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BRN Rev. 2022;8(2):93-110

BRN Reviews

REVIEW

Diagnostic and Therapeutic Challenges for Patients with Pulmonary Hypertension due to Lung Diseases

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ABSTRACT

Pulmonary hypertension (PH) associated to chronic lung disease (CLD) is relatively frequent in end-stage disease but can be also present at early stage, sometimes associated with low carbon monoxide diffusion capacity (DL_{CO}) and relatively preserved lung volume in a pulmonary vascular phenotype. PH worsens prognosis, decreases exercise capacity, and impairs quality of life. Echocardiography, chest high-resolution computed tomography (HRCT) and cardiopulmonary exercise test may help for PH screening in CLD. The diagnostic is based on right heart catheterisation. Treatment of CLD-PH includes treatment of the underlying condition, long-term oxygen therapy and lung transplantation. Pulmonary arterial hypertension (PAH)-specific medications may be useful but due to lack of evidences, heterogeneity of the studies and concerns regarding side effects, cannot be recommended. In this review, we summarize epidemiological data, clinical features and treatments of CLD-PH, especially in chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF).

Keywords: Chronic lung disease. Chronic obstructive pulmonary disease. Idiopathic pulmonary fibrosis. Pulmonary hypertension.

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Received: 08-05-2022
Accepted: 11-06-2022
DOI: 10.23866/BRNRev:2022-M0069
www.brnreviews.com

INTRODUCTION

Pulmonary hypertension (PH) is currently defined as a mean pulmonary artery pressure (mPAP) of > 20 mmHg with a pulmonary vascular resistance (PVR) of ≥ 3 Wood Units (WU) according to the 2018 World Symposium on PH (WSPH)[1]. Patients can be classified into different subgroups according to disease mechanisms and therapeutic options[2]. Group 1 refers to pulmonary arterial hypertension (PAH), typically involving different forms of PH which were originally described as displaying the histopathological hallmark of plexiform lesions. Group 2 refers to PH associated with cardiac diseases. Group 3, which will be discussed in this article, refers to PH associated with chronic lung disease (CLD)[3]. Group 4 PH is associated with thromboembolic and proximal pulmonary artery occlusions.

Virtually, all lung diseases, regardless of their aetiology, may lead to PH if they evolve to end-stage disease. However, moderate forms of CLD may also be associated with severe PH, similar to PAH. Therefore, group 3 PH may be considered as a disease spectrum going from PH associated with end-stage CLD to forms close to PAH with mild lung disease. The most common CLDs associated with PH are chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). The features of COPD and IPF may be combined in one patient, resulting in the clinical form of combined pulmonary fibrosis and emphysema (CPFE), which is frequently associated with PH. Interestingly, patients with severe PH without severe CLD frequently present with a low carbon monoxide diffusion capacity (DL_{CO}) and mild parenchymal abnormalities on chest high-resolution computed tomography (HRCT). This clinical presentation has been recently referred to as 'pulmonary vascular phenotype associated with underlying mild CLD[4].

In this review, we will discuss the various clinical features of group 3 PH especially for COPD (COPD-PH) and IPF (IPF-PH), and their diagnosis and treatment, which remain challenging.

PREVALENCE, CLINICAL FEATURES AND PROGNOSIS OF PULMONARY HYPERTENSION IN CHRONIC LUNG DISEASES

The prevalence of PH in CLD has been extensively studied. However, the results need to be interpreted according to different diagnostic methods (echocardiography or right heart catheterisation [RHC]), definitions of PH, and selection of patients (type of CLD, severity of the underlying CLD). Indeed, an important proportion of the studies has been conducted in patients evaluated for lung transplantation (LTx) and therefore present with terminal respiratory disease.

Chronic obstructive pulmonary disease

COPD is frequently associated with a mild degree of PH[5]. Structural changes related to emphysematous lungs with loss of the pulmonary vascular bed, hypoxic vasoconstriction, and inflammation due to toxic inhalation may lead to PH in COPD. Genetic factors may also play a role[6]. Remodelling of the pulmonary vessels is observed with muscularization of the pulmonary arterioles due to

proliferation and hypertrophy of smooth muscle cells[7,8]. Intimal thickening is also seen, but without the presence of plexiform lesions, as encountered in PAH. Venular remodelling with muscularization and extracellular matrix deposition has also been demonstrated.

The degree of pulmonary vascular involvement in COPD has been correlated with the severity of airflow obstruction, with the highest prevalence of PH in advanced COPD. In two cohorts of patients with severe COPD, the mean mPAP was 26 mmHg[9,10]. The prevalence of an mPAP of > 20 mmHg in COPD patients was found to be between 18% and 91% in the whole spectrum of severity of the airway obstruction[10-12]. Severe PH is not frequently encountered in patients with COPD[5] and in a large cohort of 998 patients with COPD, the mean mPAP was 20.8 mmHg and only 5.8% of the patients presented with an mPAP of ≥ 35 mmHg[13]. Interestingly, severe PH is not frequently encountered in patients with COPD[5]. In COPD patients evaluated for LTx, the prevalence of mPAP between 26–35 mmHg, 36–45 mmHg, and > 45 mmHg were 36.7%, 9.8%, and 3.7%, respectively[14]. In these patients, the prevalence of precapillary PH has been estimated at 30.4% and post-capillary PH at 17.2%[15]. A recent analysis of 99 patients with COPD and severe PH from a prospective French multicenter cohort has shown that these patients presented with marked dyspnoea (78% of the patients in New York Heart Association [NYHA] class III or IV), a moderate obstruction (mean forced expiratory volume in one second [FEV_1] value of 50%), a very low DL_{CO} (average 20%), and severe hypoxaemia associated with hypocapnia[16]. The mean survival was poor (15 months). Before developing resting PH, COPD patients may encounter abnormal circulation during exercise. Indeed, in a cohort of 131 patients with COPD without PH at rest, Kessler et al.[17] demonstrated that 25% developed mild PH over a period of six years, mainly observed in patients presenting with higher mPAP during exercise. Interestingly, the patients who developed PH also presented with more gas exchange impairment at baseline. PH in COPD is also associated with a worse prognosis[18-21]. COPD patients with an mPAP of ≥ 25 mmHg have a five-year survival of 33%, whereas the survival is 66% in patients with an mPAP of < 25 mmHg[18]. Low DL_{CO} has also been found to be a predictor of poor survival in patients with COPD-PH[22]. Besides survival, PH in COPD is also associated with symptoms and exercise intolerance[15].

