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Review

Pulmonary hypertension in chronic obstructive and interstitial lung diseases

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ABSTRACT

The purpose of the present review is to summarize the current knowledge on PH in relation to COPD and ILD from a clinical perspective with emphasis on diagnosis, biomarkers, prevalence, impact, treatment, and practical implications.

PH in COPD and ILD is associated with a poor prognosis, and is considered one of the most frequent types of PH. However, the prevalence of PH among patients with COPD and ILD is not clear. The diagnosis of PH in chronic lung disease is often established by echocardiographic screening, but definitive diagnosis requires right heart catheterization, which is not systematically performed in clinical practice. Given the large number of patients with chronic lung disease, biomarkers to preclude or increase suspicion of PH are needed. NT-proBNP may be used as a rule-out test, but biomarkers with a high specificity for PH are still required.

It is not known whether specific treatment with existent drugs effective in pulmonary arterial hypertension (PAH) is beneficial in lung disease related PH. Studies investigating existing PAH drugs in animal models of lung disease related PH have indicated a positive effect, and so have case reports and open label studies. However, treatment with systemically administered pulmonary vasodilators implies the risk of worsening the ventilation–perfusion mismatch in patients with lung disease. Inhaled vasodilators may be better suited for PH in lung disease, but new treatment modalities are also required.

1. Introduction

PH is defined as a mean pulmonary artery pressure (MPAP) ≥ 25 mm Hg.

At present, PH is classified into five groups based on similarities in pathophysiology and clinical management [1]. Group 1 is pulmonary arterial hypertension (PAH). Group 2 encompasses PH related to left heart diseases, group 3 PH related to lung diseases, group 4 chronic thromboembolic PH, and group 5 other types of PH. Group 1 PAH is relatively rare compared to group 2 and 3 PH which are considered the two largest groups, because of the frequent occurrence of left heart disease and lung diseases in the Western World [2]. However, the prevalence of PH in relation to chronic obstructive lung disease (COPD) or interstitial lung disease (ILD) is not clear due to the large number of patients and the invasive character of right heart catheterization (RHC) which is needed to ensure correct diagnosis of PH.

Currently, specific pulmonary vasodilators which target endothelial dysfunction in PAH exist, but have so far only been proven beneficial in group 1 PH [1,3]. However, evidence of endothelial dysfunction has also been shown in patients with PH related to chronic lung disease [4–6]. The literature suggests that existent pulmonary vasodilators may have beneficial effects, but on the other hand, systemic drug administration may induce vasodilation in poorly ventilated regions of the lungs [7] and lead to impaired ventilation/perfusion (V/Q) mismatch which can deteriorate the clinical condition. Therefore, administration by inhalation [8,9] and new types of drugs would be interesting to investigate.

The purpose of the present review is to summarize the current knowledge on PH in relation to COPD and ILD from a clinical perspective with emphasis on diagnosis, biomarkers, prevalence, impact, treatment and practical implications.

2. COPD and ILD

COPD is a very common disease. The prevalence varies in different geographic regions and increases with age [10]. Under-recognition of COPD, studies conducted in different age groups, and focusing on the presence of various degrees of COPD, makes it hard to conclude on the

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overall burden of COPD. However, the global prevalence has been estimated to approximately 9–10% in populations aged 40 years or more [11]. The treatment of COPD consists of smoking cessation, education, rehabilitation and pharmacological treatment targeting bronchoconstriction and inflammation, including β-adrenoceptor agonists, anticholinergics, corticosteroids, methylxanthines and phosphodiesterase type 4 (PDE-4) inhibitors [10]. In addition, long term oxygen treatment is administered to patients with hypoxemia, and lung volume reduction can be considered to relieve symptoms caused by air trapping in severe emphysematous lungs [10]. Despite the available treatments, COPD is estimated to become the third leading cause of death worldwide in 2020 [10].

