Diagnosis and management of pulmonary hypertension related to chronic respiratory disease

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Pulmonary hypertension is a recognised complication of chronic respiratory disease that is associated with significant mortality and morbidity. Treatment of the underlying lung disease and associated comorbidities is essential. https://bit.ly/3O4eoFh

Cite this article as: Krompa A, Marino P. Diagnosis and management of pulmonary hypertension related to chronic respiratory disease. *Breathe* 2022; 18: 220205 [DOI: 10.1183/20734735.0205-2022].

Received: 9 Aug 2022
Accepted: 3 Nov 2022

Abstract

Pulmonary hypertension (PH) is a recognised and significant complication of chronic lung disease (CLD) and hypoxia (referred to as group 3 PH) that is associated with increased morbidity, decreased quality of life and worse survival. The prevalence and severity of group 3 PH varies within the current literature, with the majority of CLD-PH patients tending to have non-severe disease. The aetiology of this condition is multifactorial and complex, while the prevailing pathogenetic mechanisms include hypoxic vasoconstriction, parenchymal lung (and vascular bed) destruction, vascular remodelling and inflammation. Comorbidities such as left heart dysfunction and thromboembolic disease can further confound the clinical picture. Noninvasive assessment is initially undertaken in suspected cases (*e.g.* cardiac biomarkers, lung function, echocardiogram), while haemodynamic evaluation with right heart catheterisation remains the diagnostic gold standard. For patients with suspected severe PH, those with a pulmonary vascular phenotype or when there is uncertainty regarding further management, referral to specialist PH centres for further investigation and definitive management is mandated. No disease-specific therapy is currently available for group 3 PH and the focus of management remains optimisation of the underlying lung therapy, along with treating hypoventilation syndromes as indicated.

Introduction

The development of pulmonary hypertension (PH) as a complication of chronic lung disease (CLD) and hypoxia is well documented, leading to significant morbidity (*e.g.* impaired quality of life (QoL), reduced exercise tolerance) and poor outcomes. The pathophysiology is complex, reflecting changes arising from the underlying lung disease as well as vascular remodelling and, on occasion, the presence of other important comorbidities (*e.g.* left heart disease (LHD), pulmonary emboli). Further characterisation of the prevalence, mechanisms and phenotypes is required to aid diagnosis and treatment.

Diagnostic assessment can be difficult when trying to differentiate those patients with PH in keeping with the underlying CLD *versus* those with relatively mild lung disease and a possible "idiopathic pulmonary arterial hypertension (PAH)" phenotype, in whom the role of PAH-specific therapies is still under evaluation. Expert guidance from specialist PH centres is invaluable to ensure these patients receive the most appropriate management.

The aim of this review, therefore, is to provide the clinician with an understanding of the current nature, investigation, and treatment of PH in CLD and hypoxia.

Classification and definition

PH associated with hypoxia and CLD is classified within group 3 PH by the World Health Organization (WHO), reflecting its distinct pathophysiology (table 1). It is associated with increased morbidity, increased oxygen requirements, impaired QoL, decreased exercise tolerance and a worse prognosis [2].

TABLE 1 Pulmonary hypertension related to chronic lung disease and/or hypoxia

Obstructive lung disease or emphysema
Restrictive lung disease
Lung disease with mixed restrictive/obstructive pattern
Hypoventilation syndromes
Hypoxia without lung syndromes (*e.g.* high altitude)
Developmental lung disorders

Information from [1].

These outcomes may be worse compared with idiopathic PAH (group 1 PH), while patients with a phenotype of group 1 PH complicated by relatively minor coexisting lung disease also experience significantly reduced survival [3]. The development of PH in CLD and hypoxia is both complex and varied, whilst its role in disease burden or as a marker of lung disease severity is often debated. Group 3 PH is predominantly comprised of patients with COPD and interstitial lung disease (ILD), as well as other conditions such as combined pulmonary fibrosis and emphysema (CPFE), hypoventilation syndromes, bronchiectasis (including cystic fibrosis), chronic high-altitude exposure (>2500 m) and developmental lung diseases (table 1). As highlighted in the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines [1], isolated obstructive sleep apnoea (OSA) is an uncommon cause of PH, unless there is coexisting hypoventilation with daytime hypercapnia. Diffuse parenchymal lung diseases, including sarcoidosis and Langerhans cell granulomatosis, currently lie within group 5 WHO PH due to either unclear or multifactorial mechanisms [1].

