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Management of Pulmonary Hypertension in Patients with Chronic Lung Disease

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Abstract Pulmonary hypertension (PH) is a common complication of chronic pulmonary diseases, especially in advanced disease, and is associated with greater mortality and worse clinical course. Patients with symptoms that exceed those expected by their pulmonary disease should be further evaluated by echocardiography. Confirmatory right heart catheterization is indicated in those conditions where the results of the hemodynamic assessment will determine treatment options. The treatment of choice for patients who are hypoxemic and have pulmonary hypertension associated with chronic lung disease is long-term oxygen therapy. Conventional vasodilators or drugs approved for pulmonary arterial hypertension are not recommended in patients with mild-to-moderate PH because they may impair gas exchange and because there is a lack of evidence supporting their efficacy. Patients with severe PH should be considered for referral to a center with expertise in PH and lung diseases. Ideally, these patients should be included in randomized controlled trials to determine which patients are more likely to derive benefit and which therapies are most likely to be successful.

This article is part of the Topical Collection on *Pulmonary Hypertension*

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Introduction

Pulmonary hypertension (PH) is an important complication in the natural history of chronic respiratory diseases, particularly in chronic obstructive pulmonary disease (COPD) and interstitial lung diseases (ILDs). PH, when present in these conditions, is associated with reduced survival and worse clinical course. The prevalence of PH in respiratory diseases is not negligible. It can be close to 50 % or even greater in patients with advanced disease. In most cases, PH is usually of moderate severity, without altering right ventricular function. Nevertheless, a small subgroup of patients may present with severe PH, with pulmonary artery pressure (PAP) that exceeds the severity of respiratory impairment. These patients may have a clinical picture similar to more severe forms of PH and have greater mortality.

Recent studies provide evidence on the important role of the endothelial cell and its derived mediators in the pathogenesis of PH associated with respiratory diseases [1] and have presented the rationale for the potential use of agents that modulate endothelial function in the treatment of this condition.

We review the clinical relevance of PH, its pathogenesis, diagnosis, and management, in the setting of COPD and ILD, the two most common respiratory disorders presenting this complication.

Pulmonary Hypertension in COPD

Chronic obstructive pulmonary disease is defined as airflow obstruction that results from an inflammatory process affecting the airways and lung parenchyma. Changes in pulmonary vessels represent an important component of the disease in addition to the major abnormalities that take place in the airways and lung parenchyma. Alterations in vessel structure are highly prevalent, and abnormalities in their function impair gas exchange and result in PH, which is a major factor associated with reduced survival in COPD. Studies that reveal endothelial dysfunction at early disease stages have contributed to a better understanding of the pathogenesis of PH in this disease [2, 3] and have opened a potential new approach for its treatment.

Prevalence

The actual prevalence of PH, defined by mean PAP ≥25 mmHg [4••], in COPD is unknown, because it has not been screened systematically using right heart catheterization in the wide clinical spectrum of the disease. Hemodynamic studies involving a large number of subjects have been performed most commonly in patients with advanced COPD (stage 4 of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification) [5]. In this subgroup, the prevalence of PH is high, ranging between 30 and 50 % [6•, 7, 8]. Nevertheless, in the majority of patients, PH is of mild-to-moderate severity. Severe PH is rarely seen in COPD. In a retrospective study conducted in 998 COPD patients, Chaouat et al. [9] identified only 27 patients with mean PAP >40 mmHg. Whereas 16 of them had another disease capable of causing PH, in 11 (1.1 % of the whole group), COPD was the only cause. The latter group of patients had only moderate airway obstruction, but severe hypoxemia, hypercapnia, and very low CO diffusing capacity (DLCO). These findings indicate that there is a small subset of COPD patients with severe PH that share some clinical features with idiopathic pulmonary arterial hypertension (PAH) [10]. Similar results were obtained by Thabut et al. [8], who identified in a cluster analysis a subgroup of COPD patients characterized by moderate impairment of airway function and high levels of PAP, along with severe arterial hypoxemia.

In patients with less severe disease, the prevalence of PH is lower. Hilde et al. [11] reported a PH prevalence of 5 and 27 % in GOLD stages 2 and 3, respectively. Similar rates have been observed by Portillo et al. [12], who reported a PH prevalence of 7 and 25 % in GOLD stages 2 and 3, respectively. Among COPD patients who have normal PAP at rest, many demonstrate PH during exercise and/or the development of PH later during their disease course [13].

Prognostic Significance

The rate of PH progression in COPD is normally slow (an increase of mean PAP <1 mmHg/year) [14]. The presence of PH is a strong predictor of mortality in this population. Survival is inversely related to PH severity [6•, 9].

Echocardiographic signs of right ventricular dysfunction and electrocardiographic signs of right ventricular hypertrophy or right atrial overload are also predictive of reduced survival in COPD.