ILDs are a heterogeneous group of diseases classified according to etiology and histology [12]. ILD can be caused by medication such as amiodarone, nitrofurantoin and bleomycin, by exposure to inorganic or organic dusts, or can be associated with connective tissue diseases such as scleroderma or rheumatoid arthritis [12]. In a large number of cases, the etiology is unknown, and the ILD is referred to as idiopathic. Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic ILDs [13]. The incidence of IPF has been estimated to be between 6.8 and 16.3 per 100,000 persons in the USA, but the prevalence and incidence of the whole spectrum of ILDs are unknown [14]. Currently, many ILDs are treated with immunosuppressive agents, despite lack of evidence [13]. In IPF, several trials with drugs targeting inflammation and fibrosis, for example corticosteroids, azathioprine, cyclophosphamide and INF-γ, antioxidants such as N-acetylcysteine and drugs targeting receptors suggested to promote fibrosis, e.g. the endothelin-1 antagonist bosentan, have not been able to prove favorable effects [13]. However, the anti-fibrotic agent pirfenidone seems to have a modest effect on the disease progression in IPF patients [15], and is now used for IPF in Europe. The prognosis of the different ILDs differ significantly [12]. IPF has the worst prognosis with a median survival of approximately three years [16].

All together, COPD and ILD cause extensive morbidity and mortality in the Western world. Currently, COPD and the majority of ILDs are not curable and any new treatment strategy to improve the clinical condition in the affected patients would be beneficial.

3. Pathoanatomy and pathophysiology of PH in COPD and ILD

In COPD patients with mild PH, histopathology seems to be dominated by intimal thickening of the pulmonary arteries [17], which can be found even in smokers with no evidence of COPD [4]. In COPD patients with more severe PH, medial hypertrophy is also present [17].

In ILD, pathoanatomic changes vary throughout the lungs in concert with fibrotic and non-fibrotic areas [18]. In IPF, fibrotic areas show a decreased number of vessels, whereas the number is increased in adjacent non-fibrotic tissue. The vascular changes are diverse, ranging from thickening of the muscular layer to vessels fully occluded by fibrous tissue and plexiform lesions [18] consisting of abnormally proliferated endothelial cells.

Hypoxic pulmonary vasoconstriction is considered a major driver of the development of PH in COPD and ILD [19]. In addition, evidence of endothelial dysfunction has been found in arteries from both COPD [4,5] and ILD [6] patients. For example, relaxation to acetylcholine, which stimulates endothelial release of NO and other relaxant factors, was decreased in pulmonary arteries from patients with COPD [20]. In IPF, levels of ET-1 in bronchoalveolar lavage fluid are increased [21], and in mice with bleomycin induced pulmonary fibrosis, treatment with sildenafil attenuated both the development of lung fibrosis and pulmonary hypertension [22]. Thus, it is plausible that endothelial dysfunction could be implicated in pulmonary vascular disease in both COPD and ILD. Furthermore, inflammatory infiltration of the vessels [23], abnormal angiogenesis [18] and mechanical pressure from fibrosis or hyperinflation may play a role [19]. These pathophysiological mechanisms have recently been discussed in more details [18,24]. In short, several factors contribute in complex and possibly self-enhancing interrelations (Fig. 1).

4. Diagnosis of PH in COPD and ILD

4.1. Clinical and paraclinical signs

The presence of PH in COPD and ILD is difficult to determine clinically, because dyspnea is the cardinal symptom in all of the conditions. Signs of PH on X-ray and right axis deviation on ECG are not specific for PH, and in mild PH, they are often absent [1]. Overt signs of right ventricular failure are also late manifestations. Low arterial oxygenation, and a poor 6MWT [25] should increase suspicion of PH [26–29]. African–Americans seem to have a higher propensity for PH [30].

4.2. Lung function parameters

There is an association between a low diffusion capacity (Dlco) [26] and the presence of PH in COPD [31] and ILD [29]. Although Dlco can be decreased in ILD or COPD without PH, the presence of PH was increased two-fold in IPF patients with a Dlco <30% [32]. Furthermore, among patients with COPD and ILD with severely reduced diffusion capacity corrected for alveolar volume (<40% of predicted), the prevalence of PH was high [33]. This agrees with the fact that Dlco is often decreased in PAH per se [1], and PH should be suspected in patients with a Dlco lower than expected from the derangement in other lung-function parameters.

The correlation to other lung function parameters may be poor [29,31]. In a study at a PH referral center, COPD patients with severe PH even had higher values of forced expiratory volume in 1 s (FEV1) than patients with mild PH [31].