The haemodynamic definition of PH was revised by the 2022 ESC/ERS guidelines to a resting mean pulmonary artery pressure (mPAP) of >20 mmHg. In these new PH guidelines, the definition of pre-capillary PH was also modified to reflect the presence of pulmonary vascular dysfunction by revising the pulmonary vascular resistance (PVR) threshold. The new haemodynamic definition of pre-capillary PH therefore includes: mPAP >20 mmHg, pulmonary artery wedge pressure (PAWP) ⩽15 mmHg and PVR >2 Wood units (WU) [1].

The severity of group 3 PH is now further characterised by the PVR [1]. The majority of CLD patients have either no PH (prevalence 70%) or non-severe PH (PVR ⩽5 WU, prevalence 20%), with severe PH (PVR >5 WU, prevalence 5–10%) being relatively uncommon. Patients with severe PH tend to have more profound circulatory than ventilatory exercise limitation [1].

Epidemiology

The prevalence of group 3 PH does not always correlate with the extent of the underlying lung disease, yet even the presence of non-severe PH has a negative impact on QoL and survival [1]. Epidemiology is highly dependent upon the definition of PH, the method of investigation (echocardiogram *versus* right heart catheterisation (RHC)), disease severity at the time of assessment and selection bias (*i.e.* tertiary centres *versus* general hospitals). Most studies report that patients with CLD have non-severe PH with only ∼3–4% having a mPAP >40 mmHg [4].

COPD

An accurate determination of PH prevalence in COPD is very challenging with considerable variation amongst the existing data. Subgroup analyses have shown that the prevalence of PH is related to COPD severity, with the majority (30.2%) having non-severe PH and the minority severe PH (7.2%). However, stratification according to age, sex, time of assessment and diagnostic method used showed no significant differences in prevalence ($p>0.05$) [5]. Studies in severe COPD have found that up to 90% of patients have a mPAP of >20 mmHg, with most ranging between 20 and 35 mmHg [6, 7].

PH in COPD is invariably related with worse outcomes, particularly survival, with a 5-year survival rate of 37% in COPD patients with PH *versus* 63% in COPD patients without PH [6]. Overall, while PH is a well-recognised complication in COPD, severe PH is relatively rare.

ILD

PH prevalence estimates in ILD are mainly derived from idiopathic pulmonary fibrosis (IPF) cohorts and encounter similar difficulties as described for COPD. Most patients have non-severe PH, with prevalence

increasing with disease severity. PH is again a harbinger of a worse prognosis. A mPAP ⩾25 mmHg has been reported in 14.9% of ILD patients, while prevalence was again higher in more advanced disease [8].

Shorr *et al*. [9] studied 2525 patients with pulmonary fibrosis who underwent RHC as part of lung transplant assessment. In this population, representative of more severe lung disease burden, 46.1% of patients had PH, with only 9% having severe PH. Ethnicity was found to be significantly correlated with the presence of severe PH, with African Americans being twice as likely to develop severe PH compared with Caucasians [9]. Other studies have not identified a strong correlation between PH and forced vital capacity (FVC) or radiographic fibrosis on high-resolution computed tomography (HRCT), implying that parenchymal destruction is not the single aetiology for PH progression [10]. Adverse outcomes have been observed in IPF patients with mPAP ⩾25 mmHg, including increased risk for acute exacerbations [11, 12].

More rapid progression of PH in the late stage of diffuse parenchymal lung disease has also been described. Serial mPAP measurements in patients with severe IPF awaiting transplant during initial evaluation and at the time of transplant identified an incidence of PH development of 77.8% [13].

The few studies in CPFE, defined by distinct upper lobe emphysema and lower lobe predominant fibrotic changes, have provided an estimated PH prevalence of 47% at the time of diagnosis, indicating that it is a common complication. PH is again associated with an increased risk of death in CPFE, with a 5-year survival of 25% in patients with coexistent PH on echocardiography compared with 75% in those without [14].