In addition to the prognostic significance in relation to survival, the presence of PH in COPD is associated with poor clinical evolution and more frequent use of health care resources. A mean PAP >18 mmHg is associated with an increased risk of hospitalization for COPD exacerbation [15]. In addition, the enlargement of pulmonary artery diameter seen on computed tomography (CT) also predicts hospitalization due to COPD exacerbation [16].

Pulmonary Vascular Remodeling

Remodeling of pulmonary vessels is a major cause of PH in COPD. It affects small and precapillary arteries and has been identified at different degrees of disease severity. The most prominent feature of pulmonary vascular remodeling is the enlargement of the intimal layer in muscular arteries [3, 17] (Fig. 1). Intimal hyperplasia is produced by the proliferation of smooth muscle cells (SMCs). In the arterioles, there is development of a medial coat of circular smooth muscle bounded by a new elastic lamina.

Intimal hyperplasia of pulmonary muscular arteries is apparent at all disease stages. In mild-to-moderate COPD, the majority of SMCs proliferating in areas of hyperplastic intima have a poorly differentiated phenotype, as shown by the lack of expression of contractile filaments that are characteristic of mature cells [18]. Changes in the tunica media are less evident [3, 17].

Remodeling of pulmonary arteries is not restricted to patients with an established diagnosis of COPD. Indeed, intimal thickening, the magnitude of which does not differ from that seen in patients with mild-to-moderate COPD, is also present in heavy smokers with normal lung function [18].

COPD is an inflammatory disease; hence, inflammatory cells might contribute to the alterations of pulmonary vessels. Patients with COPD have an increased number of inflammatory cells infiltrating the adventitia of pulmonary muscular arteries, as compared with nonsmokers. This inflammatory infiltrate is largely constituted by activated T lymphocytes, mostly CD8+. Interestingly, smokers with normal lung function also show an increased number of CD8+ T cells in the arterial adventitia, with a reduction of the CD4+/CD8+ ratio, as compared with nonsmokers, which does not differ from patients with mild-to-moderate COPD.

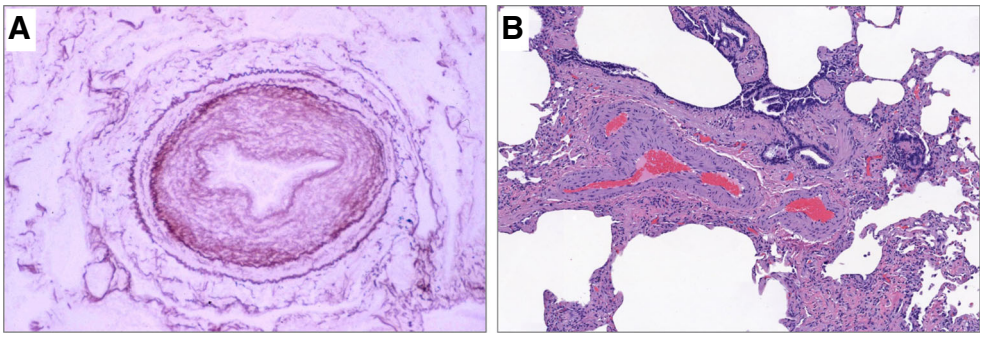

Fig. 1 **a** Photomicrograph of a pulmonary muscular artery from a patient with COPD showing prominent intimal hyperplasia and lumenal narrowing (Verhoeff-Van Gieson elastic stain, ×250). **b** Microscopic view of thickened precapillary arteries in idiopathic pulmonary fibrosis with areas of honeycombing (H&E, ×100). Images courtesy of Dr. J. Ramírez

Pathogenesis

As in other pulmonary hypertensive states, endothelial dysfunction of pulmonary arteries plays a crucial role in the pathogenesis of PH in COPD. This has been shown in patients with end-stage COPD [19] and also in patients with mild-to-moderate disease [3]. Impairment of endothelial function is associated with changes in the expression or balanced release of endothelium-derived vasoactive agents. The expression of endothelial nitric oxide synthase (eNOS) and prostacyclin synthase (PGI2-S) is significantly reduced in pulmonary arteries of COPD patients [20, 21]. Furthermore, the expression of some growth factors (vascular endothelial growth factor, VEGF) [22] or their receptors (transforming growth factor-β type II receptor) are upregulated in pulmonary arteries of COPD patients.

Hypoxia has been classically considered the main pathogenic mechanism of PH in COPD. However, its role is currently being reconsidered because pulmonary vascular remodeling and endothelial dysfunction can be observed in patients with mild COPD who do not have hypoxemia and in smokers with normal lung function [17, 18], and because long-term oxygen therapy does not fully reverse PH [23]. Furthermore, the relationship between PaO_2 and PAP is fairly weak.