4.3. High resolution computed tomography (HR-CT

On HR-CT, PH may be revealed by an increased size of the main pulmonary artery, but studies have shown that this finding was poorly correlated to MPAP in IPF patients [34]. However, HR-CT is important for classification of PH, because patients with severe precapillary PH, severe emphysema on high-resolution computed tomography, and normal spirometry have been described [35]. Therefore, HR-CT should be performed before excluding the diagnosis of PH related to lung disease. Furthermore, patients with combined fibrosis and emphysema on HR-CT have been shown to have a high propensity for PH [36] and a poor prognosis [37], which make these patients important to diagnose correctly.

4.4. Echocardiography

The best non-invasive diagnostic method for detection of PH is echocardiography [1]. The systolic pulmonary arterial pressure (SPAP) can be estimated measuring the peak velocity of a tricuspid regurgitation jet during systole. Applying the velocity (V) into a modification of the Bernouilli equation renders the SPAP: SPAP = $4v^2$ + right atrial pressure (RAP). In patients with chronic lung disease, hyperinflated or fibrotic lungs may hamper echocardiographic visualization of the heart. Several studies have shown both over- and underestimation of the echocardiographic SPAP when compared to direct measurements done by RHC [38,39]. There is currently no consensus about the upper normal limit of SPAP, or about what cut-off level of SPAP is optimal for the prediction of PH. In general, values above 36 mm Hg have been suggested to indicate that PH is possible [1], while values above 50 mm Hg indicate that PH is likely [1]. An examination for PH should not be solely relied on estimation of the SPAP, but rather on an overall judgment of the right heart

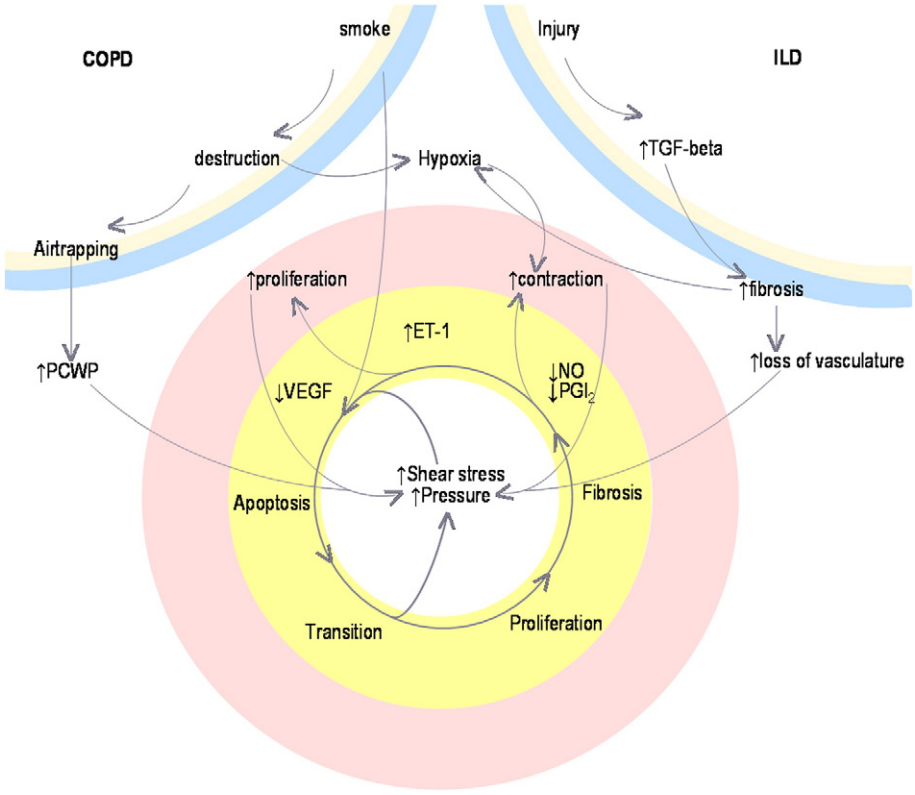

Fig. 1. Some of the proposed mechanisms contributing to PH in COPD. BMSC: bronchial smooth muscle cells, VSMC: vascular smooth muscle cells, VEGF: vascular endothelial growth factor, ET-1: endothelin-1, NO: nitric oxide, PGI_2: prostacyclin, TGF-β: tumor growth factor-β, PCWP: pulmonary capillary wedge pressure. Yellow: endothelium, Pink: vascular smooth muscle cells, Blue/Sand: respiratory wall.

including assessments of right ventricular dilatation and right ventricular function measured by the tricuspid annular plane systolic excursion (TAPSE) [39].