Sarcoidosis

Sarcoidosis-associated PH (SAPH) currently lies in group 5 due to its multisystem presentation. A recent large meta-analysis by Zhang *et al*. [15] with 632 368 sarcoidosis patients showed a pooled prevalence by transthoracic echocardiography (TTE) of 16.4%, compared with 6.4% on RHC. Increased oxygen requirements, worse functional status and increased mortality have also been observed in SAPH patients [16]. As the disease progresses with extensive lung fibrosis, prevalence may rise to over 60% [16], although PH can still develop in patients with near normal lung function tests, reflecting the different manifestations of this condition [17].

Pathophysiology

The pathophysiology of group 3 PH is multifactorial and complex, with different disease-specific mechanisms implicated (figure 1). The pulmonary circulation is a low pressure and resistance circuit that accommodates almost the entire cardiac output (CO), maintaining high blood flow. Pulmonary vessels have thinner walls without a predominant muscular layer compared with the systemic circulation, and a limited basal vascular tone. An increased CO is accommodated by vessel dilation and recruitment of previously under-perfused pulmonary vasculature. PVR is determined by several parameters including hypoxia, hypercapnia, lung volume (lower near functional residual capacity, higher in residual volume and

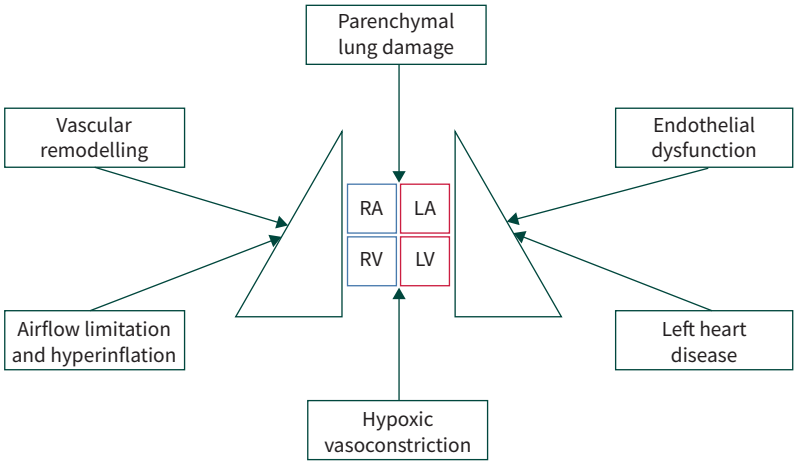

FIGURE 1 Processes involved in the pathophysiology of pulmonary hypertension in chronic lung disease and hypoxia. RA: right atrium; RV: right ventricle; LA: left atrium; LV: left ventricle.

total lung capacity), gravity, CO, and local mediators, such as hormonal and endothelium-derived factors [18, 19].

Hypoxic vasoconstriction is the homeostatic response that aims to divert perfusion to better ventilated areas during acute lung insult (*e.g.* infection, embolism) or chronic injury. Over-activation of this response has been classically related to the pathophysiology of PH in CLD and may be further precipitated by hypercapnia and acidaemia [20]. Hypoxic vasoconstriction is thought to be reversible by oxygen supplementation in the early stages of PH. Chronic hypoxia, however, leads to remodelling of pulmonary vasculature with poor response to oxygen supplementation. Vascular remodelling is mediated by an endothelium-derived vasoconstrictor–vasodilator imbalance, pathologically translating to media hyperplasia with muscularisation of the pulmonary arterioles, involving growth factors, vasoconstrictors (*e.g.* endothelin, serotonin) and transcription factors like hypoxia-inducible factor-1. Intimal hyperplasia is particularly common in COPD, which can notably share morphological changes very similar to those seen in idiopathic PAH [12, 21].

Parenchyma destruction with loss or obliteration of the pulmonary vascular bed is another important contributing factor, especially during increased CO states (*e.g.* exercise), as recruitment of under-perfused vessels is rendered impossible. Additionally, dynamic hyperinflation caused by expiratory flow limitation and air trapping in airway diseases, such as COPD, further increases PVR by stretching the intra-alveolar pulmonary capillaries, whilst over-inflation may directly compress the capillaries [19].

Increased blood viscosity from secondary polycythaemia, genetic factors (*e.g.* serotonin transporter gene polymorphism, microRNA-150 protective effect on remodelling), inflammatory mediators and direct cigarette smoking toxicity have also been implicated in the pathogenesis of group 3 PH [22–24].

