulmonary arterial tone and vascular remodelling processes; the disruption in the activity of gene expression regulators (i.e., transcription factors and transcriptional coregulators); the epigenetic processes resulting in aberrant activation of chromatin-remodelling proteins, non-coding and microRNAs; and the severe metabolic perturbations that affect transcription, post-transcriptional processes and signalling pathways (figure 6).

Dysregulation of receptor and non-receptor kinase signalling
In PH/PAH, altered expression and function of different growth factors and their respective receptor tyrosine kinases (e.g., fibroblast growth factor 2, vascular endothelial growth factor, platelet-derived growth factor, epidermal growth factor and nerve growth factor) together with inflammatory mediators (e.g., cytokines, chemokines, circulating autoantibodies and immune complexes) contribute to the phenotypic alterations of resident pulmonary vascular cells, and their accumulation in the wall of distal pulmonary arteries has been implicated.

Emerging ion channel targets
The identification of heterozygous loss-of-function mutations in the KCNK3 (potassium channel subfamily K member 3) gene that encodes TWIK-related acid-sensitive potassium channel 1 (TASK1) as a
cause for PAH has revived interest in the concept of channelopathy [62]. In addition to voltage-gated potassium channels, different types of transient receptor potential channels, calcium sensor proteins and calcium-activated chloride channels have been implicated in PAH pathogenesis [63–67]. The dysregulation of potassium channels could have a central role in the immediate and long-term regulation of pulmonary vascular function in PAH [68, 69]. This notion is consistent with the fact that restoration of potassium channel function can prevent or reverse experimental PH. For example, in vivo pharmacological activation of KCNK3 has beneficial effects in monocrotaline-induced PH [69]. Interestingly, endothelin, serotonin (5-HT), oxidative stress, BMPR2, docosahexaenoic acid and growth factors such as platelet-derived growth factor are known modulators of potassium channel activities [70]. Furthermore, inhibition of voltage-gated potassium channels could represent one potential mechanism involved in some drug-induced PH [19, 71]. The current challenge is to identify small molecules or specific strategies to restore the expression and/or activity of these ion channels in PAH dysfunctional pulmonary vasculature.

**Key transcription factors and transcriptional coregulators**

Numerous transcription factors and transcriptional coactivators (defined as a type of protein that itself has no DNA-binding activity, but can bind to a transcription factor to augment or repress the transcription factor’s ability to activate gene expression) have been implicated in PH and right ventricular dysfunction. Some of the transcription factors include PPAR-γ, myocyte enhancer factor 2 (MEF2), FoxO, p53, KLF4, HIFs, CCAAT-enhancer binding proteins (CEBP), Runt-related transcription factor 2 (RUNX2), activator protein 1 (AP-1), CtBP1, FoxM1, PKM2, NF-κB, β-catenin, the Twist family basic helix–loop–helix transcription factor 1 (TWIST1) and SLUG (figure 7) [45, 51, 72–77]. FoxO1 isoform inactivation is involved in the pro-proliferative and apoptosis-resistant phenotype of PA-SMCs, and is a known downstream mediator of different growth factors and inflammatory mediators [45]. Furthermore, the related transcription factor FoxM1 promotes PA-SMC accumulation in PH [77], suggesting that targeting the FoxO–FoxM1 axis could be a viable strategy for treatment of PH. Transcription factor coactivators have also been recently implicated in PH pathophysiology. These include PKM2 and CtBP1 [39, 72]. Importantly, normalising metabolic activity via metabolic inhibitors such as 2-deoxyglucose or directly reducing CtBP1 expression attenuates PH fibroblast proliferation and apoptosis resistance [72].

Abnormalities in other transcription factors, such as Notch3, signal transducer and activator of transcription 3 (STAT3), and the HIPPO central component large tumour suppressor 1 (LAST1) [78], and in various growth factors, underlie phenotypic changes in pulmonary vascular cells in PAH. For example, loss of PPAR-γ in pulmonary endothelial cells leads to a deficient complex with β-catenin and this results in reduced apelin, causing impaired pulmonary endothelial cell survival and angiogenesis [79]. Similarly, Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) are also emerging as key regulators of cell growth and migration in PAH and link mechanical stimuli to dysregulated vascular metabolism [80]. A comparison of two rat strains, F344 and WKY, which differ in their response to chronic hypoxia, highlighted the gene Slc39a12 that encodes the zinc transporter ZIP12 as another major regulator of hypoxia-induced pulmonary vascular remodelling [81]. Although a more complete understanding of the overall risk–benefit ratio of these different strategies needs to be evaluated, these data reveal the potential therapeutic interest for targeting particular transcription factors and/or transcription factor coactivators in PH/PAH.

**FIGURE 7** Role of transcription factors and transcriptional coregulators in the pathogenesis of pulmonary hypertension (PH). See main text for definitions. Multiple pathological stimuli, such as hypoxia, shear stress, oxidative stress, mitogens and inflammation (cytokines and chemokines), trigger downstream signalling cascades, which modulate the recruitment and activation of transcription factors and transcriptional coregulators that determine the stimulus-specific transcriptional responses in PH.
Emerging roles for epigenetic dysregulation

Altered DNA methylation of superoxide dismutase 2 and granulysin genes, histone H1 levels, aberrant expression levels of histone deacetylases (HDACs) and bromodomain-containing protein 4, and dysregulated microRNA and long-non-coding RNA networks together suggest multiple levels of epigenetic involvement in PAH pathogenesis. Recently, clinical interest in HDAC inhibition in PAH has been regenerated through the discovery that the cytosolic HDAC6 is implicated in both pulmonary arterial remodelling and right ventricular failure. Its inhibition using a HDAC6-specific inhibitor could be tested [82]. Therefore, a complete understanding of the mechanisms involved in altered gene expression in diseased cells [61] is vital for the design of novel therapeutic strategies. Mice lacking sirtuin 3 (SIRT3), a mitochondrial deacetylase, develop spontaneous PH. Interestingly, these mice have increased acetylation and inhibition of many mitochondrial enzymes and complexes, suppressing mitochondrial function. Moreover, a loss-of-function SIRT3 polymorphism is associated with PAH [83]. These studies suggest that mitochondrial products such as 2-hydroxyglutarate, α-ketoglutarate, citrate or acetyl-CoA may regulate transcription factors and epigenetic mechanisms. This metabolism–epigenetics axis facilitates adaptation to a changing environment in the pulmonary vasculature and right ventricle, providing a potential novel therapeutic target. In summary, an integrative understanding of the interplay between the molecular, metabolic, genetic and epigenetic rewiring in PH/PAH is far from complete, but conceptual themes are beginning to emerge.

Metabolic remodelling and mitochondrial dysfunction

Aberrant signalling in pulmonary vascular cells that contributes to PH/PAH development and progression may be the cause or consequence of metabolic dysregulation. Several metabolic and signalling pathways could be interesting targets for PH/PAH therapy, and those being investigated involve modulation of HIF1 and the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin pathway, mitochondrial phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1), the HIPPO and p53 signalling pathways, and inhibition of pyruvate dehydrogenase kinase (PDK), an inhibitor of the mitochondrial enzyme pyruvate dehydrogenase (PDH, the gatekeeping enzyme of glucose oxidation). Restitution of oxidative metabolism with the use of dichloroacetate in PAH patients might be efficacious in a subset of patients [84]. Lack of clinical response was associated with the presence of functional variants of SIRT3 and UCP2 (uncoupling protein 2) that predict reduced PDH function independent of PDK and greater resistance to dichloroacetate [84]. Recently, accumulation of mitochondrial heat shock protein 90 has been found to contribute to the heightened aerobic glycolysis and to the mitochondrial stress response in cultured PA-SMCs from PAH patients [85]. Even if further investigations are required to better understand the contribution of different inflammatory processes, high shear stress, chronic hypoxia and certain hormones in these metabolic dysregulations, and to identify additional and novel mechanistic targets, the use of metabolism-based therapies may be promising for PH/PAH.

Current and future perspectives

Animal model systems that mimic specific processes contributing to PH could be valuable to discover new treatment targets and to study their contribution to the disease pathogenesis at early and late phases. However, it is also clear that pulmonary vascular lesions experimentally induced do not recapitulate the full spectrum of the human disease, and there are interspecies, age, sex and environment differences in the responses to stimuli used to promote PH in these different models. In addition, there are differences in the anatomical and functional development of the immune system in animals compared with humans. The use of human tissue samples or iPSCs to derive endothelial cells or SMCs from PAH patients should thus complement animal studies in providing a path to move PH treatment into the clinic. While there are clearly limits to model PH, there are several measures that should improve predictive utility and translational efficiency: 1) define the research problem as precisely as possible; 2) identify the strengths and weaknesses of each currently available PH model; and 3) identify how they may best be used. Improvements can be made in randomising animals, consideration of both sexes, and blinding observations related to haemodynamic and structural end-points [86–88].

Considerable advances are possible by interrogating large datasets to find novel pathways, critical transcription factors, microRNAs, biomarkers and metabolic mediators of PAH as well as points of intersection that can help develop better targeted therapies. Bioinformatic approaches with established datasets can generate a PAH signature and an anti-signature that can be used to find novel or repurposed therapies, as well as to deliver them. In addition to consideration of shear stress levels, the nature of the cell matrix and the nature of cell interactions need to be incorporated. For this reason, engineering systems that use all three layers of the vessel wall and that mimic the extracellular matrix produced by these cells will be most informative. New opportunities such as three-dimensional printing can now produce extensive vascular networks.
Translating exciting pre-clinical discoveries into clinical testing presents special challenges for a rare disease like PAH. First, because of the limited number of subjects, new approaches, gleaned from the laboratory, must be used as adjuvants on top of standard-of-care therapy. An additional challenge for researchers is to find common pathways or pathophysiological processes to safely target all forms of PH/PAH. In this line of investigation, analyses of data from publicly available databases of "PAH-omics" data (most commonly transcriptomes) and from pooled PAH registries could represent promising approaches to discover common modules of genes that reveal new therapies. Another appealing approach could be to move away from common pathways to, instead, phenotype patients into "responder" and "non-responder" groups. Here, the challenge is discovering patient groups, within a group that is already small to start with, who are particularly well suited to adjuvant therapy.

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References


Genetics and genomics of pulmonary arterial hypertension

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State of the art and research perspectives in genetics and genomics of pulmonary hypertension and insights into pathobiology http://ow.ly/dkkq30mgDo2


ABSTRACT Since 2000 there have been major advances in our understanding of the genetic and genomics of pulmonary arterial hypertension (PAH), although there remains much to discover. Based on existing knowledge, around 25–30% of patients diagnosed with idiopathic PAH have an underlying Mendelian genetic cause for their condition and should be classified as heritable PAH (HPAH). Here, we summarise the known genetic and genomic drivers of PAH, the insights these provide into pathobiology, and the opportunities afforded for development of novel therapeutic approaches. In addition, factors determining the incomplete penetrance observed in HPAH are discussed. The currently available approaches to genetic testing and counselling, and the impact of a genetic diagnosis on clinical management of the patient with PAH, are presented. Advances in DNA sequencing technology are rapidly expanding our ability to undertake genomic studies at scale in large cohorts. In the future, such studies will provide a more complete picture of the genetic contribution to PAH and, potentially, a molecular classification of this disease.

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Introduction
For half a century after the mid-1900s, when cardiac catheterisation first provided clinicians the ability to safely measure pulmonary haemodynamics, idiopathic pulmonary arterial hypertension (IPAH, then termed primary pulmonary hypertension (PPH)) was recognised as a lethal pulmonary vascular disease of enigmatic origin. Near the turn of this century, new understanding was developed of the specific genetic predisposition in families with PAH and that information was a driver to revise the classification of PAH by the 3rd World Symposium on Pulmonary Hypertension in 2003. Since 2000, investigators have contributed increasing knowledge of the genetics and genomics of PAH. Technological advances in genetic sequencing have enabled inexpensive and rapid sequencing of the coding regions of the genome (whole exome sequencing (WES)), or the whole genome (whole genome sequencing (WGS)), in families and large cohorts of patients (figure 1). Insights from human genetics are increasing our understanding of the pathobiology of PAH, identifying new potential drug targets, and informing the care of patients and their families.

State of the art
Mendelian inheritance
There is a family history of PAH in 6–10% of patients not associated with other underlying disorders [1]. In 2000, genetic analysis of such families identified heterozygous germline mutations in BMPR2, the gene encoding bone morphogenetic protein receptor type 2, a member of the transforming growth factor-β (TGF-β) superfamily [2, 3]. Subsequently, mutations were also identified in IPAH [4]. It is now well established that around 70–80% of families with PAH and 10–20% of IPAH cases are caused by mutations in BMPR2 [5].

Sequencing of genes encoding BMP receptor signalling intermediaries led to the identification of rare sequence variants in SMAD1, SMAD4 and SMAD9 [6, 7]. The identification of additional SMAD9 mutations in large cohorts has confirmed its role in PAH [8]. In addition, exome sequencing of BMPR2-negative individuals with more than one family member diagnosed with PAH revealed mutations in CAV1, which encodes caveolin-1 and functions to physically colocalise BMP receptors [9]. A rare mutation in CAV1 has been associated with both lipodystrophy and PAH in a young child. KCNK3 (potassium channel subfamily K member 3) mutations were also identified by exome sequencing and encode a potassium channel that contributes to the membrane potential to determine pulmonary vascular tone [10]. Array comparative hybridisation and sequencing in childhood and (rarely) adult-onset PAH identified deletions and loss-of-function mutations in TBX4 (T-box 4), a gene that is also associated with small patella syndrome [11]. Mutations in TBX4 are among the most common genetic causes of PAH in children and suggest that PAH is at least in part a developmental lung disease when it presents early in life [12, 13]. The recognition that severe PAH can also occur in families segregating hereditary haemorrhagic telangiectasia (HHT) implicated ACVRL1 (activin receptor-like kinase 1 (ALK1)) and ENG (endoglin) mutations in PAH [14–16].

Recently, a large survey was undertaken in a collaborative European cohort of adult-onset (>18 years) patients with IPAH, familial PAH (FPAH) and anorexigen-associated PAH [8]. This study of over 1000

![Figure 1: The history of genetic discovery in pulmonary arterial hypertension. WSPH: World Symposium on Pulmonary Hypertension.](https://doi.org/10.1183/13993003.01899-2018)
patients confirmed the presence of causal mutations in BMPR2 (15.3%), TBX4 (1.3%), ACVRL1 (0.9%), ENG (0.6%), SMAD9 (0.4%) and KCNK3 (0.4%). No pathogenic coding variants in CAV1, SMAD1 or SMAD4 were identified, possibly due to the rarity of mutations in these genes in adults. The same study identified mutations in new PAH genes: ATP13A3 (ATPase 13A3; 1.1%), SOX17 (SRY-box 17; 0.9%), AQP1 (aquaporin 1; 0.9%) and GDF2 (growth differentiation factor 2/BMP9; 0.8%), and suggested additional genes that will require further validation. Mutations in all of these genes are autosomal dominantly inherited and exhibit reduced penetrance, meaning that some individuals who carry a mutation do not manifest PAH. In IPAH cases, the mutation may be inherited from an unaffected parent or occur de novo. Where parental samples are available, determining that a mutation occurred de novo can be helpful in establishing pathogenicity. Among paediatric IPAH patients without mutations in known risk genes, exome sequencing revealed a 2-fold enrichment of de novo predicted deleterious variants. De novo variants in novel genes may explain 19% of paediatric-onset IPAH cases [12]. The incomplete penetrance observed for PAH genes suggests that additional genetic, epigenetic and/or environmental factors contribute to disease risk/progression.

In 2014, biallelic mutations in EIF2AK4, a gene encoding eukaryotic translation initiation factor 2α kinase 4, were identified as a cause of heritable pulmonary capillary haemangiomatosis (PCH) [17] and pulmonary veno-occlusive disease (PVOD) [18]. PVOD and PCH are rare and pathologically distinct forms of PAH. Heritable PVOD and PCH are autosomal recessive and nearly completely penetrant, unlike other forms of PAH. Individuals diagnosed with apparently sporadic PVOD or PCH may also carry biallelic EIF2AK4 mutations in up to 25% of cases [17, 18]. Detection of biallelic pathogenic EIF2AK4 mutations establishes a precise and accurate molecular diagnosis of PVOD/PCH without requiring a lung biopsy [19].

A summary of the genes reported to date in patients with HPAH is shown in table 1. A high level of evidence needs to be established for the causal role of mutations in a particular gene before it is used in clinical screening and management.

### Common genetic variation

The role of common genetic variation contributing to the aetiology or clinical course of PAH is less well defined. To date only one genome-wide association study has been published to identify variants associated with PAH (n=625 cases). This study detected a significant association at the CBLN2 (cerebellin 2 precursor) locus mapping to 18q22.3, with the risk allele conferring an odds ratio for PAH of 1.97 ($p=7.47 \times 10^{-10}$) [20]. Another large study evaluated associations between polymorphisms in genes comprising the endothelin signalling pathway and clinical outcomes in 715 PAH patients of European descent in the STRIDE study (sitaxsentan). An association was identified between a single nucleotide polymorphism (rs11157866) in the G-protein γ subunit gene GNG2 and a combined improvement in 6-min walk distance [21]. In a smaller study, levels of serum endostatin, a potent antiangiogenic protein with the capacity to induce endothelial cell apoptosis and inhibit endothelial cell proliferation, correlated with poor functional status and was a strong predictor of mortality in group 1 patients. In contrast, a missense variant (rs12483377) in COL18A1, which encodes endostatin, was associated with lower circulating protein and reduced mortality [22]. Abnormalities of mitochondrial metabolism are now well recognised in PAH. A recent study suggests that variants in the mitochondrial genome may influence the risk of developing PAH, with a lower rate of disease associated with haplogroup L, the oldest ancestral human haplogroup [23]. Lastly, in a study of 2761 healthy adults, variants in oestriadiol metabolism (CYPIB1 (cytochrome P450 1B1)) and androgen receptor genes were associated with right ventricular function [24]. Given the significant sex disparities in PAH and previous evidence that CYPIB1 variants may modulate disease penetrance in BMPR2 mutation carriers [25], these variants warrant further study regarding a possible role in right ventricular remodelling in PAH.

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<th>Higher level of evidence</th>
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<td>BMPR2; EIF2AK4; TBX4; ATP13A3; GDF2; SOX17; AQP1; ACVRL1; SMAD9; ENG; KCNK3; CAV1</td>
<td>SMAD4; SMAD1; KLF2; BMPR1B; KCNA5</td>
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Evidence includes de novo mutation, cosegregation studies, association with replication and functional studies.

**TABLE 1 Classification of pulmonary arterial hypertension genes according to level of evidence that they play a causal role in the disease**
EIF2AK4 downregulation has been shown to inhibit BMP-mediated cellular response [33]. Under this hypothesis, EIF2AK4 fibrosis and endothelial cell proliferation observed in the lung vessels of heritable PVOD. Alternatively, inflammation [32]. It remains to be demonstrated if similar mechanisms are involved in the intimal to decreased autophagy and increased oxidative stress and its effect on inflammasome activation and proliferation, and inhibits vascular permeability. Loss of BMPR2 also favours endothelial dysfunction and promotes endothelial-to-mesenchymal transition. Given that mutations in ALK1 and ENG (usually associated with HHT) can also cause PAH, the genetic evidence strongly suggests that the pulmonary endothelial cell is an important initiating cell type in PAH pathobiology. Nevertheless, loss of BMPR2 function in other cell types (e.g. smooth muscle cells, fibroblasts and immune cells) may also contribute to disease pathobiology. For example, pulmonary artery smooth muscle cells with BMPR2 mutations are hyperproliferative and resistant to the growth-suppressive effects of BMPs, through loss of antiproliferative Smad1/5 signalling [28].

Other less common PAH mutations are also related to the BMP pathway. Smad8 (encoded by the SMAD9 gene) is a downstream mediator of BMP signalling, together with Smad1 and 5. Heterozygous mutations of SMAD9 have relatively little effect on canonical BMP signalling through Smad4, presumably due to redundancy with Smad1/5 function [29]. However, in relation to a Smad4-independent pathway that promotes microRNA maturation [30], SMAD9 mutations lead to significant loss of function, suggesting that microRNAs regulated in this manner may play an important role in PAH pathogenesis [29]. Similar results were seen in a case with congenital heart disease (CHD)-associated PAH in which pulmonary artery endothelial cells carried a somatic heterozygous deletion of SMAD9 [31].

Eif2ak4, also known as general control non-derepressible 2 (GCN2), is a serine/threonine protein kinase that phosphorylates the α subunit of eukaryotic initiation factor 2, which plays a key role in modulating amino acid metabolism in response to nutrient deprivation. EIF2AK4 senses amino acid deficiency through binding to uncharged transfer RNA. The molecular and cellular mechanisms by which loss of function of this kinase promotes the development of PVOD/PCH is under active investigation. In the Eif2ak4−/− mouse, an increased inflammatory response to stress was observed in the intestine, secondary to decreased autophagy and increased oxidative stress and its effect on inflammasome activation and inflammation [32]. It remains to be demonstrated if similar mechanisms are involved in the intimal fibrosis and endothelial cell proliferation observed in the lung vessels of heritable PVOD. Alternatively, EIF2AK4 biallelic loss of function leads to decreased TRIB3 (Tribbles-like protein 3), whose downregulation has been shown to inhibit BMP-mediated cellular response [33]. Under this hypothesis, EIF2AK4 loss of function would have similar consequences to BMPR2 or SMAD9 mutations by decreasing BMP signalling.

CAV1 is a major constituent protein of caveolae (flask-shaped invaginations of the plasma membrane) and is highly expressed in endothelial cells. BMP receptors are localised in caveolae, as well as other regions of the plasma membrane, and studies suggest that caveolae are required for initiation of BMP signalling [34]. Loss of CAV1 decreases BMPR2 membrane localisation and signalling [35]. Conversely, BMPR2 mutations can lead to caveolar trafficking defects and intracellular localisation [36]. Lastly, it is notable that even in the absence of a heritable mutation, expression levels of BMPR2 and CAV1 are reduced in PAH lung tissues [37, 38].

Factors affecting disease penetrance
Despite the fact that pathogenic BMPR2 mutations clearly cause PAH, the penetrance of the disease phenotype is incomplete. The best estimate is that penetrance in male carriers is around 14%, whereas in females it is around 42% [39]. Thus, female sex is the single most important factor influencing the penetrance of BMPR2 mutations in PAH, possibly driven by oestrogen metabolism [25]. Additional factors influencing penetrance may be genetic, epigenetic and/or environmental. Genetic factors may include the expression level of wild-type BMPR2 from the unaffected allele [40], genetic variants affecting the expression levels of TGF-β [41] or alternative splicing of BMPR2 [42]. Studies in induced pluripotent stem cells derived from affected and unaffected BMPR2 mutation carriers have suggested that genetic background, specifically differences in expression of BMP pathway-modifying genes, might contribute to penetrance [43]. Additional large-scale longitudinal studies of affected and unaffected mutation carriers are required to more systematically search for genetic and environmental modifiers of penetrance.

https://doi.org/10.1183/13993003.01899-2018
Although no study has yet addressed potential environmental factors influencing the penetrance of BMPR2 mutations in human cohorts, studies suggest that inflammatory mediators, e.g. lipopolysaccharide [44], tumour necrosis factor-α (TNF-α) [45] and 5-lipoxygenase [46], can drive the development of PH in genetically modified mice and in patient-derived pluripotent stem cells [47]. TNF-α directly suppresses BMPR2 mRNA and protein expression. In addition, epigenetic mechanisms such as hypermethylation of the BMPR2 promoter may play a role [48]. Several microRNAs have also been shown to target BMPR2 mRNA to modify expression levels of the protein, including miR-21 [49] and miR-17-92 [50].

Another factor that may contribute to penetrance is somatic mutation within lung vascular cells [51]. Several groups have identified DNA damage in endothelial and smooth muscle cells from PAH lungs in comparison with controls [51–53]. Loss of BMPR2 was associated with a deficiency of DNA repair [54], but increased DNA damage was also evident in cells from IPAH and associated PAH cases, and may be induced by environmental exposures such as methamphetamine use [55]. Further studies are needed to understand the role of DNA damage within the lung and its contribution to disease pathogenesis.

Genetic counselling/testing and management of healthy mutation carriers

Genetic counselling

Mutations in PAH genes have been identified in IPAH and FPAH, anorexigen-associated PAH, PVOD/PCH, and in children with IPAH and PAH associated with CHD. There is a medicolegal duty to inform all patients in these groups about the possibility of a genetic condition and that family members could carry a mutation that increases the risk of PAH, allowing for screening and early diagnosis. Even if genetic testing is not performed, family members should be made aware of early signs and symptoms to ensure that a timely and appropriate diagnosis is made. If a mutation is identified in a patient, the symptomatic patient should be reclassified as HPAH.

Genetic education and counselling should be performed prior to genetic testing for PAH to address the complex issues of incomplete penetrance, questions of surveillance for genetically at-risk family members, reproductive questions, concerns about genetic discrimination, as well as psychosocial issues of guilt and blame that can accompany genetically based diseases. Pre-test genetic education of the affected individual can be performed by PAH providers and/or genetic professionals, and is facilitated by focused educational videos (e.g. www.youtube.com/watch?v=36rlvtj_Qrs). In-depth genetic counselling with genetic professionals including genetic counsellors or medical geneticists is critical prior to genetic testing for asymptomatic family members. Families should also be referred to a genetic counsellor and/or clinical geneticist if they wish to consider reproductive options. The genetic counselling experience of a national reference centre on PAH shows the potential interest in genetic testing in asymptomatic family members [56].

Genetic testing in the family should begin with an affected individual whenever possible to identify the relevant mutation in the family. Otherwise, a negative genetic test result in unaffected family members is not informative. If the familial mutation is known and an unaffected family member tests negative for that mutation, the risk of PAH for that person is the same as the general population (around 1 per 1 000 000 in North America). This can provide great psychological relief to that family member and they can forgo evaluations to screen for PAH.

Genetic testing

Genetic testing can help to explain the aetiology of the disease and stratify risk for other family members and for future children. Clinical genetic testing is available in North America and Europe, and material can be sent to American or European genetic laboratories from other parts of the world. The current cost of testing ranges from approximately USD1000 to USD1500 to analyse the first member of a family. Once the family-specific mutation is known, testing other family members costs USD300–500 in the USA. The exact number of genes included, cost of testing and insurance coverage for testing varies by country and insurer. The most commonly cited reason for genetic testing for PAH is to provide information to and about children, and interest in testing is especially high for paediatric-onset PAH [57].

Targeted sequencing

As the number of genes associated with PAH increases, it has become arduous to test for each of these genes individually. The advent of next-generation sequencing has enabled the development of gene panels to interrogate several genes simultaneously. Several different technologies and platforms are available, and many are now offered on a clinical basis (www.ncbi.nlm.nih.gov/gtr/conditions/C0152171/). In addition, several of these genes can be analysed for dosage changes to detect deletions or duplications of one or more exons. Such mutations are common in BMPR2 and TBX4. An appropriate methodology, such as multiplex ligation-dependent probe amplification, should be used since these types of mutations are not
readily detected by sequencing. It is important to check the genes included in the panel at the time of testing since the composition changes as genetic discoveries advance.

**Whole exome sequencing and whole genome sequencing**

If an up-to-date panel of PAH genes fails to identify a pathogenic variant in a patient with familial PAH or in a child, WES may be appropriate to identify potentially novel genes. In the case of paediatric-onset PAH, testing should ideally include the child and both parents to allow for facile identification of de novo variants. This trio approach was used to identify both the CAV1 and KCNK3 genes [9, 10]. The largest trio analyses suggest that 19% of childhood-onset IPAH is due to de novo mutations [12]. Exome sequencing is significantly more expensive than panel gene testing and should be ordered by a genetic professional who can discuss the option of learning about incidental or secondary findings, currently comprised of 59 genes recommended by the American College of Medical Genetics and Genomics that are medically actionable and potentially life saving, including genes for hereditary cancer and sudden cardiac death [58].

On the horizon is the use of WGS, which enables the identification of variants in the non-coding regions in a patient’s genome, but is not yet routinely used on a clinical basis. Exome and genome sequencing have the advantage of iterative reanalysis over time as novel genes are identified.

**Interpretation of sequencing data**

The main problem with WES and WGS is the large number of variants identified in any individual. Interpreting the functional consequences of missense and non-coding variants is particularly challenging. Therefore, identifying potentially pathogenic variants in novel genes requires filtering out common variants based upon large databases of reference allele frequencies and bioinformatic prediction of the likely functional effects. Segregation studies within families can sometimes clarify a variant of uncertain significance (VUS), especially if the variant is de novo or if it segregates with PAH in other affected family members [58], while appreciating that penetrance is usually incomplete and that carriers may be unaffected. Only genetic variants classified as pathogenic or likely pathogenic (not VUS) can be used to genetically risk stratify unaffected family members.

**Psychosocial considerations and reproductive options**

Genetic test results may cause more harm than good in some individuals because there is currently no effective way to prevent or differentially treat hereditary forms of PAH and because of the incomplete penetrance of mutations. Identifying a mutation in a family can be associated with feelings of guilt in the parent who has passed on a mutation to their child. There are also concerns about genetic discrimination in employment and insurance. Legal safeguards against genetic discrimination vary by country. In the USA, the Genetic Information Nondiscrimination Act protects insured members against discrimination in coverage or cost of health insurance and protects against discrimination in employment, but not against discrimination in life, long-term care or disability insurance based upon a genetic predisposition. In countries with universal healthcare, the concerns about genetic discrimination are not as great and genetic testing uptake rates have been higher.

Reproductive options for those who carry pathogenic mutations include adoption, use of donor gametes, pre-natal testing, in vitro fertilisation (IVF) with pre-implantation genetic diagnosis or not considering PAH genetic status. Accessibility and insurance coverage for IVF and pre-implantation genetic diagnosis vary by country, but coverage is often not readily available due to the cost to the patient.

**Practical application of genetics and genomics**

*What is the utility of genetic diagnosis in PAH patients?*

Pathogenic PAH mutations associate with disease characteristics that influence treatment and prognosis. For example, HPAH associated with BMPR2 or ACVRL1 mutations present at a younger age, with more severe haemodynamic abnormalities, and a very low probability of acute vasoreactivity, as well as reduced survival in the current treatment era [59, 60]. Patients with a heritable form of PVOD are also younger at presentation than non-mutation carriers, but there is no significant difference in the event-free survival at 3 years [61].

Several studies have clearly shown that detection of pathogenic EIF2AK4 mutations is especially useful. The diagnosis of PVOD/PCH challenges PH clinicians, radiologists and pathologists. Identification of biallelic EIF2AK4 mutations allows confirmation of heritable PVOD/PCH without a lung biopsy and identifies a unique form of PAH that not only does not respond well to current PAH medication, but also predisposes to pulmonary oedema when these medications are administered [61]. A subgroup of individuals diagnosed with IPAH or HPAH may also carry biallelic pathogenic EIF2AK4 mutations. These individuals are characterised by presenting under the age of 50 years with a diffusing capacity of the lung...
for carbon monoxide (DLCO) <50% of predicted [62–64]. Thus, we suggest that clinicians test younger PAH patients who have a low DLCO for EIF2AK4 mutations in order to guide treatment and for risk assessment in family members [63]. Findings from genomic studies are also starting to be used to better understand the disease process and therapeutic responses. HEMNES et al. [65] identified a peripheral blood RNA expression signature in patients with a PAH subphenotype responsive to calcium channel blocker therapy, suggesting a non-invasive approach to predict drug responsiveness. Using WES, genetic variants that may underlie this subphenotype were also identified [66]. As discussed previously, common genetic variants have been associated with risk of PAH, survival and/or pharmacogenomic response to therapy. Most recently, it was shown that common functional variants in SIRT3 and UCP2 might predict the response to inhibition of pyruvate dehydrogenase kinase by dichloroacetate in a phase 2 clinical trial in PAH [67], paving the way for future precision medicine studies with this drug.

**From genes to therapies**

Molecular pathways highlighted by genetic studies are now the subject of several novel therapeutic approaches (figure 2). LONG et al. [68] reported the beneficial effects of BMP9 administration in heterozygous BMPR2 knockout mice, suggesting that compensating for BMPR2 haploinsufficiency by increasing dose of the ligand might constitute a targeted therapy for human PAH. At the receptor level, approaches include translational readthrough of nonsense mutations using ataluren to restore full-length protein [69] or slowing down lysosomal degradation of BMPR2 with chloroquine to increase receptor density at the cell surface [70, 71]. Both approaches effectively restored BMP signalling in vitro and lysosomal blockade reversed PH in experimental models. Inhibition of TNF-α with etanercept not only...
targets inflammation, but can reduce receptor shedding and proteosomal degradation of BMPR2 [45]. Elafin acts via CAV1 to promote receptor recruitment and enhance BMP signalling, reversing experimental PH [72]. Downstream of BMPR2, FK506 was found to increase BMP signalling and to reverse experimental PH, by binding FK-binding protein 12, an inhibitor of BMP signalling [73]. Phase 2a clinical trials have established safety and tolerability of low-dose FK506 in PAH [74]. Beyond the BMP pathway, KCNK3 mutations lead to reduced potassium channel conductance, which, at least for some mutations, can be recovered by the phospholipase A2 inhibitor ONO-RS-082 [10]. These studies underline the considerable progress that has been made in translating basic genetic studies into potential therapeutic modalities. While direct correction of the underlying mutations remains challenging at present, rapid advances in gene-editing technologies may make targeted mutational correction within the lung vasculature a realistic prospect in the future.

Proposed future directions

These different genomic approaches highlight potential paths forward for using molecular medicine to improve PAH patient care. Several large-scale genetics/genomics studies are currently underway in the USA and Europe. Of note, the US National Biological Sample and Data Repository for PAH (the “PAH Biobank”; www.pahbiobank.org) is generating genetic data (targeted DNA sequencing, WES and genome-wide single nucleotide polymorphisms) for 3000 group 1 PAH patients. The BRIDGE Project in the UK includes PAH as one of the rare diseases for which WGS data are being generated (https://bridgestudy.medschl.cam.ac.uk/pah.shtml). Over 1250 IPAH/familial PAH patients from Europe are being analysed to investigate the underlying genetic variation contributing to the disease. In addition, the US National Institutes of Health PVDOMICS initiative aims to define new molecular classifications across the traditional World Health Organization groups by combining deep clinical phenotyping with multiple “omics” analyses [75]. It is only through such cohorts and initiatives that we will begin to have adequate power to discover the range of genetic factors underlying PAH to provide a more complete genomic understanding of the disease. Ideally, this will lead to the identification of additional novel targets for new drugs. It also may facilitate prevention strategies for PAH and the prediction of prognosis based on a genetic classification of PAH.

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References


Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update

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State of the art and research perspectives in pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension with theoretical and practical aspects http://ow.ly/18v830mgLiP


ABSTRACT The function of the right ventricle determines the fate of patients with pulmonary hypertension. Since right heart failure is the consequence of increased afterload, a full physiological description of the cardiopulmonary unit consisting of both the right ventricle and pulmonary vascular system is required to interpret clinical data correctly. Here, we provide such a description of the unit and its components, including the functional interactions between the right ventricle and its load. This physiological description is used to provide a framework for the interpretation of right heart catheterisation data as well as imaging data of the right ventricle obtained by echocardiography or magnetic resonance imaging. Finally, an update is provided on the latest insights in the pathobiology of right ventricular failure, including key pathways of molecular adaptation of the pressure overloaded right ventricle. Based on these outcomes, future directions for research are proposed.

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The cardiopulmonary unit: more than a sum of its parts

The function of the right ventricle is of great clinical importance in severe pulmonary hypertension (PH) since it determines the outcome of the disease [1, 2]. Given the fact that right heart failure in PH is the consequence of increased (arterial) afterload and not the mere consequence of a myocardial disease, a full description of the cardiopulmonary unit is required in the study of right heart failure (figure 1a and b). The cardiopulmonary unit is composed of two main functional subsystems, i.e. the right ventricle and the pulmonary vasculature, each having their own intrinsic characteristics (figure 1b). The ventricular pressure–volume loop analysis is central in understanding right ventricular physiology, while pressure–flow analysis is central in understanding pulmonary haemodynamics. For the right ventricle, intrinsic characteristics include contractility, chamber stiffness and, although perhaps less established, the time constant of ventricular relaxation (τ), which are all load independent; for the pulmonary vascular system, resistance and compliance provide intrinsic characteristics of the steady and pulsatile load.

The interaction between the intrinsic ventricular characteristics and load results in global function, and is commonly described by cardiac output (CO) and ejection fraction (EF), on the one hand, and pressure (mean, systolic and diastolic pressure), on the other hand. The pressure gradient over the pulmonary circulation also falls into this category. Energy transfer of right ventricular to arterial load is a special form of interaction for which we reserve the term "coupling". The concept of coupling is particularly important in physiologically describing the continuum of ventricular adaptation in pulmonary arterial hypertension (PAH): well-adapted right ventricles often have preserved ventriculo-arterial coupling, while maladapted right ventricles have varying degrees of altered ventriculo-arterial coupling (figure 2). These concepts will be discussed in more detail in the following section.

This distinction between intrinsic characteristic of a subsystem and global function or system characteristics has important physiological implications. For example, despite the decrease in right ventricular EF (RVEF) in patients with PAH, right ventricle contractility as measured by ventricular characteristics has important physiological implications. For example, despite the decrease in right ventricular EF (RVEF) in patients with PAH, right ventricle contractility as measured by ventricular characteristics has important physiological implications.

Definitions

The current section presents some definitions that may help standardise important concepts relevant to the field of right ventricular adaptation and right heart failure.

- **Right heart failure** in PH can be defined as a clinical syndrome characterised by decreased right ventricular function that leads to insufficient blood flow and/or elevated filling pressures at rest or during physiologically demanding conditions, such as exercise, developmental growth or pregnancy. The cardinal symptoms of right heart failure include dyspnoea and fatigue as well as congestion. The severity of heart failure is often subcategorised according to New York Heart Association (NYHA) Functional Class and by the degree of congestion.

![Diagram](https://doi.org/10.1183/13993003.01900-2018)

**FIGURE 1** The cardiopulmonary system (CPS): a) function and b) characterisation. MVO₂: myocardial oxygen consumption; RV: right ventricle; RA: right atrium; LA: left atrium; LV: left ventricle; EF: end-systolic elastance; τ: time constant of ventricular relaxation; Eₜ: end-diastolic elastance; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance; Eₐ: arterial elastance; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; EF: ejection fraction; CO: cardiac output. Subsystems (or units: heart, respectively its load) are characterised by their intrinsic function, which can be derived from the ventricular pressure–volume relationship and the pulmonary pressure–flow relationship. The system parameters result from cardiopulmonary interaction.
Right ventricular adaptation in PH represents a continuum with an adapted right ventricle at one end and a maladapted ventricle at the other end. An adapted right ventricle in PH is characterised by a slightly dilated right ventricle with preserved stroke volume (SV), systolic function and normal filling pressures, whereas a maladapted right ventricle is characterised by a dilated right ventricle with reduced SV, systolic function and increased filling pressures. As will be discussed in the following section, adapted ventricles usually have preserved ventriculo-arterial coupling, while maladapted ventricles usually have uncoupled ventricles (figure 2).

Subsystem function (intrinsic properties of the cardiac or pulmonary vascular system): description of the right ventricle in a load-independent manner (Es and end-diastolic elastance (Ed)) or pulmonary vascular load in a manner independent of right ventricular function (pulmonary arterial vascular resistance (PVR), or arterial elastance (Ea), and pulmonary arterial compliance (PAC)).

System function results from the interaction of the two subsystems, i.e. the ventricular pump and its afterload. Interaction results in SV, CO, pressure and functional imaging parameters derived by echocardiography or cardiovascular magnetic resonance imaging (CMR). Descriptions of systolic function as RVEF or SV/right ventricular end-systolic volume (ESV) are also the result of functional interaction and not surrogates for coupling.

Coupling: the condition that occurs when right ventricular function is adapted to the pulmonary vascular load such that energy transfer is most efficient. This coupling is described by systolic and arterial elastance, Es/Ea (figures 1b and 2).

Although this article focuses on the right ventricle, it is noteworthy that ventricular interdependency plays an important role in PH. Not only the right ventricle but also the left ventricle is involved in PH since the right ventricle and left ventricle have the septum in common, are encircled with common myocardial fibres and are within a (not acutely) distensible pericardium (figure 1a) [4, 5]. This ventricular interdependency becomes visible in PH as rapid leftward bowing of the septum during early left ventricle diastole. This typical septal motion abnormality has been shown to be a consequence of a prolonged contraction of the right ventricle free wall relative to that of the septum and the left ventricle free wall, causing interventricular relaxation dyssynchrony [6, 7]. As such, the septum acts as a whistleblower of a right–left ventricular tissue load imbalance, reflecting right ventricular tissue overload in the setting of PH. This rapid early-diastolic leftward motion of the septum is also associated with septal and left ventricular myocardial stretch during late right ventricular ejection [8], causing mechanical inefficiency of the right ventricle and contributing to left ventricular underfilling [9] and atrophy [10]. The septal curvature is a useful metric in PH, reflecting both the interventricular pressure gradient and relative interventricular size, as well as dyssynchrony of contraction [7].

Assessment of the right ventricle in a load-independent manner
Right ventricular function can be characterised by the pressure–volume relation (figure 2) [11], and measurement of right ventricular volumes and pressures are therefore useful for the assessment of the

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right ventricle in PH, particularly for physiological studies. A schematic overview of an approach to right ventricle phenotyping, integrating structural imaging, haemodynamics, molecular imaging and biomarkers is given in supplementary figure S1a.

**Systole**

$E_{es}$ of the ventricle is a load-independent description of the right ventricle and the current reference measure of contractility; it depends on the contractile force of the myocyte and cardiac muscle mass (hypertrophy) [12, 13].

The derivation of $E_{es}$ is based on the pressure–volume loop (figure 2). The best method to assess $E_{es}$ is to decrease ventricular filling, e.g. by partial vena cava occlusion, and analyse the series of loops that result [14]. Connection of the end-systolic pressure ($P_{es}$)–volume points results in the $P_{es}$–volume relation and its slope is $E_{es}$. Since this approach is invasive and not widely available in the clinic, single-beat methods have been developed [13, 15]. $E_{es}$ can be increased 5-fold in PAH patients, reflecting that the right ventricle is performing at a high contractile state [16]. In addition, the elastance response to pharmacological (usually dobutamine) or physiological stress (exercise) can be useful to assess contractile reserve. In the normal right ventricle, $E_{es}$ usually increases significantly with exercise [3]. In the pressure overloaded right ventricle, although the baseline is higher than normal, the degree of increase is blunted with exercise or following dobutamine infusion [3, 17]. Contractile reserve at exercise is absent in more advanced disease states or might even decrease [3].

**Diastole**

In practice, right atrial pressure and central venous pressure are often used as surrogates for diastolic properties of the right ventricle; right atrial pressure has been consistently related to outcome in PAH starting with the original US National Institutes of Health registry study in 1991 [18]. Using load-independent metrics has the advantage of allowing a better understanding of the responsiveness to volume status or change in filling conditions. $E_{ed}$ of the ventricle is a load-independent representation of the diastolic function and is best described by a diastolic elastance curve determined by multiple pressure–volume loops obtained by decreased loading by partial vena cave occlusion. The relation is curvilinear and the most adequate description is obtained by fitting the relation with an exponential curve through the diastolic pressure–volume points, with the formula $P=\alpha e^{\beta V}$, where $\alpha$ and $\beta$ are curve-fitting constants (figure 2) [11, 19]. A single-beat method has been developed to determine $E_{ed}$ [20, 21]. $E_{ed}$ now can be calculated as $E_{ed}=\alpha e^\beta V_{ed}$, where $V_{ed}$ is the end-diastolic volume (EDV) [21]. The so-defined diastolic stiffness predicts outcome in PAH as well as the more complex $\beta$ calculation [21]. Right ventricular diastolic function is closely associated with disease severity [20], but also with $E_{es}$ [21, 22]. Right ventricle diastolic stiffness in severe PH is accompanied by fibrosis and specific biological alterations, such as reduced titin phosphorylation [20]. Although $E_{ed}$ is related to $E_{es}$, diastolic adaptability remains variable in patients with PH and whether it may serve as a biomarker of pending right ventricle failure is not completely resolved.

**Assessment of the pulmonary circulation in a heart-independent manner**

**Pulmonary vascular resistance**

When analysing the pulmonary circulation, it is useful to distinguish a steady and pulsatile component of the load. These main components of arterial load are PVR and total PAC. In the pulmonary system these two components are inversely related (see later). PVR is calculated as PVR=$P(VP−PAWP)/CO$, where $mPAP$ is the mean pulmonary arterial pressure and PAWP is the pulmonary arterial wedge pressure. A measure of total load can also be estimated from the pressure–volume loop (figure 2) as $P_{es}−P_{es}/SV$. It has been proposed to use $E_{es}−mPAP/SV$ when $P_{es}$ is not available [23]; however, this approximation should be used with caution since, especially in higher pressures ranges, $P_{es}$ is underestimated by $mPAP$ [24].

Pulmonary capillary flow is a dynamic process. In basal states, flow through an individual capillary is intermittent. Capillary recruitment occurs when the probability of a given capillary carrying flow increases. Capillary recruitment and distension both play a role in the lung’s accommodation of pulmonary arterial blood flow. At basal or moderately increased blood flows, capillary recruitment is predominant [25, 26]. At very high regional flows or pressures, after local full recruitment, capillary distension is predominant [26–29]. The local pattern of capillary recruitment/distension may vary regionally in the lung, with gravity, arterial and post-capillary venous pressures, airway pressures, and disease states all having effects [30–34].

Examining the pulmonary circulation as a whole, since in the (healthy) pulmonary circulation the arteries and veins are distensible, the assumption that the pulmonary vascular pressure difference–flow relationship is linear and crosses the origin is inaccurate. The simple formula then no longer holds and PVR can be described using two parameters: $\alpha$ (the pulmonary circulatory distensibility coefficient) and $R_0$ (a reference resistance usually
assumed to be the resistance at rest) [35, 36]. While $\alpha$ may be relevant for the detection of early pulmonary vascular remodelling and relates to exercise capacity, right ventricular function and outcome [37], it requires accurate measurement of pulmonary vascular pressure and flow at rest and at exercise. It therefore cannot be currently recommended as part of standard haemodynamic evaluation of patients referred for PH.

**Pulmonary arterial compliance**

The pulsatile load of the pulmonary circulation is most often evaluated using PAC. The best method to calculate PAC is based on a two-element Windkessel model with flow waveform and resistance as inputs to estimate the compliance value that best predicts systolic and diastolic pressures, the so-called "pulse pressure" (PP) method [38]. A simpler and accepted method to derive PAC is SV/PP [39]. This ratio assumes that the SV is buffered in the large elastic arteries in systole, without any peripheral outflow. However, there is a continuous flow toward the periphery, reducing the vascular volume increase during ejection, resulting in an overestimation of the true PAC [40]. It has been shown in intact experimental animals at various severities of induced PH that SV/PP overestimates PAC by 60–80% [40, 41]. This overestimation probably depends on patient status. CMR-determined proximal arterial compliance amounts to around 20% of PAC [42], showing the greater contribution of the smaller vessels compared with the systemic arterial vasculature.

**Time constant of the pulmonary circulation**

In the previous sections we described the steady and pulsatile components separately; however, as already mentioned, these are closely related by an inverse relationship. The PAC decay curve in diastole is determined by PVR and PAC. The combined effect can be formulated by the product of PVR and PAC. The unit of this product is time and, therefore, is called the arterial time constant (RC-time) [43].

The inverse relationship between PVR and PAC was first reported in 1971 [44]. A series of studies showed recently that PVR and PAC are inversely related, and RC-time is constant over a wide range of severities, aetiologies and treatments of PH (figure 3) [41, 45, 46]. It is noteworthy that RC-time is decreased when PAWP increases in patients with heart failure [47, 48]. The fact that PVR takes the wedge pressure into account, whereas compliance, calculated as SV/PP, does not, gives rise to an altered RC-time in post-capillary PH.

Owing to the inverse relationship between PVR and PAC, the dynamic range in PAC will be greater in patients with mild pulmonary vascular disease (PVD) (zone A in figure 3), while the dynamic range in PVR will be greater in patients with more advanced PVD (zone B in figure 3). Therefore, PAC may be more sensitive to detect changes in PVD in the early phase of disease. Moreover, several studies using linear prediction models found that PAC is an independent predictor of outcome in PAH [49–52] over a wide range of PVR [53, 54]. Another implication of this remarkable structural characteristic of the pulmonary vasculature is that it dictates the reported tight correlation between systolic PAC (sPAP), diastolic PAC (dPAP) and mPAP in normal subjects and in patients with PH of all possible aetiologies [55, 56], independently of PAWP (figure 4) [57]:

\[ sPAP = 1.61 \times mPAP \]

and

\[ dPAP = 0.62 \times mPAP \]
The first relation implies that mPAP can be calculated from Doppler echocardiographic estimates of sPAP by the formula:

\[ mPAP = 0.62 \times sPAP \]

The mPAP calculated in this way provides an estimate of mPAP in patients referred for diagnostic work-up of PH [58]. In echocardiography-based studies, different thresholds for right ventricular systolic pressure (e.g. 30, 35 or 40 mmHg) have been used for defining PH. According to the formula, a right ventricular systolic pressure of 40 mmHg would best approximate a mPAP of 25 mmHg assuming a mild right ventricular outflow tract gradient and an insonation angle <15°.

Assessment of the cardiopulmonary unit

Functional interaction

In the clinic, the description of right ventricular function in relation to its load is of high prognostic value. Most imaging parameters as measured by echocardiography or CMR reflect system function of the interaction of the right ventricle and the vascular load. At present no recommendations on the most relevant measurements of right ventricular function can be made. Further clinical research is needed, preferably multicentre and prospective, with an a priori established list of variables of interest. It should not be overlooked that adequate measurements do not only qualify based on their prognostic capability or prediction of clinical worsening; they should be reproducible and easy to assess in PH centres of expertise.