A study in patients with advanced lung disease showed that the sensitivity for PH using a combination of an SPAP above 45 mm Hg and right heart abnormalities seems to be good in patients with advanced COPD and ILD [40], and echocardiography may be regarded as a fairly, but not 100% safe method to exclude PH. It is important to notice that exacerbations of the underlying disease can temporarily increase the SPAP, and therefore echocardiography should be conducted in a stable phase. A period of 6 weeks without exacerbation is often used in clinical studies. The specificity of echocardiography in patients with lung disease tends to be low [40]. Thus, if echocardiography is suggestive of PH, the diagnosis should be confirmed by RHC, which is the only means to establish the final diagnosis [1].

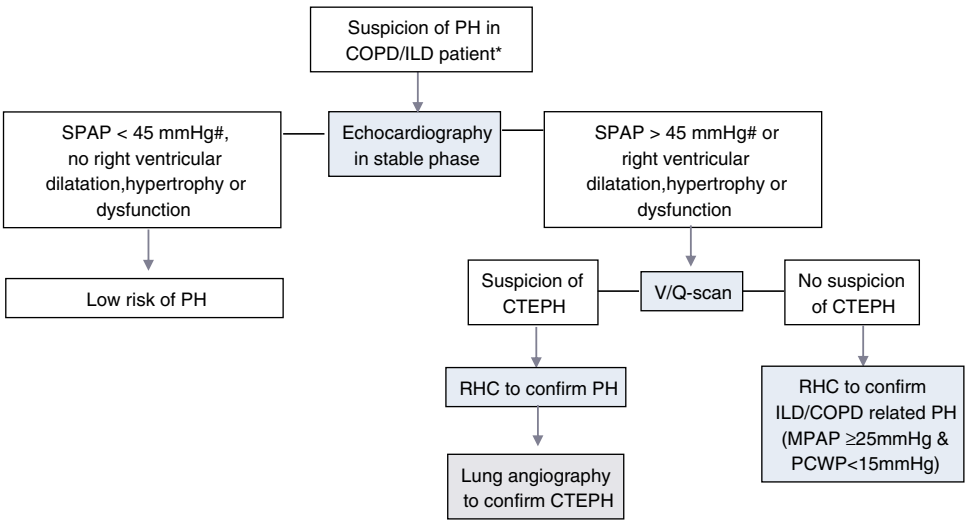

Fig. 2. Proposed algorithm for diagnosing PH in COPD and ILD. *A lower Dlco, PaO_2 or 6MWT than expected from the degree of impairment in other lung function parameters and parenchymal involvement on HR-CT, as well as overt signs of right ventricular failure, should increase suspicion, while a value of NT-proBNP < 95 ng/l reduces the probability of PH. #Note that there is no consensus about the cut-off level of SPAP that should elicit RHC. CTEPH: chronic thromboembolic pulmonary hypertension, Dlco: diffusion capacity, HR-CT: high resolution computed tomography, MPAP: mean pulmonary artery pressure, PaO_2: arterial oxygen pressure, PCWP: pulmonary capillary pressure, PH: pulmonary hypertension, PVR: pulmonary vascular resistance, RHC: right heart catheterization, SPAP: systolic pulmonary artery pressure, V/Q: ventilation/perfusion.

4.5. Ventilation/perfusion (V/Q) scan

Patients with COPD and ILD are at risk of thromboembolic disease [41,42], and if echocardiography suggests PH, V/Q scan to detect chronic thromboembolic PH (CTEPH) as surgical removal of thrombotic masses can potentially cure this type of PH [43]. Pulmonary angiography should be undertaken to confirm the diagnosis of CTEPH as depicted in Fig. 2.