Chronic high-altitude PH, usually arising above 2500 m [1], is also characterised by hypoxic vasoconstriction with resultant vascular remodelling and altered endothelial cell activity. Interestingly, genetic factors may be related to the susceptibility to high-altitude PH (*e.g.* polymorphisms in nitric oxide (NO) synthetase and angiotensin-converting enzyme (ACE)), as not all high-altitude inhabitants develop PH [25].

The following two noteworthy and clinically relevant phenotypes have also been identified.

1) The pulmonary vascular phenotype has been mainly described in COPD patients (1–4%) with severe pre-capillary PH, mild airway obstruction (forced expiratory volume in 1 s >60%), mild parenchymal impairment on HRCT, severe reduction in diffusing capacity for carbon monoxide (D_{LCO}) and profound cardiopulmonary limitation. These patients tend to develop progressive right ventricle (RV) failure and notably, share similar features with PAH. In addition, PAH may also be complicated by airway obstruction and have clinical overlap with this described phenotype. Referral to expert PH centres is recommended for further management of these patients.
2) The cardiopulmonary PAH phenotype distinguishes hypoxaemic, mainly male, elderly patients with compromised D_{LCO} (<45% of predicted value), smoking history and risk factors for LHD. This phenotype is associated with a poor response to PAH medications resulting in worsening oxygenation, along with a worse prognosis [1]. Recent studies have also described a PAH phenotype characterised by D_{LCO} impairment and diffuse parenchymal disease in older patients in conjunction with a heterozygous loss-of-function mutation in the kinase insert domain receptor (*KDR*) gene [26, 27].

When assessing CLD-PH patients, especially with severe PH, it is essential to keep in mind that the underlying lung disease may be complicated by coexistent conditions such as left heart dysfunction, thromboembolic disease, hypoventilation syndromes or rarely idiopathic PAH.

Investigation and diagnosis

Identification of group 3 PH can be challenging due to a lack of specific clinical signs and confounding symptomatology related to the underlying CLD. A high clinical index of suspicion is imperative for early diagnosis and management.

A thorough history is an essential first screening step (figure 2). Exertional limitation and dyspnoea not anticipated by the extent of the primary lung disease and/or pulmonary function tests should alert the clinician to investigate for PH. Symptomatology is initially nonspecific in PH (*e.g.* dyspnoea, chest tightness, functional limitation) and subsequently reflects RV dysfunction with chest pain, palpitations, pre-syncope, peripheral oedema, abdominal distention and haemoptysis. Indicative physical signs again

