



Pulmonary hypertension in chronic lung disease and hypoxia

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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 fulfil 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 (*FEV*₁) 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

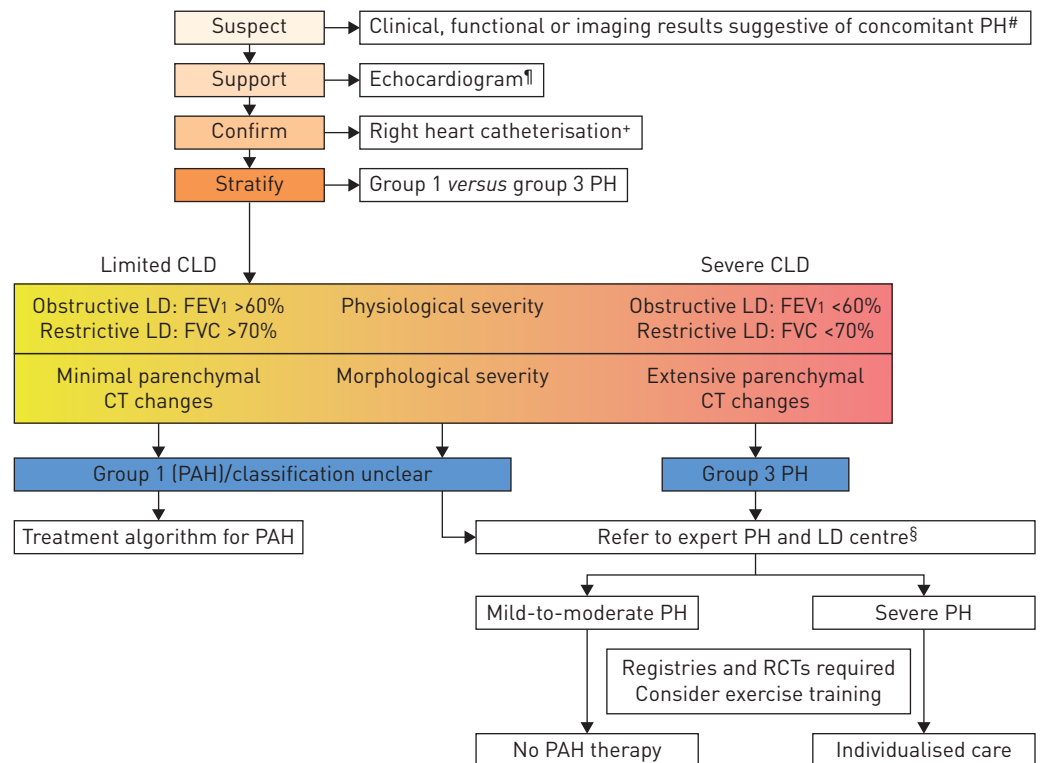


FIGURE 1 Evaluation of pulmonary hypertension (PH) in chronic lung disease (CLD). FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; CT: computed tomography; PAH: pulmonary arterial hypertension; RCT: randomised controlled trial; DLco: diffusing capacity of the lung for carbon monoxide; 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 segments, increased 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.

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

Criteria favouring group 1 (PAH)	Testing	Criteria favouring group 3 (PH due to lung disease)
Extent of lung disease		
Normal or mildly impaired: <ul style="list-style-type: none"> • FEV₁ >60% pred (COPD) • FVC >70% pred (IPF) • Low diffusion capacity in relation to obstructive/restrictive changes 	Pulmonary function testing	Moderate to very severely impaired: <ul style="list-style-type: none"> • FEV₁ <60% pred (COPD) • FVC <70% pred (IPF) • Diffusion capacity “corresponds” 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		
Moderate-to-severe PH	Right heart catheterisation Echocardiogram	Mild-to-moderate PH
Ancillary testing		
Present	Further PAH risk factors (e.g. HIV, connective tissue disease, <i>BMPR2</i> mutations, etc.)	Absent
Features of exhausted circulatory reserve: <ul style="list-style-type: none"> • Preserved breathing reserve • Reduced oxygen pulse • Low CO/<i>V</i>_{O₂} slope • Mixed venous oxygen saturation at lower limit • No change or decrease in <i>P</i>_{aCO₂} during exercise 	Cardiopulmonary exercise test ⁺ [<i>P</i> _{aCO₂} particularly relevant in COPD]	Features of exhausted ventilatory reserve: <ul style="list-style-type: none"> • Reduced breathing reserve • Normal oxygen pulse • Normal CO/<i>V</i>_{O₂} slope • Mixed venous oxygen saturation above lower limit • Increase in <i>P</i>_{aCO₂} during exercise
Predominant haemodynamic profile		Predominant obstructive/restrictive profile

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*_{O₂}: oxygen uptake; *P*_{aCO₂}: arterial carbon dioxide tension. [#]: group 2 and 4 patients are excluded 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.