4.6. RHC

By RHC, measurements of MPAP, PCWP and cardiac output (CO) can be obtained. MPAP and PCWP are affected by the intra thoracic pressure, which is often increased in pulmonary disease. This tends to raise PCWP with a risk of misclassifying the patient. Measuring end-expiratory values will diminish, but not eliminate the effect of increased intra-thoracic pressure. However, the transpulmonary pressure gradient and the pulmonary vascular resistance (PVR), which is one of the most important descriptors of pulmonary artery involvement will be correct. Importantly, CO also gives information about the degree of right ventricular deterioration.

A suggested algorithm for diagnosing PH in COPD and ILD can be seen in Fig. 2.

5. Biomarkers for PH in chronic lung disease

Due to the large number of patients with lung disease, particularly with COPD, clinical signs or biomarkers to select patients to examine further for PH, would be useful.

5.1. Brain natriuretic peptides

The only biomarkers that are currently used in practice in the field of PAH are brain natriuretic peptide (BNP) and N-terminal BNP (NT-proBNP) [1]. BNP and NT-proBNP are peptides of respectively 32 and 76 amino acids, cleaved from proBNP upon secretion into the blood stream. BNP is the active fragment and evokes vasodilatation, natriuresis and anti-fibrotic effects through activation of the membrane bound guanylyl cyclase. NT-proBNP is inactive [44,45]. The BNPs are secreted from the cardiac ventricles in response to increased workload, and it has been established that the main source of circulating BNP and NT-proBNP is the heart [44–46]. The evidence for the use of NT-proBNP as a prognostic marker for left ventricular failure [47] and PAH is significant, and NT-proBNP is accepted as a biomarker for these diseases in clinical practice [1,47].

In chronic lung disease, BNP with a cut-off value of 33.3 pg/ml has shown to have a high sensitivity and specificity for the presence of moderate to severe PH (MPAP > 35 mm Hg) [48,49]. However, the brain natriuretic peptides may not be elevated above upper normal limit in mild PH [50], and probably due to the presence of cardiac co-morbidity in especially COPD [51] which can also cause increases in BNPs, the specificity of the peptides may be low. It seems that low values (<93–95 ng/l) may exclude the presence of PH in patients with lung disease [51–53], suggesting that NT-proBNP may be suited as a rule-out test for PH in chronic lung disease (Fig. 2).

Interestingly, it has been shown that COPD patients with levels of NT-proBNP > 220 pmol/l strongly raised the 30 day mortality in acute exacerbations (OR 9, p > 0.001) [54] and NT-proBNP may thus be considered a strong prognostic factor in COPD patients with acute exacerbations.

5.2. Other proposed biomarkers

Troponin-T is released upon myocardial strain or injury and has been shown to be higher in ILD patients with PH [52]. Furthermore, the level of troponin-T has prognostic value in ILD patients [52] and in COPD patients with acute exacerbations [54,55]. In the abovementioned study, COPD patients with both elevated troponin-T and NT-proBNP had a 15-fold increased 30-day mortality risk [54].

Since cardiac involvement is secondary to the elevations of pulmonary pressure, biomarkers originating from the pulmonary arteries or parenchyma would intuitively be better suited to detect early PH. In patients with iPAH and chronic thromboembolic PH, plasma concentrations of endothelin-1 have been shown to correlate to the pulmonary arterial pressure [56,57]. In a study of 11 ILD patients, high ET-1 concentrations were related to the presence of PH [58], and a study based on echocardiography to detect PH in COPD patients, ET-1 levels also correlated to higher SPAP [59]. In the same study [59], exhaled NO was lower in patients with PH, while exhaled NO in a study of ILD patients did not correlate to PH [52]. Measurements of exhaled NO are dependent on exhaled airflow velocity, and different methods may yield various results. Asymmetrical dimethylarginine (ADMA) is an inhibitor of the nitric oxide synthase, and is elevated in idiopathic PH, thromboembolic PH, scleroderma-related PH and PH related to congenital heart disease [60–63] In patients with scleroderma, increased levels were found in patients with PH and were related to a poorer functional capacity. On the other hand, ADMA was not related to whether the patients had pulmonary fibrosis or not [60], indicating that ADMA might also be used to predict the presence of PH in patients with ILD.