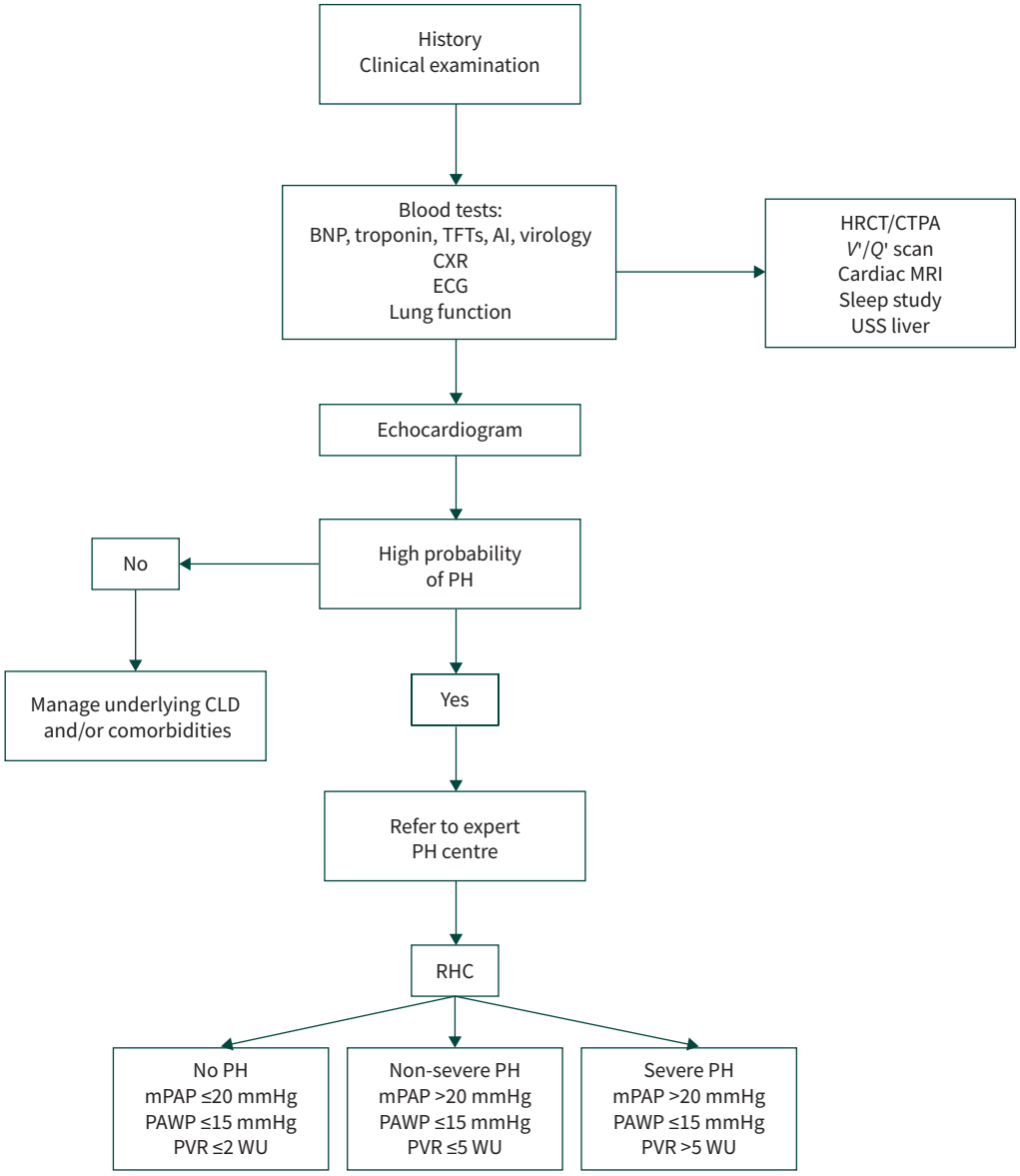

FIGURE 2 Diagnostic algorithm for the investigation of pulmonary hypertension (PH) in patients with chronic lung disease (CLD). BNP: brain natriuretic peptide; TFT: thyroid-function tests; AI: autoimmune screen; CXR: chest radiography; HRCT: high-resolution computed tomography; CTPA: computed tomography pulmonary angiogram; *V'*/*Q'* scan: ventilation/perfusion scan; MRI: magnetic resonance imaging; USS: ultrasound scan; RHC: right heart catheterisation; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; WU: Wood units.

reflect underlying RV dysfunction, including jugular venous pressure, left parasternal heave, accentuated pulmonary component of the second heart sound, a pansystolic murmur of tricuspid regurgitation, functional diastolic murmur of pulmonary regurgitation, hepatomegaly, ascites, peripheral oedema, and cool extremities [1].

Baseline investigations include pulmonary functions tests, which can show a disproportionately low D_{LCO}. Cardiac biomarkers such as brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) can help identify potential cases and monitor progress but should be interpreted with caution in the presence of coexistent LHD (*e.g.* heart failure with preserved/reduced ejection fraction, atrial fibrillation) and significant chronic renal disease. Blood tests should also include autoimmune and viral serology (*i.e.* HIV) to identify other significant causes [28].

An electrocardiograph (ECG) may be normal in the early stages but can show signs of RV strain such as right bundle branch block and right axis deviation with the development of RV dysfunction.

TTE remains the most widely used modality for initial screening and follow up, although it can be technically challenging (*e.g.* body habitus, lung hyperinflation). As a consequence, TTE may both over- and under-estimate pulmonary pressures, yet it remains a very important tool in the investigation of PH, as well as allowing concomitant assessment of LHD and structural abnormalities [29]. Great emphasis is placed on the peak tricuspid regurgitation velocity (TRV) for determining the echocardiographic probability of PH, with a peak TRV >2.8 $m \cdot s^{-1}$ suggestive of PH. In advanced lung disease, TRV frequently gives a false estimate of the pressure gradient, thus the 2022 ESC/ERS task force suggest combining TRV along with other variables such as RV size, right ventricular outflow tract diameter and RV systolic function using tricuspid annular plane systolic excursion (TAPSE) for increased accuracy [1, 22].