However, there is ample evidence that direct or indirect measurements of right ventricular EDV and ESV, derivation of SV, and filling pressures contain the foremost prognostic information. This can be explained by the pressure–volume loops derived from the adapted and failing right ventricle. In the adapted right ventricle, increased afterload in PH leads to hypertrophy and an increased contractility with more or less preserved dimensions and SV [2, 4, 11, 59], whereas in progressive right ventricular failure, the right ventricle progressively dilates and decreases its SV.

It should be noted that SV/ESV is inversely related to RVEF, as indicated by the formula SV/ESV = EF/(1–EF). Indeed, Vanderpool et al. [22] showed this inverse relation exists in patients with PH [22]. Thus, both SV/ESV and RVEF contain similar prognostic information, and should be considered as parameters of functional interaction, not coupling. RVEF and SV/ESV have been shown to be equally predictive of outcome in patients with PAH [60]. Rigorously defined cut-off values for shortened survival are 0.35 for EF [60, 61] and 0.54 for SV/ESV [22, 60]. Although theoretically RVEF and SV/ESV should have similar predictive potential, due to the hyperbolic relationship between the two, the latter may be more sensitive to early changes [62]. Then again, it is more difficult to determine ESV in an accurate manner. A large-scale head-to-head comparison of these two parameters may resolve this matter.

Coupling

Coupling implies efficiency of energy transfer from the ventricle to the arterial load and can be calculated as the ratio Es/Ea. The value will be between 1 and 2 if maximal energy transfer from ventricle to load occurs (figure 2).
Coupling has been reported in PAH patients, with single-beat calculation of the $E_{es}/E_{a}$ ratio from CMR measurements of right ventricular volumes and right heart catheterisation (RHC) measurements of right ventricular pressures [63]. Single-beat determinations of $E_{es}/E_{a}$ have been implemented in experimental animal studies to show, for example, that acutely administered prostacyclin has no intrinsic inotropic effect [64] and that β-blocker agents may either deteriorate (acutely) [11] or improve (chronically) [64] right ventricle–arterial coupling.

Compared with controls, in PH the $E_{es}/E_{a}$ was decreased, indicating insufficient contractility adaptation (“homeometric”) and impending right ventricular failure. Results have been confirmed in small cohorts of patients with either PAH or chronic thromboembolic PH, and in one case report of a patient with a systemic-like pressured right ventricle [3, 65–68]. In these studies, $E_{es}/E_{a}$ was measured either by the single-beat method [3, 63, 65, 67] or using multiple pressure–volume loops obtained by decreasing venous return through a Valsalva manoeuvre [66, 68]. $E_{es}/E_{a}$ was either maintained or decreased at rest, but consistently decreased at exercise. Decreased $E_{es}/E_{a}$ at exercise was accompanied by an increase in right ventricular EDV [68].

Coupling is maintained at resting conditions for as long as the ventricle can adapt (figure 2). Only in the late stages of pressure overload does uncoupling occur [11, 21]. Therefore, coupling is not a sensitive parameter to identify an early disease state. Although coupling measured at exercise might contain more important clinical information, the complexity of these measurements will limit clinical use.

Practical assessment of pulmonary haemodynamics
Single variables such as PAPs, SV and CO are the result of the interaction of the right ventricle to its load. This implies that from a single variable, e.g. CO, no quantitative information can be obtained on either of the subsystems, i.e. the heart or the arterial load. For this reason, a change in PAP at exercise cannot be considered as a measure of right ventricular contractility.

Measuring the pressures correctly
Measurements of PAP and PAWP during rest and especially at exercise are technically challenging because of respiratory pressure swings. To avoid spurious increases in PAWP at end-expiration during exercise caused by dynamic hyperinflation and/or decrease in lung volume, it is preferable to average the reading of pulmonary vascular pressure curves over several respiratory cycles [69]. The 2015 European Society of Cardiology/European Respiratory Society PH guidelines recommend measurements at end-expiration at rest, as is standard procedure in most catheterisation laboratories, but allow for averaging over several respiratory cycles during exercise when respiration-related phasic changes become excessive [1, 70].

Provocation of the pulmonary circulation
Provocative testing of the pulmonary circulation with exercise or a fluid challenge has been used by some centres in clinical practice for decades, but has only recently been standardised.

Exercise
The upper limit of normal of mPAP during an incremental dynamic exercise challenge is now well established at 30 mmHg at CO <10 L·min$^{-1}$ (figure 5), which corresponds to a total pulmonary resistance

**FIGURE 5** The mean pulmonary arterial pressure (mPAP)–cardiac output (CO) relationships: the ratio of $\Delta P/\Delta CO$ in health and disease. PH: pulmonary hypertension; PAH: pulmonary arterial hypertension. Reproduced and modified from [71] with permission.
constructed from a hierarchically organised series of identified independent predictors. It has been recently proposed that exercise-induced increases in mPAP >30 mmHg at CO <10 L·min⁻¹ be called “exercise PH” [69].

The cause of “exercise PH” is either an upstream transmission of increased PAWP, such as in heart failure, or an increase in PVR, such as in PVD, disturbed lung mechanics or hypoxia [37, 69, 71]. This differential diagnosis relies on a clinical probability and eventual invasive measurements of PAWP and left ventricular end-diastolic pressure. The upper limit of normal of PAWP during exercise is generally thought to be between 15 and 20 mmHg, but higher values can be recorded in athletes capable of very high CO and in elderly subjects [73]. Some consider 20 mmHg as a reasonable upper limit of normal [74]. However, a higher cut-off value of 25 mmHg has been proposed for the diagnosis of heart failure [75]. As for mPAP, a flow-corrected measure may be more appropriate, but there has been no study specifically addressing this. Since TPR normally decreases by up to 30% during exercise, the PAWP/CO slope should not exceed 2 mmHg·L⁻¹·min⁻¹. Mean PAWP/CO slopes around 1 mmHg·L⁻¹·min⁻¹ have been reported in control groups of studies on exercise testing in heart failure patients [71, 74, 75].

Fluid challenge
A fluid challenge will induce a rapid rise in PAWP in any condition associated with altered left ventricular diastolic compliance or mitral valvulopathy [76]. Fluid loading increases PAWP in healthy volunteers as a function of age, sex, amount infused and infusion rate [77]. There is an emerging consensus to infuse 500 mL of saline in 5–10 min as the best compromise between safety and stress efficacy, with 18 mmHg as the optimal PAWP cut-off to separate abnormal from normal [76–80]. This was recently underpinned by a report on 212 patients referred for PH who were challenged with 7 mL·kg⁻¹ of saline given in <5 min (corresponding to 0.5 L for a 70-kg patient) [80]. To limit the number of healthy outliers [80], a cut-off value of 20 mmHg might be preferable. Both exercise and fluid loading increase systemic venous return, but exercise has additional effects, including sympathetic nervous system activation, intrathoracic pressure changes and mixed venous or arterial hypoxaemia. These differences probably impact on their respective efficacies for diagnosis of latent disease [81].

The emerging role of non-invasive assessment of right ventricular function
The role of right ventricular function estimated by non-invasive methods such as echocardiography (two-dimensional, three-dimensional, speckle tracking-derived echocardiography) or CMR is emerging rapidly in observational studies and has been reviewed elsewhere [82]. Speckle-derived strain technology allows measurements of regional strains by either method and demonstrates heterogeneity of right ventricular strain depending on the region (e.g. apical versus mid or basal region) and occasionally significant differences between disease aetiologies, such as idiopathic PAH (IPAH) and systemic sclerosis (SSc)-associated PAH. Recent larger studies in echocardiography have demonstrated that right ventricular longitudinal strain or indices of right ventricular end-systolic remodelling in combination with N-terminal pro-brain natriuretic peptide and NYHA Functional Class provide good discrimination of outcome in PAH [83, 84].

Imaging modalities may be incorporated into large multicentre clinical trials in PH using composite morbidity and mortality end-points, which would be ideal settings to validate potential right ventricle-based surrogate end-points. Since CMR has greater sensitivity and reproducibility than ultrasound, and can detect an efficacy signal with a small sample size in a relatively short period of time, validation of specific right ventricle surrogate CMR markers (e.g. RVEF, right ventricular mass, right ventricular mass index; left ventricle size and function) in the setting of smaller phase 2 trials would be useful to help identify potentially promising therapies. This could allow the creation of prediction scores constructed from a hierarchically organised series of identified independent predictors.

Recent insights in the pathobiology of right ventricular failure
Since the 5th World Symposium on Pulmonary Hypertension report in 2013 [2], there have been major advances in understanding the underlying pathobiology of right ventricular remodelling and failure. This knowledge has been derived both from animal models, reviewed elsewhere [85], and, importantly, from human tissue. Recent work has focused on several main themes and a thorough review of the complete breadth of right ventricular failure mechanisms is beyond the scope of the current article.

First, there has been an expansion of the understanding that genetic features may affect right ventricular stress responses. It is well recognised that patients with heritable forms of PAH (HPAH) have poorer survival than their IPAH counterparts, but recent work has demonstrated that this is related to more severe right ventricular failure in HPAH due to BMPR2 (bone morphogenetic protein receptor type 2) mutation despite similar levels of afterload, suggesting a genetic contribution to right ventricular failure [86]. In a different series of investigations, BMPR2 mutation was shown to promote lipotoxicity in the
BMPR2 mutant right ventricle in rodents, in humans and in cultured cardiomyocytes with overexpression of mutant BMPR2 [87–89]. More recently, Potus et al. [90] demonstrated downregulation of miR-126 in human tissue and the monocrotaline model of right ventricular failure, with subsequent reduction in angiogenesis. Taken together, these data suggest a role for genetic regulation of right ventricular failure and may be used to develop new models of right ventricular failure.

The effect of sex hormones on the right ventricle has gained further attention. Male sex is known to be an independent risk factor for poor survival [91] and Jacobs et al. [92] found that despite a similar burden of PVD, male patients lack improvement in RVEF regardless of treatment, while their female counterparts improved RVEF. Frump et al. [93] demonstrated using the Sugen hypoxia models that oestrogen improves right ventricular function and bioenergetics, and reduces proapoptotic signalling and inflammatory cytokine expression, perhaps suggesting a protective role for oestrogen underlyng the clinically recognised sex differences.

There is improved understanding of right ventricle metabolism with recent findings that right ventricular failure is characterised by reduced fatty acid oxidation in addition to increased glycolysis [87, 88, 94, 95]. Presently, it is unknown if enhanced fatty acid oxidation or improved glucose oxidation would most successfully improve right ventricular function. Finally, there is a new perception of the contribution of altered cytoskeletal function in the right ventricle. Pulmonary artery banding was used to induce right ventricular hypertrophy and dysfunction in rats, resulting in increased myocardial stiffness with increased fibrosis- and myofibril-mediated stiffness [96]. Using the monocrotaline model, Prins et al. [97] found abnormal t-tubule architecture associated with reduced junctophilin-2 expression. Colchicine ameliorated these findings, perhaps suggesting a new therapeutic avenue for the failing right ventricle. Taken together, these studies present new data on the role of the cytoskeleton and myocardial fibrosis in promoting right ventricular dysfunction.

Animal models of right ventricular failure related to group 2 PH should be developed and may require a “multiple-hit” rather than “single-hit” approach in order to more adequately reproduce the clinical syndrome [98].

Finally, insight into the pathophysiology of right ventricular function is also emerging from human right ventricle biopsies. Isolated cardiomyocytes thus obtained may allow for deep phenotyping and mechanistic investigations of specific pathways. Using this approach in patients with end-stage PAH undergoing heart–lung transplantation, and comparing with non-failing donors, Rain et al. [20] demonstrated increased fibrosis and stiffening of right ventricle sarcomeres in conjunction with decreased titin phosphorylation in PAH. A recent study by Hsu et al. [99], using right ventricle biopsies obtained during RHC under echocardiographic guidance, revealed that patients with SSc-PAH have depressed sarcomeric function, which is manifested by a significant decline in maximal force ($F_{\text{max}}$) calcium dependence compared with non-PAH patients, while the opposite (i.e. increased calcium-activated $F_{\text{max}}$) was demonstrated for patients with IPAH, in line with data obtained by Rain et al. [20] in (non-scleroderma) PAH patients. Collectively, these findings may explain the significant differences in outcomes and survival in these two groups of patients.

**Future directions**

A summary of future directions is given in supplementary figure S1b.

Our insights into the role of the right ventricle in PH have considerably improved over recent years. These insights allow for a full assessment of right ventricular function and pulmonary vascular load based on pressure and volume measurements in patients. Such an assessment permits us to test the differential effects of future drugs on the right ventricle and pulmonary vasculature. Use of CMR should be implemented in PAH clinical trials and clinical practice when possible. Molecular imaging should be used to translate from bench to bedside (and vice versa). Novel approaches are necessary to show the clinical value of echocardiography for predicting response and tailoring therapy.

Currently, the clinical relevance of an abnormal exercise pulmonary haemodynamic response is largely unknown and requires long-term follow-up studies. If PH is present, diuretics and atrioseptostomy are the only options available to treat the right ventricle, mainly by reducing wall tension [100].

Better characterisation of normal right ventricular function, early dysfunction and irreversible failure is needed. Growing insights into how to prevent right ventricular failure at a biological level need to be translated to the clinic via well-designed trials. If right ventricular failure is present, the role of inotropic agents is unknown. Based on the finding that contractile reserve of the right ventricle is absent in advanced disease, the effectiveness of inotropic drugs in end-stage right ventricular failure needs to be re-evaluated. Finally, the optimal medical care of patients in end-stage right heart failure needs to be defined.
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References


Haemodynamic definitions and updated clinical classification of pulmonary hypertension

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State of the art and research perspectives of haemodynamic definitions and clinical classification of pulmonary hypertension
http://ow.ly/TJeR30mgWKj


ABSTRACT Since the 1st World Symposium on Pulmonary Hypertension (WSPH) in 1973, pulmonary hypertension (PH) has been arbitrarily defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest, measured by right heart catheterisation. Recent data from normal subjects has shown that normal mPAP was 14.0±3.3 mmHg. Two standard deviations above this mean value would suggest mPAP >20 mmHg as above the upper limit of normal (above the 97.5th percentile). This definition is no longer arbitrary, but based on a scientific approach. However, this abnormal elevation of mPAP is not sufficient to define pulmonary vascular disease as it can be due to an increase in cardiac output or pulmonary arterial wedge pressure. Thus, this 6th WSPH Task Force proposes to include pulmonary vascular resistance ≥3 Wood Units in the definition of all forms of pre-capillary PH associated with mPAP >20 mmHg. Prospective trials are required to determine whether this PH population might benefit from specific management.

Regarding clinical classification, the main Task Force changes were the inclusion in group 1 of a subgroup “pulmonary arterial hypertension (PAH) long-term responders to calcium channel blockers”, due to the specific prognostic and management of these patients, and a subgroup “PAH with overt features of venous/capillaries (pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis) involvement”, due to evidence suggesting a continuum between arterial, capillary and vein involvement in PAH.
Introduction
The main objectives of our Task Force were to reassess haemodynamic definitions and the clinical classification of pulmonary hypertension (PH).

Regarding definitions, we addressed two questions:
1) Should we redefine PH and pre-capillary PH?
2) Should exercise PH be reintroduced as part of the PH definition?

The other topic was to update the clinical classification, adopting some basic principles: 1) to maintain the general architecture of the current classification of PH for adults and children, 2) to provide only relevant modifications, and 3) to simplify the core of the classification.

Haemodynamic definitions

Definition of PH

In 1961, a report of the World Health Organization (WHO) Expert Committee on Chronic Cor Pulmonale mentioned clearly that the mean pulmonary arterial pressure (mPAP) does not normally exceed 15 mmHg when the subject is at rest in a lying position, and that the value was little affected by age and never exceeded 20 mmHg [1].

Since the 1st World Symposium on Pulmonary Hypertension (WSPH) organised by the WHO in Geneva in 1973, PH has been defined as mPAP ≥25 mmHg measured by right heart catheterisation (RHC) in the supine position at rest [2]. The Geneva WHO meeting was devoted to primary PH, a severe form of PH, some years after an outbreak related to the intake of the anorexic drug aminorex [3]. In the report of the meeting, it was recognised that this upper limit of normal mPAP of 25 mmHg was somewhat empirical and arbitrarily defined [2]. However, this conservative cut-off value allowed physicians to discriminate severe PH due to primary PH from other forms of PH (mainly due to lung diseases) characterised by a lower mPAP. This definition remained unchanged during the subsequent WSPH meetings from 1998 to 2013 [4–6], at least in part to preclude potential overdiagnosis and overtreatment of PH.

What is actually the upper limit of normal mPAP?

In 2009, Kovacs et al. [7] analysed all available data obtained by RHC studies in healthy individuals to determine normal values of mPAP at rest and exercise. Data from 1187 normal subjects from 47 studies were analysed. mPAP at rest was 14.0±3.3 mmHg; this value was independent of sex and ethnicity, and was only slightly influenced by age and posture. Considering this mPAP of 14 mmHg, two standard deviations would suggest mPAP >20 mmHg as above the upper limit of normal (i.e. above the 97.5th percentile). This definition is, therefore, no longer arbitrary, but based on a scientific approach.

A value of mPAP used in isolation is not accurate enough to characterise a clinical condition

Whatever the mPAP cut-off value considered for defining PH (≥25 or >20 mmHg), it is important to emphasise that this value used in isolation cannot characterise a clinical condition and does not define the pathological process per se. PAP elevation may indeed have several different causes with different management and outcomes, including increase in cardiac output (CO), left-to-right cardiac shunts, elevation of pulmonary arterial wedge pressure (PAWP) in left heart disease (LHD) and hyperviscosity. This abnormal elevation may also be due to pulmonary vascular disease (PVD) associated with structural changes of small pulmonary arteries. In the present clinical classification of PH, pre-capillary PH concerns patients from groups 1, 3 and 4, some patients from group 5, and rarely patients from group 2 with combined pre- and post-capillary PH.

To identify pre-capillary PH suggesting the presence of PVD, an above normal elevation of pulmonary vascular resistance should be included in the definition

Including pulmonary vascular resistance (PVR=(mPAP–PAWP)/CO) in the definition of pre-capillary PH is essential, allowing discrimination of elevation of PAP due to PVD from those due to elevation of PAWP or due to high CO. Since the 3rd WSPH held in 2003, pre-capillary PH of group 1 (pulmonary arterial hypertension (PAH)) has been defined by the presence of mPAP ≥25 mmHg with a normal PAWP ≤15 mmHg and elevated PVR ≥3 Wood Units (WU) [4–6]. This cut-off value of PVR ≥3 WU is also quite arbitrary since some recent data suggest that PVR >2 WU could be also considered abnormal [6]. In this sense, the use of a cut-off value of PVR ≥3 WU is conservative, suggesting the presence of a manifest pre-capillary PH. This value of PVR ≥3 WU is considered clinically relevant in different clinical situations, suggesting the presence of a significant PVD, e.g. it is already used as the threshold value for which the correction of congenital systemic-to-pulmonary shunts becomes questionable [8]. Moreover, it has been shown that elevated PVR ≥3 WU was associated with a poor survival after heart transplantation [9]. During the 6th WSPH in 2018, for patients of group 2, the Task Force on PH due to LHD recommended...
a PVR cut-off value $\geq 3$ WU to define patients with a pre-capillary component [10], so-called combined pre- and post-capillary PH, that is associated with a worse prognosis.

We propose including PVR $\geq 3$ WU not only in the definition of pre-capillary PH of group 1, but also in the definition of all forms of pre-capillary PH.

In patients with PH due to chronic obstructive pulmonary disease, those with severe PH (>40 mmHg) have a marked increase in PVR (around 10 WU); more often these patients have a mild PH (mPAP 20–30 mmHg), associated with lower PVR but remaining generally $>3$ WU [11], and this is also the case for patients with idiopathic pulmonary fibrosis [12]. In these different chronic lung diseases, even a modest elevation in mPAP (20–29 mmHg) was associated with a poor prognosis [13].

In chronic thromboembolism (group 4), a large international registry reported haemodynamic findings of severe pre-capillary PH with a mPAP of 47 mmHg and a mean PVR of 8.9 WU [14]. In this setting, even in patients with mild elevation of mPAP (20–24 mmHg), PVR is generally $>3$ WU.

**Outcome of patients with PVD and mPAP 21–24 mmHg**

Accumulating data indicate that many patients with PVD associated with an increase in mPAP but below the former threshold value defining PH ($\geq 25$ mmHg) are at risk of disease progression.

In systemic sclerosis, outcome data of patients with mPAP at diagnosis between 21 and 24 mmHg have been recently published. In 2013, a single-centre cohort study of 228 patients with systemic sclerosis who underwent RHC for suspicion of PH was reported [15]. mPAP 21–24 mmHg was documented in 86 patients at baseline; of these, 38 underwent a second RHC during the follow-up (median follow-up 48±35 months) and 16 of these (42%) developed overt PH (mPAP $\geq 25$ mmHg). The mean mPAP and PVR at baseline of these 16 patients was 22±2 mmHg and 2.9±0.6 WU, respectively; at follow-up, mean mPAP and PVR increased to 31±6 mmHg and 6.9±1.7 WU, respectively. Patients with so-called borderline mPAP at diagnosis were more likely to develop overt PAH than patients with mPAP $\leq 20$ mmHg ($p<0.001$; hazard ratio (HR) 3.7). Incident development of PAH was not benign in this cohort, with five deaths during follow-up despite the subsequent introduction of dual oral combination therapy and/or i.v. prostacyclin.

More recently, a two-centre cohort study identified 21 patients with systemic sclerosis and a mPAP at baseline of 21–24 mmHg [16]; these patients underwent a second RHC with a median follow-up of 3 years. At baseline, mean mPAP and PVR were 22±1 mmHg and 2.3±0.8 WU, respectively. At follow-up, mPAP and PVR increased to 25±4 mmHg and 3.2±1.6 WU, respectively. Among them, seven patients (33%) developed overt PH (three PAH, three pre-capillary PH associated with interstitial lung disease and one PH due to LHD) (J.G. Coghlan, Cardiology Dept, Royal Free Hospital, London, UK; personal communication).

In 2017, an Austrian group [17] published a series of 547 patients with unexplained dyspnoea and/or at risk of PH who underwent RHC. Manifest PH (mPAP $\geq 25$ mmHg) was confirmed in 290 patients, borderline PH (mPAP 21–24 mmHg) in 64 cases and 193 cases were considered as “normal” with mPAP $\leq 20$ mmHg; among them, 137 patients were defined as “lower normal” with mPAP $\leq 15$ mmHg. The median follow-up time of this cohort was 45.9 months; overall 161 patients (29%) died during the follow-up. In the multivariate model, considering age and comorbidities, both borderline PH and manifest PH were significantly associated with poor survival compared with the “lower normal” group with HR 2.37 (95% CI 1.14–4.97; $p=0.022$) and HR 5.05 (95% CI 2.79–9.12; $p<0.001$), respectively. At baseline, the group with mPAP 21–24 mmHg had a median PVR of 2.7 WU and 36% of these patients had PVR $>3$ WU.

Another instance where pre-capillary PH can be diagnosed at an earlier stage is chronic thromboembolism, as in this setting exercise limitation can occur in the absence of overt PH at rest due to the increase in dead-space ventilation resulting in a decreased ventilatory efficiency. Recently, two cohorts of 42 and 23 patients, respectively, have been reported with extensive persistent thromboembolic occlusions but without PH [18, 19]. At diagnosis, mPAP was 15–24 mmHg and PVR was 2–3 WU. These patients underwent pulmonary endarterectomy (PEA) and experienced significant improvement in WHO Functional Class, exercise capacity and quality of life, with no in-hospital mortality at 6 months. This form of chronic thromboembolism corresponded to 4% and 7% of the overall population treated with PEA in these two centres.

**Summary and perspectives**

A mPAP of 20 mmHg should be considered as the upper limit of normal value. This new definition has been recently proposed by others [20–22]. However, this abnormal elevation of mPAP in isolation is not sufficient to define PVD as it can be due to an increase in CO or PAWP.
Pre-capillary PH is best defined by the concomitant presence of mPAP >20 mmHg, PAWP ≤15 mmHg and PVR ≥3 WU (table 1), emphasising the need for RHC with mandatory measurement of CO and accurate measurement of PAWP.

For many years, the diagnosis of PH was based on an arbitrary value of mPAP ≥25 mmHg, probably because of understandable concern about overdiagnosis and overtreatment. Actually, the main cause of overdiagnosis and treatment of pre-capillary PH is the failure to confirm the diagnosis by RHC.

Conversely, the other side of this dilemma could be to undertreat some patients with abnormal elevation of PAP but not meeting the classical definition of PH. Today, there is growing evidence that in some PVDs (mainly PAH associated with systemic sclerosis, chronic thromboembolism and chronic lung diseases) patients with even a modest elevation in mPAP (21–24 mmHg) are symptomatic with exercise limitation and may have poor outcome. Nevertheless, a change in the haemodynamic definition of PH due to PVDs does not imply treating these additional patients, but highlights the importance of close monitoring in this population. Prospective trials are required to determine whether this PH population might benefit from specific management.

**Definition of exercise PH**

In 2004, PH was defined as resting mPAP >25 mmHg or exercise mPAP >30 mmHg [8]. At the 4th WSPH in 2008, however, the “exercise” part of the definition was removed [23]. This was largely due to uncertainties concerning the interrelationships between normal ageing, CO changes with exercise and pulmonary vascular physiology. This question was revisited again at the 6th WSPH in 2018.

**Why might exercise PH be relevant?**

A rise in resting PH pressure is a late event in the natural history of PVDs, because of microvascular “reserves”. PAP rises only when ≥50% of the microcirculation has been lost [24]. Much effort has been directed towards detecting PVD at an earlier (and potentially more treatable) stage. Intuitively, “unmasking” PVD by increasing CO to demonstrate increased resistance is a logical idea. Furthermore, PH patients first develop symptoms on exercise.

A number of studies have tried to unmask PVD by “stressing” the pulmonary circulation, by lung flow redistribution with upright posture [25] or by increasing CO [26]. This has led to the concept of “multipoint mPAP–CO” curves, where the rate of rise of mPAP with increasing CO has been informative (figure 1). In general, mPAP rises by ≥1 mmHg per litre of CO in normal subjects; PVD patients have a rise of ≥3 mmHg per litre of CO, reflecting increased resistance [27]. Generating such data is, however, challenging as exercise RHC measurements are time consuming, difficult, and potentially complicated by errors due to rapid respiratory cycles and inaccuracies in exercise CO and PAWP measures. Thus, generating mPAP–CO graphs for individual patients is impractical as a clinical routine.

**Why might defining exercise PH and PAH be difficult?**

A number of variables impact on the “normal” change of mPAP with exercise, which in turn complicates any attempt to establish a threshold for “exercise PH” as a pathological condition. Physiological changes occur with normal ageing [7] and mPAP also does rise with increasing CO; therefore in subjects (e.g. elite

**TABLE 1  Haemodynamic definitions of pulmonary hypertension (PH)**

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Characteristics</th>
<th>Clinical groups#</th>
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<tbody>
<tr>
<td>Pre-capillary PH</td>
<td>mPAP &gt;20 mmHg, PAWP ≤15 mmHg, PVR ≥3 WU</td>
<td>1, 3, 4 and 5</td>
</tr>
<tr>
<td>Isolated post-capillary PH (IpcPH)</td>
<td>mPAP &gt;20 mmHg, PAWP &gt;15 mmHg, PVR &lt;3 WU</td>
<td>2 and 5</td>
</tr>
<tr>
<td>Combined pre- and post-capillary PH (CpcPH)</td>
<td>mPAP &gt;20 mmHg, PAWP &gt;15 mmHg, PVR ≥3 WU</td>
<td>2 and 5</td>
</tr>
</tbody>
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mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood Units. #: group 1: PAH; group 2: PH due to left heart disease; group 3: PH due to lung diseases and/or hypoxia; group 4: PH due to pulmonary artery obstructions; group 5: PH with unclear and/or multifactorial mechanisms.
athletes) who can raise their CO to 30–40 L·min$^{-1}$ at peak exercise, mPAP can exceed previous “upper limits” of normal [28]. The greatest difficulty, however, is in using exercise to deduce the presence of PVD, because exercise also causes a rise in PAWP. Thus, if $PVR=(mPAP-PAWP)/CO$, one must measure exercise PAWP to deduce the pathogenesis of an abnormally high exercise-related PAP. As LHD is the commonest cause of resting PH and left atrial pressure rises abnormally with exercise in subjects with LHD, measuring changes in PAWP (or left atrial pressure) with exercise becomes the critical determinant for assessing PVR, in breathless patients with exercise PH.

This lack of diagnostic discrimination power (whether exercise PH is due to LHD or to PVD) has been explored by HERVE et al. [29]. Although total pulmonary resistance $>3$ mmHg per litre of CO distinguished healthy controls from those with LHD or PVD, it was impossible to distinguish LHD from PVD patients with confidence (figure 2). It should be noted that accurate measurement of exercise PAWP is technically challenging, related to the exaggerated respiratory swings in PAWP and in part to difficulties in “wedging” a balloon catheter adequately during vigorous exertion.

**Summary and perspectives**

Although there is intuitive appeal to measuring exercise haemodynamics to detect PVD at an earlier stage than can be revealed by measurements at rest, too many uncertainties persist to allow the reintroduction of a clinically useful definition of exercise PH. More information is required concerning normal changes
with ageing, high CO and especially about distinguishing exercise-related changes in PAWP (due to LHD) from changes due to PVD. We believe that these will be fruitful areas for future investigation.

Updated clinical classification of PH

The general purpose of clinical classification of PH is to categorize clinical conditions associated with PH based on similar pathophysiological mechanisms, clinical presentation, haemodynamic characteristics and therapeutic management. A comprehensive and simplified version of the clinical classification of PH in children and adults is presented in table 2. For patients with PAH associated with congenital heart disease, the four subgroups (Eisenmenger syndrome, left-to-right shunts, coincidental or small defects and post-operative/closed defects) remain the same [30] as the indications for defect closure (see the Task Force article in this issue of the European Respiratory Journal [31]). The updates of groups 2, 3 and 4 are presented in the respective Task Force articles in this issue of the European Respiratory Journal [10, 32, 33].

Update of group 1: PAH

Group 1.3: Drug- and toxin-induced PAH

We propose simplifying the characterisation of PAH associated with drugs and toxins into two subgroups to help physicians to identify drugs requiring specific surveillance. “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 with similar mechanisms of action. Based on recent data, the association of PAH with two drugs and toxins (amphetamines/methamphetamines and dasatinib) is now considered definite (table 3).

Zamanian et al. [34] reported a large series of 90 cases of PAH associated with methamphetamine-associated PAH; these subjects were less likely to be female, had more haemodynamic compromise at diagnosis and had poorer outcomes than IPAH. This analysis confirmed an association between

<table>
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<tr>
<th>TABLE 2 Updated clinical classification of pulmonary hypertension (PH)</th>
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<tbody>
<tr>
<td><strong>1 PAH</strong></td>
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<tr>
<td>1.1 Idiopathic PAH</td>
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<td>1.2 Heritable PAH</td>
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<td>1.3 Drug- and toxin-induced PAH (table 3)</td>
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<tr>
<td>1.4 PAH associated with:</td>
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<tr>
<td>1.4.1 Connective tissue disease</td>
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<tr>
<td>1.4.2 HIV infection</td>
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<td>1.4.3 Portal hypertension</td>
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<td>1.4.4 Congenital heart disease</td>
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<td>1.4.5 Schistosomiasis</td>
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<td>1.5 PAH long-term responders to calcium channel blockers (table 4)</td>
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<td>1.6 PAH with overt features of venous/capillaries [PVOD/PCH] involvement (table 5)</td>
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<tr>
<td>1.7 Persistent PH of the newborn syndrome</td>
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<tr>
<td><strong>2 PH due to left heart disease</strong></td>
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<tr>
<td>2.1 PH due to heart failure with preserved LVEF</td>
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<tr>
<td>2.2 PH due to heart failure with reduced LVEF</td>
</tr>
<tr>
<td>2.3 Valvular heart disease</td>
</tr>
<tr>
<td>2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH</td>
</tr>
<tr>
<td><strong>3 PH due to lung diseases and/or hypoxia</strong></td>
</tr>
<tr>
<td>3.1 Obstructive lung disease</td>
</tr>
<tr>
<td>3.2 Restrictive lung disease</td>
</tr>
<tr>
<td>3.3 Other lung disease with mixed restrictive/obstructive pattern</td>
</tr>
<tr>
<td>3.4 Hypoxia without lung disease</td>
</tr>
<tr>
<td>3.5 Developmental lung disorders</td>
</tr>
<tr>
<td><strong>4 PH due to pulmonary artery obstructions (table 6)</strong></td>
</tr>
<tr>
<td>4.1 Chronic thromboembolic PH</td>
</tr>
<tr>
<td>4.2 Other pulmonary artery obstructions</td>
</tr>
<tr>
<td><strong>5 PH with unclear and/or multifactorial mechanisms (table 7)</strong></td>
</tr>
<tr>
<td>5.1 Haematological disorders</td>
</tr>
<tr>
<td>5.2 Systemic and metabolic disorders</td>
</tr>
<tr>
<td>5.3 Others</td>
</tr>
<tr>
<td>5.4 Complex congenital heart disease</td>
</tr>
</tbody>
</table>

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

https://doi.org/10.1183/13993003.01913-2018
methamphetamine/amphetamine use and PAH-related hospitalisation (relative risk 2.64, 95% CI 2.18–3.2; p<0.001). Interestingly, pathological assessment demonstrated characteristic vascular changes similar to IPAH, including angiomatoid plexiform lesions, but also proliferative capillaries, as described in pulmonary capillary haemangiomatosis (PCH) or pulmonary veno-occlusive disease (PVOD). Dasatinib is a second-generation tyrosine kinase inhibitor and has been reported to be associated with PAH; the lowest estimate of incident PAH occurring in patients exposed to dasatinib in France was 0.45% [35]. Dasatinib-induced PAH frequently improves after discontinuation, but persists in over one-third of patients [35, 36].

Over the last 5 years, new drugs have been identified or suspected as potential risk factors for PAH. Several cases of deterioration or relapse of dasatinib-associated PAH after bosutinib initiation have been reported [37–39]; these cases were also characterised by an improvement of PAH after withdrawal of bosutinib. Cases of severe portopulmonary hypertension have occurred with novel strategies of direct-acting antivirals, including sofosbuvir for hepatitis C virus infection [40, 41]. Leflunomide, a disease-modifying antirheumatic drug, has been associated with several cases of PAH [42–44]. Recently, cases of potentially reversible PAH associated with natural indigo (Qing-Dai), an unapproved Chinese herbal drug, have been reported from the Japan Pulmonary Hypertension Registry [45, 46]. The active pharmaceutical ingredient of Qing-Dai is indirubin, which could induce apoptosis of pulmonary endothelial cells in vitro [46].

### Group 1.5: PAH long-term responders to calcium channel blockers

Although remodelling of small pulmonary arteries is the main pathological finding in PAH, pulmonary vasoconstriction also plays an important role in PAH pathophysiology, particularly in vasoreactive patients.

In a series of 64 patients published in 1992, Rich et al. [47] reported that patients with an acute vasodilator response to calcium channel blockers (CCBs) had dramatically improved survival when treated with long-term CCBs. In 2005, Sitbon et al. [48] demonstrated in a large series of 557 PH patients that acute vasodilator response may be observed in 12.5% of idiopathic PAH (IPAH), and overall 6.8% of patients have a long-term clinical and haemodynamic improvement on CCBs. This study identified the best criteria to identify acute vasodilator response, i.e. a reduction of mPAP ≥10 mmHg to reach an absolute value of mPAP ≤40 mmHg with an increased or unchanged CO. For vasoreactivity testing, inhaled nitric oxide at 10–20 ppm is the preferred agent, but i.v. epoprostenol, i.v. adenosine or inhaled iloprost can be used as alternatives (table 4). Long-term response to CCBs was defined by clinical

### TABLE 3 Updated classification of drugs and toxins associated with PAH

<table>
<thead>
<tr>
<th>Definite</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminorex</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>Phenylpropanolamine</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>L-tryptophan</td>
</tr>
<tr>
<td>Benfluorex</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>Methamphetamines</td>
<td>Amphetamines</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Interferon-α and -β</td>
</tr>
<tr>
<td>Toxic rapeseed oil</td>
<td>Alkylating agents</td>
</tr>
<tr>
<td></td>
<td>Bosutinib</td>
</tr>
<tr>
<td></td>
<td>Direct-acting antiviral agents against hepatitis C virus</td>
</tr>
<tr>
<td></td>
<td>Leflunomide</td>
</tr>
<tr>
<td></td>
<td>Indirubin [Chinese herb Qing-Dai]</td>
</tr>
</tbody>
</table>

### TABLE 4 Definitions of acute and long-term response

<table>
<thead>
<tr>
<th>Acute pulmonary vasoreactivity* for patients with idiopathic, hereditable or drug-induced PAH</th>
<th>Reduction of mPAP ≥10 mmHg to reach an absolute value of mPAP ≤40 mmHg Increased or unchanged cardiac output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term response to CCBs</td>
<td>New York Heart Association Functional Class I/II</td>
</tr>
</tbody>
</table>

PAH: pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure; CCB: calcium channel blocker. * nitric oxide (10–20 ppm) is recommended for performing vasoreactivity testing, but i.v. epoprostenol, i.v. adenosine or inhaled iloprost can be used as alternatives.
improvement (New York Heart Association Functional Class I or II) and sustained haemodynamic improvement after at least 1 year on CCBs only (same or better than achieved in the acute test and usually to obtain mPAP <30 mmHg with an increased or normal CO) (table 4). Pulmonary vasoreactivity testing for identification of patients suitable for CCB treatment is recommended only for patients with IPAH, heritable PAH or drug-induced PAH. In all other forms of PAH and PH the results can be misleading and long-term responders are rare [49].

Pathophysiology of PAH with vasoreactivity is largely unknown. Recently, Hemnes and co-workers have shown that PAH with vasoreactivity was characterised by a specific blood signature (microarray of cultured lymphocytes) and different gene variants (whole exome sequencing) compared with IPAH [50, 51]. These results suggest a specific entity with a distinct clinical course, characterised by significantly better prognosis, unique management and different pathophysiology (table 2).

**Group 1.6: PAH with overt features of venous/capillaries (PVOD/PCH) involvement**

Significant pulmonary venous and/or capillary involvement has been reported in many conditions which are known causes of PAH, such as systemic sclerosis. In the previous classification, PVOD/PCH was characterised as a distinct subgroup.

PVOD/PCH and PAH share similar causes and associated conditions even if some of them are more frequently associated with more pronounced venous/capillary involvement (table 5). Heritable forms of PVOD/PCH have been recognised in consanguineous families with a recessive transmission, due to biallelic mutations in the eukaryotic translation initiation factor 2α (EIF2AK4) gene [52-54]. Occupational exposure to organic solvents, particularly to trichloroethylene, has been associated with the development of pre-capillary PH with significant venous and capillary involvement [55].

Diagnosis of significant pulmonary venous/capillary involvement (PVOD/PCH) may be strongly suspected based on pulmonary function tests (decreased diffusion capacity of the lung for carbon monoxide (DLco) frequently <50% of theoretical values), arterial blood gases (severe hypoxaemia) and high-resolution computed tomography of the chest (septal lines, centrilobular ground-glass opacities/nodules and mediastinal lymph node enlargement) (table 5) [53, 54, 56]. More pronounced pulmonary venous/capillary involvement is associated with a poor prognosis, a limited response to PAH therapy and a risk of pulmonary oedema with these treatments [53, 57].

PAH and PVOD/PCH usually share a broadly similar haemodynamic profile and clinical presentation. Of note, significant pulmonary arterial remodelling has been described in biallelic EIF2AK4 mutation carriers [58] and muscular remodelling of pulmonary septal veins can be observed in BMPR2 (bone morphogenetic protein receptor type 2) mutation carriers [59]. What matters in practice are the clinical consequences of pulmonary venous/capillary involvement in pre-capillary PH. We therefore suggest that PAH and PVOD/PCH belong to a spectrum of PVDs rather than representing two clear-cut distinct entities. We propose including “PAH with overt features of venous/capillaries (PVOD/PCH) involvement” in the revised PAH (group 1) of the updated PH classification (table 2).

**Update of group 5: PH with unclear and/or multifactorial mechanisms**

Since the basis of our classification system was established in 1998, group 5 has passed through significant changes. Initially describing “disorders directly affecting the pulmonary vasculature”, then named “miscellaneous” during the 3rd WSPH in 2003 [60], and finally reaching its current presentation, this group includes forms of PH with unclear and/or multifactorial mechanisms [30, 61]. From the beginning,

![Table 5](https://doi.org/10.1183/13993003.01913-2018)
this group has represented less-studied forms of PH, in comparison with other groups; nevertheless, many of the PH forms currently in group 5 represent a significant part of the yet unrecognised worldwide burden of PH [62].

One of the central characteristics of the clinical conditions included in group 5 is that there is no identified predominant mechanism driving the development of PH and there may be multiple pathophysiological phenomena involved in this process (table 7). In this update of the classification, changes were considered only for the subtypes in which a definite relocation was supported by the available literature.

**Group 5.1: Haematological disorders**

Chronic haemolytic anaemia is clearly associated with an increased risk of PH [63]. Since the 5th WSPH in 2013, little has been added to the current understanding of the numerous presentations of PH in sickle cell disease (SCD). However, it is clear that in this setting PH is frequently multifactorial, including elevated CO, LHD, thromboembolic disease, altered blood viscosity and PVD due to endothelial dysfunction, mainly due to nitric oxide depletion [64–67]. More recently, restrictive cardiomyopathy has been better recognised and described in clinical and experimental studies [68]. These data reinforce the utmost importance of this particular form of PH and the need for continuous investigation in this field [64, 65]. In addition, over recent years, significant data have been generated regarding another important chronic haemolytic anaemia, i.e. β-thalassaemia. A better understanding about the risk factors for major complications of the disease, including PH, has been derived from significant cohorts [69]. Furthermore, DERCHI et al. [70] evaluated the prevalence of PH through invasive haemodynamic evaluation, similarly to what has been done in SCD [71–73]. In their cohort of 1309 patients that underwent screening evaluation, pre-capillary PH was confirmed in 2.1% of the cases, while a post-capillary profile was found in 0.3% [70]. Older age and splenectomy were clear risk factors associated with PH. Although this study provided important information regarding the significance of PH in this clinical condition, more data concerning the histopathology of vascular involvement as well as about pathophysiological mechanisms of PH development in these patients are still needed to better address potential management strategies.

**TABLE 6 Pulmonary hypertension (PH) due to pulmonary artery obstructions**

<table>
<thead>
<tr>
<th>4.1 Chronic thromboembolic PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2 Other pulmonary artery obstructions</td>
</tr>
<tr>
<td>4.2.1 Sarcoma (high or intermediate grade) or angiosarcoma</td>
</tr>
<tr>
<td>4.2.2 Other malignant tumours</td>
</tr>
<tr>
<td>Renal carcinoma</td>
</tr>
<tr>
<td>Uterine carcinoma</td>
</tr>
<tr>
<td>Germ cell tumours of the testis</td>
</tr>
<tr>
<td>Other tumours</td>
</tr>
<tr>
<td>4.2.3 Non-malignant tumours</td>
</tr>
<tr>
<td>Uterine leiomyoma</td>
</tr>
<tr>
<td>4.2.4 Arteritis without connective tissue disease</td>
</tr>
<tr>
<td>4.2.5 Congenital pulmonary artery stenoses</td>
</tr>
<tr>
<td>4.2.6 Parasites</td>
</tr>
<tr>
<td>Hydatidosis</td>
</tr>
</tbody>
</table>

**TABLE 7 Pulmonary hypertension with unclear and/or multifactorial mechanisms**

| 5.1 Haematological disorders |
| 5.2 Systemic and metabolic disorders |
| 5.3 Others |
| 5.4 Complex congenital heart disease |

https://doi.org/10.1183/13993003.01913-2018
Splenectomy deserves particular discussion. Following the first association of splenectomy and PH [74], it was not clear whether it represented a risk factor or a particular condition. Since then, splenectomy has been associated with the development of PH in many haematological conditions, as in the aforementioned β-thalassaemia [69, 70]. Most importantly, it has been strongly associated with the development of chronic thromboembolic PH [75]. Nevertheless, no other particular phenotype or change in clinical behaviour has been associated with the presence of splenectomy, suggesting that it should be better considered as a risk factor for PH instead of a particular condition deserving a specific classification.

Group 5.2: Systemic and metabolic disorders

It is important to emphasise that the concept supporting the classification of a clinical condition with systemic manifestations and a clear risk for PH into group 5 is, again, the lack of robust data allowing a definite recognition of predominant pathophysiological mechanisms, or describing the histopathological findings or yet, describing management strategies. For this reason, several conditions have been classified in this group, including sarcoidosis, lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis, thyroid disorders, Gaucher disease, glycogen storage disease and neurofibromatosis.

Regarding LAM, a recent screening study [76], in a significant cohort of more than 100 LAM patients, reinforced that PH in LAM is usually mild, as previously described [77]. From six patients (5.7%) presenting with pre-capillary PH, none had mPAP >30 mmHg. Moreover, the presence of PH was associated with poor pulmonary function, suggesting that the rise in pulmonary pressure is associated with parenchymal involvement, which was further reinforced by a more recent echocardiographic study [78]. Based on these findings, PH in LAM seems to be better classified together with other parenchymal lung diseases, in group 3.

Sarcoidosis is a more challenging situation, given the fact that PH might develop as a consequence of significantly different factors, from parenchymal lung disease to extrinsic compression of pulmonary vessels, direct myocardial involvement or even granulomatous arteriopathy [79]. Significant lung parenchymal disease is a highly prevalent condition in patients with sarcoidosis-associated PH [80, 81], although the presence of left ventricular dysfunction cannot be neglected [80]. It is difficult, however, to solely consider lung parenchymal involvement to reclassify sarcoidosis, given the multiplicity of other factors yet to be clarified, including the different histopathological pattern of the pulmonary vessels commonly seen in sarcoidosis, with granuloma formation in some cases [79], as opposed to other diseases in group 3. While these features are better studied, sarcoidosis remains classified into group 5.

There is a strong rationale for the concomitance of thyroid diseases and PH, from autoimmune to the presence of high or low CO, left ventricular dysfunction, or even an angio proliferation profile. The prevalence of thyroid disorders is increased in patients with PAH [82, 83]; furthermore, the level of thyroid dysfunction is also associated with prognosis in this setting [84]. Nevertheless, similarly to splenectomy, the presence of thyroid dysfunction does not necessarily characterise a specific clinical condition; it behaves more like a risk factor or a comorbidity that should be specifically controlled during the course of PH management. Until novel data prove otherwise, it was a consensus to withdraw thyroid disorders from the classification as a specific entity and better discuss their role as risk factors and/or associated comorbidities.

Many different conditions associated with PH still need better designed studies that add to the understanding of disease development. We propose that changes be made only after the generation of robust data to support such reclassification.

Conclusions

This Task Force first revisited the definition of PH, suggesting a new pressure level to define an abnormal elevation in the mPAP >20 mmHg and the need for PVR ≥3 WU to define the presence of pre-capillary PH. Furthermore, the Task Force proposed to simplify the core of the clinical classification of PH (table 2) which has been developed in additional tables. The two main changes in group 1 (PAH) include 1) the designation of a subgroup “PAH long-term responders to CCBs” and 2) the inclusion of the subgroup “PAH with overt features of venous/capillaries (PVOD/PCH) involvement”. Group 5 (PH with unclear and/or multifactorial mechanisms) was simplified with 1) the removal of splenectomy and thyroid disorders, and 2) the classification of LAM-associated PH together with other parenchymal lung diseases in group 3. Important new insights for groups 2, 3 and 4 have been addressed by the respective Task Forces in this issue of the European Respiratory Journal [10, 32, 33].

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References


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Diagnosis of pulmonary hypertension

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@ERSpublications
State of the art and research perspectives in the diagnostic procedures of patients with pulmonary hypertension including a comprehensive diagnostic algorithm http://ow.ly/Ow9730mknM6


ABSTRACT A revised diagnostic algorithm provides guidelines for the diagnosis of patients with suspected pulmonary hypertension, both prior to and following referral to expert centres, and includes recommendations for expedited referral of high-risk or complicated patients and patients with confounding comorbidities. New recommendations for screening high-risk groups are given, and current diagnostic tools and emerging diagnostic technologies are reviewed.
Introduction
There has been no meaningful decrease in the time from symptom onset to diagnosis of pulmonary hypertension (PH) in the past 20 years. Therefore, the diagnostic algorithm and guidelines for screening at-risk groups have been modified, balancing the benefits of earlier diagnosis and disease recognition against the economic healthcare burden of additional screening and increased referrals to PH centres.

Diagnostic approach in patients with clinical suspicion for PH/pulmonary arterial hypertension
PH due to parenchymal, cardiac, thromboembolic and other diseases (diagnostic groups 2, 3, 4 and 5, respectively) is associated with worse outcomes and limited treatment options, resulting in referral of these patients to PH centres. Guidelines for the diagnosis and management for these subgroups are addressed separately by the relevant 6th World Symposium on Pulmonary Hypertension (WSPH) Task Force articles in this issue of the *European Respiratory Journal* [1–3].

Clinical suspicion of PH
Symptoms
Symptoms of PH are non-specific: exertional dyspnoea, fatigue, weakness, chest pain, light-headedness/syncope and, less frequently, cough. Progressive right-sided heart failure (oedema, ascites, abdominal distension) occurs in later or more accelerated disease. Rarely, haemoptysis, Ortner’s syndrome/hoarseness (unilateral vocal chord paralysis) and arrhythmias may characterise PH.

Physical findings
Physical findings include augmented second heart sound (P2 component), right ventricular lift, jugular venous distension, hepatojugular reflux, ascites, hepatomegaly and/or splenomegaly, oedema, tricuspid regurgitant or pulmonary regurgitant murmurs, and S3 gallop.