Von Willebrand Factor (vWF) is an endothelium-derived molecule that enhances the adhesion of coagulation factors to the vessel wall. In accordance with the fact that disturbances in coagulability plays a role in PH, vWF has been shown to have conformational changes and to circulate in higher concentrations in patients with PH [64–66]. In addition, altered concentrations of the split product of fibrinogen, D-dimer, has been related to the presence and severity of PAH [67], but showed no relation to the presence of PH in ILD patients [52].

The peptide apelin has been shown to be present in pulmonary arteries, and may affect tone and angiogenesis in pulmonary arteries [68]. Apelin has also been shown to be downregulated in PAH [68,69], but is also altered in parenchymal lung disease and in hypoxic conditions, which may limit the specificity of apelin to detect PH [68].

In short, NT-proBNP is so far the best evaluated biomarker for PH in chronic lung disease, but lung derived biomarkers to detect early changes in the pulmonary arteries would be beneficial.

6. Prevalence of PH in COPD and ILD

The reported prevalence of PH in COPD patients has varied substantially in different studies [26,27,70–73]. Several studies have been performed on lung transplant candidates [28,73–75]. The advantages of these studies are that they are based on a firm diagnosis of PH established by RHC, which is performed routinely in lung transplant candidates. On the other hand, lung transplant candidates are very highly selected patients with particularly advanced lung disease, in whom PH is expected to occur more frequently. This idea is supported by a small study showing that PH occurred more frequently in COPD patients with more advanced lung disease [76]. In the studies with lung transplant candidates, PH defined as an MPAP ≥25 mm Hg, has been reported in 23% to 36% of the patients [28,74,75], while 91% of emphysematous lung transplant candidates had an MPAP ≥20 mm Hg [72]. This definition of PH has also been used in other studies from the 1990s with non-lung transplant candidates in which the prevalence was 20–35% [70,71]. In more recent studies, a prevalence of 60% in stable out-patients was found in a study based on echocardiography with the presence of PH defined by an SPAP ≥ 36 mm Hg [77]. In contrast, a study showed that 14% of 117 stable COPD out patients were screened positive by echocardiography using the criteria of a tricuspid regurgitation pressure of 40 mm Hg or right ventricular abnormalities [51]. However, only three out of six had the diagnosis confirmed on RHC, in line with the previously mentioned low positive predictive value of

echocardiography in COPD. PH in COPD is mostly mild, and only about 1–5% of COPD-lung transplant candidates has severe PH, arbitrarily defined by an MPAP above 35–40 mm Hg [31,78].

In ILD, studies investigating the occurrence of PH have focused on lung transplant candidates with IPF [79,80], patients with sarcoidosis [81,82], or scleroderma related ILD [83] These studies have suggested a prevalence of PH from 21% in patients with ILD associated to connective tissue disease to 48% in IPF transplant candidates [80] and 74% in sarcoidosis lung transplant candidates [82]. A study enrolling patients with various ILD diagnoses at a tertiary referral center, showed a prevalence of PH of 14%, indicating that the overall burden of PH is large [29]. The severity of PH is not well-described, it is probably most often mild, although pulmonary pressures can reach systemic levels [18].

In short, the prevalence of PH in COPD and ILD is unclear, and will probably remain unclear unless RHC is implemented routinely at diagnostic evaluation.

7. Clinical impact of PH in COPD and ILD

Comorbidities in COPD and ILD are generally a large problem. Cardiovascular diseases such as coronary artery disease, and obstructive sleep apnea are more common than PH in COPD and ILD [84,85], and also play an important role for the morbidity and mortality of these patients in concert with osteoporosis, gastro-esophageal reflux disease, hypertension, and metabolic syndrome. These comorbidities have recently been reviewed [84,85].

7.1. Impact of PH on mortality

Already in the 1970s, it was observed that the presence of PH was associated with a high mortality in COPD-patients [86], and during the following decades this was confirmed by several other studies [87–90]. Recently, a study showed that COPD patients with MPAP above 40 mm Hg had a significantly higher mortality than patients with COPD and mild-to-moderate PH defined as an MPAP between 25 and 39 mm Hg [31].