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*_{pO₂} 89–93%) or exercise-induced oxygen desaturation (*S*_{pO₂} <90% for ≥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].

TABLE 2 Randomised controlled trials (RCTs) with pulmonary arterial hypertension (PAH)-targeted therapy in lung disease

First author [year] [ref.]	Subjects n	Inclusion criteria	Study design	Diagnosis of PH	Baseline haemodynamics [#]	Baseline PFTs [#]	Therapy	Duration	Primary end-point result	Other outcomes
COPD										
VONBANK [2003] [86]	40	COPD on supplemental oxygen with PH by RHC	RCT (open label)	RHC: mPAP ≥25 mmHg	mPAP 27.6±4.4 mmHg, CI 2.7±0.6 L·min ⁻¹ ·m ⁻²	FEV ₁ 1.09±0.4 L, FEV ₁ /FVC 44.5%	"Pulsed" nitric oxide with oxygen vs oxygen	3 months	PVRI, improved	Improved mPAP, CO and PVR; no worsened hypoxaemia
STOLZ [2008] [53]	30	GOLD III–IV; no haemodynamic requirement	RCT (2:1)	Echo	sPAP 32 (29–38) mmHg	Not reported	Bosentan 125 mg 2 times daily	12 weeks	6MWD, no change	Worsened hypoxaemia and health-related QoL
VALERIO [2009] [50]	32	COPD with PH by RHC	RCT (open label)	RHC	mPAP 37±5 mmHg	FEV ₁ 37±18%	Bosentan 125 mg 2 times daily	18 months	No defined primary	mPAP, PVR, BODE index and 6MWD improved
RAO [2011] [87]	33	GOLD III–IV	RCT	Echo: sPAP >40 mmHg	sPAP 52.7±11.9 mmHg	FEV ₁ 32.5±11.1%	Sildenafil 20 mg 3 times daily	12 weeks	6MWD, increased 190 m	Decrease in sPAP
BLANCO [2013] [88]	60	COPD with PH by RHC or echo	RCT	RHC: mPAP ≥25 mmHg; echo: sPAP ≥35 mmHg	sPAP 42±10 mmHg, mPAP 31±5 mmHg	FEV ₁ 32±11%	Sildenafil 20 mg or placebo 3 times daily and PR	3 months	Exercise endurance time, no change	No change in 6MWD, peak V _{O₂} , QoL or oxygenation
GOUDIE [2014] [89]	120	COPD with PH by echo	RCT	Echo: pulmonary acceleration time <120 ms or sPAP >30 mmHg	Echo: sPAP 42±10 mmHg	FEV ₁ 41±16%	Tadalafil 10 mg daily	12 weeks	6MWD, no change	Decreased sPAP compared with placebo; no difference in QoL, BNP or Sa _{o₂}
VITULO [2016] [49]	28	COPD with PH by RHC	RCT (2:1)	RHC: mPAP >35 mmHg (if FEV ₁ <30%), mPAP ≥30 mmHg (if FEV ₁ ≥30%)	mPAP 39±8 mmHg, CI 2.4±0.5 L·min ⁻¹ ·m ⁻² , PVR 7±2.6 WU	FEV ₁ 54±22%, D _{Lco} 33±12%	Sildenafil 20 mg 3 times daily	16 weeks	PVR, decreased 1.4 WU	Improved CI, BODE scores and QoL; no effect on gas exchange
ILD										
HAN [2013] [90]	119	IPF with echo available (66% of the whole cohort)	RCT	Echo: RVSD	Not available	FVC 57%, D _{Lco} 26%	Sildenafil 20 mg 3 times daily	12 weeks	6MWD, less decline in patients with RVSD on sildenafil	Improvement in QoL in patients with RVSD
CORTE [2014] [60]	60	IPF or idiopathic fibrotic NSIP	RCT (2:1)	RHC: mPAP ≥25 mmHg	mPAP 37±9.9 mmHg, CI 2.2±0.5 L·min ⁻¹ ·m ⁻²	FVC 55.7±20%, K _{co} 45±22%	Bosentan	16 weeks	PVRI decrease of 20%, negative	Secondary end-points all negative; no change in functional capacity or symptoms
RAGHU [2015] [14] [†]	68	IPF with group 2 PH (14% of whole cohort)	RCT (2:1)	RHC	mPAP 30±8 mmHg	FVC 67±12%, D _{Lco} 39±15%	Ambrisentan 10 mg·day ⁻¹	Event-driven study terminated early	Disease progression, unfavourable trend	More hospitalised ambrisentan arm
NATHAN [2017] [57]	147	IIP, FVC >45%, mPAP >25 mmHg	RCT	RHC	mPAP 33.2±8.2 mmHg, CI 2.6±0.7 L·min ⁻¹ ·m ⁻²	FVC 76.3±19%, D _{Lco} 32±12%	Riociguat 2.5 mg 3 times daily	26 weeks	6MWD, no difference at study halt	Study stopped early for increased harm to riociguat arm (death and hospitalisation)