Idiopathic pulmonary fibrosis

PH is frequently associated with IPF. Pathological studies of IPF-PH have shown that the entire microvasculature can be affected by the disease process, with changes in the arteries, arterioles, capillary bed, and venules[23]. These changes are caused by the fibrotic process, as well as by the remodelling effect of hypoxia. The different structures of the pulmonary artery wall may be affected by adventitial thickening due to extracellular matrix deposition and increased presence of fibroblasts and myofibroblasts. The media is enlarged due to smooth muscle cell hypertrophy and hyperplasia, as well as accumulation of collagen and elastin. Finally, the intima is also thickened due to fibrosis. Interestingly, these changes have been found in areas of dense parenchyma fibrosis, but signs of vascular remodeling may also be present in fibrotic-spared areas

of the lung, suggesting that processes other than fibrosis and hypoxia could play a role in the vascular remodelling observed in IPF. The post-capillary compartment is also involved showing intimal proliferation and fibrosis in the pulmonary venules. Finally, capillary bed destruction is observed. In contrast, other areas of the fibrotic lung show vascular proliferation and neo-angiogenesis.

The prevalence of PH in IPF has been non-invasively evaluated between 20% and 84%[24,25]. The prevalence of precapillary PH in IPF assessed with RHC is lower, evaluated between 28% and 41% in a cohort of candidates for LTx[26-28]. In a large cohort of 2525 patients with IPF awaiting LTx, the incidence of an mPAP ≥ 25 mmHg was 46%, and severe PH with an mPAP > 40 mmHg was 9%[29]. In a large randomised control study evaluating the effect of ambrisentan on progression-free survival in IPF, including less severe patients, the prevalence of pre- and post-capillary PH in IPF was 14% and 5%, respectively[30]. PH associated with IPF can progress rapidly. A study of 45 patients with IPF on the LTx waiting list showed an mPAP increase of 3.8 mmHg/month[31]. Interestingly, a low DL_{CO} and the use of supplemental oxygen therapy were associated with a higher probability of PH, whereas lung volumes were not[26,27]. Higher systolic pulmonary artery pressures (sPAP) in IPF have been associated with a higher degree of hypoxaemia, a lower functional capacity, higher brain natriuretic peptide (BNP) levels, and increased dyspnoea[32].

In IPF, PH is associated with the risk of death[24,25,33], increasing from 5.5% to 28.8% at one year if PH is present[26]. Moreover, each 5 mmHg increase in mPAP has been associated with a 50% increase in the risk of death[28]. Many other factors are also associated with worse outcomes in IPF-PH such as right ventricle (RV) dysfunction, RV chamber enlargement[34], tricuspid annular plane systolic excursion, RV fractional area change[35], and low DL_{CO}[33].

Combined pulmonary fibrosis and emphysema

CPFE is characterised by extensive parenchymal destruction due to the association of lung fibrosis, mainly in the lower lobes, and emphysema, predominantly in the upper lobes[36-38]. However, the lung volumes are often preserved. The syndrome is frequently associated with very low DL_{CO}, hypoxaemia, and PH[39]. The reason for this particular phenotype is not well understood but is probably due to the combination of alveolocapillary membrane thickening due to fibrosis along with extensive destruction of the parenchyma due to emphysema[40]. In an echocardiographic study, the prevalence of PH in CPFE was evaluated to be 50%[38]. In a study using RHC, the mean mPAP in patients with CPFE was 40 mmHg[41]. Patients also present a severely reduced functional capacity with a mean six-minute walk distance (6MWD) of only 244 m and a poor prognosis, with a one-year survival estimated at 60%[41] and a two-year survival of only 23%[42].

Pulmonary vascular phenotype

A specific phenotype of patients with mild-to-moderate COPD and severe PH has been recently proposed[43]. Some studies have found a strong association between PH in COPD, mild lung disease, low DL_{CO}, pronounced

hypoxaemia associated with hypocapnia, and cardiovascular limitation during exercise[21,44,45]. This frequent association has led to the definition of a specific phenotype associated with COPD, referred to as pulmonary vascular phenotype[3]. The distinction between PAH and pulmonary vascular phenotype is often difficult[4,46]. This entity, which may constitute a continuum spectrum with PAH, is more frequently encountered in older male patients with a history of smoking or other toxic exposures and mild HRCT impairment[47]. Interestingly, these patients present common features in terms of poor prognosis, lung function, and demographic characteristics with CPFE patients, with the exception of radiological involvement[48]. A recent cluster analysis from 841 patients with idiopathic PAH identified a specific cluster of patients presenting low DL_{CO}, older age (mean age of 72 yrs), male predominance, history of smoking, poor response to PAH specific therapies and poor survival (five-year survival of 42%)[49]. Similar features have also been observed in post-capillary PH in a subgroup of patients with low DL_{CO}, old age, male sex, hypoxaemia, cigarette smoking status, and HRCT abnormalities[50]. The histopathological process underlying pulmonary vascular phenotype is not well understood. This could be due to a rarefaction of the lung capillary bed (also referred to as vanishing capillaries), disturbance of the alveolocapillary membrane, venular involvement, or a combination of multiple factors[51-53].