Prior studies have also shown that the presence of PH worsens the prognosis in selected groups of ILD patients with IPF or scleroderma related ILD [79,91,92]. In a study across various ILD diagnoses, the hazard ratio for death in ILD out patients with PH was approximately 8 compared to non-PH patients [29]. In a study by Hamada et al. [92] in IPF patients of whom only 5 patients had MPAP above 25 mm Hg, the best cut-off value of MPAP for prediction of mortality was 17 mm Hg. In the multivariate analysis, only Dlco turned out to be an independent predictor of death, indicating that mild PH per se did not increase mortality. However, given that PH can lower Dlco, the effect of PH may be masked in a multivariate analysis including Dlco.

Comparing PH related to chronic lung disease with other types of PH at a PH referral center, PH in chronic lung disease had a significantly worse prognosis than PAH [93]. Patients with ILD-related PH had a three-year survival of only 16% which was significantly worse than a three year survival of 41% in COPD-related PH [93]. These results emphasize the severity of PH related to lung disease, and especially to ILD. The aggravated prognosis of PH in ILD may in part be attributed to the poor prognosis of the underlying disease, especially in the case of IPF [12]. Furthermore, the prevalence of severe PH seems to be higher in severe ILD [80] than in COPD [26,73]. This might be explained by an overlap of pathophysiological factors, such as elevated ET-1 and TGF-β which play a role in both IPF and PAH [18,94].

7.2. Exercise capacity

Reports on the effect of PH on exercise capacity in COPD are somewhat conflicting. Some studies have found that PH is a limiting factor of the performance in exercise tests such as the 6MWT [75] and the cardiopulmonary exercise test (CPET) [95], while another study [96] showed no differences in 6MWT between COPD patients with or without moderate PH defined by an MPAP > 30 mm Hg. Since PH may be related to more severe lung disease, it is important to correct the effect of PH on exercise capacity for lung function, and this approach resulted in a small (6 m), but significant, difference in 6MWT between patients with and without PH in a study in lung transplant candidates [74]. Importantly, a study in COPD patients has shown that in patients with mild to moderate PH, exercise seemed to be limited by ventilation capacity, while in patients with severe PH defined by MPAP > 40 mm Hg, exercise was apparently limited by an exhausted circulatory reserve [97].

Studies investigating ILD patients agree that exercise capacity is lower in patients with PH, but adjustment for other influencing variables of the effect of PH on 6MWT has not been performed in most of them [48,98–102]. In accordance with the study in COPD patients [97], ILD out patients with severe PH (MPAP > 35 mm Hg) had a significantly lower 6MWT compared to those without PH after correction for lung function, age, sex and BMI, where as those with mild PH did not have a significantly shorter 6MWT, indicating that only severe PH restricts exercise capacity per se. A significant number of those with severe PH had echocardiographic signs of right heart failure.

In short, PH related to chronic lung disease has a poor prognosis compared to other types of PH, and the presence of PH indicates a poor prognosis in ILD or COPD, with an increasing adverse effect with increasing severity of PH. However, only severe PH seems to restrict exercise capacity per se by impairing cardiac function. This speaks in favor of specific treatment of PH with off-loading of the RV in patients with severe PH. On the other hand, in patients with mild PH with symptoms caused by impaired ventilation, pulmonary vasodilation may not relieve symptoms, but aggravate V/Q mismatch.

8. Treatment

In line with the traditional view of hypoxia as the primary cause of PH in COPD and ILD, hypoxia must be treated with long term oxygen treatment [103]. Furthermore, optimal treatment of the underlying lung disease is important. However, with the knowledge of endothelial dysfunction in PH associated to COPD and ILD, and the emergence of the pulmonary vasodilators used in PAH, interest about the usefulness of these drugs in lung disease-related PH has come forward.

Presently, three classes of specific pulmonary vasodilators are used in clinical practice to treat PAH, namely phosphodiesterase-5 (PDE-5) inhibitors, ET-1 antagonists or prostacyclin analogs.