Continued

TABLE 2 Continued

First author (year) [ref.]	Subjects n	Inclusion criteria	Study design	Diagnosis of PH	Baseline haemodynamics [#]	Baseline PFTs [#]	Therapy	Duration	Primary end-point result	Other outcomes
Sarcoidosis										
BARNETT [2009] [65]	22	Any SAPH and treatment with PAH therapy	Retrospective case series	RHC	mPAP 46.1±2.7 mmHg, CO 4.2±0.4 L·min ⁻¹	FVC 53.6±3.3%, FEV ₁ 51.2±3.7%	Bosentan, sildenafil	Median [range] 11 [5.2–46.6] months	6MWD improved by 59 m	NYHA FC improvement in nine patients
BAUGHMAN [2009] [66]	22	Any SAPH	Prospective open label	RHC	mPAP 33 [20–62] mmHg, CO 5.9 [3.1–9.5] L·min ⁻¹ , PVR 5.1 [1.96–16.3] WU	FVC 50% [41–101%], FEV ₁ /FVC 73% [53–91%]	Inhaled iloprost	4 months	6MWD unchanged 0.6±40 m	7 patients withdrew; 6 patients with ≥20% decrease in PVR and 3 patients with ≥30 m increase in 6MWD
JUDSON [2011] [91]	25	mPAP >25 mmHg, PVR >3 WU, FVC >40%, WHO FC II or III, 6MWD 150–450 m	Prospective open label	RHC	mPAP 32.7±7 mmHg, CO 4.45±0.94 L·min ⁻¹ ·m ⁻² , PVR 5.86±2.3 WU	FEV ₁ 59±21%, FVC 61.5±16.5%	Ambrisentan 10 mg daily	24 weeks	No change in 6MWD 9.8±55 m	11 patients discontinued drug at 12 weeks; 10 out of 21 patients who completed had improvements in WHO FC and QoL
BAUGHMAN [2014] [67]	39	mPAP ≥25 mmHg, NYHA FC II or III	RCT (2:1)	RHC	mPAP 36±7 mmHg, CI 2.6±0.7 L·min ⁻¹ ·m ⁻²	FVC 60±16.6%	Bosentan	16 weeks	Decrease in mPAP (to 32 mmHg)	No change in 6MWD; PVR decreased from 6.1 to 4.4 WU
KEIR [2014] [92]	33	Any SAPH	Retrospective case series	RHC	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	FEV ₁ 51.8±18.3%, FVC 64.8±22.3%	Sildenafil n=29, bosentan n=4	6 months	None identified	6MWD improved 14 m; BNP and TAPSE improved
BONHAM [2015] [93]	26	Any treated SAPH, no left-sided disease	Retrospective case series	RHC	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	FEV ₁ 48% [38–59%], FVC 48% [44–64%], DLCO 29% [25–44%]	Epoprostenol n=7, treprostinil n=6, ERA n=12, PDE5i n=20	Variable	None identified	Increased CI/CO, decreased PVR (median 12.7 months in 10 prostacyclin patients) and improved N-terminal pro-BNP

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; V_O₂: oxygen uptake; BNP: brain natriuretic peptide; S_{aO}₂: 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; K_{CO}: 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 ≥ 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 patient 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 $>35 \text{ kg}\cdot\text{m}^{-2}$ [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 $>2500 \text{ m}$ 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

TABLE 3 Recommendations and questions for the future direction of research in chronic lung disease (CLD)-associated pulmonary hypertension (PH)

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

- (Co-)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 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

COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; iPSC: induced pluripotent stem cell; CT: computed tomography; SPECT: single photon emission CT; MRI: magnetic resonance imaging; 6MWT: 6-min walk test; BNP: brain natriuretic peptide; NYHA: New York Heart Association; QoL: quality of life; IIP: idiopathic interstitial pneumonia; CPFE: combined pulmonary fibrosis and emphysema.

arterial remodelling occurs during long-term hypoxia. Both hypoxic pulmonary vasoconstriction and vascular remodelling act in concert with erythrocytosis, leading to PH at high altitude [80]. Importantly, high-altitude PH is reversible upon re-exposure to normal inspired oxygen tension (P_{iO_2}). Acute treatment studies with sildenafil and the ROCK (RhoA/Rho kinase) inhibitor fasudil reduced PAP and/or increased exercise capacity [81–83]. Only sildenafil and captopril have been investigated in long-term studies over a period of 3 months, with lowered PAP levels being noted [84, 85].

Recommendations

Re-exposure to normal P_{iO_2} is the primary treatment of high-altitude PH. Long-term treatment studies with vasodilators are largely missing.

General conclusions

The association between PH and CLD with impaired functional status and worse outcomes is well established. Whether PH is the driver of outcomes or a surrogate for the severity of the underlying CLD remains uncertain. However, given the worldwide prevalence of CLD, and the associated morbidity and

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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