Diseases associated with PH can be suggested by history and physical exam.

Established diagnostic tools
Electrocardiography
Since the US National Institutes of Health (NIH) registry report on primary PH in 1987 [4], the ECG has been considered a reliable clue to the presence of PH. ECG features in patients with pulmonary arterial hypertension (PAH) have been demonstrated to be associated with worse prognosis [5, 6]. The derivative populations for these conclusions were patients with known PAH, predominantly World Health Organization Functional Class III and IV. The utility of the ECG as a screening tool in complicated patients or those early in the course of their disease is uncertain. A normal ECG does not exclude PH.

Blood tests and immunology
Blood tests are not useful for PH diagnosis, but distinguish some forms of PH and indicate end-organ compromise. Routine biochemistry, haematology and thyroid function tests are required in all patients. Liver function abnormalities may represent congestion, primary liver disease and/or consequences of therapy. Thyroid disease is common in PAH, may develop during the disease and should be considered in cases of abrupt deterioration. Elevations of brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are associated with right ventricular overload, and are predictors of worse outcome.

Routine screening for connective tissue disease (CTD), hepatitis and HIV is required. Elevated antinuclear antibodies (ANAs) occur frequently, although in low titres (1:80). Recommended serological testing for scleroderma includes ANAs (as ELISA can be associated with false-negative tests, ANA immunofluorescence is recommended and should be considered positive at ≥1:160). If there is a high index of suspicion, consider a panel that consists of anticientromere, antitopoisomerase, anti-RNA polymerase III, double-stranded DNA, anti-Ro, anti-La and U1-RNP antibodies.

Patients with CTD (associated with thrombophilic states) and chronic thromboembolic PH (CTEPH) should undergo screening for coagulopathies and thrombophilia, including antiphospholipin antibodies, lupus anticoagulant and anti-β2-glycoprotein antibodies.

Pulmonary function tests and arterial blood gases
Pulmonary function tests are addressed in the PH lung disease Task Force article in this issue of the *European Respiratory Journal* [2], and should include total lung capacity and diffusing capacity of the lung for carbon monoxide (DLCO). In most patients with PAH there is a mild restrictive component. Marked reduction in DLCO (<60% of predicted) or severe exertional hypoxaemia can indicate pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis [7].
Cardiopulmonary exercise testing

Cardiopulmonary exercise testing (CPET) for diagnostic purposes can be done non-invasively or with haemodynamic testing [8]. CPET can quantify the degree of relative hypoperfusion of the lung and the systemic circulation that occurs during exercise in patients with PH [9], and can grade the severity of exercise limitation and assess responses to therapy [10].

Abnormalities in effort-independent ratio of minute ventilation to carbon dioxide production (\( \dot{V}_E/\dot{V}_CO_2 \)) and end-tidal carbon dioxide tension (\( PETCO_2 \)) obtained during CPET have been used to estimate the likelihood of PH (lower peak oxygen uptake (\( VO_2 \)) and/or higher \( \dot{V}_E/\dot{V}_CO_2 \) signifying an increasing likelihood of pulmonary vascular disease) [11]. Several investigators have demonstrated the utility of CPET in defining abnormal exercise responses specific to PAH [12–15]. CPET can be particularly useful in helping identify the predominant underlying cardiopulmonary pathophysiology [13, 16–19]. A detailed description of the methodologies used in CPET for PH can be found in SUN et al. [9]. Submaximal exercise testing to evaluate PAH severity using a simplified gas exchange system has also been proposed [20].

Accurate utilisation of CPET requires performance by a competent facility and interpretation by a clinician with expertise in gas exchange in conjunction with the patient’s history, physical and laboratory findings. CPET is useful for determining the nature of the exercise limitation in patients with unexplained dyspnoea, but should not be used as the sole screening tool for asymptomatic subjects at risk for developing PAH; CPET can help evaluate cardiopulmonary limitations and assess pulmonary vascular involvement in these patients; emerging evidence suggests that CPET may be useful for evaluating symptomatic patients at high risk for developing PAH [15]. In addition, CPET should be considered after diagnosis of PAH to quantify the severity of exercise impairment and to estimate prognosis.

Transthoracic echocardiography

The transthoracic echocardiogram (TTE) remains the most important non-invasive screening tool and right heart catheterisation (RHC) remains mandatory to establish the diagnosis.

The echocardiographic probability of PH was derived from previously published data in normal adults [21–23], and consolidated by expert opinion using the combination of tricuspid regurgitant velocity, right ventricular size, interventricular septal function, inferior vena cava diameter fluctuations with respiratory cycle, systolic right atrial area, pattern of systolic flow velocity and early diastolic pulmonary regurgitant velocity, and diameter of the pulmonary artery (tables 1 and 2) [24–27].

Ventilation/perfusion lung scanning

Ventilation/perfusion (V/Q) lung scanning is addressed in the CTEPH Task Force article in this issue of the European Respiratory Journal [3]. A normal V/Q scan remains the preferred diagnostic tool and rules out CTEPH. Nuclear medicine societies are recommending a transition of V/Q reporting to a binary interpretation [28, 29].

Chest computed tomography

Chest computed tomography (CT) demonstrating right ventricular dilation, right atrial dilation, enlarged main pulmonary artery (diameter ≥29 mm) or a main pulmonary artery/ascending aorta diameter ratio

<table>
<thead>
<tr>
<th>Peak tricuspid regurgitation velocity m·s⁻¹</th>
<th>Presence of other echocardiographic “PH signs”#</th>
<th>Echocardiographic probability of PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.8 or not measurable</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>2.9–3.4</td>
<td>Yes</td>
<td>Intermediate</td>
</tr>
<tr>
<td>&gt;3.4</td>
<td>Not required</td>
<td>High</td>
</tr>
</tbody>
</table>

#: see table 2. Reproduced and modified from [24] with permission.
1 is suggestive of PH [30]. High-resolution non-contrast examination can identify parenchymal lung disease and discriminate between PH lung disease and PAH (group 3 versus group 1).

Current state-of-the-art diagnostic algorithm
The modified diagnostic algorithm divides the diagnostic approach into 1) that undertaken outside the PH expert centre, including recommendations for high-risk/accelerated disease requiring expedited triage to the expert centre (figure 1), and 2) that focusing on the diagnosis of PH once referred to a PH expert centre (figure 2).

Practice recommendations (including high-risk population screening recommendations)
Patients with congenital heart disease (CHD), CTD, HIV and portopulmonary hypertension (POPH) are at increased risk for PH. As little or no progress has been made in earlier diagnosis, this Task Force recommends more aggressive assessment and screening of some of these high-risk populations.

Scleroderma (systemic sclerosis) and scleroderma spectrum
The 5th WSPH report, the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) PH guidelines and the NIH-supported 2013 CTD-PAH guidelines recommend annual screening in patients with systemic sclerosis (SSc) [24, 31, 32]. All guidelines recommend the DETECT algorithm (evidence-based detection of PAH in SSc) in patients with SSc spectrum disorders (SSc, mixed CTD or other CTDs with prominent scleroderma features (e.g. scleractyly, nail fold capillary abnormalities and SSc-specific autoantibodies)) associated with DLCO <60% of predicted and disease duration >3 years. The current diagnosis Task Force undertook a systematic review of the published literature for screening tools available for CTD-PAH [33]. The review supports incorporating TTE, DETECT (with preliminary data on its performance with those with DLCO <80% of predicted) or forced vital capacity (FVC)/DLCO ratio >1.6 and blood markers (such as NT-proBNP) in SSc spectrum disorders. Based on this data and on the published guidelines, this Task Force recommends the incorporation of DETECT, TTE or FVC/DLCO ratio with elevated NT-proBNP to screen for SSc spectrum disorders. Although the prevalence of PAH is lower in those with DLCO ≥80% of predicted, review of two large cohorts in the USA ([33] and Steve Mathai, Johns Hopkins, Baltimore, MD, USA; personal communication) suggested that PAH is present in these patients.

Recommendations
- For patients with SSc and SSc spectrum with uncorrected DLCO <80% of predicted, annual screening should be considered. The appropriate screening tools include DETECT, the 2015 ESC/ERS recommendations for TTE or FVC/DLCO ratio >1.6 (assuming none-to-mild interstitial lung disease) and ≥2-fold upper limit of normal of NT-proBNP. If any of these screening tests are positive, these patients should be referred for RHC. For those with uncorrected DLCO ≥80% of predicted, screening may be considered with TTE.

### Table 2

<table>
<thead>
<tr>
<th>A: The ventricles</th>
<th>B: Pulmonary artery</th>
<th>C: Inferior vena cava and right atrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricle/left ventricle</td>
<td>Right ventricular outflow Doppler acceleration time &lt;105 ms and/or mid-systolic notching</td>
<td>Inferior vena cava diameter &gt;21 mm with decreased inspiratory collapse (≤50% with a sniff or ≤20% with quiet inspiration)</td>
</tr>
<tr>
<td>basal diameter ratio &gt;1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flattening of the interventricular</td>
<td>Early diastolic pulmonary regurgitation velocity &gt;2.2 m·s(^{-1})</td>
<td>Right atrial area (end-systole) &gt;18 cm(^2)</td>
</tr>
<tr>
<td>septum [left ventricular eccentricity index &gt;1.1 in systole and/or diastole]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary artery diameter &gt;25 mm</td>
</tr>
</tbody>
</table>

Echocardiographic signs from at least two different categories [A/B/C] from the list should be present to alter the level of echocardiographic probability of PH. Reproduced and modified from [24] with permission.
Although the incidence of PAH in HIV is low, the large number of HIV-infected individuals worldwide makes HIV a major contributor to the worldwide incidence of PAH and a significant contributor to HIV-related death. Prior guidelines did not recommend PAH screening in HIV-infected patients, a conclusion derived from contemporary RHC-based studies in Europe [34] and the USA [35].

Preliminary data from an ongoing RHC-based study in Atlanta HIV clinics suggests a higher incidence of PH than previously reported in the USA (prevalence 2% in this US-based African-American population) (Marshaleen Henriques-Forsythe, Morehouse School of Medicine, Atlanta, GA, USA and Harrison W. Farber, Pulmonary Center, Boston University School of Medicine, Boston, MA, USA; personal communication). Risks for PAH in HIV include sex and i.v. drug use. Males are more frequently infected with HIV than females, but HIV-infected females are disproportionately diagnosed with PAH (around 2-fold). Intravenous drug use has been associated with HIV-PAH [36] in univariate analysis, although it dropped out in multivariate analysis; however, a biological rationale for this association has been demonstrated [37]. Data suggest that cocaine acts synergistically with the HIV-1 Tat (transactivator of transcription) protein [38] by suppressing bone morphogenetic protein receptor expression on pulmonary artery smooth muscle cells.

Other studies report an association between HIV-PAH and female sex [39], chronic hepatitis C virus infection (multivariate OR 3.01, 95% CI 1.2–8.2; p=0.02 [21, 40]) and origin from high-prevalence country [41].

The following higher-risk features are proposed for PAH screening in HIV to enrich the likelihood of earlier diagnosis of HIV-PAH in asymptomatic patients: female sex, i.v. drug use/cocaine use, hepatitis C virus infection, origin from high-prevalence country, known Nef (negative regulatory factor) or Tat HIV proteins and US African-American patients independent of symptoms.

**Recommendations**

- Screen for PAH in HIV patients with symptoms or with more than one risk factor for HIV-PAH.
Heritable

Recommendations in the USA for PAH genetic screening are largely ignored, misunderstood or unfunded [42]. In contrast, genetic screening and counselling offered by French PH referral centres have identified PAH mutations in 16.9% of presumed sporadic PAH patients, in 89% of patients with a family history [43] and in asymptomatic first-degree relatives of mutation carriers pre-emptively screened. Recent longevity data indicates a lifelong risk of developing disease in 14% of male and 42% of female carriers, prompting our recommendation for annual echocardiography in asymptomatic carriers [44].

Recommendations

- Genetic counselling of all idiopathic, anorexiant and familial PAH patients and first-generation asymptomatic family members of patients with known genetic mutations.
- Subsequent evaluations for PAH should be offered (e.g. CPET and TTE), in mutation-positive individuals.
- National databases for genotyping all PAH patients should be advocated by the WSPH. Biobanking of samples and/or genotyping should be mandated in future interventional studies in PAH patients and possibly in PH patients.

Other heritable PH

Hereditary haemorrhagic telangiectasia

The French hereditary haemorrhagic telangiectasia (HHT) registry [45] demonstrated the echocardiographic prevalence of PH in HHT as 4.23%, although this was usually associated with high-output left heart failure. However, the review indicated that while PAH was rare, it was associated with much poorer survival.
Recommendations

- In symptomatic patients and those with heart failure or hepatic arteriovenous malformations, with HHT or family history of HHT, genetic testing and an echocardiogram should be undertaken. If TTE positive (tables 1 and 2) or suggestive of PH, RHC should be undertaken to distinguish the aetiology of PH.

Portopulmonary hypertension

The frequency of PH in patients with liver disease varies with disease severity and duration. By time of liver transplantation 10.3% of patients had RHC-proven mean pulmonary arterial pressure (mPAP) >35 mmHg [46]. A retrospective review of the UK National Registry of all incident treatment-naïve patients with POPH suggested a prevalence of 0.85 cases per million population [47]. The prevalence of POPH in the portal hypertensive population has been previously estimated as 2–6%. Estimated median survival time was 3.75 years in this patient population, with 1-, 2-, 3- and 5-year survival of 85%, 73%, 60% and 35%, respectively.

Recommendations

- Echocardiographic screening is recommended in all patients with portal hypertension. If a tricuspid regurgitant jet of >3.4 m·s$^{-1}$ or right atrial or right ventricular enlargement or dysfunction is found, then further evaluation with RHC and referral to PH expert centre is recommended.

Congenital heart disease

In CHD, PAH can be identified in four distinct subgroups of patients: 1) Eisenmenger syndrome, 2) persistent systemic-to-pulmonary shunts, 3) those with small, coincidental defects, and 4) patients who have undergone defect correction. PAH is present by definition in subgroups 1 and 3. Thus, PAH screening in the CHD population should be undertaken in subgroup 2 and, importantly, subgroup 4.

Recommendations

- Post-operative PAH screening in subgroup 4 should include clinical and echocardiographic and ECG screening during follow-up visits 3–6 months after correction and then throughout their planned long-term cardiological follow-up. Annual screening should be planned for corrected patients who presented with increased baseline pulmonary vascular resistance or with combinations of other predisposing factors.

Novel diagnostic modalities

Innovative imaging

V/Q single photon emission CT

V/Q single photon emission CT (SPECT) has higher sensitivity compared with planar imaging and outcome studies have confirmed a high negative predictive value in excluding pulmonary embolism [48, 49]. Dual-modality techniques with varying combinations of hybrid SPECT/CT pulmonary imaging can improve the specificity of V/Q SPECT by identifying lung diseases in patients with perfusion abnormalities. The addition of low-dose CT improves the specificity of V/Q SPECT from 88% to 100% while maintaining the same high sensitivity of 97% [50]. V/Q SPECT reduces radiation exposure relative to CT [51–53]. The three-dimensional aspects of V/Q SPECT allow for data objectification and facilitate automated analysis. The perfusion redistribution index as measured by V/Q SPECT showed perceptible reduction in the normal gravity-dependent redistribution of lung perfusion in PAH patients compared with the normal population [54] and hence can be a potential marker of pulmonary vascular disease.

V/Q SPECT and hybrid pulmonary imaging are not universally available.

Dual-energy CT: pulmonary perfusion

Dual-energy CT (DECT) offers visualisation of morphological and perfusion abnormalities in the pulmonary vasculature. Perfusion alterations were less common but more homogeneous in PAH and were mainly in the form of patchy defects [55]. In CTEPH, perfusion alterations were more frequent and heterogeneous with a high level of concordance with V/Q scintigraphy. The utility of DECT in the diagnosis and prognosis of PH, particularly CTEPH, requires further evaluation.
Three-dimensional dynamic contrast-enhanced magnetic resonance: lung perfusion

Dynamic contrast-enhanced magnetic resonance estimates of perfusion are based on quantification of tissue enhancement at serial time-points after injection of gadolinium and the technique has comparable sensitivity to perfusion scintigraphy for diagnosing CTEPH [56, 57]. Although the lack of ionising radiation makes this an attractive alternative, limited availability and higher costs preclude this technique from superseding V/Q scintigraphy.

Functional magnetic resonance imaging: ventilation

The ready availability and ease of inhaled oxygen as a contrast medium makes pulmonary magnetic resonance imaging (MRI) a promising tool for assessing ventilation. In a small study, oxygen-enhanced ventilation and contrast-enhanced perfusion MRI was concordant with scintigraphy [58]. Standardisation of analyses and reproducibility of oxygen-enhanced MRI metrics is needed before routine use in clinical practice.

Subclinical right ventricular dysfunction

Parametric mapping

A review of the magnetic resonance literature found 21 magnetic resonance metrics indicative of PH [59]. Of these, the ventricular mass index (VMI) was frequently used to assess right ventricular functional and structural changes compared with RHC. A meta-analysis of VMI revealed a positive likelihood ratio of 4.894, indicating a modest ability to differentiate PH patients from healthy controls.

Late gadolinium enhancement (LGE) at the right ventricular insertion points in PH due to delayed clearance of gadolinium correlates inversely with right ventricular performance [60]; however, its utility has been called into question in recent studies as a prognostic indicator in PH [61].

T1 mapping is a non-invasive technique for extracellular volume (ECV) quantification and facilitates early detection of myocardial involvement that is not detectable by LGE. PH has been shown in a small study to be independently associated with increased right ventricular ECV even after adjustment for right ventricular dilatation and dysfunction [62].

Larger studies are required to determine if right ventricular ECV reliably predicts adverse clinical outcomes, offering the potential for risk stratification, prognostication and therapeutic efficacy assessment.

Right ventricular strain

Cardiac magnetic resonance-based right ventricular strain imaging evaluates regional myocardial function by measuring the percentage change in myocardial deformation. Cardiac magnetic resonance feature tracking has shown a significant reduction in right ventricular strain in PH patients with normal right ventricular ejection fraction, predicting subsequent clinical deterioration [63]. Magnetic resonance strain indices are similar to echocardiographic indices, but longitudinal and circumferential strain measurements are more reliable.

Pulmonary artery four-dimensional flow imaging

Time-resolved three-dimensional phase-contrast MRI, also known as four-dimensional flow magnetic resonance, visualises and quantifies cardiovascular blood flow. The pulmonary artery flow patterns can be a non-invasive early marker in those at risk for developing PH.

Main pulmonary artery flow vortices are a marker of elevated mPAP. Vortical blood flow in the main pulmonary artery >14.3% of the cardiac interval corresponds to PH with 97% sensitivity and 96% specificity [64]. The duration of the vortical flow shows a linear increase with mPAP and can be used to estimate PAPs [65]. Early onset of retrograde flow in the dorsal aspect of the main pulmonary artery is another characteristic of PAH [66].

Wall shear stress is reduced in the proximal pulmonary arteries of PAH patients, and may contribute to pulmonary endothelial cell dysfunction and PAH progression [67]. Wall shear stress can be characterised by four-dimensional flow magnetic resonance with the ability to discriminate PAH patients from normal controls [68–70].

These metrics are not available from routine RHC and therefore have potential for non-invasive PH screening and monitoring. Data extraction is complex and clinical trials are necessary to explore the benefits of four-dimensional flow magnetic resonance over standard practices.

Intravascular ultrasound and optical coherence tomography in PAH

Intravascular ultrasound and optical coherence tomography (OCT) can demonstrate intimal fibrosis, a surrogate marker of pulmonary arterial remodelling that correlates negatively with pulmonary arterial
compliance and is associated with unfavourable clinical outcomes during mid-term follow-up [71]. OCT has shown development of pulmonary arterial remodelling in patients with borderline PH and the occurrence of reverse remodelling following effective treatment [72].

**Machine learning**

Technological advances in cardiac imaging coupled with exceptional computing power and innovative analytical modelling offer an unprecedented amount of data that can contribute to the search for novel imaging biomarkers.

A recently published machine learning-based survival model had incremental prognostic power when compared with conventional parameters to more accurately predict outcomes in PH [73]. Such computational simulations can illuminate pathophysiological mechanisms of right ventricular failure, risk stratify different PH groups and identify imaging end-points following therapeutic interventions.

**Future biomarkers**

Numerous potential biomarkers (e.g. asymmetric dimethylarginine, cystatin C, volatile exhaled gases, exhaled nitric oxide (NO) fraction (FENO) and NOx derivates) [74] have been associated with endothelial cell dysfunction, inflammation, epigenetics, cardiac function, oxidative stress, metabolism, extracellular matrix and exhaled breath condensate [75, 76]; while novel, these have not yet demonstrated sensitivity and specificity for diagnosis, risk assessment or management of PH.

The future of laboratory biomarkers may hinge on the ability to use “deep phenotyping”, i.e. characteristic patterns in the genome, transcriptome, proteome and/or metabolome of the patient [77–81]. Currently metabolomics emerges as a potentially informative area of systems biology. In the future, a metabolomics fingerprint may inform treatment decisions, while changes may be considered “deep monitoring” of treatment results. Currently, however, abnormal responses versus normal responses to abnormal stimuli are indistinguishable and metabolic signatures have only been evaluated in well-defined, homogenous study populations. New research paradigms are necessary to prove their value for early detection and differential diagnosis of PAH in real life.

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Markowitz DH, Systrom DM. Diagnosis of pulmonary vascular limit to exercise by cardiopulmonary exercise testing. *J Heart Lung Transplant* 2004; 23: 88–95.


Risk stratification and medical therapy of pulmonary arterial hypertension


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Edited by N. Galiè, V.V. McLaughlin, L.J. Rubin and G. Simonneau

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State of the art and research perspectives on medical therapy of pulmonary arterial hypertension, including treatment algorithm http://ow.ly/4UKj30md5GS


ABSTRACT  Pulmonary arterial hypertension (PAH) remains a severe clinical condition despite the availability over the past 15 years of multiple drugs interfering with the endothelin, nitric oxide and prostacyclin pathways. The recent progress observed in medical therapy of PAH is not, therefore, related to the discovery of new pathways, but to the development of new strategies for combination therapy and on escalation of treatments based on systematic assessment of clinical response. The current treatment strategy is based on the severity of the newly diagnosed PAH patient as assessed by a multiparametric risk stratification approach. Clinical, exercise, right ventricular function and haemodynamic parameters are combined to define a low-, intermediate- or high-risk status according to the expected 1-year mortality. The current treatment algorithm provides the most appropriate initial strategy, including monotherapy, or double or triple combination therapy. Further treatment escalation is required in case low-risk status is not achieved in planned follow-up assessments. Lung transplantation may be required in most advanced cases on maximal medical therapy.
Introduction

Pulmonary arterial hypertension (PAH) remains a severe clinical condition despite the publication of 41 randomised clinical trials (RCTs) in the past 25 years and the regulatory approval of multiple drugs active by four routes of administration (i.v., s.c., oral and inhaled) [1, 2]. Currently approved therapies target three main pathways important in endothelial function: the prostacyclin and nitric oxide (NO) pathways, which are underexpressed in PAH patients, and the endothelin pathway, which is overexpressed in PAH patients (see the Task Force article by Humbert et al. [3] in this issue of the European Respiratory Journal). This imbalance in vasoactive mediators plays a critical role in the development and progression of the obstructive proliferative pathological changes of the distal pulmonary arteries [3], which, when untreated, will lead to heart failure and premature death (see the Task Force article by Vonk Noordegraaf et al. [4] in this issue of the European Respiratory Journal). Prostacyclin analogues (PCAs) and prostacyclin receptor agonists, phosphodiesterase type 5 inhibitors (PDE5is) and guanylate cyclase stimulators, and endothelin receptor antagonists (ERAs) are intended to correct the dysfunction of the prostacyclin, NO and endothelin pathways, respectively. Interestingly, drugs targeting the three pathways were already approved and included in the treatment algorithm for PAH patients proposed in 2003 at the 3rd World Symposium on Pulmonary Hypertension (WSPH) held in Venice, Italy [5]. The progress observed in medical therapy of PAH patients over the past 15 years is not, therefore, related to the discovery of new pathways, but to the evolution and testing of new drugs and strategies for combination therapy, and on escalation of treatments based on systematic assessment of clinical response [1, 2]. In fact, in the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines the treatment strategy was intimately linked to the baseline severity of the newly diagnosed PAH patient and recommendations for subsequent treatment escalation were founded on the patient’s conditions after a pre-specified period of therapy [1, 2]. Both the baseline assessment and the treatment response were based on a multiparametric approach to stratify the patients in low-, intermediate- or high-risk groups for 1-year mortality. The “risk” table included clinical, functional, exercise, right ventricular function and haemodynamic parameters.

This central connection between methodical risk assessment and treatment strategy in PAH patients has been recently validated by retrospective analyses of three independent registries, showing a clear prediction of survival or event-free survival based on this multiparametric approach at baseline and at follow-up [6–9].

This article will provide an updated analysis of risk stratification and its relationship with different treatment strategies available for PAH patients, including general measures, supportive therapies, monotherapy, initial and sequential combination therapy, and interventional therapies.

Risk stratification

The assessment of the prognosis of patients with PAH has been considered an important part of care since the publication of the first US National Institutes of Health idiopathic PAH (IPAH) registry nearly three decades ago [10]. Over time, different baseline and follow-up parameters, including clinical, functional, exercise, non-invasive and invasive variables, have been utilised individually or combined in formulas or calculators to predict outcome: the French Pulmonary Hypertension Network (FPHN) registry risk equation [11, 12], the PH connection equation [13, 14], the Scottish composite score [15], the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk equation [16] and risk score [17, 18], and the 2015 ESC/ERS PH guidelines risk table [1, 2]. Table 1 shows the characteristics of four registries testing the PAH risk stratification strategy of the REVEAL risk equation and of the 2015 ESC/ERS PH guidelines risk table [6–9, 17–19].

The REVEAL equation [16] and the subsequent score [17, 18], derived from a cohort of 2716 PAH patients and using 12 modifiable and non-modifiable parameters measured at baseline, provided the 12-month likelihood of survival (five strata) in incident and prevalent IPAH and associated PAH patients. If utilised at follow-up, the equation can predict outcome at 1 additional year [18]. The risk score calculator was validated internally in 504 newly diagnosed PAH patients, externally in registries and in clinical trials datasets [20, 21]. Survival up to 5 years has been reported according to baseline REVEAL score data, but not at follow-up reassessment [22]. REVEAL survival up to 5 years has also been provided for a subgroup of 1426 patients and based only on repeated high versus low brain natriuretic peptide (BNP) plasma level assessments [23]. The REVEAL registry also demonstrated the prognostic value of renal dysfunction at baseline and follow-up measurements of estimated glomerular filtration rate (eGFR) [24].

The REVEAL 2.0 risk score calculator is a refinement of the original REVEAL risk score calculator; it includes all-cause hospitalisations within the previous 6 months and eGFR, both of which have been shown to impact mortality [24, 25].
The REVEAL 2.0 risk score calculator (14 variables) has been compared [19] with the strategies utilised in the FPHN registry [8] and in the Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry [7]. In this experience the data showed that, based on the 12-month mortality, the correspondences between the low-, intermediate- and high-risk groups as defined by the 2015 ESC/ERS PH guidelines and the REVEAL 2.0 calculator (14 variables) were as follows: low risk=REVEAL score \( \leq 6 \), intermediate risk=REVEAL score 7 and 8, and high risk=REVEAL score \( \geq 9 \). The authors propose a more discriminating risk stratification provided by the REVEAL score, although it is not clear how this translates to the approach to treatment [7].

The limitations of the REVEAL score include the relatively short prediction period (1 year) when assessed at follow-up and the large number of variables required (from 12 to 14 variables). Simplified versions of the REVEAL score utilising high-yield variables seem to have a similar predictive value as the original version [26].

The 2015 ESC/ERS PH guidelines have recommended a flexible approach to PAH patient risk assessment: using a multidimensional stratification according only to modifiable clinical, functional, exercise, biochemical, echocardiographic and haemodynamic variables with known prognostic significance (ESC/ERS PH guidelines Table 13 Risk assessment in PAH). Patients were categorised as low, intermediate or high risk based on expected 1-year mortality [1, 2]. Recently, a retrospective analysis of three major registries (total of 3135 patients) provided an independent validation of this approach and showed a clear difference in 5-year survival or transplantation-free survival, depending on risk stratification category at both baseline and first follow-up [6–8]. In addition, post hoc analysis of the SERAPHIN haemodynamic substudy has shown a reduction in the morbidity and mortality end-point if low-risk haemodynamics thresholds included in the 2015 ESC/ERS PH guidelines were reached after 6 months of treatment with macitentan [27].

Interestingly, the risk stratification strategies have varied significantly among the registry studies: in the Swedish PAH Registry (SPAHR) [6] and COMPERA [7] studies (both including IPAH and associated PAH patients), individual risk was calculated at baseline and at the first follow-up by assigning a score of 1, 2 or 3 to each criterion (1=low risk, 2=intermediate risk and 3=high risk according with the 2015 ESC/ERS PH guidelines) and rounding to the mean of the available variables. In the FPHN registry [8], risk assessment was performed in incident IPAH patients according to the presence of four low-risk criteria: World Health Organization (WHO)/New York Heart Association Functional Class (FC) I or II, 2) 6-min walk distance (6MWD) >440 m, 3) right atrial pressure (RAP) <8 mmHg and 4) cardiac index \( \geq 2.5 \) L\( \cdot \)min\(^{-1}\)\( \cdot \)m\(^{-2} \). Patients were classified according to the number of low-risk criteria present at baseline (i.e. at the time of PAH diagnosis) or at the time of re-evaluation. As exploratory analyses, the additive value of BNP <50 ng\( \cdot \)L\(^{-1} \) or N-terminal pro-BNP (NT-proBNP) <300 ng\( \cdot \)L\(^{-1} \) plasma levels or mixed venous oxygen saturation (\( S_vO_2 \)) >65% as low-risk criteria was assessed in the subsets of patients for whom these data were available.

Recently, the FPHN non-invasive risk assessment strategy using three dichotomised low-risk criteria (FC, 6MWD and NT-proBNP or BNP plasma levels) has been applied to the COMPERA cohort at baseline and at the first follow-up: the authors conclude that the FPHN risk assessment strategy provides a more accurate identification of patients with an excellent long-term survival than the approach of averaging risk scores [9].

Interestingly, the variables with the highest yield in the registry analyses are similar, i.e. FC, 6MWD, NT-proBNP or BNP plasma levels, cardiac index, RAP and \( S_vO_2 \) [6–8]. These variables are appropriate at

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**TABLE 1 Summary of four registries assessing risk scores**

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<tr>
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<td>383</td>
<td>1094</td>
<td>1017</td>
</tr>
<tr>
<td><strong>Associated PAH included</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Definition of low risk</strong></td>
<td>( \leq 6 ) REVEAL score</td>
<td>( &lt;1.5 ) average score</td>
<td>( &lt;1.5 ) average score</td>
<td>3–4 out of 4 low-risk criteria</td>
</tr>
<tr>
<td><strong>1-year mortality by risk group (low/intermediate/high) %</strong></td>
<td>( \leq 2.6/7.0/\geq 10.7 )</td>
<td>1.0/7.0/26.0</td>
<td>2.8/9.9/21.2</td>
<td>1.0/NA/13.0–30.0</td>
</tr>
</tbody>
</table>

PAH: pulmonary arterial hypertension; NA: not available. #: incident patients only.

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The 2015 ESC/ERS PH guidelines have recommended a flexible approach to PAH patient risk assessment: using a multidimensional stratification according only to modifiable clinical, functional, exercise, biochemical, echocardiographic and haemodynamic variables with known prognostic significance (ESC/ERS PH guidelines Table 13 Risk assessment in PAH). Patients were categorised as low, intermediate or high risk based on expected 1-year mortality [1, 2]. Recently, a retrospective analysis of three major registries (total of 3135 patients) provided an independent validation of this approach and showed a clear difference in 5-year survival or transplantation-free survival, depending on risk stratification category at both baseline and first follow-up [6–8]. In addition, post hoc analysis of the SERAPHIN haemodynamic substudy has shown a reduction in the morbidity and mortality end-point if low-risk haemodynamics thresholds included in the 2015 ESC/ERS PH guidelines were reached after 6 months of treatment with macitentan [27].

Interestingly, the risk stratification strategies have varied significantly among the registry studies: in the Swedish PAH Registry (SPAHR) [6] and COMPERA [7] studies (both including IPAH and associated PAH patients), individual risk was calculated at baseline and at the first follow-up by assigning a score of 1, 2 or 3 to each criterion (1=low risk, 2=intermediate risk and 3=high risk according with the 2015 ESC/ERS PH guidelines) and rounding to the mean of the available variables. In the FPHN registry [8], risk assessment was performed in incident IPAH patients according to the presence of four low-risk criteria: World Health Organization (WHO)/New York Heart Association Functional Class (FC) I or II, 2) 6-min walk distance (6MWD) >440 m, 3) right atrial pressure (RAP) <8 mmHg and 4) cardiac index \( \geq 2.5 \) L\( \cdot \)min\(^{-1}\)\( \cdot \)m\(^{-2} \). Patients were classified according to the number of low-risk criteria present at baseline (i.e. at the time of PAH diagnosis) or at the time of re-evaluation. As exploratory analyses, the additive value of BNP <50 ng\( \cdot \)L\(^{-1} \) or N-terminal pro-BNP (NT-proBNP) <300 ng\( \cdot \)L\(^{-1} \) plasma levels or mixed venous oxygen saturation (\( S_vO_2 \)) >65% as low-risk criteria was assessed in the subsets of patients for whom these data were available.

Recently, the FPHN non-invasive risk assessment strategy using three dichotomised low-risk criteria (FC, 6MWD and NT-proBNP or BNP plasma levels) has been applied to the COMPERA cohort at baseline and at the first follow-up: the authors conclude that the FPHN risk assessment strategy provides a more accurate identification of patients with an excellent long-term survival than the approach of averaging risk scores [9].

Interestingly, the variables with the highest yield in the registry analyses are similar, i.e. FC, 6MWD, NT-proBNP or BNP plasma levels, cardiac index, RAP and \( S_vO_2 \) [6–8]. These variables are appropriate at
both baseline and first follow-up, and the fulfilment of low-risk criteria in three or four parameters represents a clinical response to the treatment that portends a good prognosis [8, 9]. A new risk stratification strategy based on four criteria and using these six variables has recently been proposed [28].

The limitations of the 2015 ESC/ERS PH guidelines risk table are related to the presence of “overlap patients” with prognostic parameters belonging to more than one risk designation [1, 2]. This problem has been addressed in the registry analyses with both the “score and average” method of the SPAHR and COMPERA registries and the “low-risk focused” method of the FPHN study. These methods may prove to be difficult to utilise in clinical practice, particularly for the exact distinction between intermediate- and high-risk status in individual patients. In addition, the simplified approach does not include non-modifiable or partially modifiable prognostic parameters such as age, sex, PAH type and comorbidities (renal insufficiency, diabetes mellitus, coronary artery diseases, etc.).

There are several limitations present in all risk assessment methods, including the retrospective nature of the validating analyses even when applied to prospective observational registries. In addition, data collection was not standardised in all published registries, and significant missing data and numbers of patients lost to follow-up were reported. Other important prognostic variables such as echocardiographic, cardiac magnetic resonance imaging and cardiopulmonary exercise test data were not collected systematically or analysed. Life-threatening complications such as haemoptysis, pulmonary artery aneurismal dilatation with chest organ compression, arrhythmias, etc., are not included in the current risk stratification tools. The exact influence of these parameters on the risk level designation and on the consequent treatment decisions need to be clarified in future and prospective studies. These data should be considered as part of a comprehensive risk assessment strategy which, of course, should also include clinical judgement [29].

**Clinical trials in PAH**

Figure 1 shows the time-course of the 41 RCTs performed in 9061 PAH patients and published so far [30–70]. 21 RCTs tested monotherapy versus placebo, 18 RCTs included patients already treated and tested sequential combination therapy versus background therapy plus placebo, and finally two RCTs enrolled treatment-naive patients and tested initial monotherapy versus initial double combination therapy. The different treatment strategies adopted and compared, and the diverse background therapies of enrolled PAH patients, has allowed evidence to be collected on efficacy and safety for the multiplicity of conditions encountered in clinical practice.

An important evolution in PAH RCT design is the shifting of the primary end-point from a short-term correlate such as 6MWD to a long-term true clinical efficacy measure such as clinical worsening [60, 68, 69] or clinical failure [67]. Interestingly, this change in strategy was recommended by the Task Force on Clinical Trials Design at the 4th WSPH held in Dana Point, CA, USA, in 2008 [71]. This shift has supported an increase in the level of evidence of the efficacy of the tested PAH drugs according with the scale adopted by experts [72, 73].

**FIGURE 1** Time-course of completed randomised controlled trials (RCTs) in pulmonary arterial hypertension (PAH) (n=41) according to treatment strategy. SSc: systemic sclerosis; IPAH: idiopathic PAH. Reproduced and modified from [70] with permission.

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The effect of PAH drugs on mortality was explored in a meta-analysis of 3839 patients enrolled in 25 RCTs testing monotherapy versus placebo in treatment-naive patients and reporting a risk reduction of 44% (p=0.016) in the 14 weeks of the average treatment comparison time [70, 74]. An additional meta-analysis was performed in 4095 patients enrolled in 17 RCTs that compared sequential combination therapy with monotherapy [75]; in this analysis, sequential therapy was associated with a significant risk reduction for clinical worsening (−35%; p<0.0001), but not mortality (−14%; p=0.09). The potential reasons for the lack of apparent mortality benefit include reduced statistical power of this meta-analysis for mortality as well as an overall reduced number of fatal events linked also to a short duration of the treatment comparison period [75].

In summary, based on global experience collected in the RCTs on PAH patients, the following comments can be proposed:

- **In treatment-naive PAH patients, initial monotherapy** is able to improve exercise capacity, haemodynamics and outcome compared with untreated patients [70, 74].
- **In treatment-naive and newly diagnosed (incident) PAH patients, initial combination therapy** is able to improve symptoms, exercise capacity and outcome compared with initial monotherapy [67, 76].
- **In already treated (prevalent) PAH patients, sequential combination therapy** is able to improve exercise capacity, haemodynamics and outcome compared with patients continuing with their background therapy [60, 69, 75].

**General measures and supportive therapy**

No major advances have been reported on general measures and supportive therapy since the publication of the 2015 ESC/ERS PH guidelines, and the recommendations included in the 2015 ESC/ERS PH guidelines Table 16 Recommendations for general measures and Table 17 Recommendations for supportive therapy can be referred to [1, 2]. In particular, oral anticoagulant therapy is not recommended in associated forms of PAH, while in IPAH, heritable PAH (HPAH) and drug-induced PAH the data on efficacy is more conflicting. Therefore, in this subgroup, the decision about anticoagulation has to be made on a case-by-case basis after an individual risk-benefit analysis. The 2015 ESC/ERS PH guidelines suggest that PAH patients should be advised to be active within symptom limits, but to avoid excessive physical exertion if this causes symptoms. Physically deconditioned patients who are stable on targeted medication are also advised to undertake supervised exercise training. Recently, two further RCTs and meta-analyses have been published in this regard, confirming the positive effect of training in PAH [77, 78].

**Treatment algorithm**

The recommended treatment algorithm for PAH patients is shown in figure 2.

The PAH treatment algorithm does not apply to patients in other clinical groups, and in particular it does not apply to patients with PH associated with group 2 (left heart disease) or group 3 (lung diseases). In addition, the different treatments have been evaluated by RCTs mainly in IPAH, HPAH, PAH due to drugs and in PAH associated with connective tissue disease, with Eisenmenger syndrome or with corrected congenital heart disease. The haemodynamic inclusion criteria in the majority of the RCTs were as follows: pulmonary arterial wedge pressure ≤15 mmHg, mean pulmonary arterial pressure ≥25 mmHg and pulmonary vascular resistance ≥3 Wood Units (>5 Wood Units in some RCTs). It is not clear if the efficacy/safety ratio of the PAH drugs is favourable when used in patients not fulfilling the above criteria. There is insufficient evidence to make recommendations in group 5 patients.

Since the release of the 2015 ESC/ERS PH guidelines no new RCTs leading to the approval of new PAH treatments have been published; we refer to the tables of these guidelines for the classes of recommendations and the level of evidence of the approved PAH treatments [1, 2]. In particular, the guidelines tables of interest are: **Table 1 Classes of recommendations, Table 2 Level of evidence, Table 19 Recommendations for efficacy of drug monotherapy, Table 20 Recommendations for efficacy of initial drug combination therapy, Table 21 Recommendations for efficacy of sequential drug combination therapy, and Table 22 recommendations for efficacy of intensive care unit management, balloon atrial septostomy and lung transplantation.** Amendments to these tables are required only for approvals granted by regulatory agencies after the 2015 ESC/ERS PH guidelines as follows: selexipag has been approved by the European Medicines Agency in patients with WHO FC II either as double or triple combination with an ERA and/or a PDE5i, or as monotherapy in patients who are not candidates for these therapies. The 2015 ESC/ERS PH guidelines tables provide the necessary evidence for alternative evidence-based therapeutic strategies recognising that the therapeutic approach to PAH may vary depending on local availability (and expertise) of therapeutic options in various hospitals and clinical settings. In these tables, only the compounds officially approved for PAH or under regulatory approval process in at least one
country are included. A four-level hierarchy for end-points in RCT has been proposed by experts based on level of evidence regarding efficacy [72, 73]. According to this hierarchy, drugs or combination of drugs with outcome as the primary end-point in RCTs or drugs with demonstrated reduction in all-cause mortality (prospectively defined) have been highlighted with a footnote in the 2015 ESC/ERS PH guidelines Tables 19–21.

**Treatment algorithm description**
See the treatment algorithm in figure 2.

**Initial approach**

- After confirmation of the diagnosis of the treatment-naive PAH patient in an expert centre, the suggested initial approach is the adoption of general measures and the initiation of supportive therapy (2015 ESC/ERS PH guidelines Tables 16 and 17).

- **Acute vasoreactivity testing** should be performed to predict response to calcium channel blocker (CCBs) only in patients with IPAH, HPAH, and PAH associated with drugs and toxin use. Vasoreactive patients (see the Task Force article by Simonneau et al. [79] in this issue of the European Respiratory Journal) should be treated with high doses (progressively titrated) of CCBs; adequate response should be confirmed after 3–6 months of treatment (2015 ESC/ERS PH guidelines Table 18). Adequate treatment response to high doses of CCBs is considered WHO FC I/II with sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only. Vasoreactive patients without an adequate treatment response to high doses of CCBs
should be treated with approved PAH medications according to the non-vasoreactive patients’ treatment strategy.

- **Non-responders to acute vasoreactivity testing who are at low or intermediate risk** should be treated with initial oral combination therapy with an ERA and a PDE5i (2015 ESC/ERS PH guidelines Table 20) [76, 80, 81].
- Some specific PAH subsets in which the efficacy/safety ratio of initial combination therapy is not established (table 2) should be treated with initial monotherapy.

**Recommendations for initial monotherapy** are reported in the 2015 ESC/ERS PH guidelines Table 19.

- If initial monotherapy is chosen, as head-to-head comparisons among different compounds are not available, no evidence-based first-line monotherapy can be proposed. The choice of drug may depend on a variety of factors, including approval status, labelling, route of administration, side-effect profile, potential interaction with background therapies, patient preferences, comorbidities, physician experience and cost.
- **In non-vasoreactive and treatment-naive patients at high risk**, initial combination therapy including i.v. PCAs is recommended (2015 ESC/ERS PH guidelines Table 20). Intravenous epoprostenol receives the strongest recommendation as it has reduced the 3-month rate of mortality in high-risk PAH patients also as monotherapy (2015 ESC/ERS PH guidelines Table 19) [82]. Alternative types of initial combination therapy may be considered (2015 ESC/ERS PH guidelines Table 20). Referral for lung transplantation should also be considered.

**Follow-up therapy**

- **When the initial treatment approach results in a low-risk status** within 3–6 months, the therapy should be continued and structured follow-up established (2015 ESC/ERS PH guidelines Table 14).
- **When the initial treatment approach results in an intermediate-risk status**, escalation to triple combination therapy is recommended according to the 2015 ESC/ERS PH guidelines Table 21 or to double combination in case monotherapy has been chosen. The combinations of macitentan and sildenafil [60], riociguat and bosentan [61], and selexipag and ERA and/or PDE5i [69] have the highest recommendation and evidence. PCAs should also be considered. The combination of riociguat and PDE5i is contraindicated [62]. Referral for lung transplantation should also be considered.
- **When the initial treatment approach results in a high-risk status**, maximal medical therapy including i.v. PCAs is recommended (2015 ESC/ERS PH guidelines Table 20). Referral for lung transplantation should also be considered.
- **When the second treatment step results in the low-risk status** within 3–6 months, the therapy should be continued and structured follow-up continued (2015 ESC/ERS PH guidelines Table 14). Referral for lung transplantation should also be considered according to local rules for organ allocation and average waiting time in the list.
- **When the second treatment step results in an intermediate- or high-risk status**, escalation to maximal medical therapy is recommended according to the 2015 ESC/ERS PH guidelines Table 21. Maximal medical therapy is considered to be triple combination therapy including a s.c. or an i.v. PCA (i.v. preferred in high-risk status). For patients on intermediate-risk status on double combination therapy with an ERA and a PDE5i or riociguat, the addition of selexipag should be considered [69]. For

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**TABLE 2 Potential role for initial monotherapy in specific pulmonary arterial hypertension (PAH) subsets**

| IPAH, HPAH and drug-induced PAH patient responders to acute vasoreactivity tests and with WHO FC I/II and sustained haemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only |
| Long-term-treated historical PAH patients with monotherapy (>5–10 years) stable with low-risk profile |
| PAH patients >75 years old with multiple risk factors for heart failure with preserved LVEF (high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, obesity) |
| PAH patients with suspicion or high probability of pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis |
| Patients with PAH associated with HIV infection or portal hypertension or uncorrected congenital heart disease, as they were not included in RCTs of initial combination therapy |
| PAH patients with very mild disease (e.g. WHO FC I, PVR 3–4 WU, mPAP <30 mmHg, normal right ventricle at echocardiography) |
| Combination therapy unavailable or contraindicated (e.g. severe liver disease) |

IPAH: idiopathic PAH; HPAH: heritable PAH; CCB: calcium channel blocker; PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance; LVEF: left ventricular ejection fraction; RCT: randomised controlled trial; WHO: World Health Organization; FC: Functional Class; WU: Wood Units; mPAP: mean PAP.
patients on triple combination therapy including selexipag who remain in the intermediate-risk group or progress to high risk, the substitution with s.c. or i.v. PCAs should be considered. Referral for lung transplantation should also be considered.

- **Patients on follow-up with low-risk status who deteriorate** to the intermediate- or high-risk group should be treated with double, triple or maximal combination therapy depending on the initial background treatment.

- We recommend consideration of lung transplantation in all patients on maximal triple combination therapy, with priority for those in intermediate- and high-risk groups, in accordance with local rules for organ allocation and average waiting time in the list (2015 ESC/ERS PH guidelines Table 22) (see the Task Force article by Hoepfer et al. [83] in this issue of the *European Respiratory Journal*).

- Advanced treatments for patients in severe right ventricular failure who are admitted to intensive care units are reported by Hoepfer et al. [83].

- Balloon atrial septostomy should be regarded as a palliative or bridging procedure in patients deteriorating despite maximal medical therapy.

### Transitions of PAH therapies

Clinicians might consider transitioning from one PAH-specific therapy to another for a number of reasons, including improvement of the side-effect profile and convenience or compliance with therapy. In patients who are not meeting treatment goals, transitions are considered to escalate therapy and improve patient status. Occasionally, patients have an extraordinary response to therapy and transition to a less invasive therapy is considered. As much of the literature on this topic is retrospective, prospective but observational or prospective randomised but open label, we do not recommend this approach except in rare circumstances and under close expert care. One study showed that, in carefully selected patients, the transition from *i.v.* epoprostenol to *i.v.* treprostinil was achievable around 80% of the time [84]. Transition from parenteral epoprostenol to the thermostable form was generally achievable [84].

There have been conflicting outcomes in the transition from parenteral prostacyclins to inhaled or oral prostacyclins [84]. When discontinuation of bosentan is necessary due to liver function test elevations, transitioning to ambrisentan [85] or macitentan is safe.

In case of lack of efficacy, transition from selexipag or non-parenteral PCAs to *s.c.* or *i.v.* PCAs is recommended.

There is insufficient evidence to recommend transition from sildenafil or tadalafil to riociguat for improving efficacy [86]. An additional open-label, randomised study is currently ongoing on this issue (ClinicalTrials.gov identifier NCT02891850).

### PAH complications

PAH-related hospitalisations which are usually associated with different types of complications are predictive of mortality in *post hoc* analyses of the SERAPHIN and GRIPHON studies [87]. Recommendations for the diagnosis and treatment of arrhythmias, haemoptysis and mechanical complications related to the dilatation of the pulmonary artery are already reported in the 2015 ESC/ERS PH guidelines [1, 2]. Recently, a study has reported a large series of PAH patients with angina or angina-like symptoms who underwent percutaneous coronary interventions with stenting due to severe left main coronary artery stenosis by extrinsic compression from a dilated pulmonary artery [88]. The favourable acute and long-term results of this procedure suggest increased awareness for this important and potentially catastrophic complication.

### Conclusions

Assessment of the severity of the newly diagnosed PAH patient by a multiparametric risk stratification approach is utilised for defining a low-, intermediate- or high-risk status. According to the risk status, the multiple drugs approved for PAH, interfering with the endothelin, NO and prostacyclin pathways, can be utilised with different strategies including monotherapy or combination therapies. Further treatment escalation is required in case low-risk status is not achieved in planned follow-up assessments. Low-risk patients should continue with the chosen therapy and be assessed accurately in a structured follow-up to timely identify possible deteriorations. Triple combination therapy and lung transplantation may be required in most advanced cases.