Recent observations point out that cigarette smoke products might be at the origin of pulmonary vascular impairment in COPD [2]. This suggestion arises from the observation that smokers with normal lung function show remodeling in pulmonary arteries [18], impairment of endothelial function [3], reduced expression of eNOS [24], increased VEGF expression [22], inflammatory cell infiltrates [25], and gene expression of cytokynes and angiogenic mediators [26] that are indistinguishable from those seen in patients with mild-to-moderate COPD, and clearly different from nonsmokers.

Pathophysiology and Natural History

The current hemodynamic classification of PH associated with chronic respiratory diseases distinguishes three situations [4••]:

- Chronic respiratory disease without PH (mean PAP <25 mmHg)
- Chronic respiratory disease with PH (mean PAP ≥25 mmHg)
- Chronic respiratory disease with severe PH (mean PAP ≥35 mmHg or mean PAP ≥25 mmHg with low cardiac index (<2.0 L/min/m^2))

In COPD, PH is usually of low to moderate severity, and mean PAP rarely exceeds 35 mmHg. Cases of severe PH represent only 1–3 % of patients [8, 9]. Both right atrial pressure and pulmonary artery occlusion pressure tend to be normal, as well as the cardiac output.

At their initial stage, PH in COPD may not be apparent at rest but might develop during exercise [13]. Patients with exercise-induced PH are more prone to develop resting PH in the subsequent years [13].

Pulmonary hypertension in COPD progresses slowly over time, and its severity correlates with the degree of airflow obstruction and the impairment of pulmonary gas exchange [14]. Usually, the right ventricle (RV) has time to adapt to such a modest increase in afterload, although when PAP is chronically elevated the RV dilates. The stroke volume of the RV is usually maintained, whereas its ejection fraction decreases. Yet, in clinically stable patients, RV contractility lies within normal limits irrespective of the PAP value. Decreased RV contractility in COPD has been observed only during exacerbation episodes in patients presenting marked peripheral edema [24].

In clinically stable COPD, peripheral edema is not a sign of RV failure since it might be present in patients without evidence of reduced cardiac output [24]. In COPD, peripheral edema results from a complex interaction between the hemodynamic changes and the balance between edema-promoting and edema-protective mechanisms. In patients with PH associated with chronic respiratory failure, both hypoxemia and hypercapnia aggravate venous congestion by further activating the sympathetic nervous system, already stimulated by right atrial distension. Sympathetic activation decreases renal

plasma flow, stimulates the renin-angiotensin-aldosterone system, and promotes tubular absorption of bicarbonate, sodium, and water. Vasopressin also contributes to edema formation. It is released when patients become hyponatremic and its plasma levels rise in patients with hypoxemia and hypercapnia.

Evaluation and Diagnosis

Recognition of PH in COPD is difficult, especially in its mildest form, because symptoms due to PH, such as dyspnea or fatigue, are difficult to differentiate from the clinical picture of COPD. Furthermore, the identification of some clinical signs may be obscured by chest hyperinflation or the large swings in intrathoracic pressure. Cardiac sounds may be disturbed by the presence of bronchial rales or overinflated lungs, and the typical auscultatory findings of PH are uncommon in COPD patients.

The sensitivity of chest radiography to detect PH in COPD is low (<50 %) [27], and the most characteristic radiographic pattern is an increase in size of the pulmonary vascular hilum. Other signs are enlarged right ventricle, widening of the descending right pulmonary artery diameter, and encroachment of the retrosternal airspace by the right ventricle on the lateral view. If a high-resolution CT scan is performed, it shows the characteristic airway abnormalities and an increased diameter of the pulmonary artery.

The sensitivity of the electrocardiogram to detect PH in COPD is also low (51 %) [27], although the specificity is high (86 %). Nevertheless, electrocardiographic changes are not closely related to the severity of PH. In COPD, both the S1S2S3 pattern and signs of right atrial overload have been associated with shorter survival.

Lung function testing is mandatory for the diagnosis of COPD [5]. Unfortunately, there are no specific patterns of pulmonary function impairment associated with the development of PH. Pulmonary hypertension has little effect per se on lung mechanics. In conditions of preserved lung parenchyma, PH can reduce DLCO. However, in COPD, the latter cannot be attributed to PH since it can be caused by emphysema. Indeed, COPD patients with severe PH display very low values of DLCO, along with marked hypoxemia [9].

When PH is suspected in a COPD patient, an echocardiogram should be performed, although this technique can be difficult in COPD patients because the overinflated chest may alter sound wave transmission. Furthermore, a measurable tricuspid regurgitation (TR) velocity is less likely to be observed in COPD patients [28]. Even if a TR jet is observed, echocardiographic estimates of PAP are often inaccurate and result in both false positive and false negative diagnosis of PH. Compared with right heart catheter measurements, estimations of systolic PAP by echocardiography were found to be inaccurate in 52 % cases with COPD with a tendency to overestimate PAP [29]. Indeed, 48 % patients were misclassified as having PH by echocardiography [29, 30].