SCREENING, DIAGNOSIS, AND EVALUATION OF PH IN CLD

The diagnosis of PH in patients with CLD remains challenging (Fig. 1). Clinical, radiological, and electrocardiographic signs of RV failure may be present. However, due to the non-specificity of these signs and the high frequency of mild PH not necessarily leading to clinically overt RV dysfunction, these elements are insufficient in diagnosing PH in CLD[23]. Moreover, the presence of PH in CLD, and notably in COPD, should be evaluated outside of exacerbation periods[5].

Echocardiography

Echocardiography is a good screening tool for PH. However, it has been found to be inaccurate in determining pulmonary pressure[54]. Moreover, pulmonary pressure evaluation in CLD may be challenging because of a lack of echogenicity, especially in severe emphysema[55]. In a large cohort of LTx candidates, sPAPs measured by echocardiography were significantly correlated with pressures invasively measured during RHC[56]. However, 52% of the estimated pressures were found to be inaccurate, and 48% of patients were misclassified as having PH by echocardiography, leading to a low specificity and a low positive predictive value. RV systolic pressures have also been proven to be inaccurate in estimating the presence of PH and its magnitude in IPF[57]. Furthermore, echocardiography cannot reliably distinguish between post- or pre-capillary PH. Besides pulmonary pressures, other echocardiographic parameters have been investigated and found useful for the screening and evaluation of PH in CLD. Echocardiography provided additional information on RV function[34] and other underlying cardiac conditions. However, in a cohort of patients with IPF, patients with normal RV showed a PH prevalence of more than 25%, suggesting