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References


Intensive care, right ventricular support and lung transplantation in patients with pulmonary hypertension

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Abstract Intensive care of patients with pulmonary hypertension (PH) and right-sided heart failure includes treatment of factors causing or contributing to heart failure, careful fluid management, and strategies to reduce ventricular afterload and improve cardiac function. Extracorporeal membrane oxygenation (ECMO) should be considered in distinct situations, especially in candidates for lung transplantation (bridge to transplant) or, occasionally, in patients with a reversible cause of right-sided heart failure (bridge to recovery). ECMO should not be used in patients with end-stage disease without a realistic chance for recovery or for transplantation. For patients with refractory disease, lung transplantation remains an important treatment option. Patients should be referred to a transplant centre when they remain in an intermediate- or high-risk category despite receiving optimised pulmonary arterial hypertension therapy. Meticulous peri-operative management including the intra-operative and post-operative use of ECMO effectively prevents graft failure. In experienced centres, the 1-year survival rates after lung transplantation for PH now exceed 90%.

@ERSpublications
State of the art and research perspectives on the ICU management of patients with pulmonary hypertension and right heart failure, the timing of transplant referral, and the use of extracorporeal life support http://ow.ly/pISA30mfQk4


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Introduction
The present article addresses the management of patients with advanced pulmonary hypertension (PH) or pulmonary arterial hypertension (PAH) and right-sided heart failure, focusing on intensive care, use of extracorporeal life support (ECLS) and lung transplantation. Other causes of right-sided heart failure as seen for instance in patients with acute pulmonary embolism, right ventricular infarction or right-sided heart failure secondary to left-sided heart failure will not be discussed here.

The following definitions of right-sided heart failure will be used:

1) Right-sided heart failure is characterised by low cardiac output and/or elevated right-sided filling pressures due to systolic and/or diastolic right ventricular dysfunction.
2) Right-sided heart failure is severe if it leads to secondary dysfunction of other organs and tissues, in particular liver, kidneys and gut.

This article addresses topics where robust data from large clinical trials are not available. Hence, most of the statements and recommendations are based on clinical experience and expert consensus rather than scientific evidence.

Pathophysiology of right-sided heart failure
The pathophysiology of right-sided heart failure has been described in depth elsewhere [1–3]. Here, only a couple of points will be highlighted that are considered of importance for treatment considerations.

Like left-sided heart failure, right-sided heart failure may present as isolated systolic heart failure or isolated diastolic heart failure; however, combined forms are frequently encountered in patients requiring treatment on the intensive care unit (ICU). Systolic right-sided heart failure results in left ventricular underfilling and low cardiac output, which impairs tissue perfusion and oxygenation. Diastolic right-sided heart failure results in elevated systemic venous pressure with detrimental consequences for tissue perfusion and oxygenation as well.

With increasing afterload, the right ventricle remodels, i.e. hypertrophies and eventually dilates, developing a spherical shape accompanied by increased right ventricular wall stress, impaired myocardial contractility and progressive tricuspid regurgitation, which further reduces effective cardiac output. Ventricular interdependence results in impaired left ventricular filling and function.

Severe right-sided heart failure affects all organ systems; in the ICU setting, the consequences for the liver, kidneys and gut are often most relevant. Several lines of evidence suggest that elevated venous pressures with chronic congestion are particularly damaging to these organs [4–9]. Malperfusion and congestion alter bowel wall permeability, and may cause translocation of bacteria and endotoxins from the bowel into the circulation resulting in a systemic inflammatory response or sepsis [4, 10, 11], which are common contributors to death in patients with right-sided heart failure [12].

Symptoms and signs of right-sided heart failure
Symptoms and signs of low cardiac output failure can be subtle. Tachycardia is often present, while systemic hypotension usually develops only at advanced stages. The skin may have a pale appearance; cyanosis may be present but is not obligate. Patients frequently complain about fatigue and appear tired. Agitation may be present as well and may signal imminent death. The clinical signs of right-sided backward failure such as prominent and pulsating jugular veins, ascites, and oedema are usually obvious.

Principles of ICU monitoring of patients with right-sided heart failure
ICU monitoring of patients with PH/PAH and right-sided heart failure should focus on cardiac function and the function of other organs (table 1).

In patients requiring ICU treatment, monitoring of cardiac function is essential. Right heart catheterisation, preferably with continuous cardiac output measurement, is not always necessary, but should be considered in severe and complex cases. Other tools to measure cardiac output should be considered as well.

Insertion of a central venous line is considered mandatory in patients requiring ICU treatment for right-sided heart failure. Central venous pressure measurement, which has been abandoned in most ICU patients due to poor correlation with fluid status, is pivotal in patients with right ventricular failure to determine right-sided filling pressures, keeping in mind the detrimental effects of elevated filling pressures (see earlier). In addition, central venous oxygen saturation ($SvO_2$) measurements are important to determine tissue oxygenation as $SvO_2$ correlates with cardiac output [13].

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Recommendations for ICU monitoring of patients with PH and severe right-sided heart failure

- ICU monitoring of patients with severe right-sided heart failure should include regular measurements of central venous pressure and $S_{cvO_2}$.
- Key warning signs of imminent death in patients with right-sided heart failure are a decline in $S_{cvO_2}$ accompanied by an increase in lactate and a decline in urine output.
- The use of right heart catheterisation or other devices to monitor haemodynamics and cardiac output should be considered in patients with severe right-sided heart failure and in complex situations.

ICU treatment of severe right-sided heart failure

Patients with severe right-sided heart failure require comprehensive care including treatment of factors causing or contributing to heart failure, fluid management and strategies to improve cardiac function (figure 1). If possible, such patients should be treated at expert centres capable of providing all treatment options, i.e. medical therapy, ECLS and lung transplantation. Interhospital transfer must be considered on an individual basis. Some centres provide mobile units facilitating interhospital transfer with ECLS [14].

Treatable precipitants of right-sided heart failure include infection, anaemia, thyroid dysfunction, pulmonary embolism, arrhythmia or non-adherence to prescribed medications. Supraventricular tachyarrhythmias, especially atrial flutter and atrial fibrillation, are common causes of right-sided heart failure in patients with severe PH [15] and rapid restoration of sinus rhythm should be attempted in such cases. Infection is another important contributor to death in patients with right-sided heart failure. If the source of infection is not obvious, broad-spectrum antibiotics should be considered bearing in mind that translocation from the bowel is a frequent cause of systemic inflammation and sepsis in patients with right-sided heart failure [10, 11].

Supplementary oxygen should be administered as needed to maintain peripheral oxygen saturations $>$90%. Hypercapnic patients may benefit from non-invasive ventilation [16], although caution is necessary as even non-invasive ventilation may further impair right ventricular function [17]. Whenever possible, intubation and invasive mechanical ventilation should be avoided in patients with severe right heart failure, as the induction of general anaesthesia together with a further increase in right ventricular afterload carries a high risk of death in these patients. If intubation is unavoidable, maintaining a stable blood pressure is of key importance.

Fluid management is often critical in patients with right-sided heart failure. It is a common reflex among intensivists to administer fluids to patients with hypotension or shock. Only rarely are patients with right-sided heart failure fluid-depleted as well. Most of these patients have markedly elevated right-sided filling pressures and a low cardiac output. In these patients, fluid administration may further increase right-sided filling pressures and chamber dimensions, thereby aggravating the shift of the interventricular septum to the left and increasing tricuspid regurgitation [18], all resulting in further deterioration of left...

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TABLE 1 Intensive care unit (ICU) monitoring of patients with right-sided heart failure

<table>
<thead>
<tr>
<th>Tools</th>
<th>Information provided</th>
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<tbody>
<tr>
<td><strong>Basic ICU monitoring</strong></td>
<td>Heart rate and rhythm</td>
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<tr>
<td></td>
<td>Blood pressure [non-invasive or invasive]</td>
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<td></td>
<td>Body temperature</td>
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<td>Peripheral oxygen saturation or arterial blood gases</td>
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<td>Urine output, changes in body weight</td>
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<td><strong>Central venous catheter</strong></td>
<td>Central venous pressure</td>
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<td>Central venous oxygen saturation</td>
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<td><strong>Laboratory values</strong></td>
<td>Cardiac biomarkers (N-terminal pro-brain natriuretic peptide/brain natriuretic peptide, troponin)</td>
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<tr>
<td></td>
<td>Electrolytes and renal function [estimated glomerular filtration rate, blood urea nitrogen, uric acid]</td>
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<td></td>
<td>Liver function [aminotransferases, bilirubin]</td>
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<td>Inflammation/infection [C-reactive protein, procalcitonin]</td>
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<td>Tissue damage or hypoxia [blood gases, lactate]</td>
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<tr>
<td><strong>Echocardiography</strong></td>
<td>Right and left ventricle function, valve function, pericardial effusion</td>
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<td></td>
<td>Rule out other conditions mimicking right ventricular failure, such as pericardial tamponade</td>
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<tr>
<td><strong>Right heart catheterisation</strong></td>
<td>Comprehensive haemodynamic assessment</td>
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<td>(facultative)</td>
<td>To be considered in severe or complex situations</td>
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https://doi.org/10.1183/13993003.01906-2018
ventricular filling and function, as illustrated in figure 2. In such patients, a negative fluid balance should be sought by using i.v. loop diuretics or even haemofiltration [19].

To reduce right ventricular afterload, all drugs approved for PAH may be considered in patients presenting with severe right-sided heart failure. Intravenous prostacyclin analogues (PCAs) are usually preferred because of their efficacy and a rapid onset of action. Initial triple combination therapy consisting of i.v. epoprostenol, oral phosphodiesterase type 5 inhibitors and endothelin receptor antagonists in patients with newly diagnosed PAH and right-sided heart failure has been reported with excellent short-term and mid-term results [20].

Patients with low cardiac output may initially require the use of inotropes, with dobutamine and milrinone being the most widely used agents in this setting. In animal models of right-sided heart failure, levosimendan appears more effective than dobutamine [21, 22], but reliable clinical data are lacking. Patients with a low systemic vascular resistance may need additional vasopressor treatment. Norepinephrine and vasopressin are the preferred agents. Vasopressin may be advantageous as it has pulmonary vasodilator effects [23, 24], but the clinical relevance of this property is unknown (table 2).

Recommendations for ICU treatment of patients with severe right-sided heart failure

- Patients with PAH or other forms of severe PH with right-sided heart failure requiring ICU therapy should be treated at expert centres capable of providing all treatment options, i.e. medical therapy, ECLS and advanced treatment including lung transplantation, if possible.

![FIGURE 1 Therapeutic approach to patients with severe right-sided heart failure. RV: right ventricular; PAH: pulmonary arterial hypertension; NO: nitric oxide; ECMO: extracorporeal membrane oxygenation; ECLS: extracorporeal lung support. Reproduced and modified from [80] with permission.](https://doi.org/10.1183/13993003.01906-2018)

![FIGURE 2 Effects on volume changes on cardiac function in right-sided heart failure. RV: right ventricle; LV: left ventricle; RVEDP: right ventricular end-diastolic pressure; TR: tricuspid regurgitation; CO: cardiac output. Reproduced and modified from [80] with permission.](https://doi.org/10.1183/13993003.01906-2018)
Interhospital transfer should be considered on an individual basis. Some centres provide mobile units facilitating interhospital transfer with ECLS.

ICU treatment of patients with right-sided heart failure should include treatment of underlying causes and comorbidities, supportive measures, meticulous fluid management, reduction of right ventricular afterload with drugs approved for PAH, and an individualised use of inotropes and vasopressors.

Mechanical support of the right heart
In patients with right-sided heart failure refractory to treatment, mechanical support should be considered in certain situations, i.e. in candidates for lung transplantation (bridge to transplant) and, occasionally, in patients with a treatable cause of right-sided heart failure or in hitherto treatment-naive patients (bridge to recovery).

Technical principles and features of mechanical right ventricular support
There are various devices and device configurations to support the right ventricle, and the list is constantly growing [25, 26]. At present, the most widely used techniques are peripheral veno-arterial extracorporeal membrane oxygenation (ECMO) and pumpless membrane oxygenators inserted between the pulmonary artery and the pulmonary veins or left atrium (PA-LA).

Peripheral ECMO support is usually established via the femoral vessels but upper body approaches have been used as well, the latter mostly to enable ambulation, which is not possible with lower body cannulation. The veno-arterial configuration ensures rapid and effective unloading of the right ventricle [27]. With residual pulmonary blood flow, an ECMO blood flow of 2.5–4 L·min⁻¹ is usually adequate to maintain sufficient perfusion of the entire organism, while effectively unloading the right ventricle and avoiding an unnecessary increase in left ventricular afterload. Still, this configuration is characterised by opposing blood flows in the aorta, one coming from the left ventricle, the other from the ECMO system. The area where these two blood flows meet is called the ECMO watershed, which is clinically relevant mostly for differential oxygenation [28]. In patients with femoral veno-arterial ECMO support, the lower body is supplied by blood originating from the ECMO and the upper body by blood coming from the heart. The location of the watershed is variable, and depends on the respective pressures and flows in the two circuits. While lower body oxygenation is safely maintained by ECMO, upper body oxygenation can be impaired when the blood coming from the left heart carries a low oxygen content. This affects predominantly the brain and the heart itself. While brain oxygenation can be indirectly monitored by right forearm oxygenation, it is usually not possible to measure the oxygen content in the aortic bulb and the coronary arteries. Hence, monitoring of cardiac function by regular troponin measurements and echocardiography is mandatory.

With the PA-LA approach, a membrane oxygenator is placed between the pulmonary artery and the left atrium. In patients with PH, a pump is usually not required, at least when low-resistance membranes are being used [29, 30]. PA-LA insertion is more complex than ECMO support as it requires surgery via

### TABLE 2 Inotropes and vasopressors in clinical use to treat advanced right heart failure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cardiac output</th>
<th>PVR</th>
<th>SVR</th>
<th>Tachycardia/ arrhythmia</th>
<th>Pre-clinical studies</th>
<th>Clinical studies/ experience</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inotropes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dobutamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 µg·kg⁻¹·min⁻¹</td>
<td>↑</td>
<td>\</td>
<td>\</td>
<td>→ or \</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>5–15 µg·kg⁻¹·min⁻¹</td>
<td>↑↑</td>
<td>→</td>
<td>\</td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5–5 µg·kg⁻¹·min⁻¹</td>
<td>↑</td>
<td>\</td>
<td>↑↑</td>
<td>↑</td>
<td>++</td>
<td>+/−</td>
</tr>
<tr>
<td>&gt;5 µg·kg⁻¹·min⁻¹</td>
<td>↑</td>
<td>\</td>
<td>↑↑</td>
<td>↑</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>↑↑</td>
<td>\</td>
<td>\</td>
<td>\</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>↑↑</td>
<td>\</td>
<td>\</td>
<td>\</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑↑</td>
<td>\</td>
<td>\</td>
<td>\</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><strong>Vasopressors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>↑</td>
<td>or ↑</td>
<td>↑↑</td>
<td>↑</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Vasopressin (low doses)</td>
<td>→ or ↑</td>
<td>\</td>
<td>↑↑</td>
<td>↑</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>

PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; PH: pulmonary hypertension; PAH: pulmonary arterial hypertension.

- Interhospital transfer should be considered on an individual basis. Some centres provide mobile units facilitating interhospital transfer with ECLS.
- ICU treatment of patients with right-sided heart failure should include treatment of underlying causes and comorbidities, supportive measures, meticulous fluid management, reduction of right ventricular afterload with drugs approved for PAH, and an individualised use of inotropes and vasopressors.
sternotomy or antero-lateral thoracotomy. In addition, patients with advanced right-sided heart failure often need temporary ECMO support prior to anaesthesia. The main advantages of the PA-LA approach are that 1) ambulation is feasible, 2) oxygen-enriched blood enters the left ventricle and thereby the entire systemic circulation, and 3) the pre-load of the left ventricle is increased, which helps “priming” for the haemodynamic situation after transplantation (see later).

**Right ventricular assist devices**

There are sporadic reports on isolated right ventricular assist device (RVAD) support in PAH [31]. However, successful long-term use of RVADs in patients with PAH has not yet been reported. The role of this intervention is limited given the pathophysiology of PAH, which may include aggravation of pulmonary vascular remodelling, risk of pulmonary bleeding and induction of pulmonary oedema in patients with left ventricular diastolic dysfunction [32–34]. For these reasons, isolated RVAD support should be used with utmost care or not at all in these patients. Smaller-sized devices with good ability to control the pump flow in the pulmonary circulation may open new options in the future [35].

**Indications for mechanical support of the right ventricle**

The only established option for the use of ECLS in patients with PH and right-sided heart failure is bridge to transplantation (table 3) [36, 37]. Hence, ECLS should be considered 1) if conventional treatment strategies fail in patients who 2) have already been fully evaluated for lung transplantation, who 3) have a realistic chance of receiving a donor organ in a reasonable time frame and who 4) can still be expected to have a good outcome after transplantation [26]. If possible, ECMO should preferably be used in awake, non-intubated and spontaneously breathing patients, not only to avoid the risks and complications associated with general anaesthesia and intubation in patients with right-sided heart failure, but also to prevent the negative consequences of mechanical ventilation, such as ventilator-associated pneumonia, muscular deconditioning and critical care illness. The awake ECMO strategy has proven feasible, even with bridging times of several weeks [38], and has been associated with better outcomes than historical bridging strategies that included intubation and mechanical ventilation [14, 39, 40].

The use of ECLS in patients who have not been evaluated for transplantation should be avoided unless there is a reasonable perspective for recovery. This may be the case in previously stable patients with a reversible cause of right-sided heart failure (e.g. arrhythmia or infection) or in hitherto untreated or undertreated patients with newly diagnosed PAH. Case reports demonstrating success of this approach are, however, rare [14, 41].

<table>
<thead>
<tr>
<th>First author [ref.]</th>
<th>Patients who received ECMO support</th>
<th>Patients bridged to transplant</th>
<th>Patients discharged from hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>DE PERROT [30]</td>
<td>6 (4 PA-LA, 2 VA ECMO)</td>
<td>6/6 (100%)</td>
<td>4/6 (66%)</td>
</tr>
<tr>
<td>FUEHNER [39]</td>
<td>7 (all VA ECMO)</td>
<td>6/7 (86%)</td>
<td>5/6 (71%)</td>
</tr>
<tr>
<td>HOOPES [73]</td>
<td>5 (all VA ECMO)</td>
<td>5/5 (100%)</td>
<td>4/5 (80%)</td>
</tr>
<tr>
<td>LANG [74]</td>
<td>4 (all VA ECMO)</td>
<td>4/4 (100%)</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>ROSENWEIG [41]</td>
<td>6 (all VA ECMO)</td>
<td>2/2 (100%); 4 received ECMO as bridge to recovery</td>
<td>2/2 (100%); 1/4 (25%) bridge to recovery patients survived for &gt;2 months</td>
</tr>
<tr>
<td>SHAIFI [75]</td>
<td>3 (all VA ECMO)</td>
<td>2/3 (66%)</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>CROTTI [76]</td>
<td>4 [3 VA ECMO, 1 VV ECMO]</td>
<td>4/4 (100%)</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>HOETZENECKER [77]</td>
<td>13 (9 PA-LA, 4 VA ECMO)</td>
<td>11/13 (85%)</td>
<td>7/11 (63%) survived at 1 year</td>
</tr>
<tr>
<td>SAVALE [56]</td>
<td>13 (all VA ECMO)</td>
<td>13/13 (100%)</td>
<td>8/13 (62%)</td>
</tr>
<tr>
<td>DELGREN [78]</td>
<td>2 [both VA ECMO]</td>
<td>2/2 (100%)</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>GLORION [79]</td>
<td>18 [13 VA ECMO, 3 VV ECMO, 2 PA-LA]</td>
<td>17/18 (94%)</td>
<td>15/17 (88%)</td>
</tr>
<tr>
<td>Total</td>
<td>81 (66 ECMO, 15 PA-LA); 77 as bridge to transplant</td>
<td>72/77 (94%)</td>
<td>56/72 (78%)</td>
</tr>
</tbody>
</table>

ECMO: extracorporeal membrane oxygenation; PA-LA: pulmonary artery to left atrium device; VA: veno-arterial; VV: veno-venous.
Recommendations for the use of ECLS in patients with PH and right-sided heart failure

Indications and contraindications

- Established indication: bridge to transplant in patients who have been fully evaluated and accepted for this procedure.
- Potential indications in highly selected cases:
  - bridge to transplant decision in potentially eligible patients who have not yet been fully evaluated;
  - bridge to recovery in patients with untreated or undertreated PAH, or in patients with a reversible cause of right ventricular failure.
- Contraindication: end-stage disease without a realistic chance for recovery or successful transplantation (futility).

Choice of ECLS

- Veno-arterial ECMO and the PA-LA approach are currently the only established right ventricular support strategies, but there is rapid evolution in device technologies.
- At present, veno-arterial ECMO is the most widely used ECLS strategy.
- The PA-LA approach should be considered if the expected ECLS time is of longer duration or in children with small femoral arteries.
- The choice of ECLS depends largely on centre experience.

Timing of ECLS

- All forms of ECLS are associated with potentially life-threatening complications; hence, ECLS should be used only when less invasive treatment options have been exhausted.
- ECLS should be initiated when the clinical course suggests that terminal right heart failure and/or secondary organ failure is imminent despite optimised medical therapy.
- ECLS initiated in patients with advanced PH/PAH undergoing cardiopulmonary resuscitation for right-sided heart failure will rarely result in good outcomes.

ECLS and lung transplantation

- ECLS is now an established strategy to bridge patients with right heart failure to lung transplantation.
- Centres performing lung transplantation in patients with PAH should have an established ECLS programme.

Lung transplantation

The modern era of successful lung and heart–lung transplantation started in the early 1980s with patients suffering from PH [42]. Today, due to the introduction of effective therapies for PAH and chronic thromboembolic PH, lung transplantation is performed less frequently in patients with severe PH, but remains an important treatment option for patients with refractory disease.

When to refer and when to list patients for lung transplantation

Referral to a transplant centre

General recommendations for the selection of lung transplant candidates have been published elsewhere [37]. In patients with PAH, referral to a lung transplant centre should be considered early, i.e. whenever patients display an inadequate response to treatment and are not at low risk of death despite receiving oral combination therapy (table 4). Early transplant referral is also recommended in patients who are suspected to suffer from disease variants responding poorly to medical therapy, such as pulmonary veno-occlusive disease. An early referral strategy ensures that patients have time to consider lung transplantation with all its consequences, and that centres can fully evaluate potential candidates and optimise their pre-transplant condition. In reality, patients with PAH are often referred in an advanced disease state or when they are rapidly deteriorating, which may prohibit a careful evaluation, thereby exposing them to unnecessary risks and sometimes effectively depriving them of a chance of receiving a donor organ. Early referral for transplant evaluation does not mean that patients are necessarily listed right away; a completed evaluation just allows optimal timing and rapid listing in case of clinical deterioration.

Listing patients for lung transplantation

Patients suffering from PAH should be listed for lung transplantation when they present with a high risk of death despite optimised medical therapy, which usually consists of combination therapy including s.c.
or i.v. PCAs (table 4). According to the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) PH guidelines [43, 44], patients are classified as high risk when the estimated 1-year mortality exceeds 10%. Registry data suggest that the 1-year mortality rate of these patients is in fact >20% [45, 46]. Thus, utilising risk stratification tools or scores (i.e. REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) score $\geq 10$) [47]) that denote high-risk individuals may be particularly useful in deciding when to refer a patient for evaluation. Since the 1-year mortality after lung transplantation for severe PH in experienced centres is currently around 10% [48, 49], a survival benefit can be expected for such patients.

Patients listed for lung transplantation benefit from pre-transplant rehabilitation programmes [50].

With the introduction of the lung allocation score (LAS), waiting list mortality has decreased and the odds of receiving a donor organ have increased for most major lung diseases, including PAH [51, 52]. Still, the LAS does not always adequately reflect disease severity in patients suffering from PAH [53]. In a multivariable analysis comparing mortality predicted by the LAS system to actual mortality in REVEAL, two additional variables were independently associated with increased mortality compared with the LAS: mean right atrial pressure $\geq 14$ mmHg and 6-min walk distance $\leq 300$ m [54]. These two factors, in addition to total bilirubin and cardiac index, were added to a modified LAS, released in February 2015 [55], which also reweighted weight, list urgency and post-transplant outcomes in favour of PAH. The effect of these changes on outcome should be forthcoming in the next several years.

In some countries, an "exceptional LAS" can be obtained for patients with severe PH [56]. Some other countries not using the LAS have successfully implemented high-priority programmes for these patients [57].

### Transplant procedure, post-transplant care and outcomes

Major progress has been made over the past years in lung transplantation for PAH. One of the most important innovations was the use of ECMO support during and after transplantation [58]. Meanwhile, the intra-operative use of ECMO has almost completely replaced the use of conventional cardiopulmonary bypass as it has been associated with a reduction of peri-operative complications including renal failure, a reduced need for transfusions of blood products and (in some, but not all, series) with better survival [49, 59–63]. In patients with PH and right-sided heart failure undergoing transplantation, veno-arterial ECMO is occasionally established prior to general anaesthesia to avoid haemodynamic instability.

A better understanding of the pathophysiological changes after transplantation for PH with adaptation of therapeutic strategies (e.g. achieving a negative fluid balance including use of haemofiltration when necessary and extended ECMO support) has substantially reduced the occurrence of early graft dysfunction, which was the major obstacle of post-transplant survival in these patients and the main reason why the early post-operative mortality was historically higher in patients undergoing lung transplantation for PAH than for most other end-stage lung diseases [64].

---

| **Referral** | Potentially eligible patients for whom lung transplantation might be an option in case of treatment failure  
ESC/ERS intermediate or high risk or REVEAL risk score $>7$ on appropriate PAH medication  
Progressive disease or recent hospitalisation for worsening of PAH  
Need for i.v. or s.c. prostacyclin therapy  
Known or suspected high-risk variants such as PVOD or PCH, scleroderma, large and progressive pulmonary artery aneurysms  
Signs of secondary liver or kidney dysfunction due to PAH or other potentially life-threatening complications such as recurrent haemoptysis |
|---|---|
| **Listing** | Patient has been fully evaluated and prepared for transplantation  
ESC/ERS high risk or REVEAL risk score $>10$ on appropriate PAH medication, usually including i.v. or s.c. prostacyclin analogues  
Progressive hypoxaemia, especially in patients with PVOD or PCH  
Progressive, but not end-stage, liver or kidney dysfunction due to PAH or life-threatening haemoptysis |

ESC: European Society of Cardiology; ERS: European Respiratory Society; REVEAL: Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis.
As already reported in 1999 [65], the main cause of primary graft dysfunction in these patients was not residual PH, but left ventricular failure [33]. However, the notion that the small and “unconditioned” left ventricles of patients with severe PH are prone to developing diastolic dysfunction when exposed to a normal or high pre-load after transplantation only recently came into a wider focus of interest [32, 33, 48]. Left ventricular dysfunction results in elevated left-sided filling pressures and pulmonary oedema, which tends to worsen whenever patients are awake and agitated. In the past, this has frequently led to a vicious cycle making it difficult, and sometimes impossible, to wean patients from the ventilator, thereby exposing them to the risks associated with prolonged mechanical ventilation and intensive care. To overcome this problem, several centres over many years have used combined heart and lung transplantation for patients with severe PH [66, 67]. Today, however, the post-operative prolongation of veno-arterial ECMO after transplantation effectively prevents primary graft dysfunction [48, 68]. Two different approaches have been described: 1) prolongation of ECMO with extubation first and continuation of ECMO support for 3–7 days [48] or 2) brief post-operative prolongation of ECMO in intubated patients until stabilisation of haemodynamics and normalisation of fluid balance followed by a few days of ventilation [49]. For both strategies, 1-year survival rates >90% have been reported [48, 49]. There is now consensus among experts that bilateral lung transplantation is the procedure of choice for most patients with PAH. Of note, almost any right ventricle recovers within a few weeks after transplantation, regardless of the degree of pre-transplant dilatation and dysfunction, and regardless of the severity of pre-operative tricuspid regurgitation [69–71].

Recommendations for lung transplantation in patients with PH/PAH

- Repeated risk assessment is pivotal to identify the appropriate time for initiating transplant evaluation.
- Established and validated risk prediction tools such as the REVEAL risk score or the ESC/ERS risk prediction strategy should be applied in patients with PAH to determine timing for referral to a transplant centre.
- Potentially eligible candidates should be referred for lung transplantation evaluation early, i.e. when they have an inadequate response to oral combination therapy, indicated by an intermediate or high risk according to the ESC/ERS risk stratification strategy or by a REVEAL risk score >7.
- Listing for lung transplantation should be considered in patients who present with a high risk of death according to the ESC/ERS risk stratification strategy or by a REVEAL risk score ≥10 despite receiving optimised medical therapy including s.c. or i.v. PCAs, as the expected mortality on medical therapy exceeds the expected mortality after bilateral lung transplantation. Depending on local circumstances, listing of patients at intermediate risk might be appropriate in some countries.
- Timing of listing must depend on expected local waiting time.
- Bilateral lung transplantation is the method of choice in patients with PH.
- There is no degree of right ventricular dysfunction that precludes bilateral lung transplantation in patients with PAH.
- Despite advances in ICU management and ECLS, the ideal recipient is an ambulant outpatient.
- Extended use of ECMO support should be considered after lung transplantation in patients with PH to prevent early graft dysfunction.
- Given the low number and high risk of lung transplants performed for PAH worldwide, this procedure should be concentrated in specialised centres.

Ethical considerations
Despite therapeutic progress, PAH remains a chronic, incurable and often fatal disease. Advanced ICU treatment including the use of ECLS is warranted whenever there is a clear treatment objective, be it recovery or transplantation. However, if these treatment goals are not realistically achievable, advanced intensive care will be futile and should be replaced by best supportive care, as should be the case in all patients who have reached the end of their life. It is important to consider the patient’s preferences whenever possible and to proactively discuss end-of-life matters early on. Still, patients may change their perspectives once they are no longer in a stable situation but face imminent death.

Future perspectives
In the foreseeable future, PAH will remain an incurable, chronic and progressive disease. Reverse remodelling of the pulmonary vasculopathy is a main target of ongoing research, but success in human disease has been limited so far [72]. Hence, future studies should aim at developing new drugs to affect the disease itself, but also at developing new means to support the failing right ventricle. The development of (awake) ECMO as a bridge to transplantation has been a first step. Future devices will allow an extended use of extracorporeal or intracorporeal support systems, even in outpatients, like the use of left ventricular assist devices in patients with left-sided heart failure. It is impossible to foresee if or when such devices
may obviate the need for lung transplantation. For the time being, lung transplantation remains an important treatment option for patients with otherwise refractory PAH.

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References


Clinical trial design and new therapies for pulmonary arterial hypertension

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State of the art and research perspectives in clinical trial design and new therapies for pulmonary arterial hypertension http://ow.ly/VHQ030mfRxc


ABSTRACT Until 20 years ago the treatment of pulmonary arterial hypertension (PAH) was based on case reports and small series, and was largely ineffectual. As a deeper understanding of the pathogenesis and pathophysiology of PAH evolved over the subsequent two decades, coupled with epidemiological studies defining the clinical and demographic characteristics of the condition, a renewed interest in treatment development emerged through collaborations between international experts, industry and regulatory agencies. These efforts led to the performance of robust, high-quality clinical trials of novel therapies that targeted putative pathogenic pathways, leading to the approval of more than 10 novel therapies that have beneficially impacted both the quality and duration of life. However, our understanding of PAH remains incomplete and there is no cure. Accordingly, efforts are now focused on identifying novel pathogenic pathways that may be targeted, and applying more rigorous clinical trial designs to better define the efficacy of these new potential treatments and their role in the management scheme. This article, prepared by a Task Force comprised of expert clinicians, trialists and regulators, summarises the current state of the art, and provides insight into the opportunities and challenges for identifying and assessing the efficacy and safety of new treatments for this challenging condition.

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Current state of clinical trial design and therapeutics in pulmonary arterial hypertension

With advances in our understanding of the pathobiology of pulmonary hypertension (PH) over the past 20 years, more than 10 drugs have been developed and approved for the treatment of pulmonary arterial hypertension (PAH) and one for chronic thromboembolic PH (CTEPH). Initial clinical trials performed in newly diagnosed PAH and CTEPH were single agent, placebo controlled, of short duration, focused on changes in measures of exercise capacity and comprised of relatively small populations of patients. However, over the past 5 years, clinical trial designs testing novel therapies for PAH have evolved into much larger, placebo controlled, on background therapy and upfront combination therapy trials. In addition, event-driven studies examining the effect of sequential combination therapy on clinical worsening have forced the community to search for more clinically relevant, novel efficacy end-points and trial design. Here, we review the evolution of clinical trial end-points, report on new therapeutic targets, evaluate clinical trial design and propose goals for clinical investigation.

Evolution of end-points in clinical trials of PH

6-min walk test

The 6-min walk test (6MWT), a submaximal exercise test, has been the most commonly employed primary end-point in clinical trials of PH therapies, beginning with the first randomised controlled trial (RCT) for drug registration of epoprostenol in 1990 [1]. Since that initial study, most of the registration studies for novel PAH or CTEPH therapies employed short-term change in distance achieved on the 6MWT (Δ6MWD) as the primary outcome (figure 1) [2–13]. These studies identified statistically significant differences in Δ6MWD that resulted in regulatory approval for use in PH, but the clinical relevance of these changes remained less well defined. Multiple studies examining the relationship between Δ6MWD and short- and long-term outcomes, such as need for hospitalisation, lung transplantation, initiation of rescue therapy or death, failed to consistently demonstrate significant associations [14–18]. Subsequent studies defined clinically relevant changes in 6MWD pertaining to patient-important outcomes, such as health-related quality of life and prediction of clinical deterioration [17, 19–21]. However, the utility of Δ6MWD as a primary outcome measure in clinical trials is limited, particularly in

![FIGURE 1 Duration of main registration studies (randomised controlled trials [RCTs]) for currently approved pulmonary arterial hypertension therapies. Blue bars: RCTs with change in 6-min walk distance as primary outcome measure; red bars: RCTs with morbidity and mortality composite primary outcome measure.](https://doi.org/10.1183/13993003.01908-2018)
more contemporary trials involving sequential, add-on therapy. The change is less than the clinically relevant thresholds described, despite the significance achieved by other clinical outcomes [7–10, 22, 23].

**Patient-reported outcomes**
Alternate outcome measures that are clinically meaningful end-points, measuring how a patient “feels, functions or survives”, are sought by regulatory agencies. In PH, patient-reported outcomes (PROs) now exist, but have been less responsive to therapeutic impact [24–26]. Disease-specific measures need validation in varied languages and need to be included in future clinical trials at all stages of development. The CAMPHOR (Cambridge Pulmonary Hypertension Outcome Review) questionnaire, the first PAH/CTEPH-specific questionnaire, is quite lengthy and does not track with other clinical measures over time [27]. The 10-question survey proposed by the Pulmonary Hypertension Association UK (emPHasis-10) is more efficient, but needs further study [28], and the recently reported SYMPACT study appears to be the more efficient and inclusive, but also needs additional validation [29].

**Other surrogate end-points**
PH is a disease that lacks strong surrogate end-points [30]. By definition, a surrogate end-point should be: 1) part of the causative pathway from therapy to clinical outcome, 2) its baseline value should be related to clinical outcome, 3) a change in its value should reflect a change in outcome both in direction and magnitude of change, and 4) the estimate of its clinical benefit should be independent of the nature of treatment (e.g. the relationship of change in the surrogate with the outcome should be the same regardless of the intervention that led to the change) [31]. A recent systematic review of surrogate end-points employed in clinical trials of PAH therapy between 1985 and 2013 found that inclusion of invasive measures, such as haemodynamics, as either primary or secondary end-points, significantly decreased over time, while measures of functional capacity, functional status and PROs increased significantly [32].

**Evolution to composite outcome end-points**
To address some of the limitations of the 6MWT as a primary outcome measure in clinical trials and to explore novel end-points, registration studies in the mid-2000s incorporated composite end-points reflecting time to clinical worsening (TTCW) [6, 7]. Reductions in risk of clinical deterioration noted in these studies motivated the decision to use this composite end-point of morbidity and mortality as the primary outcome in a large registration study of macitentan [22]. The significant reduction in the risk of clinical worsening noted between treatment arms was not reflected by the Δ6MWD. This suggested a distinct effect on the risk of clinical events versus improvement of functional capacity. Similar associations between treatment assignment, TTCW and Δ6MWD were noted in the RCT of selexipag [23]. Combined with data from an RCT of initial combination of ambrisentan and tadalafil versus either one alone demonstrating responsiveness of the measure in a treatment-naive cohort, TTCW is now an approved end-point for PAH therapeutic registration trials (ClinicalTrials.gov identifiers NCT01908699, NCT02932410 and NCT01824290) (table 1).

**Limitations to outcome end-points**
Future clinical trials need to be more efficient. While TTCW as the primary end-point has been widely accepted, it is not the solution. First, there is no standard definition across trials for TTCW, limiting the ability to compare treatment effects between studies (table 1). Second, each component of a composite end-point should be weighted with respect to clinical importance and frequency of occurrence; the current components of TTCW in PH are not (e.g. death is infrequent and clinical worsening is frequent) [33]. Third, the relationship between clinical worsening and subsequent survival is not well defined and not always adjudicated by an events committee with expertise in PH (table 1) [34]. A more recent analysis utilising data from the SERAPHIN [22] and GRIPHON [23] TTCW trials found a strong association between both symptomatic progression and hospitalisation and mortality at 3, 6 and 12 months [35]. Rigorous studies of the association between TTCW and subsequent events, such as survival, are still needed to fully establish TTCW as a validated surrogate for mortality.

**New drug targets for PAH**
The currently licensed drugs are directed at correcting the imbalance of vasoactive factors in PAH. There is widespread acceptance that new drugs need to address other pathological mechanisms that drive vascular remodelling. There is no shortage of novel drug targets of potential therapeutic interest; the current challenge is prioritising candidates according to likelihood of success in clinical trials, side-effects, quality of life and cost-effectiveness.

**Genetically determined targets**
Genetics is a powerful mechanism for identifying and prioritising new drug targets with confidence. Mutations in BMPR2 (bone morphogenetic protein receptor type 2), the most common susceptibility gene
for PAH, have focused attention on the transforming growth factor-β (TGF-β)/BMP signalling pathway [36]. To date, the only treatment that has been used to target BMPR2 signalling in clinical trials is FK506 (tacrolimus) [37], which is currently in phase 2 (ClinicalTrials.gov identifier NCT01647945). FK506 binds its pharmacological target FKBP12 (12-kDa FK506-binding protein) and removes it from all three BMPR type 1 receptors (ALK1, ALK2 and ALK3), including those preferred by BMPR2 (ALK1 and ALK3). It is able to activate BMPR2-mediated signalling even in the absence of exogenous ligand and BMPR2.

Strategies proposed for correcting impaired BMPR2 signalling, beyond the aspiration of gene therapy, include pharmacological approaches such as chloroquine (which prevents lysosomal degradation of the BMPR2), ataluren (with the aim of reading through missense mutations) and increasing BMP9 levels [38]. An alternative to increasing BMP signalling is to inhibit TGF-β activity using a novel activin–receptor fusion protein (sotatercept) that competitively binds and neutralises TGF-β superfamily ligands [39].

Potential targets will emerge as we better understand the genetic architecture of PAH, including ion channels (KCNK3 (potassium channel subfamily K, member 3)), aquaporin and SOX17 (SRY-box 17) [36, 40]. Further pre-clinical studies will be needed to realise how these, or their signalling pathways, might be manipulated for therapeutic benefit.

**Epigenetic modification**

Little is known of the epigenetics of PAH, but studies of histone deacetylase (HDAC) inhibitors in pre-clinical cell and animal models have reported beneficial effects, although cardiotoxicity is a concern [41]. Translating the therapeutic potential of HDAC inhibition in PAH will require a clearer insight into the HDAC subtypes involved in the vascular pathology. Likewise, a better understanding of the role of microRNAs in PAH is needed to inform how best to manipulate pharmacologically to have an impact on pulmonary vascular disease [42].

**DNA damage**

Inhibition of poly(ADP-ribose) polymerase (PARP) reverses PAH in several animal models [43]. An open-label early phase 1 study of olaparib, an orally available PARP1 inhibitor approved for the treatment of BRCA (breast cancer gene)-related breast cancer, has been proposed in PAH patients in World Health Organization Functional Class II–III on stable vasoactive therapy (ClinicalTrials.gov identifier NCT03251872).
**Growth factors**

The tyrosine kinase receptor imatinib was the first significant compound used in a large-scale trial to directly target vascular remodelling in PAH. Imatinib inhibits platelet-derived growth factor (PDGF) receptor-α and -β [44]. PDGF is a trophic factor in vascular cells and lung tissue from PAH patients shows increased expression of PDGF receptors. The phase 3 PAH trial reported a 32 m increase in mean placebo-corrected 6MWD and a reduction in pulmonary vascular resistance (PVR) without improvement in TTCW. Unfortunately subdural haematoma occurred in eight patients receiving both imatinib and anticoagulation with vitamin K antagonists [45]. However, there remains considerable interest in tyrosine kinase inhibitors, and imatinib in particular, as some patients have stabilised and even improved on imatinib treatment in anecdotal reports. Identifying the clinical and molecular characteristics of patients likely to respond is key to the success of this programme.

Clinical experience with other tyrosine kinase inhibitors urges caution. Indeed, exposure to dasatinib is associated with the development of PAH [46, 47]. In a 16-week, single-centre, open-label trial in 12 patients with PAH, the multikinase/angiogenesis inhibitor sorafenib worsened pulmonary haemodynamics and was associated with adverse events, such as moderate skin reactions on the hands and feet and alopecia [48].

**Metabolism**

Insulin resistance contributes to the morbidity and mortality of PAH [49]. This has led to interest in the use of agents such as rosiglitazone, metformin and glucagon-like peptide 1 agonists (table 2) [50, 51]. A small clinical trial with metformin is underway, with detailed study of the impact on the right ventricle and pulmonary haemodynamics. Whereas normal myocardium uses fatty acid oxidation as an energy source, the maladapted myocardium relies on glycolysis, which is much less efficient [52]. Glutaminolysis is also induced. Inhibition of fatty acid oxidation increases glucose oxidation, leading to the possibility that trimetazidine (an inhibitor of 3-ketoacyl coenzyme A thiolase), approved for angina, may have utility in PAH [53]. Ranolazine, another antianginal agent, is also an option [54].

In PAH, proliferating cells switch their metabolism from oxidative phosphorylation to glycolysis for ATP production. Dichloroacetate (DCA), which inhibits pyruvate dehydrogenase kinase, is a potential treatment for PAH [55]. Gene variants that reduce the function of SIRT (sirtuin 33) or UCP2 (uncoupling protein 2) impair the clinical response to DCA. A small clinical study with DCA has shown haemodynamic improvement in genetically susceptible patients [56].

**Inflammation and immune modulation**

Histological studies of the lung, the presence of circulating autoantibodies and high plasma levels of cytokines in PAH all point to inflammation as a driver of its pathology [57]. Direct investigation of this currently lies with a clinical trial of the anti-CD20 monoclonal antibody, rituximab, in PAH associated with connective tissue disease (ClinicalTrials.gov identifier NCT01086540), and a trial of tocilizumab, an interleukin-6 receptor antagonist in PAH (ClinicalTrials.gov identifier NCT02676947) (table 3). Elafin, an endogenously produced elastase inhibitor, has now progressed to clinical trials [58]. Elafin is pro-apoptotic and decreases neointimal lesions in lung organ culture [59].

**Oestrogen signalling**

Aromatase converts androgens to oestrogen and is evident in the pulmonary vasculature of PAH lungs. A small trial of anastrozole, an aromatase inhibitor, in PAH has reported an increase in 6MWD [60] and a further study is underway (table 4).

**Oxidative and hypoxic stress**

Oxidative stress is another mechanism that has been targeted in PAH. In contrast to animal studies [61], a phase 2 study of an inhibitor of apoptosis signal-regulating kinase 1 (ASK1) failed to show overall improvement [62]. A phase 3 study with bardoxolone methyl in scleroderma has been completed, following some signals of efficacy in phase 2 (ClinicalTrials.gov identifier NCT02036970). This drug induces the nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that regulates antioxidant proteins, and suppresses activation of the pro-inflammatory factor NF-xB.

Increased expression of hypoxia-inducible factor (HIF), specifically HIF1α and HIF2α, in the PAH lung, genetic manipulation in animals [63] and naturally occurring mutations in humans (e.g. Chuvash polycythaemia [64]) highlight the potential importance of hypoxic stress in PAH. Several groups have shown that iron deficiency in the absence of anaemia is common in PAH and is associated with reduced survival in PAH [65]. Open-label studies of i.v. iron replacement in PAH suggest an improvement in exercise capacity [66] and a double-blind study is near completion.

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RCT: randomised controlled trial; PH: pulmonary hypertension; RV: right ventricle; RVEF: right ventricular ejection fraction; MRI: magnetic resonance imaging; iPSC: induced pluripotent stem cell; LV: left ventricle; mPAP: mean pulmonary arterial pressure; PAOP: pulmonary artery occlusion pressure; PVR: pulmonary vascular resistance; RHC: right heart catheterisation; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; CPET: cardiopulmonary exercise testing; NYHA: New York Heart Association; FC: functional class; LDH: lactate dehydrogenase; FDG: ¹⁸F-2-fluoro-2-deoxy-D-glucose; PET: positron emission tomography; Nrf2: nuclear factor erythroid 2-related factor 2; ILD: interstitial lung disease; AMPK: AMP-activated protein kinase; PA: pulmonary artery.
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CTD: connective tissue disease; ILD: interstitial lung disease; POPH: portopulmonary hypertension; FC: functional class; $V'O_2$: oxygen uptake; $V'E/V'CO_2$: ventilatory response [minute ventilation/carbon dioxide production]; CPET: cardiopulmonary exercise testing; hs-CRP: high-sensitivity C-reactive protein; NT-proBNP: N-terminal pro-brain natriuretic peptide; IL-6: interleukin-6; MLHFQ: Minnesota Living with Heart Failure Questionnaire; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; MCTD: mixed connective tissue disease; PVR: pulmonary vascular resistance; RHC: right heart catheterisation; 6MWD: 6-min walk distance; WHO: World Health Organization; QoL: quality of life; RCT: randomised controlled trial; TTCW: time to clinical worsening.
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RCT: randomised controlled trial; PAH: pulmonary arterial hypertension; WHO: World Health Organization; FC: functional class; 6MWD: 6-min walk distance; RVEF: right ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; SF-36: Short Form-36; emPHasis-10: 10-question survey proposed by the Pulmonary Hypertension Association UK; TTCW: time to clinical worsening; TAPSE: tricuspid annular plane systolic excursion; PH: pulmonary hypertension; RHC: right heart catheterisation; QoL: quality of life; MLHFQ: Minnesota Living with Heart Failure Questionnaire; CPET: cardiopulmonary exercise testing; PRO: patient-reported outcome; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review.
Serotonin and humoral modulation

Serotonin (5-HT) is a potent vasoconstrictor and pro-proliferative factor in pulmonary vascular cells [67]. Terguride, a 5-HT<sub>2A/2B</sub> receptor antagonist, showed no clinical benefit in a phase 2 study in PAH [68]. This may be explained, in part, because the 5-HT<sub>1A</sub> receptor is the most highly expressed 5-HT receptor in the pulmonary arteries in PAH lungs. Tryptophan hydroxylase 1 (TPH1) is the rate-limiting enzyme in 5-HT biosynthesis and studies with a selective inhibitor of TPH1 are planned.

There is interest in further examination of the role of augmenting vasoactive intestinal polypeptide activity, despite previous disappointment with inhaled administration [69].

Careful use of β-blockers in stable PAH is safe, but which patients might benefit remains an open question [70]. While angiotensin-converting enzyme (ACE) inhibitors are importantly renoprotective in scleroderma, they have not been shown to be of benefit in PAH. The homologue of ACE, known as ACE2, converts angiotensin 1 and angiotensin II to angiotensin-(1–7), angiotensin-(1–9) and angiotensin-(1–5), and is of interest. Decreased ACE2 levels and ACE2 autoantibodies have been reported in PAH [71] and ACE2 replacement using a purified i.v. formulation of soluble recombinant human ACE2 is underway. Two prospective studies examining the effect of the aldosterone antagonist, spironolactone, are also underway.

Pulmonary artery denervation

Pulmonary artery denervation is an interventional therapy aimed at abolishing the sympathetic nerve supply to the pulmonary circulation. In a single-centre study, 13 patients underwent the procedure using a radiofrequency ablation catheter, and significant reductions of mean pulmonary arterial pressure and improvement in 6MWD were reported [72]. Several trials are ongoing to determine efficacy and safety of the procedure in PAH (table 5).

Stem cells

There are a few clinical reports of cell therapy in patients with PAH. In a 12-week open-label controlled study, infusion of autologous endothelial progenitor cells (EPCs) improved 6MWD and haemodynamic variables in adult patients with severe PAH [73]. Similar results were observed in children with idiopathic PAH [74]. In the phase 1 PHACeT trial, EPCs transduced with endothelial nitric oxide synthase were administered to patients with PAH [75]. The 6MWD improved significantly at 1, 3 and 6 months post-infusion, by 65, 48 and 47 m, respectively. During the 3-day infusion protocol, no adverse haemodynamic or gas exchange parameters were observed [75].