Systolic indices of tricuspid valve annular motion measured by tissue Doppler imaging appear to be useful for the prediction of right ventricular failure in COPD [31]. Furthermore, exercise echocardiography allows the identification of abnormal ventricular septal motion with distortion of left ventricle in COPD, findings that may help to detect occult right ventricular dysfunction [32].

Right heart catheterization is not routinely recommended in the assessment of patients with COPD. Its indication is restricted to selected cases when (1) evaluating for lung transplantation, (2) clinical worsening and progressive exercise limitation is disproportionate to ventilatory impairment, (3) progressive gas exchange abnormalities are disproportionate to ventilatory impairment, (4) an accurate prognostic assessment is deemed to be crucial, (5) severe PH is suspected by noninvasive measures and further therapy or inclusion in clinical trials or registries are being considered, and (6) there is suspicion of left ventricular dysfunction and categorization of wedge pressure might alter management [4••].

Sometimes, it is difficult to differentiate between PAH and PH associated with COPD in patients with very little airflow obstruction. In this situation, performing an incremental exercise test may help to identify those COPD patients where PH is related to their ventilatory disease. During the exercise test, COPD patients with PH may show features of exhausted ventilatory reserve, including reduced breathing reserve, normal O_2 pulse, normal CO/VO_2 slope, mixed venous O_2 saturation above lower limit and increase in $PaCO_2$ during exercise [4••].

Treatment

In patients with COPD and associated PH, the respiratory disease should be optimally treated according to existing guidelines [5]. Treatment addressed to ameliorate PH in COPD includes long-term oxygen therapy (LTOT) and vasodilators.

Long-Term Oxygen Therapy

Chronic hypoxemia plays a key role in the development of PH in COPD. Acute administration of oxygen exerts little effect on pulmonary hemodynamics in COPD, although when administered during exercise, it often improves pulmonary hemodynamics and RV performance [33].

It has been convincingly shown that LTOT prevents the progressive increase of PAP in COPD [34] and that when administered more than 18 h/day, it decreases progressively PAP [23, 35], although PAP values rarely return to normal. LTOT improves survival in COPD patients with chronic respiratory failure, although this effect is unrelated to the amelioration of pulmonary hemodynamics [34, 35]. Accordingly,

LTOT is the most appropriate treatment for PH in hypoxemic COPD patients since its administration slows down and, sometimes, reverses its progression.

Vasodilators

In COPD patients, systemic vasodilators, such as calcium channel blockers, may produce a slight improvement in pulmonary hemodynamics, but their administration is usually accompanied by worsening of gas exchange [36, 37] (Fig. 2), and there is no evidence that long-term treatment is of clinical benefit. For these reasons, they are not currently recommended for the treatment of PH associated with COPD. Selective pulmonary vasodilators, such as inhaled NO, can improve pulmonary hemodynamics but usually worsen hypoxia due to decreased ventilation perfusion matching [39, 40] and, if used, should be administered in combination with LTOT [41]. Despite some preliminary promising data, the long-term effect of selective vasodilators in terms of survival and symptom relief remains to be established.

Targeted PAH Therapy

Drugs used to treat PAH (prostanoids, ET-1 receptor antagonists, phosphodiesterase-5 inhibitors, and guanylate cyclase stimulators), which target the unbalanced release of endothelium-derived vascular mediators, improve symptoms, exercise performance, pulmonary hemodynamics, and survival in some forms of PAH. Their use in COPD might be justified on the basis of common pathogenic changes with PAH [42]; however, the limited clinical data available do not suggest a beneficial effect.

There is little information on the long-term use of intravenous epoprostenol in COPD [43]. The acute administration of epoprostenol worsens arterial oxygenation in patients with COPD due to the inhibition of hypoxic pulmonary vasoconstriction (HPV) [44]. The acute effects of inhaled iloprost have been evaluated in two studies. Dernaika et al. [45] evaluated 10 patients with COPD and a mean systolic PAP by echocardiography of 41 mmHg. The administration of 5 μg iloprost by inhalation resulted in improvement of exercise tolerance with no effect on gas exchange. In contrast, Boeck et al. [46] did not show any improvement in exercise tolerance with two different doses of iloprost, whereas gas exchange worsened at rest.

The effects of bosentan, a nonselective ET-1 receptor antagonist in COPD, were evaluated in a randomized controlled trial (RCT) [47] in patients with estimated systolic PAP ranging between 20 and 42 mmHg (Table 1). After 3 months of treatment, there were no changes in exercise tolerance or PAP assessed by echocardiography, whereas arterial oxygenation worsened significantly in the group treated with bosentan [47]. In a controlled, nonrandomized study, Valerio et al. [48] compared the effects of adding bosentan to conventional treatment in patients with COPD-associated PH, during 18 months. The study showed improvement in hemodynamics, 6-min walk distance (6MWD), and BODE index, with no deterioration in gas exchange [48] (Table 1).