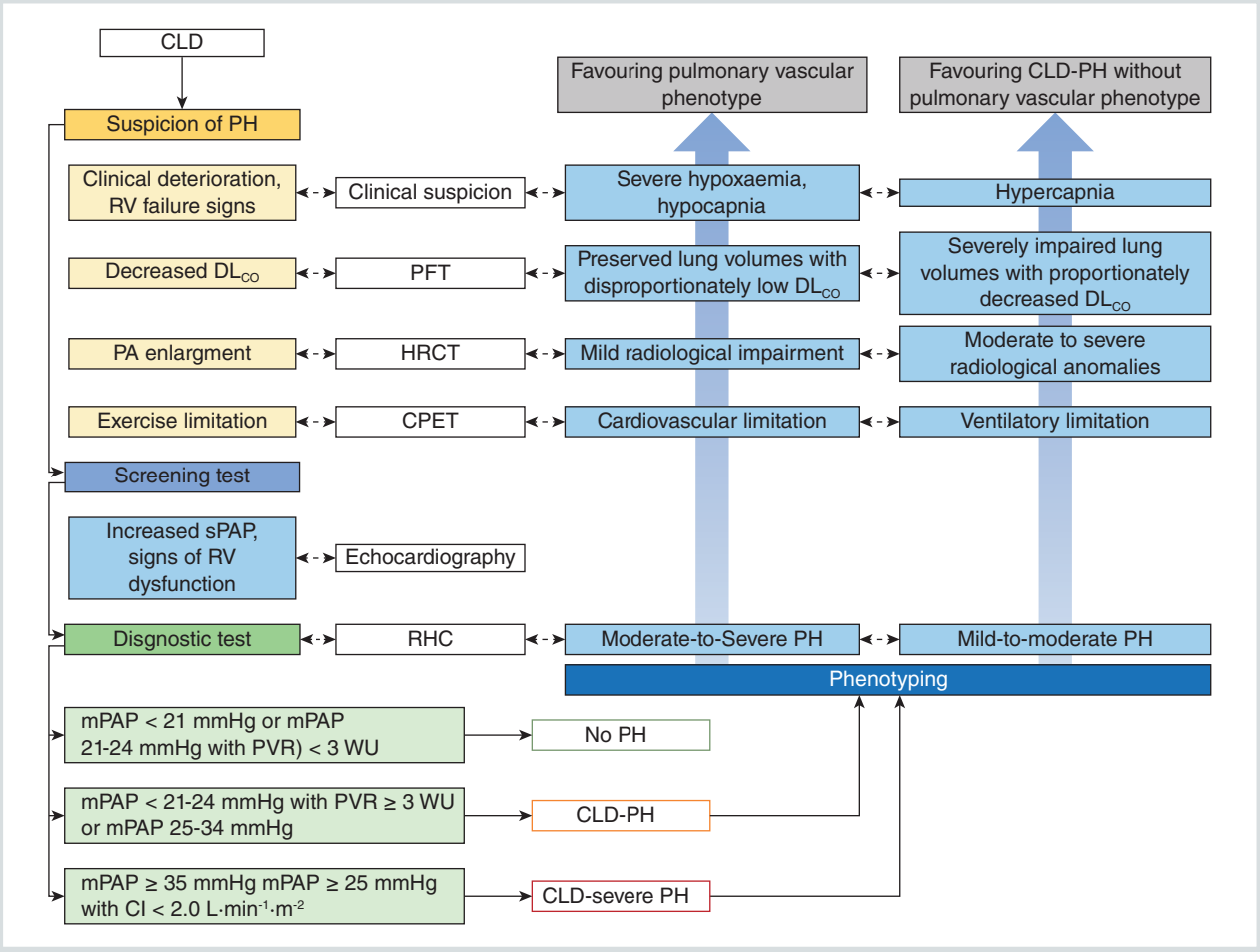

Figure 1. Algorithm for the suspicion, the screening and the diagnosis of PH in CLD.
CI: cardiac index; CLD: chronic lung disease; CPET: cardiopulmonary exercise test, DL_{CO}: diffusing capacity of the lungs for carbon monoxide; HRCT: high-resolution computed tomography; mPAP: mean pulmonary artery pressure; PA: pulmonary artery; PFT: pulmonary function test; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RHC: right heart catheterization; RV: right ventricle; sPAP: systolic pulmonary artery pressure; WU: Wood unit.

that normal RV does not exclude PH[56]. Recently, the ratio tricuspid annular plane systolic excursion (TAPSE)/systolic pulmonary artery pressure (PASP), considered as a surrogate marker of the RV-PA coupling, has been demonstrated to be able to discriminate between severe and non-severe PH associated with CLD[58]. Moreover, a value less than 0.26 mm·mmHg^{-1} was also found as a predictive marker of worse survival.

Chest high-resolution computed tomography

Chest HRCT is an important tool for the assessment of group 3 PH. First, it provides information concerning the extent of lung disease, such as the degree of fibrosis, emphysema, or a combination of both. Furthermore, it evaluates the pulmonary vasculature. Diameter enlargement of the pulmonary artery (PA) has

been found to be a risk factor for PH and a prognostic marker of worse outcomes in various CLDs. In COPD, PA enlargement[59] and vascular pruning assessed with the cross-sectional area of small pulmonary vessels less than five mm^2 has been correlated with PH[60,61]. In IPF, PA enlargement is also associated with poor prognosis[62].

Right heart catheterisation

RHC remains the gold standard for confirming a diagnosis of PH and for discriminating pre- from post-capillary PH. Indeed, the incidence of post-capillary PH increases with age and cardiovascular comorbidities, which are also associated with pulmonary diseases, especially COPD. Moreover, the chosen cut-off value of mPAP may affect the diagnosis. In addition to diagnostic, RHC is also important for assessing the severity of the disease and an accurate prognosis. Due to respiratory exaggerated variation of pulmonary pressures during the breathing cycle, the measurement and interpretation of the pressure may be challenging. Most authors recommend calculating the average pressure over several breaths instead of relying on a specific time point (that is, end expiratory pressure) for pulmonary pressure measurements[3]. The definition of PH in CLD has also recently been adapted[3]. The proceedings of the 2018 WSPH proposed a definition of CLD-PH based on an mPAP > 24 mmHg or within the range of 21 and 24 mmHg with a PVR of ≥ 3 WU. Severe PH was defined as an mPAP ≥ 35 mmHg or ≥ 25 mmHg with a reduced cardiac index < 2.0 l/min.

Few studies have evaluated the pulmonary haemodynamics during exercise in patients with CLD. In IPF, patients with an mPAP < 25 mmHg frequently encountered an mPAP at peak exercise > 45 mmHg, suggesting an abnormal response of the pulmonary circulation to exercise[63]. In COPD, patients without PH at rest but higher pulmonary pressures during exercise have a higher risk of developing PH at six years[17]. Moreover, COPD patients with exercise-induced PH displayed a higher cost of exercise in terms of oxygen uptake, ventilation, respiratory frequency, heart rate, and lactate for a given increase in workload compared to COPD with haemodynamics considered normal during exercise[64] due to an increased RV afterload and a failure to increase stroke volume[65].

Functional evaluation

A cardiopulmonary exercise test (CPET) may provide some information concerning the repercussions of PH on dyspnoea, regarding cardiac or respiratory limitations. Patients with interstitial lung disease (ILD) may frequently experience circulatory impairment and an exercise profile response compatible with pulmonary vascular disease, contributing to symptoms and disease severity[66]. Moreover, PH in IPF has been correlated with lower oxygen consumption, ventilatory inefficiency, and gas exchange impairment[67]. In COPD, PH has also been associated with lower oxygen uptake, poor exercise tolerance, ventilatory inefficiency, and desaturation during exercise[68,69]. CPET could potentially be useful as an adjunct to echocardiography for the screening and diagnosis of PH in CLD, determining the profile of dyspnoea with involvement of a respiratory or a cardiac limitation.

The 6MWD is widely used for the assessment of patients with PH. A lower 6 MWD has been associated with moderate to severe PH in IPF[26,28,70] and with death in COPD-PH[71].

Pulmonary function test

A pulmonary function test (PFT) may be used to evaluate the severity of CLD. However, the correlation between lung volumes (i.e., FEV_1 for obstructive lung diseases, total lung capacity [TLC] and/or forced vitaly capacity [FVC] for restrictive lung diseases) and PH severity is poor. Moreover, the volume may be normal or only slightly decreased in CPFE due to the combination of emphysema and pulmonary fibrosis. Patients with pulmonary vascular phenotype frequently present with mild lung volume impairment and severe PH.