There are several reasons to believe that therapy with cardiac stem cells such as cardiosphere-derived cells (CDCs) would benefit PAH patients with or without right ventricular dysfunction. CDCs have been demonstrated in pre-clinical models to ameliorate most of the major aberrations that underlie the pathobiology/pathophysiology of both the maladapted right ventricle muscle and the remodelled pulmonary vessels [76]. They are potently angiogenic, antifibrotic and antiapoptotic; they have significant anti-inflammatory effects; they attenuate both oxidative and nitrosative stress; and they attract endogenous stem cells to sites of vascular injury. Recently, the phase 1 trial ALPHA of allogeneic CDCs for PAH was initiated, with the primary objective to determine the maximum feasible dose and safety profile of CDCs administered by central infusion into the right ventricle outflow tract of patients with idiopathic PAH (table 6).

Clinical trial failures

The introduction of several new drugs for the treatment of PAH speaks to the success of drug development in this therapeutic area over the past two decades, but a growing number of clinical trials have not met their primary end-point or have reported major safety concerns (table 7). Limited data are publically available on these studies, but a deeper understanding is important to reduce risk and improve success going forward.

There is a high attrition rate as drug development progresses through its phases from first-in-human studies to pivotal registration studies. Of a total of 9985 clinical trials from 7455 development programmes between 2006 and 2015, only one in 10 progressed from phase 1 to approval [77]. For cardiopulmonary disease therapeutics the range was 6.6–12.8%. Phase transition success rate ranges for cardiopulmonary diseases are estimated at 58.9–65.3% for phase 1 to 2, 24.1–29.1% for phase 2 to 3 and 55.5–71.1% for phase 3 to new drug application. Despite this poor overall probability of success, drug development for rare disease indications remains one of the more successful programmes across all phases of development [77].

The main reason for terminating the development of a drug is lack of efficacy. 52% of programmes are stopped because of lack of efficacy compared with 21% due to safety concerns [78, 79]. Our limited understanding of the pathological drivers of PH contributes to this trial failure rate. Overemphasis on a
<table>
<thead>
<tr>
<th>Intervention</th>
<th>ClinicalTrials.gov identifier</th>
<th>Study design</th>
<th>Study duration</th>
<th>Main inclusion criteria</th>
<th>Primary outcome measures</th>
<th>Secondary outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapeutic Intra-Vascular UltraSound (TIVUS) system</strong></td>
<td>NCT02516722</td>
<td>Multicentre open-label study (TROPHY)</td>
<td>12 months</td>
<td>PAH in WHO FC III on stable double combination therapy other than parenteral PGI2</td>
<td>Safety (procedure-related AE: 1 month); safety (PAH-related AEs and all-cause death: 12 months)</td>
<td>Change in mPAP, PVR, 6MWD and QoL at 4 months</td>
</tr>
<tr>
<td><strong>Therapeutic Intra-Vascular UltraSound (TIVUS) system</strong></td>
<td>NCT02835950</td>
<td>Multicentre open-label study (TROPHY-US)</td>
<td>12 months</td>
<td>PAH in WHO FC III on stable double combination therapy other than parenteral PGI2</td>
<td>Safety (procedure-related AE: 1 month); safety [AEs, PAH-related AEs and all-cause death: 12 months]</td>
<td>Change in mPAP, PVR, 6MWD, QoL, NT-proBNP and RV function (MRI and echocardiography) at 6 months</td>
</tr>
<tr>
<td><strong>Pulmonary artery denervation</strong></td>
<td>NCT02525926</td>
<td>Multicentre single-blinded RCT versus placebo (DENERVAP)</td>
<td>24 weeks</td>
<td>PAH patients in WHO FC III–IV despite dual therapy including a PGI2 or dual oral therapy in patients unable to receive PGI2 therapy</td>
<td>Change in mPAP [RHC]</td>
<td>Change in mPAP (3 months), PVR and other haemodynamic variables (6 months), FC, 6MWD, oxygen dependence, supraventricular arrhythmia, BNP, cardiac troponin, and RV function (echocardiography)</td>
</tr>
<tr>
<td><strong>PA denervation (+sildenafil)</strong></td>
<td>NCT03282266</td>
<td>Multicentre single-blinded RCT versus placebo (PADN-CFDA)</td>
<td>24 weeks</td>
<td>PAH</td>
<td>Change in 6MWD</td>
<td>Change in haemodynamic variables (RHC), RV function (echocardiography) and PAH-related events</td>
</tr>
</tbody>
</table>

PAH: pulmonary arterial hypertension; WHO: World Health Organization; FC: functional class; PGI2: prostacyclin I2; AE: adverse event; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; 6MWD: 6-min walk distance; QoL: quality of life; NT-proBNP: N-terminal pro-brain natriuretic peptide; RV: right ventricle; MRI: magnetic resonance imaging; RCT: randomised controlled trial; RHC: right heart catheterisation.

### Table 6 Clinical trials investigating cell therapy

<table>
<thead>
<tr>
<th>Cells</th>
<th>ClinicalTrials.gov identifier</th>
<th>Study design</th>
<th>Study duration</th>
<th>Main inclusion criteria</th>
<th>Primary outcome measures</th>
<th>Secondary outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous EPCs transfected with human eNOS</td>
<td>NCT03001414</td>
<td>Multicentre double-blind crossover RCT versus placebo: phase 2 (SAPPHIRE)</td>
<td>24 weeks</td>
<td>PAH in WHO FC II–IV on stable PAH-specific therapy</td>
<td>Change in 6MWD</td>
<td>Change in 6MWD (3, 9 and 12 months) and PVR; number of deaths or clinical worsening of PAH; change in RV function (echocardiography and MRI) and QoL (SF-36)</td>
</tr>
<tr>
<td>Allogeneic human cardiosphere-derived stem cells</td>
<td>NCT03145298</td>
<td>Phase 1a: open-label; phase 1 [ALPHA] Phase 1b: double-blind RCT versus placebo: phase 1 [ALPHA]</td>
<td>1 year</td>
<td>PAH in WHO FC II–III on stable PAH-specific therapy</td>
<td>Safety (gas exchange, haemodynamics); arrhythmia; sudden death; mortality and morbidity</td>
<td>Long-term safety end-points; TTCW (including death)</td>
</tr>
</tbody>
</table>

EPC: endothelial progenitor cell; eNOS: endothelial nitric oxide synthase; RCT: randomised controlled trial; PAH: pulmonary arterial hypertension; WHO: World Health Organization; FC: functional class; 6MWD: 6-min walk distance; PVR: pulmonary vascular resistance; RV: right ventricle; MRI: magnetic resonance imaging; QoL: quality of life; SF-36: Short Form-36; TTCW: time to clinical worsening.
single mechanism and the limitations of model systems also constrain drug development [78, 80]. Pre-clinical animal models do not completely reflect true human disease. When tested in the best models, novel therapies have not been evaluated in animals on background PAH therapies. Moreover, pre-clinical studies do not employ rigours such as sample size determination and randomisation, and they have not traditionally evaluated end-points used in human trials. Finally, it is possible that therapeutic responses result from off-target effects (i.e. enhanced blood flow to skeletal muscle), which are usually not evaluated in animal models [78, 80]. Overcoming these potential pre-clinical factors will require a more complete understanding of relevant mechanisms in modern day phenotypes through initiatives such as PVDOMICS (ClinicalTrials.gov identifier NCT02980887), and advancement of technologies to improve applicability of ex vivo and in vitro assays. Establishing rigorous standards guiding pre-clinical animal model testing [80] will also likely result in improved selection of therapeutic candidates and minimise the impact of bias and false-positive results when tested in the human clinical trial environment.

Given that clinical trials are more likely to “fail” than succeed, it is important to build in plans to learn from “failure” [81]. The goals and objectives of early-phase clinical trials should be focused on safety, informative biomarkers and identification of responsive subpopulations. While bound by statistical norms, decisions in early-phase trials should not be made based on single p-value thresholds. Basing scientific, business or policy decisions in early development on a “mechanical bright-line rule” such as p-value <0.05 as a threshold of scientific claim justification can lead to incorrect conclusions [82]. Later-phase studies need to be informed by adequate data on dose–response relationships and the characteristics of patients that show an efficacy signal. However, data are generated all along the drug development pathway and it is imperative that these data are available for careful evaluation. This will inform critical analysis of study power, end-points and population selection.

Although commonly used, the term “failure” in the context of clinical trials does not distinguish between well-designed negative studies versus studies that are simply inconclusive due to flawed design or conduct. Moreover, the perception of clinical trial “failure” is complex and depends on perspective. While clinical trialists and scientists may consider interventions that do not meet relevant primary or secondary end-points as “failed”, patients may think of therapies that do not provide symptomatic improvement as unhelpful. Beyond issues of definition and perspective, data from these clinical trials are often not publically disclosed due to a multifaceted set of issues ranging from business agendas and academic disinterest to publication bias. Unsuccessful trials can be as, or even more, informative as “positive” trials. Data from the IMPRES trial serve as a good example [45]. Despite demonstrable improvement in exercise capacity and haemodynamics, the higher rate of serious adverse events and study drug discontinuation ultimately led to the decision to halt development of imatinib mesylate as add-on therapy for PAH. However, the publication and ensuing academic dialogue has empowered discussion around the methodology, dosing and approach to repurposing of therapeutics in PAH. More importantly, the data has augmented discussion of the utility of an integral biomarker as an enrichment strategy for optimum clinical trial candidate selection. The use of selected biomarkers appears to be linked with 13–21% relative increase in probability of successful transition between phases of clinical trial development [77].

Publication of all studies, irrespective of outcome, has the potential for cost reduction, improvement in future trial design, reduction in attrition rates and, most importantly, reduction in the number of clinical trial subjects exposed to ineffective drugs or enrolled in flawed clinical trial designs [83]. In fact, initiatives such as Medical Publishing Insights and Practices (www.mpip-initiative.org) and others supported by
pharmaceutical partners, the World Health Organization, and the Pharmaceutical Research and Manufacturers of America have called for transparency in publication of clinical trials protocols and results [83]. We in the PAH scientific community must recognise our ethical obligation to clinical trial subjects who allow us to expose them to investigational interventions with the hope that incremental knowledge will be gained. We are bound by this moral obligation to learn and disseminate knowledge produced by participation of each and every clinical trial subject. A transparent process for reporting and examining negative clinical trials, with the commitment to evaluation of full data sets (not only the top-line data) is essential. The process should exceed current data-sharing policies of individual institutions or medical journals and be funded to allow independently conducted analyses by scientific committees (i.e. data safety monitoring boards) with the necessary expertise (i.e. clinical trialist, ethicist and statistician). The obligation for such reporting processes should be balanced with (but not hindered by) the need for data confidentiality when analysing early-phase proof-of-concept studies.

**Challenges for future trial design**

The successful development of drugs for PAH has provided significant impact on patient outcomes, but has not yet produced a cure. The surge of novel potential options has created new challenges in clinical care and future drug development programmes. Of course, this is a “good” stress to need to overcome, but it requires thoughtful consideration of novel trial end-points and design. It also means that pharmacological interactions, pharmacodynamics and individual pharmacokinetics will become more important to incorporate into future studies. Novel biomarkers and genetic association discovery will be required to truly develop and personalise therapies. There are still considerable unknowns regarding the mechanisms of action of our current drugs, their in vivo pharmacology and their optimal usage. Additionally, larger trials will, by necessity, need to be more collaborative in order to study potential meaningfulness of disease state biomarkers. Trials in PAH starting from the pre-clinical phase through phases 1 and 2 should focus on “learning” to improve efficiency of the entire enterprise. In addition, the number of patients with an orphan disease who are available to participate in clinical trials is limited. It is imperative to gain the most knowledge with the fewest patients placed at risk.

Future therapies can no longer be studied as de novo treatments with placebo-treated comparator groups. One solution to this dilemma is to implement creative adaptive designs. Informatics technology can allow real-time “adaptation” based on clinical data received, with adjustment of enrolment stratification and outcome targets, and determination of futility [84]. In addition, this technology can allow for testing multiple therapeutic choices if all stakeholders are willing to work together to find the best therapeutic effect. The 2018 US Food and Drug Administration guidance on adaptive designs for clinical trials defined these trials as “a study design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial” [85]. It is important to recognise that once interim monitoring occurs there is little statistical cost in having frequent monitoring from that point forward [86]. These Bayesian models allow statistical inferences to take into account the data-driven adaptations and thus allow trial flexibility [87].

The easiest trial to implement is a phase 2/3 trial that allows an interim “look” to assess whether the experimental arm is effective and therefore worth continuing on to its phase 3 stage [88]. This is a faster, more efficient way to proceed but is limited to trials utilising end-points in phase 2 that occur prior to reaching the definitive end-point needed for phase 3. Issues to address in advance include setting the response rate needed to proceed to phase 3, selecting the end-points and determining if there will be a time lag to allow for data to mature prior to analysis [89]. In contrast, a less traditional approach to be considered might be a multiarm trial with multiple experimental therapies tested against a single control arm [84]. This can be done with efficacy and futility stopping rules for each therapy, and potentially only dropping some of the arms while continuing the study with others [90].

Biomarker-driven trials typically consist of randomised block, marker-enriched and marker-directed designs [87]. Block design uses the biomarker as one of many factors used for randomisation, whereas the biomarker is central to the treatment assignment in marker-directed designs. Marker-enriched designs select a prognostic marker for treatment response or a determinant of higher risk to enhance success [87]. The main adaptive platform combining these concepts is the master protocol approach. The approach or “platform” allows adding new treatment arms in the existing cohort or in new subgroups to an ongoing trial in which several treatments are being tested at once [84]. The downside is that the later added arms can only be compared with the control patients randomised from the identical time-point of enrolment. This is not an easy task to organise as multiple industry partners need to collaborate in the trial design, control and privacy of data, funding, and regulatory requirements [91].

Use of biomarkers in adaptive design can strengthen trial efficiency [92]. Umbrella or basket trials describe master protocols designed to integrate proven molecular, genetic or serological biomarkers that are
associated with treatment response. This is now possible in oncology drug development and could be a potential design for PH trials. One example could be the use of a risk assessment tool as a biomarker at enrolment or during the study to stratify subjects. Eventually, the risk tools could then be modified to yield prognosis over time with these new markers. Biomarker-defined subgroups may be small proportions of the total cohort studied with this approach. In addition, the ability to discontinue the study of ineffective therapies and add an arm if the therapy is proven beneficial increases trial efficiency. Depending on the stage of the trial, the evidence required to meet a proven threshold will vary and will need consensus prior to trial initiation [84].

Proposals for future clinical trial design in PAH

Collaboration and utilisation of existing resources are the keys to successful clinical development in PAH therapeutics. The ability to examine data upon completion in both successful and unsuccessful studies should be the rule, not the exception. Results of recent phase 1–2 studies with drugs targeting novel mechanisms of action have not yielded success, due to the heterogeneity of subjects studied, the use of myriad background therapies, the inclusion of patients with mild disease and perhaps selection of the wrong end-points. Rather than using traditional PAH clinical and haemodynamic trial end-points for targeted agents (e.g. 6MWT and PVR), the end-points should be tailored to the disease biology and anticipated mechanistic effects. This approach will allow for potential regulatory consideration of novel biomarkers.

Phase 1–2 goals

1) Pharmacokinetic and pharmacodynamics studies should be evaluated, particularly since we know little of the myriad combinations of therapies.
2) These trials should encompass biological and mechanistic markers of disease to better assess responses to therapy.
3) To improve generalisability and interpretation of the changes seen in functional capacity, early drug trials should include more homogeneous subject groups.
4) Trials should use risk tools as an enrichment strategy to better phenotype a heterogeneous group.
5) Novel efficacy markers in phase 2 (e.g. magnetic resonance imaging and PROs) should be incorporated and then utilised in phase 3.

It is clear that performing long-term composite event-driven trials will be challenging and may halt the surge of new development by committing study participants for many years [93]. Morbidity and mortality event trials require large numbers of subjects upfront to demonstrate effects even at 1 year [35, 94]. Future clinical trials in PAH will need clinically meaningful end-points that reflect morbidity and mortality as well as how patients feel and function [95]. It is known that a “low-risk” patient profile after initial treatment of PAH is associated with better survival [96–99]: a potential exploratory end-point could be the ability to reach or maintain a “low-risk” status according to the REVEAL (Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management) score [96] or the number of low-risk criteria as defined by the European Society of Cardiology/European Respiratory Society PH guidelines [94, 98, 100, 101].

Phase 2–3 goals

The overarching goal should be to improve patients’ ability to live more functional and fulfilled lives.

1) Examine time to clinical improvement instead of TTCW. This will entail defining clinically significant differences in existing end-points and allowing for derivation of these differences post-trial with novel markers.
2) Utilise change in risk as a marker of efficacy as an exploratory end-point now to examine its predictability as a clinical end-point in the future.
3) Utilise novel biomarkers (serum, plasma, genomics, metabolics and PROs) as an exploratory end-point now to examine its predictability as a clinical end-point in the future.
4) Limit unnecessary post-marketing and small investigator-initiated studies that are unlikely to enhance our scientific knowledge base or improve patient care.

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References


Pulmonary hypertension due to left heart disease

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ABSTRACT  Pulmonary hypertension (PH) is frequent in left heart disease (LHD), as a consequence of the underlying condition. Significant advances have occurred over the past 5 years since the 5th World Symposium on Pulmonary Hypertension in 2013, leading to a better understanding of PH-LHD, challenges and gaps in evidence. PH in heart failure with preserved ejection fraction represents the most complex situation, as it may be misdiagnosed with group 1 PH. Based on the latest evidence, we propose a new haemodynamic definition for PH due to LHD and a three-step pragmatic approach to differential diagnosis. This includes the identification of a specific “left heart” phenotype and a non-invasive probability of PH-LHD. Invasive confirmation of PH-LHD is based on the accurate measurement of pulmonary arterial wedge pressure and, in patients with high probability, provocative testing to clarify the diagnosis. Finally, recent clinical trials did not demonstrate a benefit in treating PH due to LHD with pulmonary arterial hypertension-approved therapies.
Introduction

Pulmonary hypertension (PH) is a common complication of left heart disease (LHD), in response to a passive increase in left-sided filling pressures, more specifically left atrial pressure [1]. It is currently defined as post-capillary PH, by an increase in mean pulmonary arterial pressure (mPAP) $\geq$25 mmHg and a pulmonary arterial wedge pressure (PAWP) $>15$ mmHg [2]. In most cases, PH-LHD (group 2 PH) is a consequence or an abnormal biomarker of the underlying cardiac disorder. However, the structure and function of the pulmonary circulation may be further affected by several mechanisms potentially leading to pulmonary arterial and venous remodelling. In heart failure, recent data even suggest that the severity of PH correlates most strongly with venous and small arteriolar intimal thickening [1–3]. In addition, the function of the right ventricle is often affected independently from the afterload increase [4–7], leading to uncoupling of the right ventricle/pulmonary artery unit [8–10] with further exercise limitation and adverse outcome. This is especially true in heart failure with preserved ejection fraction (HFpEF) [4–11]. Over the past 5 years since the 5th World Symposium on Pulmonary Hypertension (WSPH) in 2013, significant advances have improved our understanding of PH-LHD. This article summarises these findings, key challenges and proposals for the approach to this condition, with a specific focus on PH due to HFpEF.

Definition and classification of PH-LHD

At the 5th WSPH in 2013, a new terminology was adopted to distinguish isolated post-capillary PH (IpcPH) from combined post-capillary and pre-capillary PH (CpcPH), based on the diastolic pressure difference/gradient (DPG) between the diastolic PAP (dPAP) and PAWP [1]. However, this definition was found to be too restrictive and exposed to interpretation, leading to controversies about whether the DPG would [12–15] or would not [16–21] predict outcome in patients with group 2 PH. Pulmonary vascular resistance (PVR) was subsequently reintroduced to better reflect the impact of the right ventricle on outcome [2]. To date, the haemodynamic definition of PH-LHD stands as: 1) post-capillary PH when mPAP $\geq$25 mmHg and PAWP $>15$ mmHg; 2) IpcPH, when DPG $<7$ mmHg and/or PVR $\leq$3 Wood Units (WU); and 3) CpcPH when DPG $\geq$7 mmHg and/or PVR $>3$ WU. These two distinct haemodynamic phenotypes may be further defined by several variables obtained during diagnostic right heart catheterisation (RHC), none being totally independent from potential limitations [22]. The combination of recent analyses and basic physiology reveals that the haemodynamic definition of PH-LHD relies heavily on the accurate measurement of PAWP.

What is a normal PAWP and how to measure it?

In normal individuals, PAWP is close to dPAP, with a mean±SD value of 8.0±2.9 mmHg [23] for a normal range, PAWP should be measured at end-diastole to determine the pre-capillary component of PH-LHD and the calculation of PVR. In sinus rhythm, this corresponds to the mean of the a-wave. In atrial fibrillation, it is appropriate to measure PAWP 130–160 ms after the onset of QRS and before the v-wave.

Recommendations for measurement of PAWP/LVEDP in the differential diagnosis of PH

- A value of PAWP $>15$ mmHg, measured at end-expiration at rest, is considered consistent with PH-LHD. There is insufficient new data since the 5th WSPH in 2013 to recommend a change in this cut-off value.
- PAWP should be measured at end-diastole to determine the pre-capillary component of PH-LHD and the calculation of PVR. In sinus rhythm, this corresponds to the mean of the a-wave. In atrial fibrillation, it is appropriate to measure PAWP 130–160 ms after the onset of QRS and before the v-wave.
- There are no new data to suggest a change in standards for the measurement of PAWP. Therefore, we continue to recommend the assessment of PAWP at end-expiration, as averaging over of the respiratory cycle would reclassify many post-capillary PH patients to pre-capillary disease with the current PAWP cut-off value.
• Best practice suggests that RHC should be performed in stable, non-acute clinical conditions for the differential diagnosis of PH. Proper levelling at the mid-chest and "zeroing the transducer to atmospheric pressure are critical. Patients should be positioned supine with legs flat and pressures recorded during spontaneous breathing (no breath-hold). Measurements should be repeated in triplicate to obtain values within a 10% agreement.

• If PAWP is elevated and the accuracy of PAWP is in question, blood oxygen saturation should be determined in the wedge position. If the PAWP oxygen saturation is <90%, direct LVEDP measurement should be obtained.

• The presence of significant, large v-waves should be noted as this strongly suggests LHD regardless of resting PAWP.

**How to define CpcPH?**

Evidence in PH-LHD has been generated since the 5th WSPH in 2013 to 1) characterise the clinical profile, 2) describe the haemodynamic features and 3) identify outcome predictors. Indeed, the presence and the identification of a pre-capillary component in post-capillary PH are critical as it may have an impact on prognosis, can modify management and serves as the basis for clinical trial design [32]. In addition, CpcPH is associated with a reduced exercise capacity and a phenotype similar to PAH [21, 33]. Finally, it has been recently suggested that CpcPH may present a genetic profile that could be different from IpcPH [16].

Nevertheless, the populations studied in these retrospective registries are heterogeneous, from pure heart failure with reduced ejection fraction (HFrEF) cohorts [16–18], all causes of LHD [12, 15, 20, 21, 28, 34], to pure valvular heart disease (VHD) registries [13, 14]. The typical profile of PH-LHD combines an elevated PAWP (>20 mmHg), a mildly elevated mPAP (25–40 mmHg), a low cardiac index (≤2.5 L-min⁻¹-m⁻²), an elevated transpulmonary pressure gradient (TPG) (>12 mmHg), a normal DPG (<3 mmHg) and PVR ranging from 3 to 4.9 WU. In addition, right atrial pressure is consistently elevated (>10 mmHg), which may, together with elevated PAWP, suggest fluid overload or pericardial constraint. Finally, most studies reported a significant proportion (roughly one-third) of negative DPG that may be explained by the aforementioned limitations [27]. This is in keeping with a high rate of atrial fibrillation, affecting around 40% of patients.

The search for an ideal predictor of outcome in PH-LHD has led to conflicting results. On multivariate analysis, several predictors were found: a combination of mPAP and PVR [13, 16], pulmonary arterial compliance (PAC) either alone [19, 20] or in combination with mPAP and PAWP [16], or a combination of mPAP and DPG [12]. A meta-analysis identified 10 retrospective analyses using PVR, DPG and/or PAC to predict survival in PH-LHD [35]. For the purpose of consistency, and to better individuate the risk associated with each variable, independently of arbitrary cut-offs, only studies reporting the prognostic power of continuous variables were included. The analysis was done on a total of 2513 patients, followed for up to 15 years. The haemodynamic profile revealed average values of mPAP, PVR, DPG and PAC of 35 mmHg, 3.0 WU, 1.2 mmHg and 2.5 mL·mmHg⁻¹, respectively. In this analysis, DPG, PVR and PAC appeared to be associated with survival. However, both PVR and PAC were stronger predictors of outcome when compared with DPG [35]. It was suggested that a combination of variables might be better than an isolated value for prognosis purposes [35]. Interestingly, a recent analysis of three large US cohorts showed that higher pulmonary artery elastance and lower PAC are associated with increased mortality and right ventricular dysfunction, across the spectrum of heart failure and even when resistive load was normal [36]. This strongly suggests that, in CpcPH due to heart failure, the total right ventricular load is closely linked to outcome. Finally, a recent large retrospective analysis of 2587 patients with PH-HpEF showed that TPG ⩾12 mmHg, PVR ⩾3 WU and DPG ⩾12 mmHg were predictors of mortality and heart failure hospitalisations [37].

Therefore, the best way to describe the pre-capillary component of post-capillary PH remains controversial; none of the haemodynamic variables proposed to describe PH-LHD [22] are free from limitations.

**Recommendations**

• After careful consideration of the changes in the general definition of PH [36], the proposed haemodynamic definition of PH in LHD is: 1) IpcPH: PAWP >15 mmHg and mPAP >20 mmHg and PVR<3 WU; and 2) CpcPH: PAWP >15 mmHg and mPAP >20 mmHg and PVR ⩾3 WU.

• Beyond a strict haemodynamic definition, other markers of disease may be taken in consideration to better determine a patient’s prognosis. These could include an additional haemodynamic marker (e.g. DPG or PAC), cardiopulmonary exercise testing (CPET) profile (level of VE/VCO₂ (minute ventilation/oxygen uptake) slope, exercise oscillatory ventilation, end-tidal carbon dioxide tension...
(PETCO2)), indices of right ventricular function and right ventricle/pulmonary artery coupling (compliance and elastance) and biomarkers. In the context of PH due to HfPEF, ST2, a member of the interleukin-1 superfamily, may be complementary to N-terminal pro-brain natriuretic peptide (NT-proBNP) [24].

- Given the limitations of pure haemodynamic definitions, future studies should be aimed at developing biomarkers and other non-haemodynamic diagnostics to discriminate IpcPH and CpcPH.

Diagnostic approach and differential diagnosis of PH-LHD

Although RHC is the gold standard for the diagnosis of PH, it is not sufficient to make a clear distinction between idiopathic PAH (IPAH) and PH-LHD, especially when risk factors or documented history of cardiovascular disease (CVD) coexist [1, 2, 32, 34, 38]. Therefore, we propose a three-step approach to the differential diagnosis: 1) identification of a clinical phenotype to establish the characteristics of group 2 PH, 2) determination of a pre-test probability to identify which patients should move to an invasive evaluation and 3) haemodynamic characterisation, which could include provocative testing in selected cases.

Clinical phenotype of PH due to LHD

The revised clinical classification distinguishes three main entities in group 2 PH [38]: 1) PH due to HfPEF, 2) PH due to HFrEF and 3) PH due to VHD. In contrast to the other aetiologies, the distinction between PH due to HfPEF, PAH and chronic thromboembolic PH (CTEPH) may be challenging. Indeed, traditional cardiovascular risk factors may be present in patients with PAH [32, 34, 39]. Patients with systemic sclerosis may present with left ventricular involvement, independent from the presence of PH and pulmonary vascular disease (PVD) [40]. In patients with CTEPH, PAWP may be difficult to measure due to pulmonary artery obstruction and LVEDP may be elevated as patients may have concomitant cardiac involvement [41]. Finally, patients with HfPEF [32] and PH due to HfPEF [42] may present with a low diffusing capacity of the lung for oxygen (DLCO), an independent predictor of outcome [43]. All these potential confounding factors may lead to misclassification of PH.

The latter may be avoided by combining factors that are typically associated with group 2 PH, which include clinical features, echocardiographic abnormalities and other tests (e.g. magnetic resonance imaging and CPET) [1, 2, 39]. Interestingly, the prevalence of such risk factors in the COMPERA registry is high, particularly in an older subgroup of patients with cardiovascular comorbidities (referred to as “atypical PAH”) and in patients with PH due to HfPEF [34]. Importantly, a high rate of atrial fibrillation was reported at the time of diagnosis in IPAH, “atypical PAH” and PH due to HfPEF, in 10%, 42% and 54%, respectively.

Pre-test probability of PH due to LHD

As a single variable will unlikely be sufficient for accurate differential diagnosis, a combination of the previous features may help to determine a pre-test probability of group 2 PH. Composite scores integrating clinical and non-clinical features were derived from retrospective single-centre analyses [44–48], lacking external validation. A proposal to integrate these features is shown in table 1, some being markers of high probability of PH-LHD (previous cardiac interventions, presence of atrial fibrillation at diagnosis, evidence for structural LHD and CPET abnormalities). This approach is in line with the current strategy for the general diagnosis of PH [2, 49] and has also recently been suggested in the assessment of HfPEF [50].

Haemodynamic evaluation of PH-LHD

As a general rule, the decision for invasive confirmation of PH-LHD assumes the presence of an intermediate to high probability of PH based on symptoms and echocardiographic features, following the revised diagnostic algorithm [51]. In patients with a high probability of LHD as a cause of PH, the general management should be guided according to the recommendation for the underlying condition. In patients with an intermediate probability, invasive characterisation may be performed in patients with risk factors for PAH (e.g. systemic sclerosis), CTEPH or in cases of unexplained dyspnoea. The presence of right ventricular abnormalities also requires invasive assessment as it may have an influence on management (figure 1a). Due to the presence of multiple confounding factors and the complexity of the interpretation of invasive measurements, RHC should be performed in expert centres [2]. Provocative testing during RHC may be useful in the distinction between healthy subjects and HfPEF [51–54] or to uncover PH-LHD in patients with PAWP at the upper limit of normal (ULN) (i.e. 13–15 mmHg) [55–58]. For this purpose, both exercise testing and fluid loading are used in clinical practice (table 2).

The ULN of mPAP during an incremental dynamic exercise challenge has been suggested at >30 mmHg with a cardiac output (CO) <10 L·min⁻¹, which corresponds to a total pulmonary vascular resistance (TPR=mPAP/CO) of 3 WU [59, 60]. The ULN of PAWP during exercise is thought to be between 15 and
25 mmHg, but higher values can be recorded in elderly subjects [59, 60]. In addition, other factors may influence the interpretation of PAWP during exercise, including body position (supine versus upright, with supine values being 5 mmHg higher than upright on average), age, sex, duration of exercise and timing over the respiratory cycle [60, 61–64]. Many of these issues are discussed in a recent position paper [60].

Recent data suggest that initial increases in PAWP and mPAP in middle-aged healthy individuals do not necessarily reflect abnormal cardiopulmonary physiology, as pressures may normalise within minutes [61]. The ULN to detect an abnormal response of PAWP to exercise is therefore unknown. Some authors suggest a cut-off value of 25 mmHg for the diagnosis of heart failure [51–54], although PAWP >25 mmHg has been found in elderly individuals free of apparent CVD [61]. Finally, different cut-offs may be used according to age and sex [55, 62, 63]. Therefore, a flow-adjusted measure of PAWP may be more appropriate than PAWP alone [59, 60], with recent work suggesting a PAWP/CO slope >2 mmHg·L⁻¹·min⁻¹ is associated with reduced functional capacity, higher NT-proBNP and reduced heart failure-free survival [61].

As measurements of pressures during exercise are technically difficult and require specialised equipment, a fluid challenge may be easier to standardise and more readily available. Any condition associated with reduced left ventricular diastolic compliance or VHD will be associated with a rapid increase in PAWP when challenged with an increased systemic venous return [53, 54]. Although not as profound, fluid loading also increases PAWP in healthy volunteers as a function of age, sex, amount infused and infusion rate [52]. Thus, the standardisation of the test cut-off values for PAWP has raised controversies [53–55, 65, 66]. It has been shown that up to 20% of patients with pre-capillary PH may present an increase in PAWP >15 mmHg after fluid loading [56, 57, 65]. However, current evidence suggests a PAWP of 18–20 mmHg after infusion might represent the ULN (table 2) [53, 66]. The advantages and limitations of exercise testing and fluid loading are presented in table 3.

**Recommendations**

- The nomenclature of “PAH with cardiovascular risk factors” should be preferred over any other, to account for their coexistence without suggesting that risk factors may be influencing the cause of the PVD. The role of comorbidities in the disease process of PAH is not demonstrated and remains unclear.
- A three-step approach should be followed to perform the differential diagnosis between group 2 PH (mainly HFpEF) and PAH: 1) identification of a clinical phenotype suggesting PH-LHD, 2) determination of a pre-test probability for PH-LHD and 3) haemodynamic characterisation.
- Invasive assessment should be performed in patients with intermediate probability of PH-LHD, presence of right ventricular abnormality and when risk factors for PAH/CTEPH coexist (figure 1b).
- In patients with a PAWP 13–15 mmHg and high/intermediate probability of PH-HFpEF, provocative testing should be considered to uncover PH due to HFpEF. For technical reasons and reliability of pressure recording, a fluid challenge is preferred over exercise in the approach to differential diagnosis.
- PAWP >18 mmHg immediately after administration of 500 mL of saline over 5 min is considered abnormal.

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**TABLE 1 Pre-test probability of left heart disease (LHD) phenotype**

<table>
<thead>
<tr>
<th>Feature</th>
<th>High probability</th>
<th>Intermediate probability</th>
<th>Low probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;70 years</td>
<td></td>
<td>60–70 years</td>
<td>&lt;60 years</td>
</tr>
<tr>
<td>Obesity, systemic hypertension, dyslipidaemia, glucose intolerance/diabetes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Previous cardiac intervention#</td>
<td>Current</td>
<td>Paroxysmal</td>
<td>Normal or signs of RV strain</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Present</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Structural LHD</td>
<td>LBBB or LVH</td>
<td>Mild LVH</td>
<td>No</td>
</tr>
<tr>
<td>ECG</td>
<td>LA dilation; grade &gt;2 mitral flow</td>
<td>No LA dilation; grade &lt;2 mitral flow</td>
<td>No</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Mildly elevated V′E/V′CO₂ slope; EOV</td>
<td>Elevated V′E/V′CO₂ slope or EOV</td>
<td>High V′E/V′CO₂ slope; no EOV</td>
</tr>
<tr>
<td>Cardiac MRI</td>
<td>LA strain or LA/RA &gt;1</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

LBBB: left bundle branch block; LVH: left ventricular hypertrophy; RV: right ventricular; LA: left atrial; E/e′: early mitral inflow velocity/mitral annular early diastolic velocity ratio; CPET: cardiopulmonary exercise testing; V′E: minute ventilation; V′CO₂: carbon dioxide production; EOV: exercise oscillatory ventilation; MRI: magnetic resonance imaging; RA: right atrial. #: coronary artery and/or valvular surgical and/or non-surgical procedures, including percutaneous interventions.
However, how this should impact management is unknown. If PAH-specific therapies are initiated in patients with an “abnormal” response, caution should be exercised, including close monitoring of response and side-effects.

Clinical trials and therapy for PH due to LHD

Pathways involved in the development of PAH may contribute to the pathogenesis of heart failure and PH due to LHD, providing a rationale for investigating the role of their modulation in this setting [1, 2, 32, 39]. Until recently, most studies were performed in HFrEF patients, leading to disappointing results [1, 2, 32, 39]. The results of the ENABLE trials with bosentan were recently published, confirming that blocking endothelin-1 has no effect on outcome in patients with HFrEF [67]. The SOCRATES programme assessed the role of vericiguat, a guanylate cyclase stimulator, in HFrEF [68] and HfPEF [69]. In SOCRATES-Reduced, vericiguat did not change the NT-proBNP level at 12 weeks compared with placebo [68]. Similar results were observed in SOCRATES-Preserved, with no effect on left atrial volume index, the coprimary end-point [69]. Inhaled sodium nitrite has been shown to acutely decrease left-sided filling pressures and PAP at rest [70] and exercise [71]. However, the multicentre INDIE-HFpEF trial (ClinicalTrials.gov identifier NCT02742129) did not show a benefit of the compound on exercise capacity in HFpEF after 12 weeks [72]. Since 2013, several randomised controlled trials have been completed in patients with PH-LHD (table 4). The effects of 60 mg sildenafil 3 times a day were compared with placebo in 52 patients with PH due to HFpEF at 12 weeks [73]. No effect was observed on the primary end-point of mPAP, while a decrease in PVR and an improvement in exercise capacity were previously shown in a single-centre trial [74]. Riociguat, a guanylate cyclase stimulator, did not improve mPAP after 12 weeks in patients with PH due to HFrEF [75].

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The MELODY-I study was the only study specifically including patients with CpcPH [76]. Patients were randomised to placebo or macitentan 10 mg. The main end-point assessed a composite of significant fluid retention (weight gain ≥5% or ≥5 kg because of fluid overload or parenteral diuretic administration) or worsening in New York Heart Association Functional Class (NYHA FC) from baseline to end of treatment. Exploratory end-points included changes in NT-proBNP and haemodynamics at week 12. Treatment with macitentan was associated with a 10.1% increased risk of fluid retention versus placebo, although this did not reach statistical significance. The Kaplan–Meier estimates for survival without admission due to heart failure were 0.76 and 0.86 in the sildenafil and placebo group, respectively, mostly within the first month. At week 12, the macitentan group showed no change in PVR, mean right atrial pressure or PAWP with respect to placebo.

Finally, the SIOVAC trial aimed to determine whether treatment with sildenafil improves outcomes of patients with persistent PH after correction of VHD [77]. Patients who had undergone a successful valve replacement or repair procedure at least 1 year before inclusion were randomised to 40 mg sildenafil 3 times daily (n=104) versus placebo (n=96) for 6 months. The primary end-point was a composite clinical score combining death, hospital admission for heart failure, change in NYHA FC and patient global self-assessment. Improvement in the clinical score was significantly more frequent in the placebo group (44 versus 27 patients receiving sildenafil). In contrast, worsening was more common in the sildenafil group (33 versus 14 patients in the placebo group). The Kaplan–Meier estimates for survival without admission due to heart failure were 0.76 and 0.86 in the sildenafil and placebo group, respectively, although this did not reach statistical significance.

The typical profile of patients included in the trials modulating the nitric oxide/cGMP pathway shows an elderly (70 years) female predominance, with a high rate of atrial fibrillation at baseline (44–77%) and a high rate of atrial fibrillation at baseline (44–77%).
preserved ejection fraction in more than half of the cases. With the exception of the MELODY trial, patients had IpcPH, as shown by a combination of DPG around 2 mmHg and PVR below or slightly above 3 WU [73, 75, 77]. In contrast, the patients recruited in the MELODY trial had a typical CpcPH profile, which was associated with higher baseline NT-proBNP, reflecting worse right ventricular function [76]. Several studies using PAH therapies/pathways in PH-LHD are underway (table 5).

**PH and vasoreactivity testing in end-stage heart failure**

In the context of heart transplantation, PH is associated with an increased 30-day mortality in patients with TPG >15 mmHg and PVR >5 WU [78]. A continuous risk of morbidity and mortality increases with progressive elevation in mPAP, TPG and PVR [79]. Finally, PH reverses soon after heart transplantation, the most pronounced reduction in PVR occurring within 1 month post-transplant [80]. Implantation of a left ventricular assist device (LVAD) rapidly reduces “fixed” PH in heart transplant candidates, with survival outcomes comparable to patients without [81]. In addition, right ventricular afterload almost always declines with LVAD insertion and does so rapidly [82]. It is therefore recommended to perform RHC in all candidates before listing and at 3–6-month intervals in listed patients, especially in the presence of reversible PH or worsening heart failure [83]. LVAD recipients with at least one post-implant RHC without PH likely require less frequent assessments [84]. The current recommendations for heart transplantation suggest that an acute vasodilator challenge should be performed if sPAP >50 mmHg, and either TPG \( \geq \) 15 mmHg or PVR >3 WU and systemic systolic arterial pressure >85 mmHg [83]. However, 

| **TABLE 3** Limitations and advantages of exercise testing and fluid loading in the assessment of pulmonary hypertension |
|-----------------------------|-----------------------------|
| **Exercise testing** | **Fluid loading** |
| Clinical relevance for symptom assessment | +++ |
| Clinical relevance for differential diagnosis | + |
| Main advantages | Respects the pathophysiology; comprehensive test, allowing for additional insights in pulmonary vascular disease (dynamic pulmonary vascular resistance); complementary with cardiopulmonary exercise testing |
| | Easy to perform, no specific setting; minimal risk of misinterpretation of pressures reading; better established cut-off defining abnormal increase in pulmonary arterial wedge pressure |
| Main limitations | Requires a specific complex setting; expertise in conducting the test; pressure reading during exercise; range of normal response uncertain |
| | Unknown response in disease state; age dependency of response |
| Standardised protocol | +/- |
| | ++ |

| **TABLE 4** Recently completed randomised controlled trials targeting the phosphodiesterase type 5 inhibitor/nitric oxide and endothelin pathways in pulmonary hypertension due to left heart disease |
|-----------------------------|-------------|-------------|-------------|-------------|-------------|
| **First author or study [ref.]** | **Study drug** | **Dose** | **Subjects** | **Duration** | **Population** | **Primary outcome** | **Result** |
| Guazzi [74] | Sildenafil | 50 mg 3 times a day | 44 | 12 months | HFpEF | PVR, RV performance, CPET | Improvement |
| LEPHT [75] | Riociguat | 0.5, 1 or 2 mg 3 times a day | 201 | 16 weeks | HFrEF | mPAP versus placebo | No change |
| Hoendermis [73] | Sildenafil | 60 mg 3 times a day | 52 | 12 weeks | HFpEF | mPAP versus placebo | No change |
| SIOVAC [77] | Sildenafil | 40 mg 3 times a day | 231 | 24 weeks | VHD | Composite clinical score* | Worsening in active group |
| MELODY-1 [76] | Macitentan | 10 mg once daily | 48 | 12 weeks | HF (EF >30%); 75% HFpEF | Safety and tolerability | +10% fluid retention in active group |

Recommendations

- There is still no multicentre trial that suggests targeting PH-LHD with PAH-specific drugs is beneficial. Therefore, we maintain a strong recommendation against the use of PAH therapies in group 2 PH.
- In addition, a safety signal should be acknowledged: 1) the use of sildenafil in the context of PH post-VHD intervention is associated with an increased risk of clinical deterioration and death, and 2) the use of macitentan in CpcPH due to heart failure is associated with an increased risk of fluid retention.
- Following the MELODY-1 trial, new standards have been proposed to explore the role of PAH-approved therapies in the context of group 2 PH. If pursued, such trials should be limited to PH due to HFP EF with CpcPH. The agent of choice should ideally be a HFP EF disease-modifying drug. Finally, a proof-of-concept study should be performed first, with safety and tolerability, haemodynamic and/or CPET efficacy end-points.
- Vasoreactivity testing is not recommended in patients with PH-LHD, outside of the context of assessment for heart transplantation.

Conclusions

PH is common in LHD; it is not a disease, although a subset of patients present with significant pulmonary vascular changes. Clinical research and prospective long-term multicentre analysis of PH-HFpEF cohorts may help to better identify risk factors for CpcPH and provide insights on outcome predictors. A pre-test probability assessment of LHD should be part of the diagnostic approach of PH. Further studies are needed to develop a multidimensional prediction score. Invasive confirmation on RHC requires attention to accurate resting PAWP measurement, at end-diastole and end-expiration. An increase of PAWP >18 mmHg after fluid loading, in patients with resting values between 13 and 15 mmHg and

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**TABLE 5** Planned and ongoing trials in pulmonary hypertension (PH) due to left heart disease

<table>
<thead>
<tr>
<th>Study#</th>
<th>Study drug</th>
<th>Dose</th>
<th>Subjects</th>
<th>Duration</th>
<th>Population</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERENADE (NCT03153111)</td>
<td>Macitentan</td>
<td>10 mg once daily</td>
<td>300</td>
<td>52 weeks</td>
<td>LVEF &gt;40% and ESC-defined HFpEF; HF hospitalisation within 12 months and/or PAWP or LVEDP &gt;15 mmHg within 6 months; elevated NT-proBNP; PVD or RVD</td>
<td>% change from baseline in NT-proBNP at week 24</td>
</tr>
<tr>
<td>SOPRANO (NCT02554903)</td>
<td>Macitentan</td>
<td>10 mg once daily</td>
<td>78</td>
<td>12 weeks</td>
<td>LVAD within 45 days; PH by RHC with PAWP ≤18 mmHg and PVR &gt;3 WU</td>
<td>PVR ratio of week 12 to baseline</td>
</tr>
<tr>
<td>DYNAMIC (NCT02744339)</td>
<td>Oral riociguat</td>
<td>1.5 mg 3 times a day</td>
<td>114</td>
<td>26 weeks</td>
<td>HFpEF; mPAP &gt;25 mmHg and PAWP &gt;15 mmHg</td>
<td>Change in CO</td>
</tr>
<tr>
<td>Oral treprostinil (NCT03037580)</td>
<td>Oral treprostinil</td>
<td>Oral</td>
<td>310</td>
<td>24 weeks</td>
<td>LVEF &gt;50%; RHC within 90 days of randomisation; 6MWD &gt;200 m</td>
<td>Change in 6MWD from baseline to week 24</td>
</tr>
<tr>
<td>PASSION (not registered)</td>
<td>Oral tadalafil</td>
<td>40 mg once daily</td>
<td>320</td>
<td>NA</td>
<td>HFpEF; PH with PAWP &gt;15 mmHg and mPAP &gt;25 mmHg and PVR &gt;3 WU</td>
<td>Time to first event defined as HF-associated hospitalisation (independently adjudicated) or death from any cause</td>
</tr>
</tbody>
</table>

#: ClinicalTrials.gov identifier numbers are provided where possible. LVEF: left ventricular ejection fraction; ESC: European Society of Cardiology; HF: heart failure; pEF: preserved ejection fraction; PAWP: pulmonary arterial wedge pressure; LVEDP: left ventricular end-diastolic pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; PVD: pulmonary vascular disease; RVD: right ventricular dysfunction; LVAD: left ventricular assist device; RHC: right heart catheterisation; PVR: pulmonary vascular resistance; mPAP: mean pulmonary arterial pressure; CO: cardiac output; 6MWD: 6-min walk distance; NA: not available.
intermediate/high probability of HFpEF, may be considered abnormal. However, we strongly encourage further study of this population as well as non-haemodynamic, alternative strategies to differentiate IpcPH and CpcPH. The CpcPH haemodynamic presentation is now defined by PVR >3 WU on top of a post-capillary PH phenotype. Finally, multicentre randomised trials using PAH therapies in PH-LHD have not demonstrated benefit and have raised safety concerns. Their use is still not recommended in PH-LHD.

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Pulmonary hypertension in chronic lung disease and hypoxia

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State of the art and research perspectives in pulmonary hypertension in chronic lung disease and hypoxia http://ow.ly/XcW730meWxy


ABSTRACT Pulmonary hypertension (PH) frequently complicates the course of patients with various forms of chronic lung disease (CLD). CLD-associated PH (CLD-PH) is invariably associated with reduced functional ability, impaired quality of life, greater oxygen requirements and an increased risk of mortality. The aetiology of CLD-PH is complex and multifactorial, with differences in the pathogenic sequelae between the diverse forms of CLD. Haemodynamic evaluation of PH severity should be contextualised within the extent of the underlying lung disease, which is best gauged through a combination of physiological and imaging assessment. Who, when, if and how to screen for PH will be addressed in this article, as will the current state of knowledge with regard to the role of treatment with pulmonary vasoactive agents. Although such therapy cannot be endorsed given the current state of findings, future studies in this area are strongly encouraged.

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Introduction
This article provides an update on pulmonary hypertension (PH) associated with chronic lung disease (CLD), with the main focus being on chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) [1]. There is evidence that PH is associated with other CLDs such as cystic fibrosis and bronchopulmonary dysplasia [2, 3]. CLD-associated PH (CLD-PH) is clearly linked with reduced functional status and worse outcomes [4, 5]. Even in patients who fulfill diagnostic criteria for group 1 pulmonary arterial hypertension (PAH), the presence of minor lung disease affects survival [6]. Moreover, there is data suggesting that mean pulmonary arterial pressure (mPAP) ≤25 mmHg is associated with worse outcome in CLD-PH [7, 8]. Whether the presence of PH is causative or a surrogate of other factors affecting outcomes remains largely uncertain.

PH in the context of acute exacerbations of the various CLDs will not be discussed. However, it is important that defining PH should not be undertaken during an acute exacerbation, but under stable conditions. For purposes of consistent nomenclature, the lung condition will be mentioned first, followed by “-PH” since mostly it is the lung condition which initially manifests clinically.

Epidemiology and clinical relevance of PH in lung disease

Chronic obstructive lung disease
The prevalence of PH in COPD (COPD-PH) is in general dependent on the severity of the disease, but also on the definition of PH and the method of diagnostic assessment. Specific genetic signatures are also linked with the development of PH in COPD [9]. Several studies in patients with spirometric Global Initiative for Chronic Obstructive Lung Disease stage IV showed that up to 90% have mPAP >20 mmHg, with most ranging between 20 and 35 mmHg. Approximately 1–5% of COPD patients have mPAP >35–40 mmHg at rest [10]. Even under moderate exercise conditions, COPD patients may show a rapid rise in mPAP, indicating loss of lung vasculature, vascular distensibility and/or vessel recruitment capability. In addition, exercise PH in COPD may be due to comorbid left heart disease. There is a cluster of patients representing a “pulmonary vascular COPD phenotype”, characterised by less severe airflow limitation, hypoxaemia, very low diffusing capacity of the lung for carbon monoxide (DLCO), normo- or hypocapnia and a cardiovascular exercise limitation profile [11]. Interestingly, the vascular lesions in COPD-PH patients are morphologically similar to those in idiopathic PAH (IPAH). It has previously been established that the presence of PH has a stronger association with mortality in COPD than forced expiratory volume in 1 s (FEV1) or gas exchange variables [1]. In addition, an enlarged pulmonary artery diameter, as detected by computed tomography (CT) scan, predicts hospitalisation due to acute COPD exacerbation [4, 12].