In COPD patients, the acute administration of the phosphodiesterase-5 inhibitor sildenafil improves pulmonary hemodynamics but, at the same time, worsens gas exchange due to the inhibition of HPV [38•] (Fig. 2). Three RCTs with sildenafil have been recently reported (Table 1). Rao et al. [49] reported a decrease in PAP and increase in 6MWD in 33 COPD patients with PH treated with sildenafil during 12 weeks. In contrast, Lederer et al. [50], who evaluated 10 COPD patients without PH that were treated with sildenafil and placebo during 1 month with a cross-over design, did not find any effect on 6MWD or peak VO_2, whereas arterial

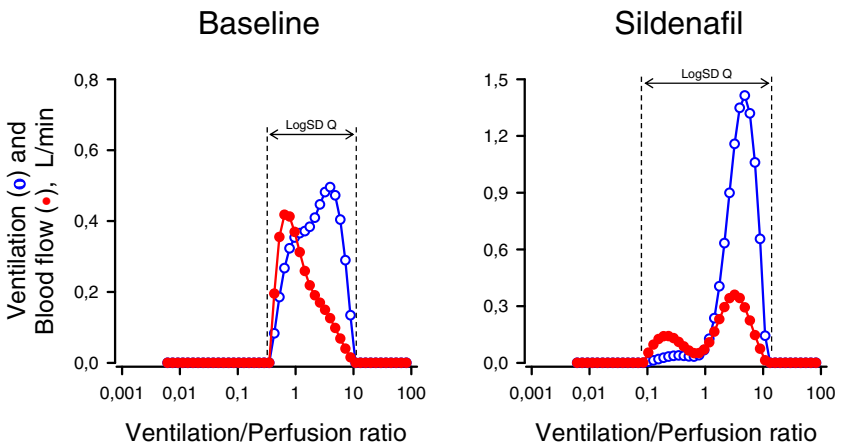

Fig. 2 Acute effects of sildenafil in patients with COPD and pulmonary hypertension on ventilation-perfusion (V_A/Q) relationships. Graphs show V_A/Q distributions, assessed with the multiple inert gas elimination technique, in a patient with COPD, at baseline and after 20 mg sildenafil. The amount of ventilation (*open blue* symbols) and blood flow (*solid red* symbols) in units with different V_A/Q ratios (log scale) in each condition are shown. Sildenafil diverted blood flow to units with low V_A/Q ratio with the development of a second mode in the blood flow distribution, thereby increasing its dispersion (LogSD Q) (Adapted from Blanco et al. [38•])

Table 1 Randomized controlled trials with targeted pulmonary hypertension therapy in COPD

Author (year)	Number	Drug dose	Follow-up	PH status	Primary end point	Results
Stolz [47] (2008)	30	Bosentan 125 mg bid	12 weeks	No PH	Δ6MWD	NS
Valerio [48] (2009)	32	Bosentan[a] 125 mg bid	18 months	Yes mPAP 37 mmHg	PAP, FC, 6MWD	↓PAP, ↓FC, ↑6MWD
Rao [49] (2011)	33	Sildenafil 20 mg tid	12 weeks	Yes sPAP 53 mmHg	6MWD	↓PAP, ↑6MWD
Lederer [50] (2012)	10	Sildenafil 20 mg tid	4 weeks	No PH	6MWD Peak VO_2	NS
Blanco [51•] (2013)	60	Sildenafil[b] 20 mg tid	3 months	Yes mPAP 31 mmHg	Endurance time	NS
Goudie [52•] (2014)	120	Tadalafil 10 mg qd	12 weeks	Yes mPAP 30 mmHg	Δ6MWD	NS

PH pulmonary hypertension, *PAP* pulmonary artery pressure, *sPAP* systolic PAP estimated by Doppler echocardiography, *mPAP* mean PAP assessed by right heart catheterization, *6MWD* distance covered in the 6-min walk test, *Peak VO_2* oxygen consumption at peak exercise, *FC* functional class, *bid* two times a day, *tid* three times a day, *qd* one time a day, *NS* not significant

[a] Unblinded

[b] Added to pulmonary rehabilitation

oxygenation and quality of life worsened during the sildenafil treatment period. A recent RCT of sildenafil added to a pulmonary rehabilitation program also failed to show improvement in exercise tolerance and quality of life in patients with severe COPD and moderate PH [51•] (Table 1). More recently, Goudie et al. [52•] reported the results of a RCT conducted in 120 patients with COPD and moderate PH, treated during 12 weeks with tadalafil (10 mg daily) or placebo. This trial failed to show any improvement in 6MWD. The effect of extended treatment (long-term) of targeted PAH therapy on oxygenation in patients with COPD is variable, with some studies demonstrating worsening of hypoxemia (Table 3).

In summary, LTOT is the treatment of choice in patients with PH associated with COPD who are hypoxemic. In the subgroup of patients who have severe PH, PAH-targeted therapy might be a consideration, although ideally this should be addressed in the setting of clinical trials. Using PAH-targeted therapy in patients with COPD and moderate PH is currently discouraged because there is no consistent evidence of efficacy in the RCTs published so far and there is compelling evidence indicating that these drugs might worsen pulmonary gas exchange.