DL_{CO} is a robust marker of PH and may suggest pulmonary vascular involvement[26]. A DL_{CO} < 30% in IPF has been associated with a doubled risk of PH[27]. A low DL_{CO} has been frequently associated with CLD-PH[25,26]. Decreased DL_{CO} in CLD-PH reflects the combined effects of alveolar membrane abnormality (due to emphysema or fibrosis) and capillary blood volume reduction[52]. The microvasculopathy associated with PH could further reduce the capillary blood volume, decreasing more strongly the diffusion capacity[72]. The association of low DL_{CO}, poor survival and PH has been recognized in COPD, IPF and CPFE suggesting a common association in the spectrum of CLD which may reflect common pathophysiological process in these diseases[13,22,33].

Biomarkers

Biomarkers such as BNP have been found to be useful in the diagnosis and assessment of CLD-PH. An elevated BNP > 33.3 pg/mL may discriminate between moderate-severe and no or mild PH in patients with IPF with a sensitivity of 100% and a specificity of 89%[70]. High BNP levels have also been associated with a worse prognosis in IPF-PH[35,73]. However, a high BNP level may be encountered in various cardiac diseases, and a normal BNP level does not exclude a mild PH without RV failure, limiting the use of BNP in the diagnosis of CLD-PH.

TREATMENT

General treatment of the underlying lung disease remains important, although it is limited in severe COPD and IPF. Pharmacological treatment of respiratory condition, respiratory rehabilitation, and prevention of exacerbations are important. In addition to these general interventions, different treatments targeting pulmonary vasculature include long-term oxygen therapy (LTOT), PAH-specific medications, and LTx.

Long-term oxygen therapy (LTOT)

LTOT addresses the hypoxic pulmonary vasoconstriction component which worsens PH. LTOT can improve prognosis in COPD if administered for at least 16 h per day and can reverse the progression of PH in COPD[74]. Evidence in IPF is limited. A recent review showed no effects of LTOT on symptoms and quality of life (QoL) in patients with ILD, although exercise capacity was increased[75].

PAH-specific therapy

PAH-specific medications have been evaluated in group 3 PH, with various study designs, outcomes, and patient populations. Until now, no PAH-specific medication has been approved for the treatment of group 3 PH due to lack of efficacy and safety concerns. However, compassionate treatment of well-selected patients with severe CLD-PH in experienced centres has led to encouraging results but may not be widely generalised and recommended.

In COPD, endothelial dysfunction has been largely studied with findings suggesting a reduction in the expression of endothelial nitric oxide (NO) synthase and prostacyclin synthase and increased expression of endothelin-1 in PA of patients with COPD[76-78]. Endothelin-1 has also been found to correlate with sPAP in COPD[79].

Sildenafil is the most frequently studied drug in group 3 PH. It was found to reduce hypoxia-induced PH and pulmonary vascular remodelling in animal models[80,81] and to reduce hypoxia-induced PH in healthy volunteers[80]. However, by inhibition of the hypoxic pulmonary vasoconstriction, pulmonary vasodilators may increase the ventilation perfusion mismatch, creating functional shunting and worsening hypoxaemia[82].

Sildenafil was found to improve mPAP at rest and during exercise[82,83] but had no effect on cardiac function[84]. However, the use of this vasodilating agent was accompanied by a loss of hypoxic vasoconstriction, an increase in ventilation-perfusion mismatch, and a degradation of gas exchange[82]. In a double-blind, randomised controlled trial of 63 COPD patients with moderate PH, sildenafil administered in association with rehabilitation for 12 weeks failed to improve exercise capacity or QoL[85]. Interestingly, there was no increase in hypoxaemia. A recent meta-analysis of nine randomised control trials of sildenafil use in COPD-PH involving 579 patients showed that sildenafil was able to significantly improve 6MWD in these patients[86]. However, there was no significant improvement in the QoL or symptoms. In a multicentre randomised control study including 28 patients with severe COPD-PH (mean mPAP 39 mmHg), sildenafil improved PVR, body-mass index (BODE) score, and QoL without deleterious effects on gas exchange after 16 weeks[87]. Altogether, these results suggest a hemodynamic improvement with limited effect on QoL and a relatively safe profile, especially regarding the effect on gas exchange. The results variability could be due to the variability of inclusion criteria (i.e., severe or non-severe PH) and study designs (duration, outcomes studies, number of patients enrolled).

Other medications targeting the NO pathway have been investigated in COPD-PH. In a randomised control trial of 120 patients with mild COPD, tadalafil did not demonstrate improvement in exercise capacity or QoL[88]. Riociguat, a soluble guanylate cyclase stimulator, was also investigated in animal models of COPD-PH and in patients. In a mouse model of smoke-induced PH and emphysema, riociguat was found to reduce PH and emphysema[89]. A single dose of riociguat decreased PVR and mPAP in a dose-dependent manner in patients with COPD exhibiting mild PH, without deleterious effects on gas exchange[90]. Riociguat was also retrospectively evaluated

in seven patients with COPD-PH, showing that it was able to reduce PVR and airway resistance[89]. These results are relatively limited and further studies are requested to evaluate the effect and the safety profile of riociguat in COPD-PH.

Endothelin pathways has also been studied in COPD-PH, mainly with bosentan, a dual endothelin receptor antagonist. Bosentan has been assessed in a 12-week randomized control trial including 30 patients with COPD exhibiting moderate PH[91]. There was no improvement in the 6MWD, and the authors noticed increased hypoxaemia in patients treated with bosentan. However, in another 18-month randomized open study of 40 patients with COPD, the authors found an improvement in exercise tolerance, haemodynamics, and BODE index[92]. Ambrisentan, a selective type A endothelin antagonist receptor, was evaluated in a large cohort of patients with diverse types of PH, of whom 24 had COPD-PH and 21 had ILD-PH. There was a trend towards a decreased 6MWD and BNP, suggesting a progression of the pulmonary lung disease rather than the pulmonary vascular disease[93]. Gas exchange was not studied, and the study design precludes firm conclusions in group 3 PH. Due to lack of evidence, absence of effect in randomized control trials and safety concern regarding gas exchange, endothelin receptor antagonists are not recommended to treat COPD-PH.