Idiopathic pulmonary fibrosis and other idiopathic interstitial pneumonias
Most of the data on the prevalence and impact of PH complicating fibrotic lung disorders emanates from the idiopathic pulmonary fibrosis (IPF) literature. In IPF, mPAP ≥25 mmHg has been reported in 8–15% of patients upon initial work-up, with greater prevalence in advanced (30–50%) and end-stage (>60%) disease [13–15]. Additionally, echocardiography studies have suggested a high prevalence of PH [16]. However, echocardiography and other non-invasive measures, including an enlarged main pulmonary artery on CT scan, are limited in their accuracy to detect PH in lung diseases, thus serving as screening tools only [16, 17]. Nonetheless, both of these modalities have been shown to provide independent prognostic information in patients with fibrotic lung disease. In most patients, PH is mild to moderate, but may also be severe [14]. One longitudinal study suggested that mPAP increases by around 1.8 mmHg per year, but rapid progression of PH has also been reported in late-stage IPF patients [18]. Intriguingly, there is limited correlation between PH severity and lung function impairment or high-resolution CT fibrosis score [14–16, 19, 20], whereas distinct gene signatures have been observed in IPF-PH lungs [21]. PH may also be associated with an increased risk for acute exacerbation in advanced IPF [22]. Adverse outcomes with mPAP thresholds ≥25 mmHg have been reported in IPF. Indeed, the prognosis of fibrotic idiopathic interstitial pneumonia (IIP) with PH is worse than IPAH [23].

Combined pulmonary fibrosis and emphysema, and other lung diseases
Combined pulmonary fibrosis and emphysema (CPFE) is currently defined by the simultaneous presence of emphysema in the upper lobes and fibrosis in the lower lobes on chest CT. Patients with CPFE are particularly prone to develop PH, with estimates suggesting a prevalence of 30–50% [24]. Typically, normal or mildly abnormal lung volumes and the absence of airflow obstruction are accompanied by a markedly impaired diffusion capacity, significant hypoxaemia and PH. The PH appears to contribute to the functional limitation in CPFE and is associated with poor survival [24, 25].
Sarcoidosis

The prevalence of PH in sarcoidosis ranges from 5.7% to 74% [26]. Sarcoidosis-PH has a reported 5-year survival of 50–60% [27, 28]. While the vast majority of patients with sarcoidosis-PH have extensive parenchymal disease, it may also occur in patients without pulmonary fibrosis [27–29]. The mechanisms underlying PH in sarcoidosis are complex, and include fibrosis-associated remodelling and obliteration of pulmonary vessels, extrinsic compression of central pulmonary vessels by lymphadenopathy or mediastinal fibrosis, pulmonary veno-occlusive-like lesions, granulomatous involvement of pulmonary vessels, left ventricular dysfunction, and portopulmonary hypertension [27].

Other CLDs

The prevalence of PH in patients with pulmonary Langerhans cell histiocytosis is high, with haemodynamic features frequently resembling PAH, while PH complicating lymphangioleiomyomatosis tends to be mild to moderate and mostly related to the extent of parenchymal involvement [30, 31]. PH may complicate the course of adults with a history of bronchopulmonary dysplasia and cystic fibrosis [2, 3]. PH may also develop in patients with chronic hypersensitivity pneumonitis and, possibly, lung cancer [32, 33].

Detection of PH in CLD

Non-invasive modalities that might raise suspicion for the presence of PH in CLD include circulating biomarkers, pulmonary function testing, echocardiography and imaging (figure 1). Plasma levels of brain

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**FIGURE 1** Evaluation of pulmonary hypertension (PH) in chronic lung disease (CLD). FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; CT: computed tomography; PAH: pulmonary arterial hypertension; RCT: randomised controlled trial; DLCO: diffusing capacity of the lung for carbon monoxide; KCO: transfer coefficient of the lung for carbon monoxide. #: suggestive findings include: 1) symptoms and signs (dyspnoea out of proportion, loud P2, signs of right heart failure, right axis deviation on ECG, elevated natriuretic peptide levels); 2) pulmonary function test abnormalities (low DLCO e.g. <40% of predicted), elevated %FVC/%DLCO ratio (low KCO); 3) exercise test findings (including decreased distance, decreased arterial oxygen saturation or increased Borg rating on 6-min walk test and decreased circulatory reserve, preserved ventilatory reserve on cardiopulmonary exercise testing); and 4) imaging findings (extent of LD, enlarged pulmonary artery/aorta diameter ratio >1 on CT). ¶: signs supporting the diagnosis of PH include elevated systolic pulmonary arterial pressure and signs of right ventricular dysfunction. However, echocardiography measures are only suggestive and have limited accuracy in patients with CLD. §: strongly consider referring the patient to a PH expert centre. ¶: expert centres should comprise multidisciplinary teams. Any decision for individualised treatment should follow a goal-orientated approach with predefined treatment targets, to be stopped if these targets are not met after a predefined time period.
natriuretic peptide (BNP) or N-terminal pro-BNP are elevated in severe CLD-PH, but have less sensitivity and specificity for moderate PH and may be confounded by left heart abnormalities [34, 35]. In both ILD and COPD, PH is generally associated with a lower DLCO, diminished exercise capacity and more impaired gas exchange at rest or during exercise than expected based on ventilatory impairments [14, 16, 19, 36, 37].

Echocardiography is considered the best non-invasive modality to screen for CLD-PH. However, the ability to determine peak tricuspid regurgitation velocity to estimate the right ventricular systolic pressure is limited in these patients [38]. Alternate echocardiographic measures including right ventricular outflow tract diameter, tricuspid annular plane systolic excursion, and qualitative assessment of right chamber structure and function have been advocated in IPF and COPD [39, 40].

The ratio of the main pulmonary artery to ascending aorta diameter on imaging may predict PH in both COPD and IPF, with a ratio >1 (range 0.9–1.1) suggested as a threshold [12, 41, 42]. Combining the pulmonary artery/aorta diameter ratio and other non-invasive measures (including echocardiographic and physiological variables) improves the accuracy of predicting PH [36, 41].

Right heart catheterisation (RHC) remains the gold standard for the diagnosis of CLD-PH. However, suspicion for underlying PH does not always mandate performance of RHC in patients with established lung disease if there is no therapeutic or management consequence.

**Recommendations**

**When to perform RHC**

RHC should be performed in patients with CLD when significant PH is suspected and the patient’s management will likely be influenced by RHC results, including referral for transplantation, inclusion in clinical trials or registries, treatment of unmasked left heart dysfunction, or compassionate use of therapy.

RHC may be considered when:

1. Clinical worsening, progressive exercise limitation and/or gas exchange abnormalities are not deemed attributable to ventilatory impairment.
2. An accurate prognostic assessment is deemed sufficiently important.

**Pressure measurements during RHC**

As a result of exaggerated changes in intrathoracic pressures during the breathing cycle in patients with lung disease, a floating average over several breaths (without a breath hold) is suggested for measurement of mean pressures, including the pulmonary capillary wedge pressure.

We suggest adapting the definition for PH in the context of CLD-PH:

1. CLD without PH (mPAP <21 mmHg, or mPAP 21–24 mmHg with pulmonary vascular resistance (PVR) <3 Wood Units (WU)).
2. CLD with PH (mPAP 21–24 mmHg with PVR ≥3 WU, or mPAP 25–34 mmHg) (CLD-PH).
3. CLD with severe PH (mPAP ≥35 mmHg, or mPAP ≥25 mmHg with low cardiac index (<2.0 L·min⁻¹·m⁻²)) (CLD-severe PH).

The rationale for the choice of mPAP ≥35 mmHg as a cut-off for severe PH follows previously presented evidence [1]. There are currently no valid data to support the routine use of acute vasodilator testing in CLD-PH.

The randomised controlled trials (RCTs) in group 1 for PAH therapies set exclusion criteria using pulmonary function testing in the following ranges: total lung capacity <60–70% of predicted, FEV1 <55–80% of predicted or FEV1/forced vital capacity (FVC) ratio <50–70%. PAH studies have not previously utilised chest imaging to exclude patients with lung disease; indeed, it is possible that a number of patients with lung volumes above these inclusion thresholds might have an underappreciated burden of parenchymal lung disease. However, lung diseases (especially COPD) are common conditions and PAH developing in such patients may not be attributable to these diseases, but may be coincidental. Criteria for discrimination between group 1 and group 3 PH are summarised in table 1. The spectrum of severity of both the pulmonary vascular and parenchymal lung disease is likely a continuum, which often makes the distinction between group 1 and group 3 PH very difficult. When there is uncertainty whether to classify a patient with lung disease and PH into group 1 or group 3, then the patient should be referred to centres with expertise in both PH and CLD.

**Treatment of PH due in CLD: evidence for appropriate risk–benefit balance of PAH-targeted therapy**

The underlying lung disease should be optimally treated according to current guidelines. Long-term oxygen treatment (LTOT) makes intuitive sense in patients with lung disease who are hypoxaemic.
However, it has only been prospectively evaluated in COPD. In stabilised hypoxaemic COPD patients, LTOT for 15 h per day prevented the progressive increase of mPAP and when used for >18 h per day produced a slight decrease of mPAP [43, 44]. However, in COPD patients with moderate resting oxygen desaturation (\(S_pO_2 89–93\%\)) or exercise-induced oxygen desaturation (\(S_pO_2 <90\%\) for \(\geq 10\) s), LTOT does not provide benefit in terms of survival or hospitalisations [45]. Evidence for the beneficial effect of LTOT in ILD is less clear than in COPD and there are no studies addressing the impact of LTOT on PH associated with this group of diseases [46].

Safety and efficacy of PAH-targeted therapy in CLD-PH has been evaluated in recent years; however, there have only been a few RCTs in ILD, COPD and sarcoidosis. Pertinent studies which included more than 20 participants are shown in table 2.

### COPD

**Effect on pulmonary haemodynamics**

Long-term use of PAH-targeted therapy improves pulmonary haemodynamics in COPD patients with PH, as shown in two different meta-analyses [47, 48]. Beneficial haemodynamic effects with long-term PAH therapy, assessed by RHC, have been demonstrated with both sildenafil and bosentan [49, 50].

**Effect on exercise tolerance, symptoms and quality of life**

The effect of PAH-targeted therapy on exercise capacity in patients with COPD-PH is less apparent. Two meta-analyses failed to show significant improvement in 6-min walk distance (6MWD), whereas a third reported an improvement in 6MWD in COPD patients with demonstrated PH [47, 48, 51].

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**TABLE 1 Criteria favouring group 1 versus group 3 pulmonary hypertension (PH)**

<table>
<thead>
<tr>
<th>Criteria favouring group 1 (PAH)</th>
<th>Testing</th>
<th>Criteria favouring group 3 (PH due to lung disease)</th>
</tr>
</thead>
</table>
| **Extent of lung disease** | Pulmonary function testing | Moderate to very severely impaired:  
FEV1 <60% pred (COPD)  
Low diffusion capacity in relation to obstructive/restrictive changes |
| Absence of or only modest airway or parenchymal abnormalities | High-resolution CT scan | Characteristic airway and/or parenchymal abnormalities |
| **Haemodynamic profile** | Right heart catheterisation | Mild-to-moderate PH |
| **Ancillary testing** | **Present** | **Absent** |
| Features of exhausted circulatory reserve:  
Preserved breathing reserve  
Reduced oxygen pulse  
Low CO\(\text{/V'O}_2\) slope  
Mixed venous oxygen saturation at lower limit  
No change or decrease in \(P_{OCO_2}\) during exercise | Cardiopulmonary exercise test* | Features of exhausted ventilatory reserve:  
Reduced breathing reserve  
Normal oxygen pulse  
Normal CO\(\text{/V'O}_2\) slope  
Mixed venous oxygen saturation above lower limit  
Increase in \(P_{OCO_2}\) during exercise |

\(P_{OCO_2}\): arterial carbon dioxide tension. *: based on the diagnostic criteria of these groups; ¶: parenchymal changes linked to pulmonary veno-occlusive disease may be discriminated from those associated with diffuse parenchymal lung diseases; +: features of a limited circulatory reserve may be noted in severe COPD-PH and severe IPF-PH.

PAH: pulmonary arterial hypertension; FEV1: forced expiratory volume in 1 s; COPD: chronic obstructive pulmonary disease; FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis; CT: computed tomography; BMPR2: bone morphogenetic protein receptor type 2; CO: cardiac output; \(V'O_2\): oxygen uptake; \(P_{OCO_2}\): arterial carbon dioxide tension.
<table>
<thead>
<tr>
<th>First author [year] [ref.]</th>
<th>Subjects</th>
<th>Inclusion criteria</th>
<th>Study design</th>
<th>Diagnosis of PH Baseline haemodynamics*</th>
<th>Baseline PFTs*</th>
<th>Therapy</th>
<th>Duration</th>
<th>Primary end-point result</th>
<th>Other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td><strong>VONBANK</strong> (2003) [86]</td>
<td>40</td>
<td>COPD on supplemental oxygen with PH by RHC</td>
<td>RCT (open label)</td>
<td>RHC; mPAP ≥25 mmHg</td>
<td>mPAP 27.6±4.4 mmHg, CI 2.7±0.6 L·min⁻¹·m⁻²</td>
<td>FEV₁ 0.9±0.4 L, FEV₁/FVC 44.5%</td>
<td>“Pulsed” nitric oxide with oxygen vs oxygen</td>
<td>3 months</td>
</tr>
<tr>
<td><strong>STOLZ</strong> (2008) [53]</td>
<td>30</td>
<td>GOLD II–IV; no haemodynamic requirement</td>
<td>RCT (2:1)</td>
<td>Echo</td>
<td>sPAP 32 (29–38) mmHg</td>
<td>Not reported</td>
<td>Bosentan 125 mg 2 times daily</td>
<td>12 weeks</td>
<td>6MWD, no change</td>
</tr>
<tr>
<td><strong>VALERIO</strong> (2009) [50]</td>
<td>32</td>
<td>COPD with PH by RHC</td>
<td>RCT (open label)</td>
<td>RHC</td>
<td>mPAP 37±5 mmHg</td>
<td>FEV₁ 37±18%</td>
<td>Bosentan 125 mg 2 times daily</td>
<td>18 months</td>
<td>No defined primary</td>
</tr>
<tr>
<td><strong>RAO</strong> (2011) [87]</td>
<td>33</td>
<td>GOLD III–IV</td>
<td>RCT</td>
<td>Echo</td>
<td>sPAP 52.7±11.9 mmHg</td>
<td>FEV₁ 35±18%</td>
<td>Sildenafil 20 mg 2 times daily</td>
<td>12 weeks</td>
<td>6MWD, increased 190 m</td>
</tr>
<tr>
<td><strong>BLANCO</strong> (2013) [88]</td>
<td>60</td>
<td>COPD with PH by RHC or echo</td>
<td>RCT</td>
<td>RHC; mPAP ≥25 mmHg; echo: sPAP ≥35 mmHg</td>
<td>sPAP 42±10 mmHg, mPAP 31±5 mmHg</td>
<td>FEV₁ 32±11%</td>
<td>Sildenafil 20 mg or placebo 3 times daily and PR</td>
<td>3 months</td>
<td>Exercise endurance time, no change</td>
</tr>
<tr>
<td><strong>GOODE</strong> (2014) [89]</td>
<td>120</td>
<td>COPD with PH by echo</td>
<td>RCT</td>
<td>Echo: pulmonary acceleration time &lt;120 ms or sPAP &gt;30 mmHg</td>
<td>Echo: sPAP 42±10 mmHg</td>
<td>FEV₁ 41±16%</td>
<td>Tadalafil 10 mg daily</td>
<td>12 weeks</td>
<td>6MWD, no change</td>
</tr>
<tr>
<td><strong>VITULO</strong> (2016) [49]</td>
<td>28</td>
<td>COPD with PH by RHC</td>
<td>RCT (2:1)</td>
<td>RHC; mPAP &gt;35 mmHg (if FEV₁ &lt;30%)</td>
<td>mPAP 39±8 mmHg, CI 2.4±0.5 L·min⁻¹·m⁻², PVR 7±2.6 WU</td>
<td>FEV₁ 54±22%, D₁CO 35±12%</td>
<td>Sildenafil 20 mg 3 times daily</td>
<td>16 weeks</td>
<td>PVR, decreased 1.4 WU</td>
</tr>
<tr>
<td><strong>HAN</strong> (2013) [90]</td>
<td>119</td>
<td>IPF with echo available (66% of the whole cohort)</td>
<td>RCT</td>
<td>Echo: RVSD</td>
<td>Not available</td>
<td>FVC 57%, D₁CO 26%</td>
<td>Sildenafil 20 mg 3 times daily</td>
<td>12 weeks</td>
<td>6MWD, less decline in patients with RVSD on sildenafil</td>
</tr>
<tr>
<td><strong>CORTE</strong> (2014) [40]</td>
<td>60</td>
<td>IPF or idiopathic fibrotic NSIP</td>
<td>RCT (2:1)</td>
<td>RHC; mPAP ≥25 mmHg</td>
<td>mPAP 37±9.9 mmHg, CI 2.2±0.5 L·min⁻¹·m⁻²</td>
<td>FVC 55.7±20%, D₁CO 45±22%</td>
<td>Bosentan</td>
<td>16 weeks</td>
<td>PVRI decrease of 20%, negative</td>
</tr>
<tr>
<td><strong>RAO</strong> (2015) [14]</td>
<td>68</td>
<td>IPF with group 2 PH (14% of whole cohort)</td>
<td>RCT (2:1)</td>
<td>RHC</td>
<td>mPAP 30±8 mmHg</td>
<td>FVC 67±12%, D₁CO 39±15%</td>
<td>Ambrisentan 10 mg·day⁻¹</td>
<td>Event-driven study terminated early</td>
<td>Disease progression, unfavourable trend</td>
</tr>
<tr>
<td><strong>NATHAN</strong> (2017) [57]</td>
<td>147</td>
<td>IIP, FVC &gt;45%, mPAP &gt;25 mmHg</td>
<td>RCT</td>
<td>RHC</td>
<td>mPAP 33.2±8.2 mmHg, CI 2.6±0.7 L·min⁻¹·m⁻²</td>
<td>FVC 76.3±19%, D₁CO 32±12%</td>
<td>Riociguat 2.5 mg 3 times daily</td>
<td>26 weeks</td>
<td>6MWD, no difference at study halt</td>
</tr>
</tbody>
</table>
Sarcoidosis

<table>
<thead>
<tr>
<th>First author [year] [ref.]</th>
<th>Subjects</th>
<th>Inclusion criteria</th>
<th>Study design</th>
<th>Diagnosis of PH</th>
<th>Baseline haemodynamics</th>
<th>Baseline PFTs</th>
<th>Therapy</th>
<th>Duration</th>
<th>Primary end-point result</th>
<th>Other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnett (2009) [65]</td>
<td>22</td>
<td>Any SAPH and treatment with PAH therapy</td>
<td>Retrospective case series</td>
<td>RHC</td>
<td>mPAP 46.1±2.7 mmHg, CO 4.2±0.4 L·min⁻¹</td>
<td>FVC 53.6±3.3%, FEV1 51.2±3.7%</td>
<td>Bosentan, sildenafil</td>
<td>Median (range) 11 (5.2–46.6) months</td>
<td>6MWD improved by 59 m</td>
<td>NYHA FC improvement in nine patients</td>
</tr>
<tr>
<td>Baughman (2009) [66]</td>
<td>22</td>
<td>Any SAPH</td>
<td>Prospective open label</td>
<td>RHC</td>
<td>mPAP 33 [20–62] mmHg, CO 5.9 [3.1–9.5] L·min⁻¹, PVR 5.1 [1.96–16.3] WU</td>
<td>FVC 50% [41–101%], FEV1/FVC 73% [53–91%]</td>
<td>Inhaled iloprost</td>
<td>4 months</td>
<td>6MWD unchanged 0.6±40 m</td>
<td>7 patients withdrew; 6 patients with ≥20% decrease in PVR and 3 patients with ≥30 m increase in 6MWD</td>
</tr>
<tr>
<td>Judson (2011) [91]</td>
<td>25</td>
<td>mPAP &gt;25 mmHg, PVR &gt;3 WU, FVC &gt;40%, WHO FC II or III, 6MWD 150–450 m</td>
<td>Prospective open label</td>
<td>RHC</td>
<td>mPAP 32.7±3 mmHg, CO 4.4±0.94 L·min⁻¹, PVR 5.86±2.3 WU</td>
<td>FEV1 59±21%, FVC 61.5±16.5%</td>
<td>Ambrisentan 10 mg daily</td>
<td>24 weeks</td>
<td>None identified</td>
<td>11 patients discontinued drug at 12 weeks; 10 out of 21 patients who completed had improvements in WHO FC and QoL</td>
</tr>
<tr>
<td>Baughman (2014) [67]</td>
<td>39</td>
<td>mPAP &gt;25 mmHg, NYHA FC II or III</td>
<td>RCT (2:1)</td>
<td>RHC</td>
<td>mPAP 36±7 mmHg, CI 2.6±0.7 L·min⁻¹·m⁻²</td>
<td>FVC 60±16.6%</td>
<td>Bosentan</td>
<td>16 weeks</td>
<td>Decrease in mPAP to 32 mmHg</td>
<td>No change in 6MWD; PVR decreased from 6.1 to 4.4 WU</td>
</tr>
<tr>
<td>Keir (2014) [92]</td>
<td>33</td>
<td>Any SAPH</td>
<td>Retrospective case series</td>
<td>RHC</td>
<td>mPAP 44±8.6 mmHg, PVR 10±5.1 WU, CI 2.1±0.6 L·min⁻¹·m⁻², TAPSE 17±5 [8–27] mm</td>
<td>FEV1 51.8±18.3%, FVC 64.8±22.3%</td>
<td>Sildenafil n=29, bosentan n=4</td>
<td>6 months</td>
<td>None identified</td>
<td>6MWD improved 14 m; BNP and TAPSE improved</td>
</tr>
<tr>
<td>Bonham (2015) [93]</td>
<td>26</td>
<td>Any treated SAPH, no left-sided disease</td>
<td>Retrospective case series</td>
<td>RHC</td>
<td>mPAP 46 [38–56] mmHg, CI 2.1 [1.8–2.6] L·min⁻¹·m⁻², PVR 8.3 [5.7–11.1] WU</td>
<td>FEV1 48% [38–59%], FVC 48% [44–64%], DLCO 27% [25–44%]</td>
<td>Epoprostenol n=7, treprostinil n=6, ERA n=12, PDE5i n=20</td>
<td>Variable</td>
<td>None identified</td>
<td>Increased CI/CO, decreased PVR (median 17.2 months in 10 prostacyclin patients) and improved N-terminal pro-BNP</td>
</tr>
</tbody>
</table>

PH: pulmonary hypertension; PFT: pulmonary function test; COPD: chronic obstructive pulmonary disease; RHC: right heart catheterisation; mPAP: mean pulmonary arterial pressure; CI: cardiac index; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PVR(I): pulmonary vascular resistance (index); CO: cardiac output; GOLD: Global Initiative for Chronic Obstructive Lung Disease; sPAP: systolic PAP; 6MWD: 6-min walk distance; QoL: quality of life; BODE: body mass, airflow obstruction, dyspnoea, exercise capacity; echo: echocardiography; PR: pulmonary rehabilitation; V0₂: oxygen uptake; BNP: brain natriuretic peptide; SaO₂: arterial oxygen saturation; WU: Wood Units; DLCO: diffusing capacity of the lung for carbon monoxide; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; RVSD: right ventricular systolic dysfunction; NSIP: non-specific interstitial pneumonia; KCO: transfer coefficient of the lung for carbon monoxide; IIP: idiopathic interstitial pneumonia; SAPH: sarcoidosis-associated PH; NYHA: New York Heart Association; FC: Functional Class; WHO: World Health Organization; TAPSE: tricuspid annular plane systolic excursion; ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor. #: for RCTs, the data for the treatment arm are reported as mean±SD or median (interquartile range); ¶: subgroup analysis of the ARTEMIS-IPF trial (study performed to evaluate the antifibrotic effects of the study medication, not all patients had PH).}

PH: pulmonary hypertension; PFT: pulmonary function test; COPD: chronic obstructive pulmonary disease; RHC: right heart catheterisation; mPAP: mean pulmonary arterial pressure; CI: cardiac index; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PVR(I): pulmonary vascular resistance (index); CO: cardiac output; GOLD: Global Initiative for Chronic Obstructive Lung Disease; sPAP: systolic PAP; 6MWD: 6-min walk distance; QoL: quality of life; BODE: body mass, airflow obstruction, dyspnoea, exercise capacity; echo: echocardiography; PR: pulmonary rehabilitation; V0₂: oxygen uptake; BNP: brain natriuretic peptide; SaO₂: arterial oxygen saturation; WU: Wood Units; DLCO: diffusing capacity of the lung for carbon monoxide; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; RVSD: right ventricular systolic dysfunction; NSIP: non-specific interstitial pneumonia; KCO: transfer coefficient of the lung for carbon monoxide; IIP: idiopathic interstitial pneumonia; SAPH: sarcoidosis-associated PH; NYHA: New York Heart Association; FC: Functional Class; WHO: World Health Organization; TAPSE: tricuspid annular plane systolic excursion; ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase type 5 inhibitor. #: for RCTs, the data for the treatment arm are reported as mean±SD or median (interquartile range); ¶: subgroup analysis of the ARTEMIS-IPF trial (study performed to evaluate the antifibrotic effects of the study medication, not all patients had PH).
The effect of PAH-targeted therapy on dyspnoea or quality of life measures in COPD-PH is also generally disappointing when evaluated in RCTs [47, 48]. However, one recent study conducted in COPD patients with severe PH showed that sildenafil significantly improved the BODE (body mass, airflow obstruction, dyspnoea, exercise capacity) index, the modified Medical Research Council scale and the Short Form-36 general health domain [49]. Taken together, the available studies do not provide clear evidence that the effect of PAH-targeted therapy on pulmonary haemodynamics in COPD-PH translates into an improvement in exercise tolerance and symptoms.

**Effect on oxygenation**

Vasodilator treatment may worsen gas exchange due to the inhibition of hypoxic pulmonary vasoconstriction, thereby increasing ventilation/perfusion mismatching in COPD [52]. Evidence for a long-term benefit of PH therapy in COPD-PH is heterogeneous [47]. While deterioration of gas exchange was shown in some studies with the long-term use of bosentan or sildenafil, no change was observed in others using sildenafil or tadalafil [49, 53, 54] and rarely resulted in treatment withdrawal [55]. It is important to note that any reduction in oxygenation related to pulmonary vasodilation might be compensated for by an increased cardiac output that may maintain or even improve tissue oxygen delivery, especially with exercise.

**Conclusion**

Although preliminary evidence suggests that currently available vasoactive medications may have a benefit in COPD-PH patients with mPAP $\geq 35$ mmHg, further studies are required before PAH therapies can be recommended. Therefore, these patients should be a target population for larger prospective studies. This does not preclude COPD patients with lower mPAP being enrolled in future studies, especially if the cardiac index is low or PVR is significantly elevated.

**Idiopathic interstitial pneumonias**

**Safety**

Treatment with PAH-targeted therapies in patients with IIP has yielded important safety signals in some RCTs. The ARTEMIS study was terminated prematurely because an interim analysis indicated that ambrisentan-treated patients with IPF were more likely to have disease progression, particularly hospitalisations due to respiratory events [56]. Thus, ambrisentan is contraindicated in patients with IPF. The RISE-IIP trial evaluated the effect of riociguat on 6MWD in patients with IIP. The study was terminated early on the basis of interim results showing increased mortality and risk of serious adverse events in the riociguat group [57]. Accordingly, riociguat is contraindicated in patients with IIP-PH.

**Effect on pulmonary haemodynamics**

Uncontrolled studies have shown improvement in pulmonary haemodynamics in patients with IIP-PH using riociguat and treprostinil [58, 59]. However, RCTs have failed to substantiate such an improvement in this population. The BPHIT study did not show significant changes in pulmonary haemodynamics in patients with IIP-PH treated with bosentan during 16 weeks [60]. The ARTEMIS-IPF trial also failed to show any significant effect of ambrisentan on pulmonary haemodynamics in the subgroup of patients who underwent a second assessment with RHC [14].

**Effect on exercise tolerance**

A recent meta-analysis did not show improvement in 6MWD in patients with ILD-PH treated with PAH-targeted therapy [48]. The STEP-IPF study, which was enriched for underlying IPF-PH by the inclusion of patients with DLCO $<35\%$ of predicted, failed to meet its primary end-point of a 20\% increase in the 6MWT distance [61]. In contrast, open-label studies with sildenafil, riociguat and treprostinil did show significant improvements in 6MWD, with an average increase of 46 m over baseline [48]. The largest observational study to date of severe IIP-PH patients (n=151) found that the improvement in 6MWD at 6 months in response to PAH therapy was equivalent to that seen in IPAH patients [23].

**Effect on symptoms and quality of life**

The effect of PAH-targeted therapy on symptomatic burden in patients with PH-ILD has been assessed in two RCTs and three open-label studies [48]. The STEP-IPF study also demonstrated a positive effect of sildenafil on quality of life compared with the placebo arm, while one study showed significant improvement in shortness of breath using treprostinil [59, 61]. The remaining studies failed to show significant change in quality of life questionnaires or dyspnoea scales [48].
**Effect on oxygenation**

In ILD, the acute administration of aerosolised iloprost, inhaled nitric oxide or sildenafil does not worsen ventilation/perfusion relationships. In contrast, acute administration of i.v. epoprostenol causes deterioration of gas exchange due to increased perfusion in non-ventilated alveolar units [62–64]. In longer-term studies, treatment with PAH-targeted therapy did not result in worsening of gas exchange in patients with ILD [48].

**Conclusion**

Riociguat and ambrisentan are both contraindicated in IIP-PH. There is no evidence of benefit for other endothelin receptor antagonists in IIP-PH. Data on the use of sildenafil in IIP-PH is conflicting, while evidence for prostanoid therapy is too limited for any current recommendations. Further RCTs are encouraged.

**Combined pulmonary fibrosis and emphysema**

Treatment options remain limited with currently little evidence to support PAH therapies in this disease.

**Sarcoidosis**

There is still a lack of data on the safety and efficacy of drugs approved for PAH in sarcoidosis-PH patients. Case series have suggested beneficial effects of various compounds (table 2) [28, 65, 66]. However, only a single RCT has been performed in this group of patients and the results were inconclusive [67]. At present, no PAH-targeted therapy can routinely be recommended for patients with sarcoidosis-PH.

**Other CLDs**

Clinical experience and case series suggest beneficial effects of drugs approved for PAH in some patients with pulmonary Langerhans cell histiocytosis and lymphangioleiomyomatosis, but the lack of robust data precludes firm recommendations for any of these other conditions [31, 68].

**Retrospective survival analysis in group 3 PH**

The impact of PAH-targeted therapy on survival in group 3 PH has been assessed in retrospective studies, which included patients with different CLDs and usually with severe PH. One study found a survival benefit in severe PH-COPD patients with a favourable haemodynamic and functional response after 3 months of therapy, while two studies showed longer survival in patients treated with PAH-targeted therapy (mostly phosphodiesterase type 5 inhibitors) compared with patients who did not receive PAH-targeted treatment [69–71]. In one of these studies, the survival benefit was apparent in patients with severe PH, but not mild-to-moderate PH [70]. These studies need to be interpreted with caution given the nature of their study design with no RCTs as yet attesting to a survival benefit.

**Recommendations for treatment of different patient groups with CLD and PH**

Further long-term RCTs focusing on, but not limited to, patients with CLD-severe PH and COPD or ILDs are needed. Due to the major differences in underlying pathophysiology, obstructive and restrictive lung diseases should be investigated separately. Combining different groups with lung fibrosis is one potential clinical trial approach, with the advantage of increased patient numbers and abrogation of the diagnostic dilemma that often accompanies fibrotic lung disorders. This might be disadvantageous in view of the differing aetiologies, but there are precedents for this approach in PAH where IPAH has typically been combined with other group 1 subgroups in RCTs. This problem may be addressed by detailed phenotyping of the patients and predefined subgroups to be analysed separately in addition to the overall analysis. Based on physiological testing (lung function, haemodynamics and exercise) as well as CT morphology, the following groups of PH patients may be distinguished with respect to classification and management recommendations (summarised in table 1 and figure 1):

1) **Patients with mild obstructive or restrictive lung disease, in whom CT analysis shows no gross parenchymal or airway abnormalities and who present with clinically relevant PH.** Whether such patients have PAH (group 1) with concomitant lung disease or PH due to lung disease (group 3) remains a diagnostic dilemma (see earlier). Therefore, these patients should be referred to an expert centre.

2) **Patients with more severe obstructive and/or restrictive lung disease (IPF with FVC <70% of predicted, COPD with FEV1 <60% of predicted) and accompanying less severe PH (mPAP 20–24 mmHg with PVR ≥3 WU, or mPAP 25–34 mmHg).** These groups represent the majority of patients presenting with CLD-PH. Current data do not support therapy with PAH-approved drugs in these patients. Moreover, as the limitation in exercise capacity in these patients is largely due to ventilatory and not circulatory impairment, any functional benefit from PAH treatment is questionable. Vascular changes
may, however, contribute to disease progression and future studies addressing this aspect of the disease may be a worthy endeavour.

3) **Patients with more severe obstructive and/or restrictive lung disease and severe PH as defined earlier (mPAP $\geq 35$ mmHg, severe COPD-PH, severe ILD-PH, severe CPFE-PH).** These patients have a poor prognosis and should be referred to a centre with expertise in both PH and CLD for individualised care. These patients should preferably be included in RCTs if available.

4) **Patients with “end-stage” obstructive and/or restrictive lung diseases and associated PH.** In these advanced cases, life-preserving measures, such as mechanical ventilatory or extracorporeal membrane oxygenation support, should only be considered as a bridge to transplantation. Patients in any of these groups may be candidates for lung transplantation, an option that should be part of the management algorithm if all else fails and they are otherwise appropriate candidates. RCTs should address whether PAH-approved drugs may improve functional ability, quality of life, prolong time to clinical worsening, improve survival or provide a bridge to transplantation. In the absence of such trials, decisions on individualised patient care should be made in the context of expert centres.

### Specific aspects of PH in systemic sclerosis

PH in patients with systemic sclerosis (SSc) can be multifactorial. These patients are at high risk of developing isolated PAH, but they may also develop significant parenchymal lung disease and/or a component of left heart disease. There is often difficulty in discriminating group 1 PAH from group 3 PH in SSc patients, since quite commonly these patients have evidence of parenchymal lung disease on high-resolution CT, which may or may not be accompanied by restrictive physiology. SSc patients with combined pulmonary fibrosis and PH have a particularly high mortality risk [72]. Both PH severity and the extent of pulmonary fibrosis can vary widely. Patients with pre-capillary PH and mild fibrosis are usually classified as having PAH, and have been included in most of the RCTs of PAH medications. However, assessment of the degree of fibrosis was usually based on pulmonary function testing and not scrutiny of the extent of fibrosis on high-resolution CT. Patients with preserved lung volumes can be safely treated with PAH drugs, but there is no evidence for treatment of PH-SSc with more advanced ILD.

### Recommendations

While there are clearly SSc patients who are “pure” group 1, there are others who are group 2 or 3. There is likely a significant grey zone of these patients with features of more than one group. To best evaluate the extent of lung disease in relation to the patient’s haemodynamic profile requires lung imaging rather than reliance on pulmonary function test criteria only. In the absence of RCTs, SSc patients with PH and more than minimal fibrosis on high-resolution CT should be referred to expert centres for individualised treatment.

### Hypoventilation and hypoxia-associated PH

Chronic PH in obstructive sleep apnoea is rare and most commonly mild. In marked contrast, a significant proportion of patients with obesity–hypoventilation syndrome (OHS) or overlap syndrome (combination of obstructive sleep apnoea and COPD) present with PH [73, 74]. This represents an important group of patients given that current estimates suggest that around 0.4% of the US population suffers from OHS, reaching up to 31% among hospitalised patients with a body mass index $>35$ kg m$^{-2}$ [75]. Although variable, PH is frequently severe in these patients, being commonly associated with right ventricular failure and poor outcomes [76]. In addition to the improvements in gas exchange and sleepiness, one RCT and two series documented near normalisation of pulmonary haemodynamics, right ventricular function and exercise capacity after 3–6 months of non-invasive ventilation [73, 74, 76]. Similar findings were reported in a series of patients with PH associated with restrictive thoracic diseases treated with non-invasive ventilation [77].

### Recommendations

The mainstay treatment of OHS is non-invasive ventilation, which does not, however, always correct the PH.

### PH at high altitude

High altitude is defined as an elevation of $>2500$ m above sea level. 140 million people permanently reside at high altitudes and $>40$ million visitors reach high-altitude levels yearly [78]. Data on prevalence of high-altitude PH, defined as mPAP $\geq 30$ mmHg by the International Society for Mountain Medicine [79], are rare and figures range from 5% to 23%, dependent on the geographic region and sex. Thus, hypoxia-induced PH is a major health problem at high-altitude regions of the world [78, 79]. Low ambient oxygen induces hypoxic pulmonary vasoconstriction, which increases PVR. In addition, pulmonary
Development of better animal models of PH in both COPD and ILD encouraged
- Differential molecular mechanisms (parenchymal versus vascular)
- Identification of novel molecular targets

Novel techniques employing ex vivo cultured human lung tissue to identify the key cellular and molecular drivers of pathological lung and vascular remodelling and for individualised drug testing
- 3D-cultured human pulmonary vascular cells, viable human lung slices, ex vivo grown or iPSC-derived human lung organoids

Research into biomarkers for group 3 PH encouraged
- Classical circulating peptides, circulating RNA subsets, monocyte/leukocyteomics, volatile exhaled compounds, exhaled "genomic fingerprint"
- Shared access to existing biobanks/biosamples from disparate registries, trials including industry-sponsored studies, regulatory agency involvement
- Patients enrolled into future clinical trials should be consented to enable sharing of their biospecimens

Clinical variables for enrolment in group 3 clinical trials require more sophisticated "deep phenotyping"
- Image phenotyping of parenchymal and vascular changes, novel imaging techniques including CT "vascular morphometry", SPECT/CT, PET "metabolomics", four-dimensional MRI, artificial intelligence machine learning ("radiomics")
- Nature, extent and spatial distribution of the parenchymal and vascular abnormalities

Optimal patient phenotype for trials of therapy
- Best haemodynamic variable(s) and threshold to define the patient phenotype; evaluation of right ventricular dysfunction for enrolment; extent of permissible parenchymal lung disease?
- Combination of pulmonary function testing, haemodynamic profile and imaging required

Clinical trial end-points in PH with underlying lung disease
- Phase 2 studies: physiological variables (e.g. right ventricular function, haemodynamics, 6MWT) and biomarkers (e.g. BNP) acceptable
- Phase 3 studies: comprehensive patient centric clinical outcomes preferable: composite end-point, time to clinically meaningful change (clinical worsening and/or improvement)
- Clinical worsening events may include: mortality, hospitalisation (cardiopulmonary), categorical changes in a functional test (e.g. 6MWT), QoL measures, NYHA Functional Class change, need for supplemental oxygen, disease exacerbation, lung transplantation

6MWT: improve its group 3 informative value ("integrate" distance, deoxygenation, Borg dyspnoea score, heart rate recovery?)

Encourage cardiopulmonary exercise testing for more elaborate distinction between respiratory versus circulatory limitation (problem: supplemental oxygen dependency)

Haemodynamic assessment while exercising is encouraged and is to be standardised

Inclusion spectrum in group 3 in view of different aetiology, molecular pathology and clinical course: "narrow versus broad"?

IIP can be studied together with chronic hypersensitivity pneumonitis and occupational lung disease

Sarcoidosis-PH sufficiently different and should be studied independently

COPD-PH should be studied independently

CPFE-PH included in ILD-PH studies; permissible provided the extent of their emphysema is not too great; or risk for confounding signal?

Studies employing inhaled PH therapies are an attractive option as this may enable better ventilation/perfusion matching and limit systemic side-effects

Future studies should focus on the prevention/inhibition/reversal of vascular remodelling in addition to vasodilation CLD-PH

Future studies should also target the role of the vascular compartment in driving parenchymal abnormalities ("vascular therapy beyond PH")

Further studies of the role of pulmonary rehabilitation [exercise training] in lung disease complicated by PH are encouraged
mortality of CLD-PH, this area is one of great unmet medical need where future research should be strongly encouraged and supported (table 3).

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References


Chronic thromboembolic pulmonary hypertension

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State of the art and research perspectives in chronic thromboembolic pulmonary hypertension, including treatment algorithm http://ow.ly/C3Hy30mflUy


ABSTRACT Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of pulmonary embolism and a major cause of chronic PH leading to right heart failure and death. Lung ventilation/perfusion scintigraphy is the screening test of choice; a normal scan rules out CTEPH. In the case of an abnormal perfusion scan, a high-quality pulmonary angiogram is necessary to confirm and define the pulmonary vascular involvement and prior to making a treatment decision. PH is confirmed with right heart catheterisation, which is also necessary for treatment determination. In addition to chronic anticoagulation therapy, each patient with CTEPH should receive treatment assessment starting with evaluation for pulmonary endarterectomy, which is the guideline recommended treatment. For technically inoperable cases, PH-targeted medical therapy is recommended (currently riociguat based on the CHEST studies), and balloon pulmonary angioplasty should be considered at a centre experienced with this challenging but potentially effective and complementary intervention.

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Introduction
Since the 5th World Symposium on Pulmonary Hypertension (WSPH) in 2013, major progress has occurred in the understanding and management of chronic thromboembolic pulmonary hypertension (CTEPH). First, the link between CTEPH and acute pulmonary embolism, and some of the challenges associated with making the connection, will be reviewed. Key diagnostic steps in establishing early and accurate diagnosis will be emphasised. Each component of the current CTEPH treatment approach will be overviewed. Finally, an updated treatment algorithm is proposed taking into account the advances since 2013.

CTEPH and pulmonary embolism
CTEPH is classified within group 4 PH [1], and is characterised pathologically by organised thromboembolic material and by altered vascular remodelling initiated or potentiated by a combination of defective angiogenesis, impaired fibrinolysis and endothelial dysfunction [2–4]. These changes lead to PH and ultimately right ventricular failure [5, 6]. The precise pathogenesis of CTEPH remains unclear, but appears to be incited by acute pulmonary embolism [7].

However, classic risk factors for venous thromboembolism do not appear to increase the risk of CTEPH [8] and there are clear geographic differences in CTEPH epidemiology. An international CTEPH registry (Europe and Canada) indicated that 75% of patients with CTEPH had a documented antecedent history of acute pulmonary embolism [9], while in Japan, the rates of acute pulmonary embolism preceding CTEPH range from only 15% to 33% [10, 11]. There is an 80% female preponderance of CTEPH in Japan; these statistics differ significantly from the USA and Europe [9]. A number of abnormal autoimmune, inflammatory and thrombophilia markers have been found in CTEPH patients [2]; it is feasible that variability in this underlying pathological milieu contributes to the variability in the worldwide CTEPH epidemiology. Furthermore, variable gene expression has been demonstrated in pulmonary artery endothelial cells from patients with CTEPH compared with normal controls [12].

In published prospective studies with the diagnosis confirmed by right heart catheterisation (RHC) the incidence of CTEPH after symptomatic acute pulmonary embolism is reported to range from 0.4% to 6.2% [13–25], giving a pooled incidence of 3.4% (95% CI 2.1–4.4%) [7]. Since that analysis, a new report from Switzerland screened 508 patients after acute pulmonary embolism over 2 years and found a cumulative incidence of CTEPH confirmed with RHC of just 0.79% [26].

Determining the precise CTEPH incidence is complex. CTEPH is likely both underdiagnosed and the incidence of CTEPH after acute pulmonary embolism prone to overestimation, making the actual incidence difficult to quantify. Non-specific symptoms, variable rates of antecedent acute pulmonary embolism and the expertise required to read computed tomography pulmonary angiography (CTPA) contribute to underdiagnosis [27, 28]. Underdiagnosis is further compounded by the infrequent use of lung ventilation/perfusion scintigraphy (V/Q scan) despite guideline recommendations [29, 30].

Approximately 30000 acute pulmonary embolism cases are diagnosed annually in France, with the CTEPH incidence estimated at 3.4% [31]. GUÉRIN et al. [22] suggested a CTEPH incidence of 4.8%. Neither of these estimates is consistent with the current frequency of newly diagnosed CTEPH. A limitation of the numerous CTEPH incidence reports after acute pulmonary embolism may be attributed to an unrecognised amalgam of incident and prevalent cases [22].

In terms of reducing the risk of CTEPH following acute pulmonary embolism, no prospective randomised acute pulmonary embolism trials have examined systemic or catheter-based thrombolysis or clot extraction with RHC as an outcome measure in patients with persistent symptoms. Claims have been made that the incidence of CTEPH in patients receiving thrombolytic therapy is reduced, but end-points such as an echocardiogram-derived systolic pulmonary arterial pressure (sPAP) of 40 mmHg do not define PH or CTEPH [32]. Systemic thrombolysis failed to reduce the risk of CTEPH in intermediate/high-risk (submassive) pulmonary embolism patients in the 3-year follow-up of the PEITHO trial (average sPAP at follow-up was around 31 mmHg in each group) [33]. To date, there is no proof that aggressive treatment of acute pulmonary embolism can prevent CTEPH.

Chronic thromboembolic disease
Chronic thromboembolic disease (CTED) is characterised by similar symptoms and perfusion defects, but without PH at rest. Currently a new threshold for PH (mean PAP (mPAP) >20 mmHg) and pre-capillary PH (combination of mPAP >20 mmHg, pulmonary arterial wedge pressure ≤15 mmHg and pulmonary vascular resistance (PVR) >3 Wood Units) has been proposed by the 6th WSPH Task Force on PH diagnosis and classification [1]. While there is good evidence to suggest these new thresholds, the consequences for CTEPH and CTED, respectively, are not yet established. In the future, however, these new thresholds might also be applied to group 4 PH. Exercise limitation in CTED has been attributed either to exercise-induced PH, with an increased slope of the pulmonary arterial pressure–flow relationship, or to
dead-space ventilation, with increased ventilatory equivalents for carbon dioxide [34, 35]. Both new and worsened dyspnoea and persistent perfusion defects are often encountered after acute pulmonary embolism, in, respectively, 30% and 30–50% of patients, which makes the recognition of CTED challenging [18, 36, 37]. Cardiopulmonary exercise tests and echocardiographic evaluations are recommended to exclude patients in whom symptoms are related to lung disease, left heart disease, obesity or deconditioning. A tentative, comprehensive definition of CTED is proposed in table 1. Selected patients with CTED may benefit from pulmonary endarterectomy (PEA) as shown in a series of 42 patients out of 1019 who underwent surgery in the UK reference centre [38]. Post-operative improvement in symptoms, functional class and quality of life were reported. However, while there was no in-hospital mortality, major complications occurred in 40% of the cohort (small subdural haematomas, tracheostomy). Although endarterectomy is aimed to prevent subsequent disease, the natural history of CTED is unknown and there is no evidence that CTED evolves to CTEPH. At present, patients with CTED represent a group in need of both symptom relief and better understanding of their disorder. CTEPH treatment guidelines should not be applied to CTED.

### Diagnosis of CTEPH

A normal V/Q scan effectively excludes CTEPH with a sensitivity of 90–100% and a specificity of 94–100% [39, 40]. In a study of confirmed cases of CTEPH, V/Q scan was found to be superior to CTPA with a sensitivity of 97.4% versus 51% [39]. This difference has narrowed as CT technology and interpretation have advanced. Indeed, a more recent study has shown that both V/Q scan and CTPA are accurate methods for the detection of CTEPH with excellent diagnostic efficacy (100% sensitivity, 93.7% specificity and 96.5% accuracy for V/Q scan; 96.1% sensitivity, 95.2% specificity and 95.6% accuracy for CTPA) [40]. However encouraging, V/Q scan remains the preferred initial imaging test for CTEPH screening [5, 29]. Recent retrospective studies have also assessed the diagnostic accuracy of three-dimensional dynamic contrast-enhanced lung perfusion magnetic resonance imaging (MRI) against planar V/Q scan or SPECT (single photon emission CT) scan as a screening tool for CTEPH [41, 42]. These studies demonstrated that dynamic contrast-enhanced lung perfusion MRI has a similar sensitivity (97%) for diagnosing CTEPH when compared with planar V/Q scan and a higher sensitivity (100% versus 97%) when compared with SPECT scan. Prospective studies examining the value of lung perfusion MRI and SPECT scan as a screening test for CTEPH are required to address the clinical utility (including their costs) and diagnostic performance of these modalities.

Digital subtraction angiography (DSA) had been considered the gold standard for characterising vessel morphology in CTEPH, but is being challenged by advances in non-invasive modalities. CTPA is currently widely used for assessment of operability. CTPA in more recent reports has a high sensitivity and specificity in detecting chronic thromboembolic lesions at the main/lobar (89–100% and 95–100%, respectively) and segmental (84–100% and 92–99%, respectively) levels [43–45]. CTPA can also be valuable by revealing bronchial artery collaterals, which can correlate with more central disease [46], and by evaluating the lung parenchyma and mediastinum. Advanced CT technologies, including dual-energy CT (DECT), ECG-gated area detector CT (ADCT), cone-beam CT (CBCT) and contrast-enhanced magnetic resonance pulmonary angiography, are emerging as valuable modalities for detailing the pulmonary vasculature. With advances with distal endarterectomy and the advent of balloon pulmonary angioplasty (BPA), and general focus on more distal vascular assessment, conventional DSA may not always be suitable for providing fine details. More selective segmental angiography, CBCT and ADCT may be better for pre-BPA planning by providing greater resolution than conventional DSA, particularly in the more distal vessels [47]. These imaging techniques are not widely available and require expertise.