Pulmonary Hypertension in Interstitial Lung Disease

Interstitial lung diseases (ILDs) consist of a group of diffuse parenchymal lung diseases that share similar clinical, radiologic, and pulmonary function characteristics, resulting from the damage of lung parenchyma by varying patterns of inflammation and fibrosis [55]. The majority of ILDs have been associated with PH, although its prevalence varies greatly depending on the underlying disease. The most extensive available data refer to idiopathic pulmonary fibrosis (IPF) associated PH.

Epidemiology

The prevalence of PH in patients with severe IPF ranges between 32 and 46 % [56–59]. PH is more prevalent in patients with worse lung function, although other factors including age, duration of the disease, need for supplemental oxygen, and reduced exercise tolerance are also associated with the presence of PH in IPF. Combined pulmonary fibrosis and emphysema is associated with a higher prevalence of PH [60].

In sarcoidosis, the presence of PH is often associated with advanced fibrotic disease and with the development of hypoxemia. One study reported a 28 % prevalence of PH in patients with sarcoidosis [56]. The prevalence of PH in other ILDs is unknown. It has been reported rarely in LAM and in Langerhans' cell hystiocitosis.

Combined Pulmonary Fibrosis and Emphysema

Combined pulmonary fibrosis and emphysema (CPFE) has been recently identified as a distinct clinical entity [60]. The prevalence of PH in this condition is very high, in the range of 60–70 % [60, 61], and its presence is associated with poor prognosis.

Although the pathophysiology of this condition is not well known, it has been related to smoking habit as tobacco is a common risk factor for both emphysema and fibrosis. CT scan shows a combination of emphysema in the upper zones and diffuse parenchymal lung disease with fibrosis in the lower zones. As compared with patients with isolated COPD or isolated IPF, patients with CPFE show severe dyspnea,

subnormal lung function, more severe impairment of gas exchange, higher prevalence of PH, and shorter survival [62].

In summary, when managing with patients with ILD, diagnosing this entity has clinical relevance, because it carries an increased risk of developing PH with increased mortality.

Prognostic Significance

The presence of PH has prognostic importance in IPF. The rate of PH progression in ILD is rapid as compared with COPD. Nadrous et al. [63] reported shorter survival in patients with IPF and systolic PAP >50 mmHg, assessed by echocardiography, than patients below this value. Furthermore, Lettieri et al. [56] showed that in patients with IPF listed for lung transplantation, the presence of PH was associated with greater mortality. Considering that mean survival after the diagnosis in IPF is only 3 years [64], the presence of associated PH represents a sign of very poor prognosis in this condition.

Pathology and Pathogenesis

There is probably no single pathologic mechanism that links ILD to PH. The vasculopathy of IPF consists of medial and intimal enlargement of pulmonary arteries (Fig. 1). In addition, intimal lesions can progress to fibrosis with the consequent luminal obliteration. Presumably, the most important mechanism involved in the pathogenesis of PH in IPF is the destruction of lung tissue, with the consequent loss of vasculature, and vessel fibrosis in the affected regions (Fig. 1). Fibrotic areas have markedly reduced vascular density, as shown by the absence of endothelial cell markers in fibroblastic foci [65].

A weak correlation between PAP and PaO_2 suggests a potential role of hypoxemia in the development of PH in IPF [66]. However, the pattern of vascular remodeling, the lack of reversibility with oxygen, and the presence of PH in patients with mild hypoxemia suggest that hypoxemia per se is not the only cause of this complication.

Alterations in the synthesis and release of certain endothelium-derived vasoactive mediators may be involved in the pathogenesis of IPF-associated PH. Among those, ET-1 appears to play a prominent role, since it is abundantly expressed in the lung tissue of patients with IPF [67]. It is interesting that ET-1 immunoreactivity and mRNA are present in pulmonary vascular endothelial cells in patients with associated PH [67]. Furthermore, patients with IPF have increased plasma levels of ET-1, and its concentration correlates with disease progression and the presence of PH [68].

Pathophysiology

Generally, in IPF, PH is of mild-to-moderate severity, with only few subjects developing severe PH, usually at the end-stage of the disease. In these patients PH may progress rapidly. Nathan et al. [69] reported an increase of mean PAP of 10± 8 mmHg in less than a year in patients with IPF listed for lung transplant. At the time of transplant, the prevalence of PH had doubled with respect to the period of evaluation, 86 and 39 %, respectively [69].

Pulmonary vascular involvement in ILD affects the efficiency of gas exchange. Agustí et al. [70] showed that the increase in mean PAP, along with the decline in PaO_2, and the impairment of V_A/Q distributions during exercise, was related to the severity of structural vascular changes.