Drugs targeting the prostacyclin pathway have also been tested in COPD-PH. Some of them have the particularity to be available for inhalation, which could be particularly relevant in COPD-PH. Indeed, their deposition will occur preferentially in the well-ventilated areas of the lungs, reducing the potential negative effect of vasodilatory drugs on gas exchange. Inhaled iloprost was found to acutely improve haemodynamics in COPD-PH, with a more pronounced effect in severe PH, without a relevant effect on gas exchange[94]. In a small study of nine mild COPD-PH patients, inhaled treprostinil after 16 weeks seemed to have no relevant impact on arterial oxygenation, but the authors noticed a decline in lung function[95]. However, the very small number of patients precluded firm conclusions. Another three-month retrospective study with inhaled treprostinil, including 22 patients with COPD with moderate PH, demonstrated an improvement in functional class and exercise tolerance without deleterious effects on gas exchange[96]. Until now, due to lack of evidence, there is no indication for medication targeting the prostacyclin pathway. However, due to these encouraging results, these medications should be considered for future clinical trials.

Combination therapies have also been assessed in COPD-PH. Two retrospective studies of patients with COPD exhibiting severe PH, assessed with serial RHC, and receiving various medications including combination therapies, showed a significant improvement in haemodynamics (mPAP, cardiac output [CO], PVR) but no difference in exercise capacity, symptoms, oxygenation, or NT-proBNP levels[97,98].

Despite some encouraging results, the prognosis of medically treated patients with COPD-PH remains poor and inferior to that of patients with PAH, with one-, three-, and five-year survivals of only 86%, 55%, and 38%, respectively[71]. Table 1 gives an overview

Table 1. Results of the main randomized control trials of PAH-specific medications in COPD

Study (ref)	Therapy	Subjects included (n)	Diagnostic	Primary outcome	Other outcomes	Effect on drug on hypoxaemia
Blanco I et al. 2013[85]	Sildenafil 20 mg tid	63	COPD with sPAP > 34 mmHg or mPAP ≥ 25 mmHg	Negative. No significant change in cycle endurance time in the constant work-rate exercise test	No difference in incremental exercise test, 6MWD, QoL	No worsening of hypoxaemia
Goudie AR et al. 2014[88]	Tadalafil 10 mg/d	120	COPD with pulmonary acceleration time < 120 ms or RVSP > 30 mmHg	Negative. No significant difference in 6MWD at 12 weeks	No improvement in QoL	No worsening of hypoxaemia
Vitulo P et al. 2017[87]	Sildenafil 20 mg tid	28	COPD with mPAP ≥ 30 mmHg	Positive. Significant decrease in PVR.	Improvement in QoL, DLCO, BODE index	No worsening of hypoxaemia
Stolz D et al. 2008[91]	Bosentan 125 mg bid	30	Severe COPD (FEV_1 < 50%)	Negative. No significant improvement in 6MWD at 12 weeks.	No effect on dyspnoea or BNP; decrease in QoL in patients treated with bosentan	Worsening of hypoxaemia with bosentan

6MWD: six-minute walk distance; BNP: brain natriuretic peptide; BODE: body-mass index, airflow obstruction, dyspnoea, and exercise; COPD: chronic obstructive pulmonary disease; DLCO: diffusing capacity of the Lung for Carbon monoxide; FEV1: forced expiratory volume in 1 second; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; QoL: quality of life; RVSP: right ventricle systolic pressure; sPAP: systolic pulmonary artery pressure.

of the main randomized clinical trials regarding treatment with PH-specific medications in COPD. These results have also been pooled in meta-analyses to investigate the global effect of medical treatment. The results of two meta-analyses were discordant. In a recent meta-analysis of PAH-specific medication in COPD-PH, the authors analysed five randomised controlled studies including 257 patients with COPD-PH. The study found a non-significant increase in the 6MWD (+ 43 m) without worsening of hypoxaemia[99]. In another meta-analysis involving nine clinical trials and 365 patients with COPD-PH, the authors found a significant improvement in exercise capacity with a 66 m improvement in 6MWD[100]. There was no significant impact on oxygenation, QoL, or symptoms. Due to conflicting but encouraging results, further well-designed studies with specific attention to the type of patients enrolled are required.

PH-specific medications have also been evaluated in patients with ILD. Due to potential effects on the fibrotic process, some of them have also been assessed independently of the presence of PH, directly to target the pulmonary fibrosis. In IPF, treatments targeting the NO pathway have been extensively studied. At the cellular level, sildenafil was found to reduce pulmonary endothelial dysfunction and decrease PA smooth cell proliferation in human cells[101,102]. In animal models, sildenafil has been found to decrease RV hypertrophy and fibrosis and decrease pulmonary vascular remodelling[103]. In an *ex vivo* study, sildenafil showed an inhibitory effect on 5-HT-induced contraction to be significantly higher in arterial rings of patients with IPF-PH than in arterial rings of patients with IPF without PH[104]. Due to promising results in preclinical studies, sildenafil was also evaluated in clinical trials. In patients with IPF without overt PH, sildenafil was demonstrated to be