### Table 1 Chronic thromboembolic disease (CTED) compared with chronic thromboembolic pulmonary hypertension (CTEPH)

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>CTEPH</th>
<th>CTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Exercise dyspnoea</td>
<td>Exercise dyspnoea</td>
</tr>
<tr>
<td>PH</td>
<td>Present at rest</td>
<td>Absent at rest</td>
</tr>
<tr>
<td>RHC at exercise</td>
<td>Any mismatched perfusion defect</td>
<td>mPAP/CO slope &gt;3 mmHg·L⁻¹·min⁻¹</td>
</tr>
<tr>
<td>V/Q scan</td>
<td>Typical findings of CTEPH</td>
<td>Any mismatched perfusion defect</td>
</tr>
<tr>
<td>Angiography (CTPA or DSA)</td>
<td></td>
<td>Typical findings of CTEPH</td>
</tr>
<tr>
<td>CPET</td>
<td></td>
<td>Excluding ventilatory limitation, deconditioning</td>
</tr>
<tr>
<td>TTE</td>
<td></td>
<td>Excluding left ventricular myocardial or valvular disease</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>At least 3 months</td>
<td>At least 3 months</td>
</tr>
</tbody>
</table>

RHC: right heart catheterisation; V/Q: ventilation/perfusion; CTPA: computed tomography pulmonary angiogram; DSA: digital subtraction angiogram; CPET: cardiopulmonary exercise test; TTE: transthoracic echocardiogram; mPAP: mean pulmonary arterial pressure; CO: cardiac output.

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Pulmonary endarterectomy
PEA should be offered to all eligible patients with CTEPH. The international registry of incident cases of CTEPH reported 3-year survival of 90% in those operated and 70% in those not having surgery [48]. Long-term follow-up of a large cohort reported 10-year survival of 72% (average age 58 years) [49]. Death was attributed to unrelated causes in 49% of patients; residual PH with PVR $\geq 425$ dyn·s·cm$^{-5}$ correlated with worse survival [49]. Strict objective definitions of operability remain elusive, but certain features are more likely to predict a good surgical outcome (table 2). While select patients may be technically operable, they may not benefit from endarterectomy due to significant comorbidities; the best treatment for such cases remains uncertain. The traditional routine of inserting an inferior vena cava filter (IVC) device prior to endarterectomy has not been formally studied and has been abandoned at the leading surgical centres. In the international registry, IVC filter prior to surgery did not influence long-term survival [48]. The most important surgical advance has been in redefining the distal limits of endarterectomy [50, 51]. In expert centres, surgery can be performed successfully in patients with distal chronic thromboembolism [51]. The advances in diagnostics and growing surgical experience have contributed to this success. As a result, the previously published intra-operative classification [52] has been refined to better reflect the current surgical approach and level of revascularisation (table 3) [50]. This also means not all surgical centres will view operability in the same manner [53]. A three-step stratified definition of expert surgical centre has been proposed which factors the following important goals: surgical mortality (<5%), surgical volume (more than 50 PEA per year) and ability to perform segmental endarterectomy [53]. Furthermore, in this era of a comprehensive approach to CTEPH, an expert centre should be capable of evaluating and offering any/all established treatment modalities according to individual need.

The place of PH-targeted medical therapy and BPA relative to surgery is dependent on the anatomical distribution of disease and is not fully defined. Combining endarterectomy with BPA either as a hybrid or stepwise approach is being evaluated at select expert programmes [54]. In the CHEST-1 study, riociguat was beneficial for patients with residual PH after endarterectomy [55]. A trial is needed to clarify if PH-targeted medical therapy prior to endarterectomy in operable patients confers harm or benefit (ClinicalTrials.gov identifier NCT0327357).

Balloon pulmonary angioplasty
BPA has evolved into an important component of the CTEPH treatment algorithm since the 2012 reports from Japan [56–58]. BPA has been reported to improve haemodynamics, symptoms, exercise capacity and right ventricular function, with significantly lower rates of major complications than compared with the report from 2001 [59–62]. In retrospective analyses, the benefits of BPA also appear to be maintained in the medium term [10, 63]. Subsequent publications from Europe report similar results [64–66]. The recent BPA series from Germany is unique as these centres started BPA alongside a well-established PEA programme [67]. Although their complication rates were similar to those from Japan, the magnitude of efficacy (e.g. PVR reduction) was less in comparison with the reports from Japan. The potential explanations offered included the possibility of differences in operability threshold and the variability in the types of patients treated with BPA between centres.

Although these results of BPA are encouraging, the reports are from expert centres and may not be generalisable. Even with the technical refinements, there remains a steep learning curve in order to safely, effectively and consistently perform BPA [68]. A successful BPA requires extensive training and case experience. BPA should be reserved for expert centres, where it should be considered for symptomatic

TABLE 2 Favourable risk–benefit assessment for pulmonary endarterectomy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lower risk with predictable good long-term outcome</th>
<th>Higher risk with less predictable long-term outcome (not contraindications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>History of DVT/PE</td>
<td>No history of DVT/PE</td>
</tr>
<tr>
<td>Examination</td>
<td>No signs of right heart failure</td>
<td>Signs of right heart failure</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>None</td>
<td>Significant concomitant lung or left heart disease</td>
</tr>
<tr>
<td>Functional limitation</td>
<td>Functional class II or III</td>
<td>Functional class IV</td>
</tr>
<tr>
<td>Imaging</td>
<td>Clear disease concordant on all images</td>
<td>Inconsistency on imaging modalities</td>
</tr>
<tr>
<td>Type of disease</td>
<td>Bilateral lower lobe disease</td>
<td>No disease appreciable in lower lobes</td>
</tr>
<tr>
<td>Haemodynamics</td>
<td>PVR &lt;1000 dyn·s·cm$^{-5}$, in proportion to site and number of obstructions on imaging; higher PA pulse pressure</td>
<td>PVR &gt;1200 dyn·s·cm$^{-5}$, out of proportion to site and number of obstructions on imaging; higher PA diastolic pressure</td>
</tr>
</tbody>
</table>

DVT: deep vein thrombosis; PE: pulmonary embolism; PVR: pulmonary vascular resistance; PA: pulmonary artery.

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CTEPH patients ineligible for PEA due to distal chronic thromboembolism or persistent/recurrent PH after surgery. The role of BPA for those with technically operable disease, but who are unsuitable for surgery due to subjective determination or patient refusal, has not been established.

BPA patient selection at an expert centre starts with a multidisciplinary review of all available and pertinent data. Anatomical and functional assessment of pulmonary arteries and lung perfusion are critical to identify the target vessels [69]. A selective pulmonary angiogram of the target vessels will show more details and serves as confirmation prior to intervention during BPA. A selective angiogram may not capture all the distal lesions potentially amenable to BPA, necessitating multiple complementary imaging modalities such as intravascular imaging and pressure gradient analysis to aid in lesion assessment and balloon sizing [70].

BPA complications should be defined and uniformly reported. Unlike reperfusion lung injury after PEA which can be delayed for days before onset [71], the injury associated with BPA appears to be more vascular injury related to the intervention than the capillary leak syndrome described post-PEA [72]. Table 4 is proposed as a guide for BPA centres for classification of complications. Injury caused by wire perforation or interruption of the diseased vessel is the most common [69]. Lung injury by wire perforation or balloon overdilatation in the setting of severe PH risks potentially fatal massive infiltration and/or haemorrhage which may require mechanical ventilation or extracorporeal support. Classic reperfusion lung injury is rare with BPA. Published low BPA complications reflect limited experience confined to experienced BPA centres. In experienced hands, BPA has emerged as a promising and established treatment for inoperable CTEPH.

**PH-targeted medical therapy**

While PEA remains the treatment of choice for most patients with CTEPH, around 40% of the patients in the international CTEPH registry were considered inoperable due to concern for inaccessible vascular obstruction, PAP out of proportion to morphological lesions and significant prohibitive comorbidities [9]. A large number of small studies and three large randomised controlled trials (table 5) have demonstrated varying improvements with targeted medical therapy in technically inoperable patients [55, 73, 74].

<table>
<thead>
<tr>
<th>TABLE 3 University of California San Diego chronic thromboembolism (CTE) surgical classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical levels</strong></td>
</tr>
<tr>
<td>Level 0</td>
</tr>
<tr>
<td>Level I [Level IC]</td>
</tr>
<tr>
<td>Level II</td>
</tr>
<tr>
<td>Level III</td>
</tr>
<tr>
<td>Level IV</td>
</tr>
</tbody>
</table>

Information from [50].

<table>
<thead>
<tr>
<th>TABLE 4 Balloon pulmonary angioplasty complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During the procedure</strong></td>
</tr>
<tr>
<td>Vascular injury* with/without haemoptysis</td>
</tr>
<tr>
<td>Wire perforation</td>
</tr>
<tr>
<td>Balloon overdilatation</td>
</tr>
<tr>
<td>High-pressure contrast injection</td>
</tr>
<tr>
<td>Vascular dissection</td>
</tr>
<tr>
<td>Allergic reaction to contrast</td>
</tr>
<tr>
<td>Adverse reaction to conscious sedation/local anaesthesia</td>
</tr>
<tr>
<td><strong>After the procedure</strong></td>
</tr>
<tr>
<td>Lung injury¶ (radiographic opacity with/without haemoptysis, with/without hypoxaemia)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Access site problems</td>
</tr>
</tbody>
</table>

\*: signs of vascular injury: extravasation of contrast, hypoxaemia, cough, tachycardia, increased pulmonary arterial pressure; ¶: causes of lung injury: vascular injury much greater than reperfusion lung injury.
TABLE 5 Pulmonary hypertension-targeted medical therapy randomised controlled trials in chronic thromboembolic pulmonary hypertension

<table>
<thead>
<tr>
<th>Trial [ref.]</th>
<th>Study drug</th>
<th>Duration weeks</th>
<th>Subjects n</th>
<th>NYHA FC</th>
<th>6MWD m</th>
<th>6MWD effect m</th>
<th>PVR baseline dyn·s·cm⁻⁵</th>
<th>PVR effect %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENEFIT [73]</td>
<td>Bosentan</td>
<td>16</td>
<td>157</td>
<td>II–IV</td>
<td>342±84</td>
<td>+2²ns</td>
<td>783 (95% CI 703–861)</td>
<td>–24</td>
</tr>
<tr>
<td>CHEST-1 [55]</td>
<td>Riociguat</td>
<td>16</td>
<td>261</td>
<td>II–IV</td>
<td>347±80</td>
<td>+46</td>
<td>787±422</td>
<td>–31</td>
</tr>
<tr>
<td>MERIT-1 [74]</td>
<td>Macitentan</td>
<td>16 (24⁸)</td>
<td>80</td>
<td>II–IV</td>
<td>352±81</td>
<td>+34</td>
<td>957±435</td>
<td>–16</td>
</tr>
</tbody>
</table>

Data are presented as n or mean±SD, unless otherwise stated. NYHA FC: New York Heart Association Functional Class; 6MWD: 6-min walk distance; PVR: pulmonary vascular resistance; NS: non-significant. All three trials had an adjudication process for operability. ⁸: 6MWD measured at 24 weeks.

However, data are lacking for patients with medical contraindications or those refusing surgery. Riociguat is the currently approved medical therapy in many countries for inoperable CTEPH based on the CHEST trials [55, 75]. Recently, the MERIT-1 trial of macitentan in the treatment of inoperable CTEPH showed improvements of the primary end-point (PVR (p=0.041)) and of other end-points (e.g. 6-min walk distance (p=0.033) and N-terminal pro-brain natriuretic peptide (p=0.040)) [74]. This last study provided the first evidence on combination drug therapy in CTEPH. 61% of the included patients were already treated with phosphodiesterase type 5 inhibitors and/or oral/inhaled prostanooids at inclusion, and addition of macitentan showed similar efficacy compared with the drug-naïve patients. Accordingly, macitentan is being considered for potential CTEPH registration. Event-driven morbidity/mortality studies have not been performed in CTEPH.

Patients with persistent/residual post-operative PH were also included in BENEFIT and CHEST-1, representing around 30% of the study population [55, 73]. Both studies included patients with mPAP ≥25 mmHg and PVR ≥300 dyn·s·cm⁻⁵ at >6 months after endarterectomy. This can be put in perspective with real-life data from the large UK national cohort, in which 3–6 months after PEA: 1) 51% of the patients had mPAP ≥25 mmHg, 2) mPAP ≥30 mmHg predicted initiation of PH-targeted medical therapy, and 3) mPAP ≥38 mmHg and PVR ≥425 dyn·s·cm⁻⁵ correlated with worse long-term survival [49].

Using medical therapy as a “bridge to PEA” is more controversial, and is felt to delay timely surgical referral and, therefore, definitive treatment. In the international registry and in a University of California San Diego cohort, 28% and up to 37%, respectively, of the patients were on some form of PH-targeted drug(s) at the time of surgical referral [9, 76]. In both cohorts, the delay between diagnosis and surgery was doubled in the pre-treated patients, without demonstrable clinical benefit. In the international registry, pre-treatment even independently predicted worse outcome (hazard ratio 2.62; p=0.0072) [48]. Key limitations of these reports are with inherent referral bias and the possibility of medical therapy potentially stabilising otherwise deteriorating cases (unknown and not tested). In order to provide the missing evidence, a phase 2 study will soon commence to include CTEPH patients with high PVR for pre-operative treatment with riociguat versus placebo (ClinicalTrials.gov identifier NCT0327357). Using medical therapy as a “bridge to BPA”, although not studied, has become common practice and in keeping with the indication for riociguat for technically inoperable disease. A study is currently ongoing which compares riociguat versus BPA for technically inoperable CTEPH, followed by an opportunity to crossover after 6 months (ClinicalTrials.gov identifier NCT02634203).

CTEPH treatment algorithm

The newly proposed CTEPH treatment algorithm is provided in figure 1 and starts with lifelong anticoagulation. Antiplatelet therapy is not an alternative to anticoagulation in patients with CTEPH. Data differentiating the best form of anticoagulation therapy is lacking in CTEPH. Traditional anticoagulation has been with oral vitamin K antagonists. Whether the newer oral anticoagulants or chronic injectable anticoagulants are adequate in CTEPH is unknown. The algorithm emphasises the need for a multidisciplinary assessment, including a surgeon experienced with PEA, PH specialist, BPA interventionist and CTEPH-trained radiologist. A PH referral centre was previously defined and recommended as a minimum volume of 50 pulmonary arterial hypertension or CTEPH patients managed per year [77]. However, given the highly specialised nature of CTEPH treatment, additional factors should be considered when gauging clinical expertise.

In the CHEST-1 trial, central adjudication exemption and local operability assessment were allowed provided a participating centre performed more than 20 PEA operations per year [78]. However, the majority of the operability adjudication occurred with the central committee whose members each
performed well in excess of 50 operations per year. In addition, the central adjudication committee had double the rate of operability determination than the local adjudication committee (15% operable versus 7% operable, respectively). From the international CTEPH registry, a trend with the best in-hospital and 1-year post-operative mortality was observed from centres performing higher volumes of PEA, with the best results observed from centres performing more than 50 operations per year [79]. This observation likely does not take into account the relative differences in case complexity, with potentially more challenging cases referred to higher-volume programmes. Additional emphasis on the importance of surgical centre experience was reported in the UK national registry of patients undergoing PEA [49]. In this report, significantly lower in-hospital mortality was observed in the second group of consecutive 500 operated cases compared with the initial group of 500 operated cases. In addition, the ability for high-volume centres to perform more distal endarterectomy necessitates stratification of surgical centre expertise [53]. A similar observation applies to BPA success; the safety and efficacy reports of the refined BPA techniques from Japan are from centres performing the highest volume of procedures (typically more than 100 per year) [58, 59]. In summary, an expert CTEPH centre should be able to assess and deliver all established treatment modalities with outcomes similar to or exceeding those published.

Patients with operable CTEPH should receive PEA as the treatment of choice. For those deemed inoperable, the best level of evidence supports initiating medical therapy and consideration of BPA. Patients with persistent/recurrent symptomatic PH following PEA should receive medical therapy and be considered for BPA or re-do endarterectomy in cases of significant re-occlusion [80]. Lastly, given the subjectivity of operability assessment, it is possible for a patient initially deemed to be inoperable to receive PEA with or without treatments for inoperable CTEPH. The new algorithm therefore allows for fluidity between these treatment modalities as information and expertise is gained.

Conclusions

PEA remains the treatment of choice for patients with operable CTEPH. Two additional recognised treatments are now available (i.e. targeted medical therapy and BPA). A multimodal, individualised approach to treatment at expert centres integrating surgical, interventional, imaging and medical PH expertise with the development of clear outcomes analyses is mandatory going forward.

Conflict of interest: N.H. Kim reports personal fees for consultancy, steering committee work and speaker bureau membership from Actelion and Bayer; personal fees for consultancy from Merck; and is a board member of the International CTEPH Association, CTEPH.com. M. Delcroix is an investigator, speaker, consultant or steering committee member for Actelion, Bayer AG, Bellerophon, Eli Lilly, GSK, MSD, Pfizer and Reata; and has received an institutional research grant from Actelion. X. Jais received grants and personal fees from Actelion, GSK, Bayer and MSD. M.M. Madani has received consultancy fees from MSD/Bayer, Wexler Surgical and Actelion, and is an executive board member of the International CTEPH Association, CTEPH.com. H. Matsubara has received lecture fees from
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Incidence of venous thromboembolism: a community-based study in Western France.


Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management

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State of the art and future perspectives in paediatric pulmonary hypertension with special emphasis on classification, diagnosis and treatment http://ow.ly/uVPo30mksOj


ABSTRACT Paediatric pulmonary arterial hypertension (PAH) shares common features of adult disease, but is associated with several additional disorders and challenges that require unique approaches. This article discusses recent advances, ongoing challenges and distinct approaches for the care of children with PAH, as presented by the Paediatric Task Force of the 6th World Symposium on Pulmonary Hypertension. We provide updates of the current definition, epidemiology, classification, diagnostics and treatment of paediatric PAH, and identify critical knowledge gaps. Several features of paediatric PAH including the prominence of neonatal PAH, especially in pre-term infants with developmental lung diseases, and novel genetic causes of paediatric PAH are highlighted. The use of cardiac catheterisation as a diagnostic modality and haemodynamic definitions of PAH, including acute vasoreactivity, are addressed. Updates are provided on issues related to utility of the previous classification system to reflect paediatric-specific aetiologies and approaches to medical and interventional management of PAH, including the Potts shunt. Although a lack of clinical trial data for the use of PAH-targeted therapy persists, emerging data are improving the identification of appropriate targets for goal-oriented therapy in children. Such data will likely improve future clinical trial design to enhance outcomes in paediatric PAH.

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Introduction

Pulmonary hypertension (PH) in children is associated with diverse diseases with onset at any age. The distribution of aetiologies in paediatric PH is quite different to that of adults, with children having a greater predominance of idiopathic pulmonary arterial hypertension (IPAH), pulmonary arterial hypertension (PAH) associated with congenital heart disease (PAH-CHD) and developmental lung diseases. Differences in aetiology, presentation and outcomes require a unique approach in children. The management of children remains challenging because treatments have long depended on evidence-based adult studies and the clinical experience of paediatric experts. Although there is still a lack of data on effectiveness, formulation, pharmacokinetics, optimal dosing and treatment strategies, data are emerging that allow for the definition of appropriate treatment targets and goal-oriented therapy in children. Nevertheless, children with PAH are currently treated with targeted PAH drugs with benefit. We provide an overview of recent updates in the current definition, epidemiology, classification, diagnostics and treatment of PAH in children, and identify current needs based on discussions and recommendations from the Paediatric Task Force of the 6th World Symposium on Pulmonary Hypertension (WSPH) in Nice, France (2018).

Definitions

Historically, the definition of PH in children has been the same as in adults, *i.e.* mean pulmonary arterial pressure (mPAP) ≥25 mmHg. In the normal fetal circulation, PAP is similar to systemic pressure and rapidly falls after birth, achieving levels that are similar to the adult by 2–3 months of age. Due to variability in pulmonary haemodynamics during post-natal transition, paediatric PH has been defined as mPAP ≥25 mmHg after 3 months of age. In paediatric PH, especially in association with CHD, it is recommended to use pulmonary vascular resistance (PVR) as indexed to body surface area (PVRI) in order to assess the presence of pulmonary vascular disease (PVD), as defined by PVRI ≥3 WU·m⁻².

The 6th WSPH proposed to modify the definition for PH in adults as mPAP >20 mmHg and to include PVR ≥3 WU to identify pre-capillary PH. Whether or not the same findings of high normal or “borderline PH” with mPAP of 21–24 mmHg in subgroups of adult PH such as scleroderma, chronic obstructive pulmonary disease and interstitial lung disease is a risk factor for developing PAH and related morbidities in children as in adults will require further study [1]. However, in order to speak a universal language and facilitate transition from paediatric to adult PH care, the Paediatric Task Force chose to follow the newly proposed adult definition of PH and encourages further study of these patients. The proposed use of PVR to assess PVD at the 6th WSPH had already been included previously in the haemodynamic assessment of PH in children. The Paediatric Task Force further reinforced the need for indexing of PVR in children.

Vasoreactivity

In IPAH/heritable PAH (HPAH), acute vasodilator testing (AVT) is recommended to identify patients who are likely to have a good long-term prognosis when treated with long-term calcium channel blocker (CCB) therapy. In the recent past, positive vasoreactivity was believed to be more common in children with IPAH when compared with adults and that specific response criteria were indicated for children. However, using the same criteria for adult and paediatric subjects with IPAH/HPAH showed that the proportion of AVT responders was similar in both age groups [2]. A recent large study including 382 patients showed a substantial discrepancy in how AVT is performed and interpreted in children, and that standardisation is required [2]. As in adults, inhaled nitric oxide at 10–80 ppm is the preferred agent, but *i.v.* epoprostenol, *i.v.* adenosine or inhaled iloprost may be used as alternatives. However, optimal dosing in small children is not well defined for the latter drugs. As recently reported, the *Sitbon criteria for positive AVT*, as defined by a decrease in mPAP by at least 10 mmHg with sustained cardiac output that is commonly used in adult IPAH/HPAH, have been shown to identify children who will show sustained benefit from CCB therapy [2, 3]. Positive AVT in subjects with mPAP <40 mmHg at baseline is defined by a drop of at least 10 mmHg without a fall in cardiac output. Based on these data it is advised to use the Sitbon criteria for AVT in children. Since it has been shown that only half of the adult responders have a long-term haemodynamic and clinical improvement on CCB therapy, close long-term follow-up is required.

*Can AVT predict operability if resting PAP and PVR are elevated in children with CHD and open systemic-to-pulmonary shunts?*

In CHD-associated PH, AVT is often performed for other reasons than determining the potential use of CCB therapy and predictor of outcome, as shown in IPAH/HPAH. AVT is also used to distinguish between reversible and progressive PAH in patients with PAH-CHD, and thus potential operability [4]. However, specific criteria for defining a positive AVT response or specific haemodynamic targets that predict reversal of PAH and good long-term prognosis following surgical correction remain lacking.
In fact, other factors beyond the haemodynamic response to AVT have been shown to be associated with PAH reversal after surgical repair, including age, type of cardiac lesion, comorbidities, resting and exercise saturation, and clinical history. In the absence of robust data on haemodynamic predictors, current guidelines suggest criteria for operability of CHD in the presence of PAH that are based on expert opinion. The Paediatric Task Force agreed on general guidance for assessing operability in CHD-PAH, but emphasises that the long-term impact of defect closure in the presence of PAH with increased PVR is unknown (table 1).

Updates in paediatric PH epidemiology and classification
Current epidemiological data on paediatric PH are mainly derived from registry cohorts; as a result they are affected by study design, logistics and the scope of clinical practice underlying patient selection for these registries. Geographic coverage, referral patterns, inclusion criteria and disease definitions may differ between registries, leading to potential selection bias that can affect reported incidence and prevalence rates. The estimated incidence of sustained PH in all categories was reported at 4–10 cases per million children per year with a prevalence of 20–40 cases per million in Europe (Spain, the Netherlands) and 5–8 cases per million children per year and 26–33 per million children in the USA [5–7]. A Dutch nationwide epidemiological study, that minimised potential bias by including all hospitals in the country by combining hospital registries with local paediatric cardiology databases over a 15-year period, reported an annual incident rate of PH in children of 63.7 per million children [6]. The majority of children (2845 out of 3262) had “transient” PAH and were infants with either persistent PH of the newborn (PPHN) or repairable cardiac shunt defects. Of the remaining children, 27% had other forms of PAH (IPAH, PAH-CHD, PAH associated with connective tissue disease (CTD) and pulmonary veno-occlusive disease (PVOD)), while a significant proportion (34%) had PH associated with developmental lung disease, including bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH) and congenital pulmonary vascular abnormalities [6].

**Group 1: PAH**
**Group 1.1: IPAH**
Estimated incidence rates for IPAH vary from 0.47 to 1–2 cases per million children, with estimated prevalence rates from 2.1 to 4.4 cases per million children [5–9].

**Group 1.2: HPAH**
As in adult PAH, gene mutations that have been implicated in the pathogenesis of HPAH have been identified in 20–30% of paediatric sporadic PAH cases and 70–80% of familial PAH cases. These include known mutations such as those in BMPR2 (bone morphogenetic protein receptor type 2) and ACVRL1 (activin receptor-like kinase 1). However, compared with adult PAH, the genetic architecture of paediatric PAH differs and seems enriched in TBX4 and ACVRL1 mutations [10–13]. Whether mutation carriers in paediatric PAH have a different phenotype or clinical course than non-carriers remains to be demonstrated [11]. Furthermore, paediatric PAH is frequently associated with chromosome and syndromic anomalies, in which the mechanistic basis for PAH is generally uncertain. A recent exome sequencing study in paediatric PAH suggests that de novo variants in novel genes may explain approximately 19% of paediatric-onset IPAH cases. The prevalence of known PAH gene mutations in PAH-CHD is controversial as several studies have not detected PAH mutations in these patients, whereas other groups have identified BMPR2 mutations in patients presenting with PAH after correction of a defect [11, 14], and a recent study shows variants in SOX17 associated with PAH-CHD [15]. Genetic testing is still not performed routinely in all paediatric PH as it may lead to significant psychological impacts, particularly in asymptomatic

<table>
<thead>
<tr>
<th>Pulmonary vascular resistance index WU·m²</th>
<th>Pulmonary vascular resistance WU</th>
<th>Correctability/favourable long-term outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>&lt;2.3</td>
<td>Yes</td>
</tr>
<tr>
<td>4–8</td>
<td>2.3–4.6</td>
<td>Individual patient evaluation in tertiary centres</td>
</tr>
<tr>
<td>&gt;8</td>
<td>&gt;4.6</td>
<td>No</td>
</tr>
</tbody>
</table>

WU: Wood Units. Special considerations include: age of patient, type of defect, comorbidities, resting or exercise-induced desaturation is a concern and PAH therapy [treat with intent-to-repair approach has not been proven].
individuals, especially in the setting of incomplete penetrance. Genetic testing should be combined with genetic counselling by experts in this field so that families have all information before and after testing.

The genetics of PH and genetic testing specifically in paediatrics requires further work and should be performed in expert centres with a genetic counselling group.

**Group 1.3: Drug- and toxin-induced PAH**

Several cases of transient PAH that resolved after discontinuation of diazoxide have been described in the literature, suggesting that hyperinsulinaemic and hypoglycaemic neonates treated with diazoxide require echocardiographic surveillance [16]. The US Food and Drug Administration (FDA) issued a warning about diazoxide and PAH in neonates in 2015 [17].

**Group 1.4: Associated PAH**

**Group 1.4.1: PAH associated with CTD**

PAH-CTD in children is uncommon, but deterioration is usually rapid when associated with PAH. PAH-CTD occurs in 0–4% of patients in PH clinics [5–7, 18–21]. In a multinational cohort of 389 children with systemic juvenile arthritis from the CARRA registry, 16 (4%) were diagnosed with PAH [18]. A recent study suggests that PAH was diagnosed by echocardiography in 2% of a cohort of 850 children with systemic lupus erythematosus within the first 2 years of diagnosis. These patients with PH were mostly asymptomatic and, in some cases, the PAH resolved or improved [19].

**Group 1.4.2: PAH associated with HIV infection**

PAH-HIV in children appears to be rare outside of endemic areas, with one case in each of the Spanish, Dutch and UK registries [5, 6, 22].

**Group 1.4.3: PAH associated with portal hypertension**

Patients with liver disease suffer from two distinct pulmonary vascular complications: hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH). Whereas HPS is characterised by increased pulmonary blood flow, low PVR and hypoxaemia, POPH has striking pulmonary vascular remodelling that adversely affects the outcome of orthotopic liver transplantation [23]. POPH appears to be rare in children, with 0–2% of cases reported in PH registries [5, 6, 22, 24].

**Group 1.4.4: Congenital heart disease**

Group 1.4.4 PAH includes patients with simple operable and inoperable CHD, subgrouped as those with Eisenmenger physiology, those with PAH and left-to-right shunts, those with PAH thought to be incidental to their CHD and those with postoperative/closed defects. This classification for PAH associated with cardiac or arterial shunt has not changed since the previous WSPH 2013 classification [25]. Transient PH following repair of congenital heart disease occurs in 21.9 cases per million and is one of the commonest forms of PAH in children, second only to persistent pulmonary hypertension of the newborn [6]. Complex heart diseases have been assigned to group 5.4.

**Group 1.4.5: Schistosomiasis**

Schistosomiasis is uncommon in developed countries and lacks studies of targeted PH therapy in children.

**Group 1.5: PAH long-term responders to CCBs**

As in adults, a subgroup of children with IPAH can be identified who are positive AVT responders and would now be classified as “PAH long-term responders to CCBs” [25]. Based on the Sitbon criteria, this subgroup is estimated to include roughly 8–15% of the children with IPAH.

**Group 1.6: PAH with overt features of venous/capillaries (PVOD/PCH) involvement**

PAH with overt features of venous/capillaries (PVOD/pulmonary capillary haemangiomatosis (PCH)) involvement in children appears to be rare. PVOD and/or PCH was diagnosed in 0.7–2% cases of PAH in the Spanish, Dutch and TOPP registries [5, 6, 26]. The EIF2AK4 (eukaryotic translation initiation factor 2α kinase 4) mutation was present in two-thirds of children diagnosed with PVOD in France [11].

**Group 1.7: Persistent PH of the newborn syndrome**

PPHN is the most common cause of transient PAH (30.1 cases per million children per year) and may be increasing in frequency [7]. In the era before inhaled nitric oxide therapy, PPHN occurred in approximately 2 per 1000 live births [27]. In contrast, between 2003 and 2012, the prevalence of PPHN among 12954 extremely pre-term infants enrolled was 8.1% (95% CI 7.7–8.6%), with the trend increasing annually, in part due to increased survival of extremely low-birthweight infants and growing awareness of
PPHN in pre-terms. The proportion of newborns with PPHN is inversely related to gestational age, with an incidence of 18.5% (range 15.2–22.4%) for infants born at 22–24 weeks compared with 4.4% (range 3.8–5.2%) for those born at 27 weeks [28]. The current WSPH Paediatric Task Force emphasised that PPHN is a syndrome with multiple associated conditions (table 2). Although multifactorial in origin, recent epidemiological studies show that PPHN is associated with ante-natal events, including pre-eclampsia, chorioamnionitis and other peri-natal events, leading to abnormal pulmonary vascular growth and function, and perhaps increasing the risk for PAH later in life [26].

**Group 2: PH due to left heart disease**

Very little epidemiological data are available on this condition in children; however, left ventricular diastolic dysfunction and impaired myocardial performance can contribute to PH severity in diverse settings, including PPHN, BPD and CDH. Congenital left heart inflow/outflow obstructions are common in children with CHD, and outcome is dependent on aetiology and the stage in pulmonary vascular development that the obstruction occurs. Pulmonary vein stenosis, which has a very poor prognosis, can complicate the course and is emerging as an important cause of sustained PH, especially in the setting of ex-premature infants with BPD [29–32]. Table 3 shows congenital post-capillary obstructive lesions most frequent in childhood now classified as group 2.4 PH

**Group 3: PH due to lung diseases and/or hypoxia**

**Group 3.5: Developmental lung disorders**

This category comprises an important and increasingly recognised proportion of children with PH. BPD is a common developmental disorder of prematurity that is characterised by impaired alveolar and vascular growth and maturation. Fast registry data report that 10–12% of children with PH have associated lung disease, with BPD being the most common disorder [26, 33]. This might likely be an underrepresentation of its frequency due to bias in registry enrolment, as previously mentioned. The Netherlands epidemiological study revealed that 34% of patients with sustained PH have developmental lung disease. The incidence and prevalence of severe BPD and PH increase with increasing survival of 23–26-week pre-terms. In a prospective study, PH at 7 days of age was present in 42% of premature babies (birthweight 500–1250 g) and was associated with late PH (at 36 weeks corrected age) in 14%, worse severity of BPD, longer need for mechanical ventilation and neonatal intensive care unit hospitalisation, and higher mortality [34, 35]. In children with BPD, PH can resolve with respiratory and PH-targeted drug therapy over time; however, even in the surfactant era the morbidity and mortality of PH in BPD infants remains high. Recent meta-analyses found that the presence of PH in premature born infants was strongly associated with mortality (risk ratio 4.7) with an accumulative estimated mortality rate of 16% prior to discharge and of 40% during the first 2 years of life. However, the same meta-analyses identified that most reports have studied selected patient populations, and accurate estimates of incidence and prevalence rates later in life are lacking [36]. No trials have yet been conducted to formally assess the effect of PH-specific therapies on children with BPD.

### Table 2 Persistent pulmonary hypertension of the newborn (PPHN) and associated disorders

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Associated disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic PPHN</td>
<td>Myocardial dysfunction (asphyxia, infection)</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>Structural cardiac diseases</td>
</tr>
<tr>
<td>Meconium aspiration syndrome</td>
<td>Hepatic and cerebral arteriovenous malformations</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>Associations with other diseases:</td>
</tr>
<tr>
<td>Transient tachypnoea of the newborn</td>
<td>Placental dysfunction (pre-eclampsia, chorioamnionitis, maternal hypertension)</td>
</tr>
<tr>
<td>Pneumonia/sepsis</td>
<td>Metabolic disease</td>
</tr>
<tr>
<td>Developmental lung disease</td>
<td>Maternal drug use or smoking</td>
</tr>
<tr>
<td>Peri-natal stress</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 Congenital post-capillary obstructive lesions [group 2.4]

<table>
<thead>
<tr>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary vein stenosis</td>
</tr>
<tr>
<td>Isolated</td>
</tr>
<tr>
<td>Associated (bronchopulmonary dysplasia, prematurity)</td>
</tr>
<tr>
<td>Cor triatriatum</td>
</tr>
<tr>
<td>Obstructed total anomalous pulmonary venous return</td>
</tr>
<tr>
<td>Mitral/aortic stenosis (including supra/subvalvular)</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
</tr>
</tbody>
</table>
Table 4 provides a summary of developmental lung disorders that share the common feature of developmental vascular disturbances.

**Group 4: PH due to pulmonary artery obstructions**
Chronic thromboembolic PH remains uncommon as a cause of PAH in children, at around 0–1.4% of cases [22, 26]. In contrast, pulmonary artery obstructions occur in a number of CHDs, either congenitally or acquired after corrective surgery [25].

**Group 5: PH with unclear and/or multifactorial mechanisms**

**Group 5.4: Complex CHD**
This group includes haematological disorders, systemic and metabolic disorders, others, and complex CHD. Of specific interest for the paediatric age group are complex heart diseases that are associated with congenital anomalies of the pulmonary vasculature such as segmental disorders, single ventricle physiology and the scimitar syndrome (table 5). PH in these settings is extremely difficult to define or classify [37]. After extensive discussion at the 5th WSPH in 2013, the Paediatric Task Force agreed to classify several anomalies with differential pulmonary blood flow under the category of "segmental PH", indicating the distinct nature of these entities when compared with other forms of PH [38, 39].

During the current 6th WSPH, the Paediatric Task Force also considered including patients with single ventricle physiology as representing yet another difficult group to define; this group continues to increase and represents a significant proportion of subjects with PVD at major medical centres. At various stages these patients may have increased or decreased pulmonary blood flow, and as they reach an age suitable for the Fontan procedure or total cavo-pulmonary connection these subjects have variable degrees of PVD and bronchopulmonary collaterals. Subsequently, the chronic non-pulsatile pulmonary circulation associated with a Fontan circulation likely induces a very specific form of PVD that is dissimilar to PVD in other diseases associated with PH [40]. Patients with Fontan circulation do not usually fulfil the definition of PH with mPAP >20–25 mmHg and, accordingly, these patients were previously excluded from the official WSPH classification. Nevertheless, these patients develop PVD that markedly impacts survival and, according to the Paediatric Task Force, PVD in the setting of single ventricle physiology deserves inclusion and has been classified with other forms of group 5 PH. The nature and mechanisms underlying the pathobiology of PVD in this setting urgently require further investigation.

### Table 4: Developmental lung disorders associated with pulmonary hypertension

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td></td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia</td>
<td></td>
</tr>
<tr>
<td>Down syndrome</td>
<td></td>
</tr>
<tr>
<td>Alveolar capillary dysplasia with “misalignment of veins” (FOXF1)</td>
<td></td>
</tr>
<tr>
<td>Lung hypoplasia, acinar dysplasia</td>
<td></td>
</tr>
</tbody>
</table>
| Surfactant protein abnormalities | Surfactant protein B deficiency
Surfactant protein C deficiency
ABCA3
TTF1/NKX2-1
TBX4 | |
| Pulmonary interstitial glycogenosis | |
| Pulmonary alveolar proteinosis | |
| Pulmonary lymphangiectasia | |

### Table 5: Complex congenital heart disease (group 5.4)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
</table>
| Segmental pulmonary hypertension | Isolated pulmonary artery of ductal origin
Absent pulmonary artery
Pulmonary atresia with ventricular septal defect and major aorto-pulmonary collateral arteries
Hemitruncus
Other | |
| Single ventricle | Unoperated
Operated
Scimitar syndrome |
In these complex CHD categories (group 5.4), the general definition of PH does not suffice and should be customised. At present, there is insufficient data showing that targeted therapies are safe and efficient in this population, and further studies are required [41, 42].

Additional special considerations for paediatric clinical classification

The WSPH classification for PH was originally designed for adults with PH. The rationale for a clinical classification includes the ability to strengthen clinical practice, including enhanced diagnostic and management strategies, and to help provide guidance for prioritising laboratory, translational and epidemiological research questions. In addition, goals for improving classification systems include the need for clarification of disease phenotype, encouraging new thinking on causation and disease pathobiology, enhancement of diagnostic evaluations, improvements in correlations of phenotype and therapeutic responsiveness, and enhancement of clinical trial design.

While the major categories of PH as classified by the WSPH have been shown to be helpful also in neonates and children, there are persistent and important gaps that should be considered to improve their utility in these specific age groups.

In 2013, the first WSPH Paediatric Task Force reasoned that a common classification for both adults and children is preferred, since children with PH who were diagnosed in the neonatal through adolescent age ranges are now surviving into adulthood and such classification will facilitate transition from paediatric to adult services. They then proposed several modifications in order to highlight aspects of paediatric disorders and better address specific features of paediatric PH within the core of the existing classification. These modifications included the designation of PPHN as a subclass within group 1 disorders, more detailed categorisation of PAH in CHD, the addition of congenital left heart inflow and outflow tract to group 2, and the introduction of the category of “developmental lung disease” to group 3 and of “segmental PH” to group 5.

In 2018, the WSPH Paediatric Task Force aimed to further capture specific paediatric features in the WSPH clinical classification, while preserving the main core of the classification as given in table 2 of the Task Force article by Simonneau et al. [25] in this issue of the European Respiratory Journal. They proposed additional further refinements of these groups as discussed in the previous subsections, including a separate designation for congenital/acquired cardiovascular conditions leading to post-capillary PH (group 2.4), developmental lung disorders (group 3.5), other pulmonary artery obstructions (group 4.2) and complex CHD (group 5.4).

Recent observational paediatric data reveal that PAH in “older” children, despite specific differences, shares many common features with adult PAH. However, PH presenting in neonates is often associated with developmental vascular abnormalities and responses, and in the current classification is assigned to group 3 PH associated with lung disease and/or hypoxia. These PVDs are much less comparable to adult PH, since the impact of PH on the immature, developing lung is recognised as a major factor integral to the presentation, diagnosis, response to therapy and outcome, both immediate and long term. It is clear that although paediatric and adult PH share common features, the aetiology, epidemiology and presentation of neonatal and paediatric PVD differ significantly from those in adults. One of the distinguishing features of PH in children is the injury of the developing fetal, neonatal and paediatric lung circulation [43]. Another distinguishing feature is the frequent association with chromosome, genetic and syndromic anomalies (11–52%), and the phenotypic associations that may result in multifactorial causes of PH in up to 33% of cases [5, 44].

The current WSPH Paediatric Task Force therefore proposed to designate the developmental (vascular) lung disorders as a special subcategory within group 3 PH (group 3.5). In addition to the recognised frequency and importance of PVD and PH in disorders such as BPD and CDH, this category includes a rapidly expanding list of newly recognised genetic developmental lung disorders, including surfactant abnormalities, pulmonary interstitial glycogenesis, alveolar capillary dysplasia, TBX4 mutations and others (table 4).

Paediatric PVDs are often associated with multiple comorbidities that may contribute to PH severity and dictate overall outcomes. As discussed, the genetic background of paediatric PH appears to differ from that of adult PH, and accompanying genetic disorders, syndromes and growth abnormalities are frequent in children with PH. Whether these latter should be regarded as causally related, disease modifiers or innocent bystanders is often not clear. Therefore, accurate phenotyping of children with PH and assessment of the effect on outcome of comorbidities remains of crucial importance in any classification.

Down syndrome

An illustrative example of the complex role of comorbidities in paediatric PH warranting further attention is Down syndrome. This Paediatric Task Force discussed the unique clinical phenotype of neonates, infants and children with Down syndrome, and the potential role for PH screening in this group.
Down syndrome, or trisomy 21, is associated with significant cardiovascular and pulmonary morbidity and mortality in children, including PH, chronic hypoxaemia and recurrent respiratory illnesses. Newborn infants with Down syndrome are at high risk of developing severe PPHN at birth and often have more aggressive PVD secondary to CHD or airways obstruction than do subjects without Down syndrome. Mechanisms that increase the susceptibility of infants and children with Down syndrome to develop worse PH and cardiopulmonary disease are incompletely understood. Past studies have shown that infants dying with Down syndrome can have evidence of lung hypoplasia as demonstrated by decreased alveolarisation, peripheral lung cysts and persistence of the double-capillary network [45]. These early abnormalities of arrested lung development may contribute to increased susceptibility for more aggressive cardiovascular and respiratory diseases in Down syndrome. Although mechanisms for abnormal lung and lung vascular development are uncertain, recent work has shown that three antiangiogenic (anti-vascular endothelial growth factor) genes are present on chromosome 21, and are each overexpressed in human fetal and infant lung tissue, including endostatin, RCAN-1 (regulator of calcineurin-1) and β-amyloid peptide. Experimentally, early disruption of angiogenic signalling decreases vascular growth and increases the risk for PH, and also impairs distal airspace (alveolar) growth [46, 47]. Overall, these laboratory and clinical findings suggest that subjects with Down syndrome are highly susceptible to decreased lung vascular and alveolar growth, which may increase the risk for PH and lung hypoplasia. Impaired lung vascular growth may increase the risk for environmental stimuli, such as haemodynamic stress, especially with associated CHD, intermittent or sustained hypoxia with obstructive apnoea or lung disease, viral infection, aspiration and other factors, to induce more accelerated PH in subjects with Down syndrome than others. Thus, the genetic consequences of Down syndrome may be linked with disruption of lung vascular and alveolar growth, suggesting that Down syndrome represents a "developmental lung disease". The current WSPH Paediatric Task Force agreed that the phenotype of Down syndrome-related PH is variable and does not universally fit into a single classification group, but that children with Down syndrome will be classified as group 3 in the absence of CHD (group 1 or 2).

Diagnosis of paediatric PH

Since the aetiology of PH is very diverse, a methodical and comprehensive diagnostic approach is crucial to reach an accurate diagnosis and treatment plan. Moreover, IPAH is a diagnosis "per exclusion" and can be made only by excluding known causes of PH. Despite this, recent registries have shown that most children do not undergo a complete evaluation [48]. An updated comprehensive paediatric diagnostic algorithm is shown in figure 1. Special situations may predispose to the development of PAH and should be considered.

Right heart catheterisation

The Paediatric Task Force addressed several questions regarding the risks and benefits of right heart catheterisation (RHC) in confirming the diagnosis of PH or PAH in children, and which children may be at highest risk for adverse events during RHC.

RHC remains the gold standard for the definitive diagnosis and nature of PAH, performing AVT, and providing useful data for risk stratification. This necessity should be balanced with associated risks. Major complications associated with RHC in children with PH have been reported to be 1-3%, and are generally associated with clinical condition and young age (newborns and young infants) [49–52]. As a result, cardiac catheterisation in paediatric PAH is strongly recommended to be performed in experienced paediatric PH centres using strategies to prevent these potential complications and having the ability to manage complications including PH crisis with aggressive interventions such as extracorporeal life support (ECLS). In rare instances, a child may be too sick to undergo cardiac catheterisation safely (e.g. World Health Organization Functional Class (WHO FC) IV). In these cases, when the suspicion of PAH is high and the non-invasive imaging is highly supportive, one should stabilise first and cautiously initiate appropriate PH therapy under careful observation, most often in the intensive care unit setting. RHC can then be performed more safely when the patient is sufficiently stabilised. Every attempt should be made for children with IPAH/HPAH to undergo RHC and AVT safely so one can determine whether they are acutely responsive to vasoreactivity testing and could benefit from CCB treatment. For those robustly responsive, but with poor cardiac function, a CCB would not be utilised unless the function improved.

Indications for repeat cardiac catheterisation in children with PH are not well defined, but include assessment of treatment effect, clinical deterioration, detection of early disease progression, listing for lung transplantation and prediction of prognosis. It has, however, not been shown whether changes in haemodynamic parameters are associated with change in clinical outcome and therefore these parameters do not meet the requirements to serve as established treatment goals.
Treatment strategies and clinical end-points

Currently, a goal-oriented treatment strategy is suggested for the treatment of paediatric PAH. Despite the absence of validated treatment goals in paediatric PAH, various treatment guidelines were proposed for children with PAH, predominantly based on expert opinion [53–56]. An apparent lack of consensus in these opinions resulted in important differences in reported paediatric treatment recommendations, stressing the need for evidence.

In 2013, the Paediatric Task Force of the 5th WSPH summarised determinants of higher risk in children, which included clinical evidence of right ventricular failure, progression of symptoms, syncope, failure to thrive, WHO FC III or IV, significantly elevated or rising brain natriuretic peptide (BNP) levels, echocardiographic signs of severe right ventricular enlargement or dysfunction, pericardial effusion, and haemodynamic parameters such as mPAP/mean systemic arterial pressure (mSAP) ratio >0.75, mean right atrial pressure (mRAP) >10 mmHg and PVRI >20 WU·m² [54]. A recent systematic review and meta-analyses concluded that WHO FC, N-terminal pro-BNP (NT-proBNP)/BNP, mRAP, PVRI, cardiac index and acute vasodilator response are consistently reported as useful prognostic factors for assessing long-term outcomes in paediatric PAH, and thus could be used for initial risk stratification and as such incorporated in recommendations and guidelines [57, 58].

However, parameters with prognostic capabilities are not automatically suitable to serve as a treatment goal. Treatment goals are either clinically meaningful parameters that reflect how a patient feels or functions and can thus be a target for treatment, or should be surrogates for survival. Surrogates for
survival by definition are parameters with a strong correlation with survival, which can be changed by treatment, while such change should indicate disease worsening or improvement and should be predictive of long-term outcome.

WHO FC, used in children with PAH and indicating how the child feels and function, has been demonstrated to be also a strong predictor of transplant-free survival. Moreover, WHO FC has been shown recently in paediatric PAH to be also a surrogate for survival and as such WHO FC qualifies as a treatment goal, despite its disadvantage of being a potentially subjective assessment [53]. A functional class designed specifically for children was proposed in 2011, but is still being considered because of its complexity and influence by comorbidities, and therefore has not yet reached broad use [59, 60].

In adults with PAH the 6-min walk test (6MWT) has been used to demonstrate drug efficacy. Although its ability to serve as a surrogate end-point for late outcomes is debatable, the 6MWT may be useful as a treatment goal in paediatric patients developmentally able to perform the test (children ≥6 years of age) [61, 62]. Unfortunately, younger children cannot reliably perform the test, making this a suboptimal primary end-point in a study of the full age range of children. Cardiopulmonary exercise testing (CPET) is even more demanding with respect to developmental skills and paediatric reference values for CPET in association with outcome are lacking [63].

Echocardiography seems an obvious tool to monitor treatment effect in children with PH. It provides functional and structural assessment of the heart and estimates of pulmonary haemodynamics, and is widely available, non-invasive and well tolerated by children. Unfortunately, echocardiography is also subject to significant operator and interpretation variability [64]. Where several echocardiographic variables have been suggested as predictors of outcome in paediatric PAH, today only tricuspid annular plane systolic excursion (TAPSE) has been shown as strongly associated with improved survival during treatment, indicating its potential utility as a treatment goal [53]. New echocardiographic modalities for evaluating right ventricular function (three-dimensional echocardiography, strain and strain rate, and right ventricular stroke work) as well as magnetic resonance imaging (MRI) assessment of right ventricular volume and function both hold promise here, but more data in the paediatric population are needed to determine the value of these techniques regarding establishment of predictive value or surrogacy for clinical outcomes [65, 66].

In addition to right ventricular function, right ventricular pulmonary vascular coupling reflects right ventricular afterload, and is regarded to be an important measure for the cardiovascular state and thus prognosis in patients with PH. MRI and echocardiography are potential candidates for non-invasive monitoring of this coupling state.