Radiographic imaging may also raise the index of suspicion with respect to PH. Chest radiographs may show RV enlargement, pruning of pulmonary vessels and increased diameter of the main pulmonary arteries. Chest CT can be indicative of PH, identifying a ratio of the pulmonary artery to ascending aorta diameter >1, as well as right heart enlargement and RV outflow hypertrophy [1, 23].

Combining the above modalities has the highest diagnostic yield [1].

Functional assessment with cardiopulmonary exercise testing may help to discriminate the presence of pulmonary vascular disease and other potential causes (*e.g.* LHD), as well as guiding further investigation.

RHC remains the gold standard for the diagnosis of group 3 PH. It is an invasive procedure that requires great expertise, especially with the variable changes in intrathoracic pressure that can be encountered due to the underlying lung disease. Potential indications for RHC are [1]:

1) clinical deterioration (*i.e.* worsening dyspnoea, exercise capacity and gas exchange) and/or symptoms out of keeping with the underlying lung disease;
2) to determine suitability for surgical treatment, such as lung transplantation and lung volume reduction, and clinical trials enrolment;
3) suspected severe PH on TTE;
4) to diagnose suspected concomitant idiopathic PAH or chronic thromboembolic PH (CTEPH);
5) to unmask suspected LHD; and
6) cases where further haemodynamic information will aid phenotyping of disease and consideration of therapeutic interventions.

It is important to note that a diagnosis of PH should not be made during an exacerbation but only when a patient's condition is stable, to avoid potential confounding from the transient elevation in pulmonary pressure and PVR that can occur [24].

All patients with clinical or echocardiographic signs of severe PH and/or RV dysfunction should be referred to an expert PH centre for further management and individualised care. Additionally, fast-track referral to a PH centre is suggested at any point of recognising warning signs (*e.g.* malignancy, history of pulmonary embolism, essential thrombocythaemia) with an increased suspicion of PAH or CTEPH [1].

Treatment

The main axiom in the management of group 3 PH has been optimisation of the treatment of the underlying CLD according to current guidance [1]. PAH-specific therapies have not been advocated previously, though the identification of a "pulmonary vascular" phenotype may provide scope for such therapies in the future.

Optimising the underlying lung disease

The current ERS/ESC guidelines highlight this as the mainstay in the management of group 3 PH by trying to mitigate bronchospasm, improve ventilation/perfusion (V'/Q') mismatch and gas exchange, as well as addressing other comorbidities (*i.e.* LHD, pulmonary embolism, sleep disordered breathing).

Long-term oxygen therapy

Long-term oxygen therapy (LTOT) is a cornerstone of managing hypoxaemic patients with CLD-PH. Evidence arises mainly from COPD patients, showing improved pulmonary haemodynamics and a partial delay in PH progression, yet pulmonary artery pressures are rarely normalised once vascular remodelling is

established [30]. Evidence in ILD-PH is less well established due to the paucity of randomised controlled trials (RCTs). The current recommendation for LTOT in COPD-PH patients is an arterial oxygen tension <60 mmHg or peripheral oxygen saturation <91% at rest, and for it to be used at least 15 h a day [30, 31].

Oxygen therapy is also recommended for high-altitude PH, although the ideal course of action is relocation to low-altitude areas [32].

Management of RV dysfunction

Although right heart failure (RHF) shares some common neuro-humoral pathophysiology with left heart failure, there is no evidence to support analogous treatment (ACE inhibitors, β-blockade, aldosterone antagonists) or the use of systemic vasodilators (*e.g.* amlodipine, diltiazem) [33].

Diuretics are recommended for managing fluid overload and symptomatic relief in decompensated RHF, whilst closely monitoring renal function.

Digoxin has been classically used in RHF as an RV inotrope. Early studies with digoxin identified an acute increase in RV ejection fraction [34], but a recent meta-analysis did not find a significant clinical and haemodynamic improvement [35]. Despite this paucity of data, digoxin is still sometimes used long term in patients with RHF [35]. Digoxin may also be used for rate-control in atrial arrhythmias [1].

Pulmonary rehabilitation

Pulmonary rehabilitation has been shown to be safe, particularly in COPD patients, with potential beneficial effects in exercise capacity, respiratory training, and QoL [28]. This has led to it being recommended in CLD-PH patients.