ineffective in improving exercise capacity[105,106] but had a positive effect on oxygenation, DL_{CO}, and QoL[106]. Studies with a limited number of patients have shown that sildenafil was effective in improving haemodynamics in IPF, with a substantial reduction in PVR[107] and improved exercise capacity[107,108]. A randomised controlled, open-label trial in 16 patients with IPF demonstrated that sildenafil was able to reduce PVR by 32.5% without deleterious effects on gas exchange, in comparison with epoprostenol[109]. In a randomised placebo-controlled study, sildenafil was found to improve 6MWD and QoL in patients with IPF and RV dysfunction[110]. A recent double-blind, randomised, placebo-controlled trial consisting of the addition of sildenafil to pirfenidone in patients with IPF and echocardiographic suspicion of PH or an mPAP > 20 mmHg did not demonstrate a benefit with a negative primary outcome consisting of a disease progression composite endpoint[111]. Another trial including 274 patients with IPF and associating nintedanib and sildenafil was also negative regarding the primary outcome (improvement of QoL)[112]. As found for COPD-PH, the effect of sildenafil in IPF-PH seems to be relatively safe and could be favourable in some subsets of patients. Further studies are required with a specific attention to design, methods of evaluation of PH and selection of patients.

Riociguat has also been evaluated for the treatment of ILD-associated PH in a randomised control trial[113]. Due to the higher proportion of adverse events and death in the treated group, the study was stopped earlier and according to this results riociguat is now contra-indicated for the treatment of ILD-associated PH.

Endothelin pathway is also a relevant target for PH associated to fibrotic respiratory diseases. Endothelin-1 has been associated with PH development, but is also a profibrotic agent[114]. In an IPF-PH bleomycin rat model, macitentan, a second generation dual endothelin receptor antagonist, was found to prevent pulmonary vascular remodelling, RV hypertrophy, and cardiomyocyte diameter increase, whereas bosentan did not[115]. In a small retrospective monocentric study, bosentan and IV epropostenol were found to be efficacious in improving WHO functional class and 6MWD in a heterogeneous population of patients with ILD-PH[116]. A small randomised control trial of 24 patients with IPF and mild PH showed a significant increase in survival in the treated group compared to the non-treated group[117]. However, in larger randomised trials, bosentan was not able to improve 6MWD[118], QoL, symptoms[119], or IPF progression free survival[120]. In a randomised controlled trial of 60 patients with IPF or non-specific interstitial pneumonia and RHC-proven PH, bosentan was not able to reduce indexed PVR, exercise capacity, or symptoms[121]. Altogether, these results seem to indicate that bosentan is probably not effective in most of the patients with IPF-PH. Macitentan was evaluated in a randomised control trial for the treatment of IPF[122]. Although well tolerated, macitentan was not able to demonstrate a positive effect on the decrease in FVC in 178 patients. However, the study did not evaluate the potential pulmonary vascular effects. Ambrisentan has been evaluated in a large randomised control trial in 492 IPF patients to for its ability to decrease disease progression[123]. However, the study was negative, with an increased risk of disease progression and hospitalisations in the ambrisentan-treated

group. Most of the patients had mild PH, with only 4% having an mPAP > 35 mmHg. There was no difference in the rate of development of PH in subjects without PH at baseline, suggesting that ambrisentan was not able to prevent PH development in IPF-PH. However, in patients with PH who received ambrisentan and who were repeatedly assessed by RHC, an mPAP decrease of 5 mmHg was observed in comparison with an mPAP decrease of 1 mmHg for patients without PH. However, due to the increased risk of serious adverse events in the treated group, ambrisentan is contra-indicated in IPF patients.

To avoid the deleterious effect of vasodilatation of the area of the lung subjected to hypoxic vasoconstriction and to maintain an optimal ventilation-perfusion ratio, inhaled vasodilatory therapies have been assessed in IPF. The effects of intravenous prostacyclin and inhaled NO and aerosolised prostacyclin were compared in a clinical study[124]. Inhaled prostacyclin significantly decreased mPAP and PVR without increasing shunting and without systemic vasodilatory effect, whereas shunting was significantly increased during perfusion with intravenous prostacyclin, and the decrease in mPAP was significantly less pronounced with systemic vasodilatory effect, suggesting a beneficial effect of inhaled medication targeting the prostacyclin pathway. The Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE (INCREASE) study, a 16-week randomized control trial of inhaled treprostinil in patients with ILD-PH, recently demonstrated a benefit in ILD-PH, with an improvement in 6 MWD, NT-proBNP, and a reduction in the risk of clinical worsening[125]. Interestingly, a post-hoc analysis demonstrated a significant increase in FVC, especially in the patient subgroup with IPF[126].

Finally, a recent meta-analysis of PAH-specific medication involving 2124 patients, of whom 1274 received PH-specific medications, was not able to demonstrate a benefit in terms of survival, lung function, dyspnoea, or exercise capacity, but showed a small but significant improvement in QoL[127]. Table 2 gives an overview of the main randomized clinical trials regarding treatment with PH-specific medications in IPF/ILD.

In CPFE, the recent clinical trial INCREASE evaluating inhaled treprostinil in patients with ILD has enrolled 25% of patients with CPFE[126]. The positive results of the study suggest that inhaled treprostinil could be also efficient for patients with CPFE. Due to the severity and the dramatic prognosis of CPFE, these patients should be promptly referred for LTx.