Evaluation and Diagnosis

Similar to what occurs in COPD, clinical symptoms of PH appear late in the course of ILD and may be masked by the underlying pulmonary disorder. Suspicion of the disease might be raised by conventional examinations such as ECG, usually showing right ventricular hypertrophy and right atrial dilatation, and chest X-ray that may show proximal pulmonary artery and/or right ventricular enlargement.

In patients with ILD, the DLCO falls because of the enlargement of the interstitial space and the vascular disease [71]. In these patients, a reduction in DLCO disproportionate to the reduction in lung volumes might suggest underlying pulmonary vascular disease. Indeed, in IPF, the prevalence of PH is higher in subjects with DLCO values below 40 % predicted [55].

As in other conditions, Doppler echocardiography is the essential tool for the detection of PH. Nevertheless, its accuracy in ILD is low. In one study, only 40 % of echocardiographic measurements accurately reflected the value of systolic PAP, as compared with right heart catheterization measurements [57], with a trend to overestimate systolic PAP. The sensitivity of echocardiography in detecting catheter-proven PH was 73 % and the specificity 45 %, considering a cutoff value of systolic PAP >40 mmHg [57]. The diagnostic performance of Doppler echocardiography improved slightly when it was considered together with the 6MWD and the results of pulmonary function testing [57].

Accordingly, right heart catheterization is mandatory to confirm the diagnosis of PH in ILD. The procedure should be reserved for those patients in whom the result of the hemodynamic assessment will determine treatment options (e.g., listing or priorization for lung transplant) or cases potentially suitable for PAH-targeted therapy.

Treatment

There is no specific information on the hemodynamic effects of LTOT in patients with ILD and associated PH. Conceivably, LTOT might be of clinical benefit, especially in patients experiencing oxygen desaturation during exercise or nocturnal hypoxemia.

Table 2 Randomized controlled trials with targeted pulmonary hypertension therapy in interstitial lung disease

Author (year)	Disease	Number	Drug dose	Follow-up	PH status	Primary end point	Results
King [77] (2008)	IPF	158	Bosentan 125 mg bid	12 months	No PH	Δ6MWD	NS
Seibold [78] (2010)	SSc-ILD	163	Bosentan 125 mg bid	12 months	No PH	Δ6MWD	NS
IPFnet [54] (2010)	IPF	180	Sildenafil 20 mg tid	12 weeks	Unknown	↑6MWD >20 %	NS
King [79•] (2011)	IPF	616	Bosentan 125 mg bid	20 months	Unknown	Time to disease progression	NS
Raghu [80•] (2013)	IPF	178	Macitentan 10 mg qd	15 months	Unknown	ΔFVC	NS
Raghu [81•] (2013)	IPF	492	Ambrisentan 10 mg qd	35 weeks	10 % had PH	Time to disease progression	Negative[a,b]
Han [82] (2013)[c]	IPF	119	Sildenafil 20 mg tid	12 weeks	Based on RV hypertrophy or systolic dysfunction	Δ6MWD	Yes
Corte [53•] (2014)	IPF/NSIP	60	Bosentan 125 mg bid	16 weeks	Yes mPAP 36 mmHg	↓PVRI >20 %	NS

IPF idiopathic pulmonary fibrosis, *SSc* systemic sclerosis, *NSIP* non-specific interstitial pneumonia, *bid* two times a day, *tid* three times a day, *qd* one time a day, *PH* pulmonary hypertension, *mPAP* mean pulmonary artery pressure, *6MWD* distance covered in the 6-min walk test, *FVC* forced vital capacity, *PVRI* pulmonary vascular resistance index, *NS* not significant

[a] Worse in the ambrisentan-treated group

[b] Similar results in the subgroup with PH

[c] Substudy of the IPFnet study conducted in patients who had Doppler echocardiography

A number of trials have evaluated the effects of systemic vasodilators (hydralazine, calcium channel blockers) for the treatment of PH in ILD. All of them had negative results [72]. Regarding the effects of vasodilators on gas exchange in ILD, current data indicate that they may not produce further impairment in gas exchange, since the underlying mechanisms of hypoxemia differ from those in COPD [73].

Few studies have evaluated the efficacy of PAH-targeted therapy in patients with ILD and associated PH. Ghofrani et al. [74] evaluated the acute effects of inhaled NO, intravenous epoprostenol, and oral sildenafil in 16 patients with ILD-associated PH. Whereas all three agents decreased PVR, patients receiving intravenous prostacyclin experienced a decrease in PaO_2, largely because of an increase in V_A/Q mismatching. By contrast, the administration by inhaled route of the prostacyclin analogue iloprost resulted in a significant decrease of PVR without deteriorating pulmonary gas exchange [75].