Continuous positive airway pressure/noninvasive ventilation

PH in the context of OSA/obesity hypoventilation syndrome may be potentially reversible with treatment of the underlying sleep disordered breathing by using continuous positive airway pressure/noninvasive ventilation, resulting in decreased pulmonary vasoconstriction and vascular resistance through correction of chronic hypoxaemia, hypercapnia and acidaemia [36].

Pulmonary vasodilator therapies

Drugs used in PAH management have not been advocated in CLD-PH patients based on previously conflicting data and the relatively few large RCTs [1].

Phosphodiesterase-5 inhibitors

Cyclic guanosine monophosphate (cGMP) is the second messenger of NO that stimulates pulmonary arterial smooth muscle relaxation. It is normally inactivated by the phosphodiesterase-5 (PDE-5) isoenzyme that is most commonly expressed in the lung. Sildenafil and tadalafil are selective PDE-5 inhibitors and their use in trials with CLD-PH has elicited contradictory data.

Only a single RCT by Vitulo *et al.* [37], in COPD patients with severe PH who received sildenafil, observed improved pulmonary haemodynamics, BODE index (body mass index, airflow obstruction, dyspnoea, exercise capacity), airflow obstruction, dyspnoea and QoL, with no significant effect on arterial oxygenation. No benefit in exercise tolerance or QoL was seen in COPD-PH patients enrolled on pulmonary rehabilitation and receiving sildenafil [38]. Similarly, no significant effect on exercise capacity was seen in COPD-PH patients receiving tadalafil [39].

An early study in ILD-PH patients showed improved pulmonary haemodynamics and gas exchange in a small cohort of patients with severe lung fibrosis receiving sildenafil [40]. The STEP-IPF study (180 IPF patients that received either sildenafil or placebo) then found no significant improvement in 6-min walking distance (6MWD), gas exchange, symptoms or QoL. Co-administration of sildenafil with antifibrotic agents was investigated in the INSTAGE study. This double-blind RCT randomised IPF patients (some with RV dysfunction) to receive nintedanib with either sildenafil or placebo. A subgroup analysis showed no significant differences in QoL or FVC in the dual therapy group, although BNP did stabilise implying a potential haemodynamic effect in IPF patients with RV stress [40–42].

Endothelin receptor antagonists

Endothelin (ET)-1 is a very potent pulmonary vasoconstrictor with mitogenic properties. The endothelial vasoconstrictive effect is driven by two receptors, ETa and ETb.

In a RCT in severe COPD patients, those given bosentan showed no improvement in 6MWD or pulmonary haemodynamics, whilst gas exchange and functional status worsened compared with patients on placebo [43].

With respect to ILD-PH, the B-PHIT study, a double-blind RCT that compared bosentan to placebo in patients with fibrotic idiopathic interstitial pneumonia (IIP) and PH, found no difference in invasive pulmonary haemodynamics, functional status or symptom burden after 16 weeks [44].

The ARIES-3 trial in COPD and ILD patients showed no benefit in patients with PH of mixed aetiologies, whilst the ARTEMIS-IPF trial was halted after an interim analysis revealed that ambrisentan-treated patients were more likely to meet the trial's primary end-point criteria for disease progression, clinical worsening with increased hospitalisations due to respiratory infections. Consequently, ambrisentan is contraindicated in IPF-PH [1, 45, 46].

Prostacyclin analogues

Prostacyclin is produced by endothelial cells. It is a potent pulmonary and systemic vasodilator, as well as inhibiting platelet aggregation and the release of growth factor from the endothelium.

Few studies have examined the effect of prostacyclin derivatives in treating PH associated with COPD. A pilot study, in 15 patients with advanced IPF and PH associated with RV dysfunction, showed that treatment with treprostinil could improve right heart haemodynamics and echocardiographic function without affecting systemic oxygen saturation [47].

The use of inhaled agents may improve V'/Q' mismatch and oxygenation, circumventing the problem of indiscriminate pulmonary vasodilation associated with other therapies. Promising data have come from a recent phase 3 RCT (the INCREASE study) in 326 patients with ILD-PH trialling inhaled treprostinil. The drug was well tolerated, with improvements in 6MWD and FVC, while the NT-proBNP level was decreased 15% from baseline, compared with those receiving placebo [48]. As further long-term data are required, inhaled treprostinil was mentioned in the 2022 ESC/ERS PH Guidelines as a class III recommendation with level B of evidence for ILD-PH patients [1]. Conversely, a study using inhaled iloprost in COPD patients showed no benefit in terms of exercise tolerance or dynamic hyperinflation, although a reduction in alveolar dead space fraction was noted [48, 49].