At the pulmonary arterial side of ventricular–arterial coupling, pulmonary arterial stiffness parameters are gaining interest as prognostic indicators in PAH. Recently, pulmonary vascular stiffness indices have been shown to predict the development of advanced PAH and mortality in paediatric PVD [67–71].

Serum biomarkers have the advantage of being relatively easy to obtain in peripheral blood and several biomarkers have been studied in paediatric PAH. Two serum biomarkers have been repeatedly shown to have prognostic capabilities in paediatric PAH: NT-proBNP and uric acid. A recent meta-analysis confirmed that NT-proBNP correlated strongly and consistently with survival in children with PAH, and thus can be used for risk stratification in this population. However, to be used as a treatment target or clinical end-point, biomarkers should be representative of the disease process and its evolution, which is often difficult to demonstrate. Nevertheless, changes in NT-proBNP levels following treatment initiation were recently shown to be predictive for survival in paediatric PAH, indicating that NT-proBNP qualifies as a treatment goal [72, 73]. Baseline uric acid levels had previously been shown to correlate with survival in paediatric PAH [74]. More recently, it was shown that the development of uric acid levels over time correlates with outcome in paediatric PAH [75]. These findings show that uric acid is capable of predicting outcome not only at baseline, but also during the disease course of PAH, and therefore may also qualify to be a treatment goal.

Recently, clinical worsening has been introduced as a composite end-point for large randomised controlled trials (RCTs) in adults with PAH. Components of clinical worsening included unambiguous events such as death or lung transplantation, which are combined with softer events, including hospitalisations, need for additional therapy and worsening of function. The use of clinical worsening as an end-point has been validated in adults with PAH and the soft clinical worsening end-point components were shown to be highly predictive for subsequent mortality. These results have now been reproduced in the paediatric PAH population using clinical worsening components: death, lung transplantation, non-elective PAH-related hospitalisations, including hospitalisations for atrial septostomies, initiation of i.v. prostanoids and functional deterioration (worsening of WHO FC, ≥15% decrease in 6MWD or both) [76]. Moreover, this
study showed that clinical worsening occurred with a high event rate in paediatric PAH, indicating that clinical worsening may serve as a suitable end-point in future paediatric trials.

Monitoring daily physical activity has also been suggested as an alternative tool to assess functional capacity in children. A recent pilot study using three-axis accelerometry in 29 children with PAH and 60 controls showed that physical activity was markedly decreased in children with PAH, and that accelerometer output correlated with clinical disease severity markers and predicted outcome [77]. Larger studies are in progress to validate the use of accelerometer output as a clinically meaningful end-point for clinical trials in paediatric PAH.

In summary, the emerging paediatric data provide increasing evidence and support for the risk stratification model proposed by the WSPH Paediatric Task Force in 2013, with some minor modifications in 2018. For example, the prognostic significance of syncope could not be demonstrated and is therefore questioned as a high-risk factor for poor outcomes. Importantly, upcoming evidence suggests that in paediatric PAH striving for a low-risk profile using this WSPH paediatric risk assessment tool might also be used as treatment target, as has recently been suggested in adults [78–80].

**Updates to the paediatric treatment algorithm**

The prognosis of children with PAH has improved in the past decade owing to new therapeutic agents and aggressive treatment strategies. However, the use of targeted pulmonary PAH therapies in children is almost exclusively based on experience and data from adult studies, rather than evidence from clinical trials in paediatric patients. Due to the complex aetiology and relative lack of data in children with PAH, selection of appropriate therapies remains difficult. We propose a pragmatic treatment algorithm based on the strength of expert opinion that is most applicable to children with IPAH (figure 2). The ultimate goal of treatment should be improved survival and to facilitate normal activities of childhood without self-limitation.

Background therapy with diuretics, oxygen, anticoagulation and digoxin should be considered on an individual basis. Care should be taken to not overly decrease intravascular volume due to the pre-load dependence of the right ventricle. Following the complete evaluation for all causes of PH, AVT is recommended to help determine therapy.

In children with a positive AVT response, oral CCBs may be initiated [2–4]. In the child with a sustained and improved response, CCBs may be continued, but patients may deteriorate, requiring repeat evaluation and additional therapy [81]. Clinical experience suggests that these children remain on CCBs in addition to targeted PAH therapy. For children with a negative AVT response or in the child with a failed or

FIGURE 2 Paediatric idiopathic/familial pulmonary arterial hypertension treatment algorithm. CCB: calcium channel blocker; ERA: endothelin receptor agonist; PDE5i: phosphodiesterase type 5 inhibitor. #: deterioration or not meeting treatment goals.
non-sustained response to CCBs, risk stratification should determine additional therapy (table 6). Although the specific number of lower- or higher-risk criteria to drive therapeutic choices is not yet known, a greater proportion of either should be considered as justification for therapy. As in adult patients, determinants of higher risk in children include clinical evidence of right ventricular failure, progression of symptoms, WHO FC III or IV, significantly elevated or rising BNP/NT-proBNP levels, severe right ventricular enlargement or dysfunction and pericardial effusion. Additional haemodynamic parameters that predict higher risk include mPAP/mSAP ratio >0.75 [82], mRAP >10 mmHg and PVRI >20 WU·m² [83]. Additional high-risk parameters include failure to thrive. In the child with a negative acute vasoreactivity response and lower risk, initiation of oral monotherapy is recommended. Treatment of choice is an endothelin receptor antagonist (bosentan [83–90], ambrisentan [91, 92]) or phosphodiesterase type 5 (PDE5) inhibitor (sildenafil [93–100], tadalafil [101, 102]). Children who deteriorate on either endothelin receptor antagonists or PDE5 inhibitors may benefit from consideration of early combination therapy (add-on or up-front). If the child remains in a low-risk category, addition of inhaled prostacyclin (iloprost [103–106], treprostinil [107]) to background therapy may be beneficial. It is crucial to emphasise the importance of continuous repeat evaluation for progression of disease in children on any of these therapies. In children who are at higher risk, initiation of oral monotherapy is recommended. Treatment of choice is an endothelin receptor antagonist (bosentan [83–90], ambrisentan [91, 92]) or phosphodiesterase type 5 (PDE5) inhibitor (sildenafil [93–100], tadalafil [101, 102]).

Interventional palliative bridges

Atrial septostomy

Atrial septostomy in children with IPAH has been performed to treat syncope, and improve cardiac output and systemic oxygen carrying capacity, especially in countries without easy access to targeted PH drugs or in IPAH refractory to medical therapy, or as a bridge to lung transplantation [114]. Atrial septostomy improves symptoms and quality of life in paediatric PAH, and may serve as a bridge to lung transplantation [56]. It appears to be safe in centres with experience, and one study reported lung transplantation-free and repeat-balloon atrial septostomy (BAS)-free survival at 30 days, 1 year and 5 years was 87%, 61% and 32%, respectively [115]. However, in most cases BNP levels do not change after BAS and it seems likely that the creation of the Potts shunt (see following subsection) may ultimately be the preferred procedure as in contrast to BAS it unloads the pulmonary vascular bed, as well as the right ventricle with preserved oxygenation to the upper

| TABLE 6 Determinants of paediatric idiopathic/heritable pulmonary arterial hypertension risk |
|-----------------------------------|-----------------------------------|-----------------------------------|
| Lower risk | Determinants of risk | Higher risk |
| No | Clinical evidence of RV failure | Yes |
| No | Progression of symptoms | Yes |
| >350 | 6MWT (>6 years old) m | <350 |
| Normal | Growth | Failure to thrive |
| I, II | WHO FC | III, IV |
| Minimally elevated | Serum BNP/NT-proBNP | Significantly elevated |
| | | Rising level |
| | | |
| | | Echocardiography |
| | | RA/RV enlargement |
| | | Reduced LV size |
| | | Increased RV/LV ratio |
| | | Reduced TAPSE |
| | | Low RV FAC |
| | | Pericardial effusion |
| Systemic CI >3.0 L·min⁻¹·m⁻² | Haemodynamics | Systemic CI <2.5 L·min⁻¹·m⁻² |
| Systemic venous saturation >65% | | mRAP >10 mmHg |
| Acute vasoreactivity | | PVRI >20 WU·m² |
| | | Systemic venous saturation <60% |
| | | PACI <0.85 mL·mmHg⁻¹·m⁻² |

RV: right ventricle; 6MWT: 6-min walk test; WHO: World Health Organization; FC: Functional Class; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; RA: right atrium; LV: left ventricle; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; CI: cardiac index; mRAP: mean right atrial pressure; PVRI: pulmonary vascular resistance index; WU: Wood Units; PACI: pulmonary arterial compliance index.
body including coronary and cerebral vessels. Relative contraindications for atrial septostomy include 1) mRAP >20 mmHg, 2) resting arterial oxygen saturation <90%, 3) severe right ventricular failure and 4) patients with impending death.

Atrial septostomy may be considered in the child with worsening PAH despite optimal medical therapy, but should be considered before the later stages with increased risk. Atrial septostomy can be considered in patients with WHO FC III and IV symptoms and recurrent syncope on combined medical therapy, as palliative bridge to transplant, increasing the chance for survival while waiting for a donor organ.

Reversed Potts shunt

The Paediatric Task Force also discussed whether the reversed Potts shunt should be offered to children with severe IPAH/HIPAH who are refractory to medical therapy.

Surgical creation of a palliative reversed Potts shunt (left pulmonary artery to descending aorta) has been described as a new option for severely ill children with suprasystemic IPAH [56, 116]. This surgical procedure implies the creation of a connection between the left pulmonary artery and the descending aorta, which allows right-to-left shunting, similar to a patient with patent ductus arteriosus-related Eisenmenger syndrome. The use of a reversed Potts shunt in suprasystemic PH is considered advantageous compared with atrial septostomy as it provides high oxygen saturated blood to the coronary arteries and the central nervous system, and only causes desaturation of the lower body. Another benefit arises from its effect on haemodynamics by the relief of right ventricular pressure overload in systole and, in part, also in diastole, with a subsequent reduction in shifting of the interventricular septum towards the left ventricle with an improvement in systolic and diastolic left ventricular performance. A run-off through the Potts shunt, if too big, with decreased pulmonary perfusion and extreme desaturation of the lower body, with subsequent undersupply of the myocardium and the brain, should be avoided. The procedure may be considered in patients with suprasystemic PH refractory to any medical treatment, including combined therapy presenting with WHO FC IV symptoms.

The largest series published consisted of 24 children with drug-refractory PAH in which a permanent Potts shunt was created (19 surgical left pulmonary artery–descending aorta, six via stenting of a persistent ductus arteriosus) [117]. Six patients experienced severe post-operative complications and there were three early deaths related to low cardiac output. After a median follow-up of 2.1 years, the 21 survivors showed persistent improvement in functional capacities and none of the patients had syncope or overt right ventricular failure [76]. These favourable long-term results suggest that creation of a Potts shunt can be a valuable alternative, or bridge to bilateral lung transplantation, at least in selected cases.

Recently, several case series demonstrated the feasibility of the pure catheter-based interventional implementation of the connection between the left pulmonary artery and the descending aorta [118]. The most elegant method is obviously the implantation of a stent in a still patent persistent ductus arteriosus, which is not infrequently present in infants and young children. This procedure is an established method in CHD with duct-dependent circulation and can be established with considerable low peri-procedural risk in experienced centres. The interventional de novo creation of a left pulmonary artery–descending aorta connection with a covered stent from the left pulmonary artery or descending aorta side [119] has been shown to be feasible, but currently must be considered a high-risk procedure in patients with end-stage PAH who are too sick to undergo surgery and only in a programme with expertise in performing this procedure. Salna et al. [120] described a novel successful approach to the Potts shunt in a young adult with IPAH using a unidirectional valved shunt from the main pulmonary artery to the descending aorta, which has the advantage of preventing any back flow from the aorta when the PAP is subsystemic and during diastole. Whether this will prove to be a preferred approach remains to be seen. The current WSPH Paediatric Task Force decided to include the Potts shunt in the treatment algorithm, but caution that it should only be done in selected patients in a centre with the expertise to perform the procedure, including ECLS back-up (figure 2). Whether this is preferred over an atrial septostomy will require further experience and study.

Clinical trial design

The Paediatric Task Force further discussed whether we can develop new paediatric-specific clinical end-points in clinical trial design.

Our understanding of the pathobiology and treatment of children with PH has improved considerably during the past 20 years, but treatment is still based on clinical trial evidence of efficacy from clinical trial data in adults, individual clinical experience, registry data, short-term trials and open-label studies. RCTs have not been conducted. Clinical trials in adults are most helpful when conducted on the most homogeneous, “purest” form of the disease, i.e. IPAH, but this is rare in children. Growth and
development entail constant hormonal and metabolic change necessitating age-related study, understanding the effect on long-term outcome is crucial and choice of end-points is difficult [121]. The European Medicines Agency (EMA) and US FDA both require RCTs, but the EMA emphasises the need for pharmacokinetic and safety studies, which have been done in some instances, while the US FDA seeks to include a clinical end-point for evidence of efficacy. Relevant clinical end-points include death, transplantation and hospitalisation, and determining how the child feels. The traditional means of evaluation in adults, such as the 6MWT, are obviously not applicable to young children. Potential surrogate end-points in children include weight, echocardiography, biomarkers (primarily NT-proBNP), MRI and exercise testing. None of these possibilities have been fully validated. Haemodynamic evaluation does not seem to be an appropriate end-point since there are ethical considerations and sequential studies are not known to relate to long-term outcome. Recruitment, retention and evaluation of a continually maturing small population of children is a considerable challenge.

However, since the 5th WSPH, paediatric-specific biomarkers, such as functional classification, TAPSE and NT-proBNP, growth and composite clinical end-points have been evaluated. TAPSE, NT-proBNP and WHO FC identified transplant-free survival in 70 children with PAH [53]. Height for weight was also identified as a clinical end-point [122]. The Panama “Paediatric Functional Class” correlated well with outcome [60]. A composite end-point of clinical worsening composed of death, lung transplantation and initiation of parenteral prostanoid therapy was identified [53, 76]. A novel approach to clinical evaluation of treatment efficacy or disease progression may be the use of home accelerometers and a pilot study suggested that there is a difference in spontaneous physical activity in children with PAH compared with controls [77]. Thus, paediatric-specific clinical end-points and trial design are evolving.

Conclusions

Despite many unique characteristics, children with PH are often assessed and managed based on adult PH guidelines. This current WSPH Paediatric Task Force had an opportunity to further highlight some of the inherent differences between children and adults with PH, novel findings in paediatric PH since the 5th WSPH meeting in 2013, and develop additional current paediatric-specific recommendations. The current 2018 6th WSPH classification incorporates the growing population of children with developmental lung diseases, such as BPD and CDH, complex CHD, and novel mutations. The Paediatric Task Force addressed a new definition for PAH and AVT in children, a novel palliative bridge approach with the reversed Potts shunt, and clinical trial design. The field of paediatric PH still requires future paediatric-specific clinical trials in order to develop specific treatment strategies and clinical end-points for children with PH.

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References


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The importance of patient perspectives in pulmonary hypertension


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@ERSpublications
Analysis and discussion on the importance of patients’ perspectives in pulmonary hypertension
http://ow.ly/edOt30mgYoI


ABSTRACT The assessment of objective measurement of cardiopulmonary status has helped us achieve better clinical outcomes for patients and develop new therapies through to the point of market access; however, patient surveys indicate that more can be done to improve holistic care and patient engagement. In this multidisciplinary review, we examine how clinical teams can acknowledge and embrace the individual patient’s perspective, and thus improve the care for individual patients suffering from pulmonary hypertension by cultivating the importance and relevance of health-related quality of life in direct clinical care. At the individual level, patients should be provided with access to accredited specialist centres which provide a multidisciplinary approach where there is a culture focused on narrative medicine, quality of life, shared decision making and timely access to palliative care, and where there is participation in education. On a larger scale, we call for the development, expansion and promotion of patient associations to support patients and carers, lobby for access to best care and treatments, and provide input into the development of clinical trials and registries, focusing on the patients’ perspective.

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Introduction

This article provides an overview of the role of the patient’s perspective in understanding and managing pulmonary hypertension (PH). “Patient perspective” is the patient’s experience of PH and its impact on him/her and caregivers, including symptomatic, intellectual, psychosocial, spiritual and goal-oriented dimensions of the disease and its treatment. Implicit in the concept of perspective is how it can be effectively communicated, understood and acted upon by others involved with the patient, including primary and subspecialty healthcare providers (HCPs), adjunctive professional providers (e.g. mental health and spiritual counsellors), family and social network, and health-related influencers (e.g. government, insurers and medical industry).

Assessing the patient perspective

Surveys

Surveys of pulmonary arterial hypertension (PAH) patients provide insights into patients’ perceptions of impactful aspects of their disease [1–5]. A general conclusion among surveys is that although the clinical definition of the severity of disease appropriately includes symptomatology, exercise capacity, biomarkers, invasive and non-invasive haemodynamic measurements, and survival, these parameters do not capture the extensive realm of physical, emotional and psychosocial issues which affect patients and their caregivers (figure 1).

Health-related quality of life measures

Generic and disease-specific measures of “health-related quality of life” (HRQoL) have been evaluated in PH patients (table 1) [6–18]; physical/functional, emotional and social aspects of HRQoL are negatively impacted by PH [19–21]. PH therapies produce a variable benefit in HRQoL (table 2) [22–42]. Some measures of HRQoL may also correlate with survival prognosis [43]. Importantly, medications directed towards concomitant health issues (e.g. depression, anxiety and sleep disorders) [44] or non-pharmacological therapies (e.g. exercise programmes, psychosocial counselling, health coaching and access to nurse specialists or palliative care strategies) [45–51] may improve HRQoL.

FIGURE 1 Surveys of patients and caregivers suggest that traditional parameters of pulmonary hypertension severity may be the “tip of the iceberg” when the broader range of patient concerns is considered.
Current status

“Patient perspective” can be viewed through two different but related lenses: 1) the individual’s perspective as it relates to each patient’s individual situation and 2) the aggregate perspective of the PH population, i.e. a perspective of common denominators despite unique individual variations.

Individual patient perspective

Recognition of the importance of the individual patient’s perspective regarding their experience of PH is exemplified by the evolving patient/HCP clinical interaction. The traditional model of this relationship (exploration of symptoms and physical findings with tests culminating in a diagnosis and treatment recommendations) has been the subject of algorithms and guidelines [45, 52–54]. The management of PH is increasingly complex, including medications administered by different routes with unpredictable degrees of beneficial and adverse effects, options for invasive or surgical interventions, differences in practice settings and access to treatment from centres to community practices, decreased time spent with patients, and considerations of cost and follow-up. Increasing recognition of this complexity of PH and its treatment, and of the importance of the individual patient’s perspective, including their understanding of PH and appreciation of the burden of their illness and impact on their HRQoL, requires a bidirectional exchange of opinions and objectives between patients and HCPs, in order to promote integration of the patient perspective into the patient/HCP relationship. This patient-centred collaborative care approach is finding expression in concepts such as narrative medicine, shared decision making and palliative care, leading to greater patient engagement, involvement and empowerment in management of their illness [55].

Narrative medicine

A key feature of patient-centred medicine in chronic conditions such as PH is that the patient presents with a spectrum of symptoms and associated psychological responses which occur within a sociological and cognitive framework unique to that patient, and which contribute to the patient’s fears, coping mechanisms and goals. Treatment focused exclusively on the underlying disease often fails to address the ripples of impact provoked by PH which may become the main source of concern to the patient. The ability of HCPs to “acknowledge, absorb, interpret, and act on the stories and plights of others” has been referred to as narrative competence, the foundation of narrative medicine [56]. The intention of narrative

Table 1: Summary of measures of health-related quality of life used in pulmonary arterial hypertension (PAH)

<table>
<thead>
<tr>
<th>Measure [ref.]</th>
<th>Domains</th>
<th>Items n</th>
<th>Recall period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 [9]</td>
<td>Physical functioning, role limitations physical, bodily pain, general health, vitality, social functioning, role limitations emotional, mental health</td>
<td>36</td>
<td>Now to past 4 weeks</td>
</tr>
<tr>
<td>EQ-5D [10]</td>
<td>Health state description: mobility, self-care, usual activities, pain/discomfort, anxiety/depression; overall health status (visual analogue scale)</td>
<td>51</td>
<td>Today</td>
</tr>
<tr>
<td>NHP [11]</td>
<td>Mobility, pain, social isolation emotional reactions, energy level, sleep</td>
<td>38</td>
<td>At the moment</td>
</tr>
<tr>
<td>HADS [12]</td>
<td>Anxiety, depression</td>
<td>14</td>
<td>At the moment</td>
</tr>
<tr>
<td><strong>PAH specific</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAMPHOR [13]</td>
<td>Overall symptoms (energy, breathlessness, mood), functioning, quality of life</td>
<td>65</td>
<td>Today</td>
</tr>
<tr>
<td>MLHFQ [14]</td>
<td>Physical, emotional</td>
<td>21</td>
<td>4 weeks</td>
</tr>
<tr>
<td>LPH [15]</td>
<td>Physical, emotional</td>
<td>21</td>
<td>1 week</td>
</tr>
<tr>
<td>CHFQ [16]</td>
<td>Dyspnoea, fatigue, emotional function, mastery</td>
<td>20</td>
<td>2 weeks</td>
</tr>
<tr>
<td>emPHasis-10 [17]</td>
<td>Unidimensional</td>
<td>10</td>
<td>At the moment</td>
</tr>
<tr>
<td>PAH-SYMPACT [18]</td>
<td>Respiratory symptoms, tiredness, cardiovascular symptoms, other symptoms, physical activities, daily activities, social impact, cognition, emotional impact</td>
<td>41</td>
<td>24 h for symptoms; 7 days for impacts</td>
</tr>
</tbody>
</table>

SF-36: Medical Outcomes Study 36-item short form; EQ-5D: EuroQol Group 5-Dimension Self-Report Questionnaire; NHP: Nottingham Health Profile; HADS: Hospital Anxiety and Depression Scale; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; MLHFQ: Minnesota Living with Heart Failure Questionnaire; LPH: Living with Pulmonary Hypertension questionnaire; CHFQ: Chronic Heart Failure Questionnaire; emPHasis-10: 10-question survey proposed by the Pulmonary Hypertension Association UK. Information based on and expanded from [6].
<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>Subjects</th>
<th>Drug</th>
<th>HRQoL</th>
<th>Time to</th>
<th>Domains significantly improved#</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIES-1 [26]</td>
<td>201</td>
<td>Ambrisentan 2.5–10 mg</td>
<td>SF-36</td>
<td>Physical: none; mental: none</td>
<td></td>
</tr>
<tr>
<td>ARIES-2 [26]</td>
<td>192</td>
<td>Ambrisentan 2.5–5.0 mg</td>
<td>SF-36</td>
<td>Physical: function; mental: none</td>
<td></td>
</tr>
<tr>
<td>EARLY [27]</td>
<td>185</td>
<td>Bosentan</td>
<td>SF-36</td>
<td>24 weeks</td>
<td>Physical: none; mental: none; health transition index</td>
</tr>
<tr>
<td>SERAPHIN [29]</td>
<td>742</td>
<td>Macitentan 3 or 10 mg</td>
<td>SF-36 version 2</td>
<td>6 months</td>
<td>Physical: function, role, pain; mental: vitality, social function, emotional role, mental health</td>
</tr>
<tr>
<td><strong>PDE5 inhibitors and sGC stimulators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sildenafil in PPH [32]</td>
<td>22</td>
<td>Sildenafil 25, 50 or 100 mg</td>
<td>CHFQ</td>
<td>6 weeks</td>
<td>Dyspnoea, fatigue</td>
</tr>
<tr>
<td>SUPER-1 [31]</td>
<td>278</td>
<td>Sildenafil (pooled 20, 40 or 80 mg doses)</td>
<td>SF-36</td>
<td>12 weeks</td>
<td>Physical: function, general health; mental: vitality; Utility index score</td>
</tr>
<tr>
<td>PHIRST [30]</td>
<td>405</td>
<td>Tadalafil 40 mg</td>
<td>SF-36</td>
<td>EQ-5D</td>
<td>Physical: function, role, pain, general health; mental: vitality, social function; Visual analogue scale; UK utility index score; USA utility index score</td>
</tr>
<tr>
<td>PATENT-1 [28]</td>
<td>443</td>
<td>Riociguat</td>
<td>EQ-5D</td>
<td>LPH</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Prostanoids and prostacyclin receptor agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoprostenol in PPH [34]</td>
<td>81</td>
<td>Epoprostenol</td>
<td>CHFQ</td>
<td>NHP</td>
<td>Dyspnoea, fatigue, emotional function, mastery</td>
</tr>
<tr>
<td>Treprostinil s.c. in PAH [39]</td>
<td>470</td>
<td>Treprostinil</td>
<td>MLHFQ</td>
<td></td>
<td>Emotional reaction, sleep</td>
</tr>
<tr>
<td>Iloprost for severe PH [37]</td>
<td>203</td>
<td>Inhaled iloprost</td>
<td>EQ-5D</td>
<td></td>
<td>Physical score</td>
</tr>
<tr>
<td>Beraprost for PAH [33]</td>
<td>116</td>
<td>Beraprost</td>
<td>MLHFQ</td>
<td>3, 6, 9 and 12 months</td>
<td>Overall health status (visual analogue scale)</td>
</tr>
<tr>
<td>Treprostinil in CTD-PAH [38]</td>
<td>90</td>
<td>Treprostinil</td>
<td>MLHFQ</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>GRIPHON [41]</td>
<td>1156</td>
<td>Selexipag</td>
<td>None reported</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td><strong>Combination therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACES [40]</td>
<td>267</td>
<td>Sildenafil added to epoprostenol</td>
<td>SF-36</td>
<td>Physical: function, role, general health; mental: vitality, social functioning, mental health</td>
<td></td>
</tr>
<tr>
<td>TRIUMPH [36]</td>
<td>235</td>
<td>Treprostinil added to oral bosentan or sildenafil therapy</td>
<td>MLHFQ</td>
<td></td>
<td>Global, physical scores</td>
</tr>
<tr>
<td>AMBITION [35, 42]</td>
<td>500</td>
<td>Upfront ambrisentan and tadalafil</td>
<td>None initially reported; CAMPHOR, SF-36</td>
<td></td>
<td>Improved only health transition score in SF-36 versus monotherapy; both arms improved all domains of both instruments</td>
</tr>
</tbody>
</table>

ERA: endothelin receptor agonist; SF-36: Medical Outcomes Study 36-item short form; PDE5: phosphodiesterase type 5; sGC: soluble guanylate cyclase; PPH: primary pulmonary hypertension; CHFQ: Chronic Heart Failure Questionnaire; EQ-5D: EuroQol Group 5-Dimension Self-Report Questionnaire; NS: non-significant; LPH: Living with Pulmonary Hypertension questionnaire; NHP: Nottingham Health Profile; MLHFQ: Minnesota Living with Heart Failure Questionnaire; CTD: connective tissue disease; SF-12: Medical Outcomes Study 12-item short form; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review. #: compared with placebo. Information condensed and updated from [22].
Shared decision making

The definition of shared decision making is succinctly stated in commonsense terminology: “a conversation between the clinician [and others, such as pastoral counsellor and social worker] and the patient in which they figure out together what to do to address the patient’s situation” [62]. This concept incorporates components that are “iterative and interactive steps in a conversational dance”, which include: clarifying the patient’s situation; identifying the aspect of the situation that requires action; recognising that more than one way of addressing the situation exists; discussing the pros and cons of the available approaches with the patient and caregivers; and gaining understanding of what the patient values about these options, and why [62].

For the patient perspective to be valid and relevant, it must be informed by an accurate comprehension by the patient of the facts of the situation. In some medical disciplines, decision aid tools have been developed to facilitate the patient’s understanding of the clinical context and potential outcomes of alternative treatment strategies, including those which are probabilistic in nature. Decision aids promote the patient’s knowledge, estimation of treatment risk and engagement in the discussion. However, there has not yet been a demonstrable benefit in terms of outcome [62]. Standardised decision aids have not been developed for PH management.

Palliative care

Palliative care was traditionally a change in the focus of care at the end of life away from therapies intended to cure or slow the progression of disease, to management of physical symptoms (e.g. pain) and emotional distress. Palliative care is currently better understood as an interdisciplinary approach to promoting quality of life and reducing suffering at any stage of chronic disease [63]. Palliative care has been defined as “patient and family-centered care that optimizes quality of life by anticipating, preventing, and treating suffering. Palliative care throughout the continuum of illness involves addressing physical, intellectual, emotional, social, and spiritual needs and to facilitate patient autonomy, access to information, and choice” [64].

In a survey of 774 PAH patients, 276 analysable responses revealed that awareness of and access to palliative care resources were low despite marked impairment of HRQoL, physical and emotional wellbeing, social activity, and pain control [49]. This degree of diminished HRQoL is consistent with that found in other studies [20, 49, 65–69]. Since PH-targeted therapies do not usually alleviate all physical symptoms or necessarily improve patients’ psychosocial function, a role for integrating palliative care techniques and expertise early to optimise HRQoL has been advocated [70].

Obstacles to expanding the use of palliative care in PH patients are lack of awareness of its purpose (e.g. symptom management and psychological wellbeing), inadequate local medical payer coverage, misunderstanding palliative care as synonymous with hospice care and implies “giving up” or being resigned to an imminent death, and not understanding that PH-targeted medications can continue within a palliative care strategy [63]. Therapies for PH have side-effects which may negatively impact HRQoL despite achieving benefits in terms of haemodynamics and some symptoms. Thus, strategies to focus on HRQoL during otherwise beneficial treatment arguably become even more imperative.

PAH population perspective

Patients and caregivers need support from others, which can take many different forms: awareness that others are confronting similar struggles, sharing experiences and information, suggesting solutions to
shared challenges, attending formal educational events, participating in collaborative efforts to advance care, and unifying around shared needs and goals to raise awareness.

**Patient associations**
Organisations have been created to facilitate the expression of the PH population perspective and to aid in dealing with the needs of PH patient communities worldwide (table 3).

**Support groups**
Support groups are smaller local patient networks with less infrastructure and expense which provide informal interactions to offer empathetic sharing of experiences and education. Support groups may be independent or promoted by medical institutions or pharmaceutical companies, and may receive logistical or financial assistance from national patient associations. Such local/regional support groups exist in many countries especially in North America (e.g. more than 240 identified by the Pulmonary Hypertension Association (PHA) in the USA), but also in a number of European, Latin American, Asian and African nations.

**Education/awareness**
Acquiring information about PH is an essential coping mechanism for many patients. In addition, the perception that others lack awareness and knowledge about their disease is distressing. Insights provided to patients in subspecialty clinics by dedicated staff helps address these needs [50, 71], but public dissemination of information also is central to patient organisations' mission. A pivotal component of this effort has been to increase awareness of PH both in HCPs and the general population in order to improve the timeliness and accuracy of PH diagnosis in patients presenting with suggestive symptoms (e.g. the "Early Diagnosis" campaign of the US PHA), catalysed by observations that there is a significant interval between symptom onset and definitive diagnosis [4, 5, 72].

The annual World Pulmonary Hypertension Day was first held on May 5, 2012 in Madrid, Spain to raise global awareness and this was adopted by PHA Europe (http://worldphday.org). The World Pulmonary Hypertension Day has gained increasing momentum, with 86 global partner organisations involved in an international awareness campaign in 2018. Through its involvement of national political and health authorities, academia, HCPs, and celebrities, World Pulmonary Hypertension Day has generated media interest and awareness across the world.

Evaluation of patients at referral centres frequently identifies aspects of pre-referral management that do not align with best practices and guidelines [73]. Concerned physicians and patients in the PH community re-emphasised the need for professional education, including periodic international symposia (e.g. the World Symposia on Pulmonary Hypertension (WSPH) [74] and the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for PH [45], culminating in publications of state-of-the-art knowledge summaries, management guidelines and algorithms), web-based educational programmes, on-site preceptorships and PH-focused publications.

**Access to healthcare/coverage**
Disparity in healthcare access is a worldwide issue which patient organisations address on behalf of their constituencies. A major concern of patients, their families and primary HCPs is where the patient should be most effectively managed. This concern embodies many elements: how can qualified experts and well-resourced medical facilities be identified; how can geographical and financial constraints be navigated; by whom are complex treatment strategies best prescribed, managed and followed; and what is the best approach to medical emergencies? The answers are largely dependent on the geographical location and nationality of the patient.

In the USA, under the aegis of the PHA, the PH Care Centers (PHCC; https://phassociation.org/phcarecenters) programme of site accreditation was developed to identify facilities which are staffed and equipped to deliver patient management that meets expert consensus for best practices.

The European Reference Networks (ERNs; https://ec.europa.eu/health/ern_en) for rare diseases, launched in 2017, introduced a European Union (EU) accreditation system for centres of expertise for rare diseases to whom referrals can be made for “virtual” consults. The EU initiative is intended to facilitate cross-border sharing of knowledge, experience, medical research, teaching, training and resources. Patients are closely involved and each ERN has a Patient Advisory Group (ePAG) which advises on strategy, policy and organisational processes. PHA Europe has three representatives on ERN Lung.

Latin American and Asian countries also confront difficulties with early diagnosis and access to treatment for PH patients due to lack of knowledge and insufficient legal frameworks to protect the right to good
<table>
<thead>
<tr>
<th>Organisation (website)</th>
<th>Region; beginning</th>
<th>Constituency</th>
<th>Mission</th>
<th>Major activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Hypertension Association [<a href="https://phassociation.org">https://phassociation.org</a>]</td>
<td>USA; 1991</td>
<td>PAH and CTEPH patients, caregivers, physicians and allied health professionals, researchers; membership: &gt;16000</td>
<td>“To extend and improve the lives of those affected by PH”</td>
<td>Research funding support; advocacy; patient support and education, medical education and public awareness and education; PH care centre accreditation</td>
</tr>
<tr>
<td>Pulmonary Hypertension Association Canada [<a href="http://www.phacanada.ca">www.phacanada.ca</a>]</td>
<td>Canada; 1999 as Pulmonary Hypertension Society of Canada, renamed PHA Canada in 2008</td>
<td>All PH patients and their caregivers, physicians and allied healthcare professionals; engagement: &gt;1000 (note no formal membership)</td>
<td>“To empower the Canadian PH community through awareness, advocacy, education, research and patient support”</td>
<td>Patient/caregiver support and education; advocacy; medical education; public awareness and education; research funding support</td>
</tr>
<tr>
<td>Pulmonary Hypertension Association Japan [<a href="http://www.pha-japan.ne.jp">www.pha-japan.ne.jp</a>]</td>
<td>Japan; 1999</td>
<td>PAH and CTEPH patient, caregivers; membership: &gt;200</td>
<td>“Promotion of social awareness and understanding about PH”</td>
<td>Advocacy; patient support and education, public awareness; promoting early diagnosis and access to new drugs</td>
</tr>
<tr>
<td>Pulmonary Hypertension Association UK [<a href="http://www.phauk.org">www.phauk.org</a>]</td>
<td>UK; 2000</td>
<td>PAH and CTEPH patients, caregivers, physicians and allied health professionals, researchers; membership: &gt;4000 patients and &gt;200 HCPs</td>
<td>To advance the education and awareness of the general public and medical professionals of the condition known as PH; the relief of need of sufferers of PH, their families and carers through the provision of financial assistance towards, but not exclusively, respite care, travel grants and equipment grants at the discretion of the executive committee, as and when resources allow</td>
<td>Patient and family support, high-quality online/printed support materials, support and advocacy for all patients with all forms of PH, increasing disease awareness within all areas of healthcare and general public; reduce the time to diagnosis for PH; improve the health wellbeing and quality of life of patients with PH and their kinship; ensure equity of access in the UK to evidence-based PH treatments for all; reduce the financial hardship incurred by living with PH</td>
</tr>
<tr>
<td>Pulmonary Hypertension Association Europe [<a href="http://www.phaeurope.org">www.phaeurope.org</a>]</td>
<td>Europe; 2003</td>
<td>Umbrella organisation for 40 patient associations in 33 countries</td>
<td>“Promotion of social awareness and understanding about PH”</td>
<td>Improve access to expert care, improve awareness and screening, encourage clinical research and innovation, empower patient groups, ensure the availability of psychosocial support</td>
</tr>
<tr>
<td>Latin Society of Pulmonary Hypertension (Sociedad Latina de Hipertensión Pulmonar) [<a href="http://www.sociedadlatinahp.org">www.sociedadlatinahp.org</a>]</td>
<td>Latin America; 2005</td>
<td>Umbrella organisation for 21 Latin American patient associations in 16 countries</td>
<td>“To raise awareness about PH throughout Latin America”</td>
<td>Promoting optimal level of care for PAH patients, availability of quality treatments, research on new drugs and therapies, awareness and public policies; umbrella organisation supporting regional patient organisations; awareness campaigns include: “Labios Azules” (“Blue Lips”) (2011); “Sin Aliento” (“Short of Breath”) (2012); “Quedate sin Aliento” (“Stay Breathless”) (2014) and “Un Aliento para Vencer” (“Breathe to Win”) (2016)</td>
</tr>
<tr>
<td>Organisation (website)</td>
<td>Region; beginning</td>
<td>Constituency</td>
<td>Mission</td>
<td>Major activities</td>
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<tr>
<td>Pulmonary Hypertension Association of Australia ([<a href="http://www.phaaustralia.com">www.phaaustralia.com</a>])</td>
<td>Australia; 2005</td>
<td>All categories of PH patients, caregivers, family and supporters, pre- and post-transplant patients; HCPs are non-participant members trying to understand the patient/family side of the disease; membership &gt;7000</td>
<td>&quot;To provide hope, support and education, and to promote awareness and to advocate for the PH community&quot;</td>
<td>Administered by volunteers for 18 years (no paid staff); patient, caregiver and family education; public awareness and education through website and several social media platforms; advocate for the PH community; bereavement support; immediate phone support for those in a PH-related crisis; immediate online support through their secure Facebook support group; work closely with Australian specialists through the Pulmonary Hypertension Society of Australia and New Zealand ([<a href="http://www.phsanz.org">www.phsanz.org</a>]) to ensure best outcome for patients</td>
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<tr>
<td>iSEEKPH Hope Center ([<a href="http://www.iseek.org.cn">www.iseek.org.cn</a>])</td>
<td>China; 2011</td>
<td>Patients, caregivers, physicians, medical professionals, researchers; membership: &gt;5000</td>
<td>&quot;To advocate for patients’ equal rights and improve their quality of life&quot;</td>
<td>Advocacy; patient education and support; public awareness; education; research</td>
</tr>
</tbody>
</table>

PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic PH; HCP: healthcare professional. #: for a comprehensive listing of international PH associations, see https://phassociation.org/phinternational.
healthcare by World Health Organization criteria. Scarcity of referral centres, inconsistency among health systems, wide distribution of patients, geographical barriers, economic disparity and limited accessibility to medical records have made it difficult to generate awareness of PH.

Advocacy and empowerment

Patient-centred organisations acknowledge patients’ needs within a supportive environment and provide opportunities for patients and caregivers to advocate for themselves by being proactive in defining their situations, proposing solutions, participating in political activity to promote those solutions, being engaged in their own self-care and counselling each other [55]. Patients’ understanding of their illness and engagement in the care process appears to contribute to improved coping ability [71] and outcomes [75, 76] in a variety of chronic diseases. Patient associations and individual patients in many parts of the world are active advocates for better access to treatment, organ transplant and greater attention to quality of life.

PHA Europe has been successful in involving members of the European Parliament, top EU officials, members of the ESC and ERS, and representatives of influential public health European non-governmental organisation in PH-related issues, including for two European Parliament meetings (2012 and 2016). PHA Europe is also active in the context of larger European organisations, and gives support and strategic advice to national advocacy activities.

Lacking a national single-payer system, the US PHA undertakes simultaneous efforts to educate policy makers at both the federal and state levels, and inform and educate federal and state regulatory agencies (e.g. Centers for Medicare & Medicaid Services and the US Food and Drug Administration (FDA), and state health and insurance agencies) and commercial payers. The US PHA uses a combination of advocacy staff, volunteer PH patients and caregivers, and coalitions of patient organisations with similar advocacy goals to influence policy makers.

The Latin Society of Pulmonary Hypertension (Sociedad Latina de Hipertensión Pulmonar (SLHP)) has supported improved living conditions of patients. One result of this is the Framework Law approved by the Health Commission of the Latin Parliament in 2015 and by other legislative forums to promote national laws that protect the Human Right to Health. This law regulates the healthcare for people with rare diseases in Latin America. However, the diversity, complexity, fracture and corruption of the health systems make it difficult to achieve a direct impact.

Role in research/registries

Patients have had a vital role in PAH-related clinical trials and registries, almost exclusively as study subjects. An early manifestation of the relevance of the patient perspective in research is the concept of patient-reported outcome (PRO) as a meaningful measurement of treatment effect of investigational drugs. In 2009, the US FDA stated that “A PRO is any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else” [77]. The 4th and 5th WSPH, in 2008 and 2013, respectively, advocated that PROs be included as a secondary end-point in clinical drug studies [78, 79]. Patient input is needed to understand their perspective and experience so that PROs can be developed as relevant end-points in clinical trials [80]. The US FDA launched the Patient-Focused Drug Development initiative to assess and integrate patient perspectives into the early phases of drug development in a range of diseases [81]. A meeting involving PAH patients and representatives was held in 2014, and emphasised the impact of PAH on the individual patient’s life beyond the physical burden of symptoms, including loss of independence, inability to perform routine daily activities and fully participate in relationships with significant others and children, embarrassment, fear of being alone, and impact of treatment side-effects on HRQoL [82]. This initiative represents an important step in incorporating patient perspective and engagement at an early stage of clinical trial design.

Future directions

In order to advance the role of patients, both as individuals and as a demographic group, to a position of empowerment and engagement in all aspects of their PAH experience with the goal of enhancing overall wellbeing [55], we suggest several areas in which to focus future attention (table 4). The common denominator of these suggestions is to cultivate the importance of HRQoL in the care PH patients.

Clinical management

Promote access to optimal management

Optimal care must be multidimensional to address the physical, psychological, social and informational needs of patients and caregivers, alongside their clinical needs. This approach is suggested by the latest ESC/ERS clinical guidelines: “[expert] Referral centres are recommended to provide care by an
interprofessional team ...

interprofessional team ...” [45]. Nevertheless, guidelines are largely silent about the desirability of patient/HCP bidirectional interactions that address patients’ need for emotional support conducted by a collaborative team at a “tempo” which permits the patients to understand the HCP’s information and to convey their perspectives, concerns and goals. Future guidelines should point out that HRQoL objectives require a culture of shared decision making and narrative competence to support patient and caregiver emotional resilience. This should include access to focused psychological management, social work, palliative care, spiritual counselling and physical therapy (figure 2).

Optimal care must be accessible to the patient. Mechanisms, such as ERNs and the PHCC, to evaluate and identify sites able to provide clinical management consistent with consensus guidelines are important steps. The next challenge is to promote restriction of care to such centres once sufficient numbers have been identified to serve the PH population. This is most likely to be achieved in systems with a single payer/commissioner, usually state provided.

In Latin America and in developing countries, future advances are particularly challenging because of the barriers noted earlier. A primary objective of patient organisations both in Latin America and worldwide will be to overcome these barriers and advocate for social, political and legal measures to procure accessible healthcare for PH patients. “Twinning relationships” between individual centres of expertise and centres seeking consultative input could be a means of promoting optimal care in needy regions. The regional disparity of care available to PH patients mandates that governments, insurers, the pharmaceutical industry, and patient and professional organisations promote global accessibility and affordable treatment for all PH patients. For a compelling narrative regarding the need for globalisation of PH care, please watch the Jenna Lowe Trust video at: https://phassociation.us13.list-manage.com/track/click?u=acd152c7c169b59aaec993284&id=4874e4af3a&ec=99080b0e01.

**Empower patients’ participation in their management**

PH patients and HCPs collaboratively make decisions which have a major impact and require an understanding by all parties of the components and priorities involved in achieving an appropriate course of action. To achieve the necessary mutual understanding requires a complexity, duration and frequency of interaction that poses a challenge within the time constraints of medical practices. The process may be facilitated by incorporating formal principles of shared decision making, including the use of decision aid tools. A synthesis of the qualitative precepts of narrative medicine and the implementation of more quantitative HRQoL instruments in clinical practice might also enhance the physician’s awareness of the patient’s needs and systematically reflect aspects of illness that are not otherwise measured.

Patient associations frequently offer educational materials which complement the role of the HCP by providing information about the disease, treatment options and day-to-day issues in living with PH. Since 2015, over 200 resources in 24 languages have been collected in the “PH Library” (www.ourphlibrary.com),

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### TABLE 4  Cultivate the importance of health-related quality of life (HRQoL) in the care of those affected by pulmonary hypertension (PH)

<table>
<thead>
<tr>
<th>Clinical management</th>
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<tbody>
<tr>
<td>Promote access to optimal care</td>
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<tr>
<td>Expand MDT approach</td>
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<tr>
<td>Accreditation of PH centres</td>
</tr>
<tr>
<td>Twinning of expert and developing centres</td>
</tr>
<tr>
<td>Empower patient participation in management</td>
</tr>
<tr>
<td>Multimedia patient information/materials</td>
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<tr>
<td>Create and endorse methods to enhance HCP and patient/caregiver communication:</td>
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<tr>
<td>Shared decision making</td>
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<tr>
<td>Narrative-based medicine</td>
</tr>
<tr>
<td>Palliative care techniques</td>
</tr>
</tbody>
</table>

**Provider development**

Integrate concepts of narrative-based medicine, shared decision making and HRQoL into clinical training

**Clinical research**

Support, expand and harmonise HRQoL databases
Prioritise HRQoL as a distinct end-point in clinical trials
Foster patients’ input into clinical study design and outcome measurements

**Patient associations**

Promote the mission and role of PH patient organisations worldwide

MDT: multidisciplinary team; HCP: healthcare provider.
an online joint project of PHA in the USA and PHA Europe, which should be continued and expanded. An additional role that patient organisations and support groups might play is to help patients develop narrative medicine knowledge and skills so they can be more effective during their limited time with HCPs.

**Role and timing of palliative care**

The assimilation of palliative care principles into the PH management strategy at an earlier phase of disease should be encouraged to promote all means of improving HRQoL by pain management, symptomatic improvement of dyspnoea, addressing psychological issues and sleep disturbances, and assisting in end-of-life concerns. Equating the term “palliative care”, which is currently burdened with the notion of “end-of-life” care, with “holistic” or “quality-of-life” care will be an important strategy for reorienting perceptions about this discipline.

**Provider development**

Integrate concepts of patients’ perspectives into medical education

Medical education has recognised the importance of the patient perspective to a degree, incorporating concepts of shared decision making, narrative-based medicine and HRQoL into educational curricula. Narrative medicine can potentially increase efficiency and bring economic benefits to healthcare systems. A closer and more collaborative patient–doctor relationship can improve treatment compliance and satisfaction, and reduce unnecessary tests and medicolegal disputes.

It is important to further integrate these concepts into all clinical disciplines, including PH management, at all levels of medical education from medical school to continuing medical education of all HCPs.

**Clinical research**

Support, expand and harmonise HRQoL databases

Surveys of patient perspectives are an important source of information by which HCPs can orient themselves to their patients’ multiple and complex needs. Since perspectives may vary as the treatment milieu changes over time, it will be important to periodically reassess using updated survey instruments.
Information derived from patient surveys can differ by geographical location. This suggests that the use of surveys in other regions of the world would be informative in terms of comparisons and would also provide new insights into the attitudes of previously unexamined populations, including those in Latin America, the Middle East, Africa and Asia.

Surveys of patient perceptions should be integrated with traditional clinical database registries. Incorporation of these variables into a single or cross-linked case report form would potentially simplify (unify) data collection. Ultimately data analyses might better determine whether treatment strategies and traditional outcome measures (e.g. hospitalisation and survival) correlate with HRQoL. It is likely that these analyses would be hypothesis generating and lead to further formal study.

It would be useful if registries and/or patient surveys were designed to prospectively harmonise data variables in such a way that global analyses could be performed without resorting to post hoc statistical adjustment.

Incorporate patients’ perspectives early into clinical study design and outcome measurements

Based on information gleaned from surveys, including patients in the clinical trial design process may increase the importance of “overall wellbeing” as a central objective of medical care and potentially as a clinical trial outcome on an equal footing with more traditional end-points. HRQoL could be included as an end-point by itself or as part of a multiparameter score, rather than simply a surrogate for other end-points such as survival or clinical deterioration.

The PAH patient and caregiver community needs to be cognisant of the developing opportunity to participate in relevant advisory and steering committees in order to advocate for the patients’ perspective in clinical trial design. This might be best pursued by patient organisations by advocating for and facilitating patients to serve as steering committee members, patient liaisons or focus group members for study designs, as an outgrowth of US FDA and European Medicines Agency initiatives to promote “patient-focused drug development”.

Patient associations

Recognise and enhance the role of PAH patient organisations/professional organisations

As noted, existing patient organisations (e.g. in the USA, Europe and elsewhere) work as a loose confederation with a similarity of general objectives adapted to their constituencies’ specific realities and needs (table 3). Such patient associations have a track record of providing a voice and support for the PH patient community. Thus, continued development of these organisations should be supported and similar associations should be established in underserved areas. Obstacles to globalisation of PH patient organisations are significant and include: funding, geographic dispersion of rare disease patients, communication barriers, questions of organisational governance and substantial differences in delivery of medical care. The commonality of objectives and needs of PH patients suggest that stronger networking for the purposes of educational efforts and sharing of productive strategies should be promoted. An important step forward in this direction was taken in 2017 when the US PHA, SLHP and PHA Europe decide to join forces for the first time in organising the World Pulmonary Hypertension Day, which, in turn rallied many other associations from other parts of the world, including from Canada, Africa, Asia and Australia. Social media can play an increasing role in the future in breaking down geographical barriers and having a unifying function, and other avenues for collaboration should be explored.

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