The effects of bosentan have also been evaluated in IPF. Acutely, bosentan decreased PAP slightly without altering pulmonary gas exchange [76]. Nevertheless, the administration of bosentan during 3 months to patients with IPF and borderline PH (mean PAP, 22 mmHg) did not improve exercise tolerance [76]. Based on the potential role that ET-1 might have in the pathogenesis of IPF, the efficacy of bosentan was

Table 3 Long-term effects of targeted pulmonary hypertension therapy on gas exchange in lung disease

Author (year)	Disease	Number	Follow-up	PH status	Variable	Drug	Change from baseline	*P* value
Lederer [50] (2012)	COPD	10	4 weeks	Excluded	PaO_2	Sildenafil Placebo	+1 mmHg +5 mmHg	0.06
Blanco [51•] (2013)	COPD	60	3 months	Yes	PaO_2	Sildenafil Placebo	−3.6 mmHg −4.0 mmHg	NS
Goudie [52•] (2014)	COPD	120	12 weeks	Yes	SaO_2	Tadalafil Placebo	−0.9 % −0.7 %	NS
Stolz [47] (2008)	COPD	30	12 weeks	No	PaO_2	Bosentan Placebo	−4.5 mmHg −0.4 mmHg	0.03
Corte [53•] (2014)	IPF/NSIP	60	16 weeks	Yes	SaO_2	Bosentan Placebo	−0.8 % −0.5 %	NS
IPFnet [54] (2010)	IPF	180	12 weeks	Unknown	PaO_2	Sildenafil Placebo	−0.6 mmHg −3.6 mmHg	0.02

COPD chronic obstructive pulmonary disease, *IPF* idiopathic pulmonary fibrosis, *NSIP* nonspecific interstitial pneumonia, *NS* not significant

evaluated in a RCT conducted in 158 patients with IPF and normal PAP [77] (Table 2). After 12 months, patients treated with bosentan did not show greater exercise capacity, as compared with placebo, although there was a trend in delayed disease progression and improvement in quality of life [77]. More recently, a RCT with bosentan in patients with IPF or nonspecific interstitial pneumonia showed no difference in invasive pulmonary hemodynamics, functional capacity, or symptoms between the bosentan and placebo groups over 16 weeks [53•] (Table 2). The effects of ambrisentan were evaluated in a RCT conducted in almost 500 patients with IPF. An interim analysis indicated a low likelihood of showing efficacy for the primary end point, and ambrisentan-treated patients were more likely to meet the prespecified criteria for disease progression. A subgroup of 48 patients (10 %) with IPF and PH revealed similar results for the primary end point [81•]. For these reasons, the trial was prematurely terminated and regulatory agencies discourage the use of ambrisentan in patients with IPF. Macitentan, a novel endothelin-1 receptor antagonist, has also been evaluated in patients with IPF, showing no effect on forced vital capacity or time to IPF worsening or death [80•] (Table 2).

The effects of sildenafil were evaluated in an open-label study, conducted in patients with IPF and associated PH, that showed improved 6MWD [83]. In contrast, a RCT with sildenafil conducted in 180 patients with IPF failed to show any improvement in the 6MWD [54]. Nevertheless, a subanalysis in patients of the same cohort who had echocardiographic assessment of right ventricular function showed that in patients with IPF and right ventricular systolic dysfunction, sildenafil resulted in better preservation of exercise capacity and improvement in the quality of life, as compared with placebo [82].

A RCT with riociguat, a soluble guanylate cyclase stimulator, in ILD-associated PH is currently under way. Results of this trial will provide information on the potential usefulness of this new class of drug in ILD.

Long-term effects of PAH-targeted therapy on gas exchange in patients with ILD are shown in Table 3. Available data suggests that in ILD, they do not exert the deleterious effect on arterial oxygenation shown in COPD.

Pending on the results of ongoing trials, the use of targeted PAH therapy might be considered only in those cases of ILD with disproportionally elevated PH. As with COPD, patients who have severe PH in the setting of ILD should be considered for entry into clinical trials or registries and or referral to centers with expertise in PH and lung disease.

Conclusion

The development of PH is a poor prognostic sign in patients with chronic pulmonary diseases. For this reason, PH must be suspected early on the basis of disproportionate symptoms in patients with moderate ventilatory impairment. The treatment of choice in patients with hypoxemia is LTOT. Treatment with conventional vasodilators or drugs used to treat PAH is discouraged due to the lack of consistent efficacy observed in the majority of RCTs conducted so far, and because there is compelling evidence indicating that these drugs may worsen pulmonary gas exchange, particularly in COPD. The subgroup of patients with severe PH should be ideally managed in centers with expertise in both PH and chronic lung diseases and included in randomized controlled trials if available. Treatment with targeted-PAH therapy might be considered in patients with severe PH in a compassionate basis due to the poor prognosis of this condition, with careful monitoring of gas exchange and should be included in prospective registries.

Compliance with Ethics Guidelines

Conflict of Interest Joan Albert Barberà reports grants and personal fees from Actelion, Bayer, GlaxoSmithKline, and Pfizer. Isabel Blanco declares grants and personal fees from Actelion and Bayer.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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