Soluble guanylate cyclase activators

This most recent class of PAH therapy acts directly on the enzyme soluble guanylate cyclase to increase the production of cGMP thereby promoting pulmonary vasodilation. Riociguat, the first drug in this class approved for use clinically in CTEPH and idiopathic PAH, was trialled in IIP patients with PH in the RISE-IIP study [50]. The study was however stopped early after an interim analysis showed increased mortality and hospitalisations in those receiving riociguat. It is therefore contraindicated in IIP-PH [1].

Treatment: conclusions

Overall, despite some favourable data on PAH-targeted therapies on specific CLD-PH patients, robust evidence is lacking as most studies are limited by small sample sizes, lack of randomisation and controls. Larger, well-designed multicentre RCTs are required before these therapies can be recommended.

Optimisation of the underlying disease and treatment of RV dysfunction and hypoventilation syndromes remain the key steps in management. Patients with PH disproportionate to their lung parenchymal impairment should be referred to specialist PH centres with expertise in both conditions for further assessment [12].

Future development

Further studies will help address three key issues with respect to our understanding and management of group 3 PH:

- Continued investigation of the underlying mechanisms involved to better characterise the clinical phenotypes present, as well as potentially identify new targets for future therapies.
- Identification of new disease-specific biomarkers that will help in screening, diagnosis, and surveillance.
- Large RCTs to determine the effectiveness of existing and new PH-specific therapies in the individual CLDs (*i.e.* ILD, COPD, sarcoidosis).

Conclusion

PH is a recognised complication of chronic respiratory disease that is associated with significant mortality and morbidity. Treatment of the underlying lung disease and associated comorbidities is essential. Further research is required to characterise the underlying mechanisms and clinical phenotypes, as well as determine the effectiveness of PAH-specific therapies.

Key points

- Group 3 PH is a common complication of CLD with significant morbidity and mortality, constituting a considerable socioeconomic healthcare burden.
- It is a heterogeneous condition (*e.g.* hypoxic pulmonary vasoconstriction, lung destruction, hyperinflation, vascular remodelling), often complicated by other causes such as LHD, pulmonary emboli and sleep disordered breathing.
- No specific treatments are currently available and management at present should focus on optimising treatment of the underlying lung disorder.
- Patients with potential CLD-PH should be referred to specialist PH centres with expertise in both conditions for further assessment to determine if group 1 or 3 PH is present.
- Further research is required to aid the characterisation of clinical phenotypes as well as the need for large, double-blind RCTs to determine if PAH-specific therapies are clinically effective.

Self-evaluation questions

1) What is the haemodynamic definition of severe group 3 PH according to 2022 ESC/ERS guidelines for the diagnosis and treatment of PH?
   a) mPAP >25 mmHg, PAWP ⩽15 mmHg and PVR ⩾2 WU
   b) mPAP >20 mmHg, PAWP ⩽15 mmHg and PVR >5 WU
   c) mPAP >20 mmHg, PAWP ⩾15 mmHg and PVR ⩽2 WU
   d) mPAP >25 mmHg, PAWP ⩾15 mmHg and PVR ⩽5 WU
2) Which of the following are implicated in the development of group 3 PH?
   a) Vascular remodelling, drugs and toxins, HIV
   b) Hypoxic vasoconstriction, parenchymal destruction and vascular remodelling
   c) Coexistent left heart and thromboembolic disease
   d) Hypoxic vasoconstriction, vascular remodelling, haematological disorders and sarcoidosis
3) What is the most appropriate screening test for group 3 PH?
   a) NT-proBNP plasma levels
   b) TTE
   c) CTPA
   d) RHC
4) What is the currently advised treatment strategy for non-severe group 3 PH?
   a) Optimise underlying lung disease management and RV dysfunction
   b) LTOT only
   c) Digoxin
   d) PAH-targeted drugs

Conflicts of interest: A. Krompa has no conflicts of interests or disclosures. P. Marino has received honoraria and travel bursaries from MSD, GlaxoSmithKline, Actelion and Janssen Pharmaceuticals, as well as education, research and service development grants from Actelion and Janssen Pharmaceuticals.

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Suggested answers

1. b.
2. b.
3. b.
4. a.