Lung transplantation

LTx is the definitive treatment for various forms of CLD with respiratory failure. Pulmonary fibrosis and COPD are the most frequent indications. Patients with severe disease without relevant comorbidities and young age may be potential candidates for LTx. Severe PH associated with CLD is an indication for LTx due to its poor prognosis. However, in some studies, severe PH in CLD has been associated with a higher risk of primary graft dysfunction and postoperative bleeding, and with a poorer 90 day survival after LTx[128]. Moreover, the presence of PH is a contraindication for unilateral transplantation.

Table 2. Results of the main randomized control trials of PAH-specific medications in IPF/ILD

Study (ref)	Therapy	Patients included (n)	Diagnostic	Primary outcome	Other outcomes	Effect on drug on hypoxaemia
BUILD-1[118]	Bosentan 125 mg bid	158	IPF	Negative (no difference in 6MWD up to 12 months)	A trend in favor of bosentan in the time to death or disease progression; possible positive effect on QoL and dyspnoea	No effect
BUILD-3[120]	Bosentan 125 mg bid	616	IPF of less than three years duration, confirmed by surgical biopsy	Negative (no effect on time to IPF worsening or death)	No effect on QoL or dyspnoea; possible positive effect on the decline rate of FVC and DLCO	Not reported
MUSIC[122]	Macitentan 10 mg/d	178	IPF of less than three years duration, confirmed by surgical lung biopsy	Negative (no difference in FVC decline at 12 months)	No effect on time to first occurrence of IPF worsening or death; no significant effect on DLCO or dyspnoea	Not reported
ARTEMIS-IPF[123]	Ambrisentan 10 mg/d	492	IPF < 5% honey combing on HRCT	Negative. Stopped earlier due to increased risk for disease progression in the ambrisentan-treated group		Not reported
STEP-IPF[106]	Sildenafil 20 mg tid	180	IPF (DLCO < 35%)	Negative (no improvement in 6MWD at 12 weeks)	Positive effect on DLCO and QoL; no effect on dyspnoea	Positive effect of sildenafil on PaO_2
INSTAGE[112]	Nintedanib 150 mg bid plus sildenafil 20 mg tid	274	IPF (DLCO < 35%)	Negative (no significant difference in the SGRQ total score at 12 weeks)	Lower risk of an absolute decline in the FVC in the treated group; no effect on dyspnoea or exacerbations rate	No effect on saturation at 12 weeks
Behr et al. 2021[111]	Sildenafil 20mg tid added to pirfenidone (1602-2403mg/d)	177	IPF with DLCO < 40% and precapillary PH (mPAP ≥ 20 mmHg) or intermediate/high probability of PH on echocardiography	Negative (no difference in progression-free survival at 52 weeks)	No effect on QoL, FVC, 6MWD, NT-proBNP	Not reported
RISE-IIP[113]	Riociguat 0·5 mg up to 2·5 mg three times daily	229	Idiopathic interstitial pneumonia with FVC ≥ 45%, precapillary PH confirmed by RHC	Negative. Stopped earlier due to increased in serious adverse events and mortality in patients receiving riociguat		No negative effect of riociguat on gas exchange
INCREASE[125]	Inhaled Treprostinil 72 µg qid (maximum dose)	326	ILD with precapillary PH assessed by RHC (PVR ≥ 3 WU, mPAP ≥25 mmHg)	Positive (significant difference 6MWD at 16 weeks in the Treprostinil group)	Positive effect on NT-proBNP and risk of clinical worsening; no effect on QoL	No negative effect of inhaled treprostinil on gas exchange

6MWD: Six-minute walk distance; DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; HRCT: High-resolution computed tomography; ILD : interstitial lung disease; IPF: idiopathic pulmonary fibrosis; mPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal prohormone of Brain natriuretic peptide; PaO2: partial pressure of oxygen in arterial blood; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; QoL: quality of life; RHC: right heart catheterisation; SGQR: St George's Respiratory Questionnaire; WU: Wood units.

CONCLUSION AND PERSPECTIVES

As presented in this review, adequate diagnosis, evaluation, and treatment of group 3 PH remain challenging owing to the heterogeneity of this entity.

RHC remains the definitive gold standard for diagnosis. However, it is an invasive technique, and due to the lack of recommended drugs in group 3 PH, the decision to perform RHC should be based on the perspective of a relevant clinical decision: compassionate use of specific PAH medication, unexplained clinical degradation, enrolment in a clinical trial or referral for LTx. The decision of which patients should be referred for RHC and when, remains difficult. Echocardiography has been considered as the best screening test for PH. However, assessment of pulmonary pressures, RV function, and morphology with echocardiography in CLD remains particularly difficult and frequently inaccurate. Therefore, there is a crucial need to develop screening algorithms, including HRCT, CPET, PFT, and biomarkers.

Clinical trials are also highly heterogeneous in terms of patient selection, PH diagnosis, type and administration of treatments, precluding firm conclusions regarding medical treatment. Due to the lack of evidence and risk of clinical degradation, medical treatment of CLD-PH may not be systematically recommended and should be reserved only at experienced centres. Some studies point to a higher benefit of sildenafil in CLD-PH[42]. Due to its relatively low cost, the possibility of titration and studies suggesting improvement without gas exchange deterioration, it could be considered as the first choice in CLD-PH. Moreover, the emerging role of inhaled Treprostinil in PH associated with ILD has to be underlined. Indeed, it is the first therapy that has proved efficacy in a multicenter randomized, double-blind, placebo-controlled trial. However, there is still a crucial need for well-designed studies for patients with CLD-PH for whom the PH phenotype has been precisely determined, especially for patients with severe PH and patients with pulmonary vascular phenotype.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose related to this work.

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