8.1. PDE-5 inhibitors

PDE-5 inhibitors inhibit the breakdown of cyclic guanylyl monophosphate (cGMP) which is the second messenger downstream to NO. These drugs primarily target the pulmonary circulation because the concentration of PDE-5 is very high in the lungs [104]. The PDE-5 inhibitors used for PAH count sildenafil and tadalafil which differ somewhat with respect to selectivity for the different subtypes of phosphodiesterases and pharmacokinetics. Sildenafil was the first drug on the market, and several animal studies have shown a beneficial effect of sildenafil in models of PH related to lung disease; a positive effect has been shown in rats with hypoxia induced pulmonary hypertension [105–107] and in rats with bleomycin induced pulmonary fibrosis and PH [22]. In addition, in vitro studies in cultured human pulmonary endothelial cells showed that sildenafil ameliorated endothelial cell function after exposure to cigarette smoke extracts [108].

In humans, the acute effects of sildenafil has been studied in patients with lung fibrosis and PH [109], in which sildenafil was shown to decrease the pulmonary pressure selectively without impairing the match between ventilation and perfusion (V/Q). However, in COPD patients with MPAP > 20 mm Hg [7], sildenafil worsened the V/Q mismatch

and resulted in lower arterial oxygen pressure in some of the patients at rest. On the other hand, sildenafil decreased the pulmonary pressure both at rest and during exercise capacity [7].

In a retrospective study, forty-three COPD patients with severe PH at a PH referral center were treated with PAH-drugs [31]. Sildenafil was used in the majority of patients. There was no difference in mortality between those treated with PAH drugs and those not treated. However, those who were treated had more advanced PH and COPD. Other open-label studies or case-reports suggest a beneficial effect of sildenafil [110,111]. Controlled long-term studies of the effect of sildenafil in PH related to lung disease are yet to come. From the point of view that some degree of PH is present in many COPD patients, at least during exercise, the effect of three months of treatment with sildenafil [112] has been investigated in patients with COPD. However, patients were not selected on the basis of the presence or absence of PH. This study showed no effect on exercise capacity or stroke volume during exercise. In the same manner, sildenafil was tested in IPF patients with advanced fibrosis, but also without knowledge about the patients' PH status [113]. This trial was negative with respect to the primary end-point, which was the 6WMT, but showed some positive trends in some of the secondary end-points towards a beneficial effect of sildenafil. Thus, this trial actually encourages further investigations in patients with a firm diagnosis of PH rather than it eliminates an effect of sildenafil in IPF-related PH.

8.2. Endothelin-1 antagonists

ET-1 exerts vasoconstriction and stimulates cell proliferation through activation of the ETA receptor which is localized in the vascular smooth muscle cells. ET-1 also binds to the ETB receptor which is situated in vascular smooth muscle where it evokes vasoconstriction, but the ETB receptor is also situated in vascular endothelial cells, where it stimulates release of NO and prostacyclin [114]. The currently approved ET-1 receptor antagonists for PAH are the non-selective ETA and ETB receptor antagonist bosentan, and the selective ETA receptor antagonist ambrisentan.

Bosentan was the first developed ET-1 receptor antagonist, and experimental studies have shown that bosentan inhibits the development of PH in chronic hypoxic rats [115] and in bleomycin induced PH [116]. Also, in human pulmonary arteries, exposure to smoke extracts resulted in up-regulation of ETA and ETB receptors, proliferation and increased vasoconstriction. These effects were counteracted by bosentan [117].

A beneficial effect of bosentan treatment in patients with ILD and PH has been observed in case-series [118,119]. In COPD patients who were not selected on behalf of the presence of PH, three months of treatment with bosentan did not improve exercise capacity, and an impairment of arterial oxygenation was observed [120]. However, in a study in COPD patients with a diagnosis of PH confirmed by RHC, 18 months of treatment with bosentan improved the 6 minute walk test without worsening arterial oxygenation [121]. This study had 16 completing patients in the treatment and the placebo group, respectively, and was randomized, but not double-blinded. However, it suggests a positive effect, and should encourage larger scale studies in COPD patients with a firm diagnosis of PH.

8.3. Prostacyclin analogs

Epoprostenol, treprostinil and iloprost are prostacyclin analogs used for PAH [1]. Epoprostenol has a very short half-life and is administered by continuous IV infusion. Treprostinil has the longest half-life of the parenteral formulations. Both treprostinil and iloprost and can be administered by IV or SC injection as well as by inhalation. The prostacyclin analogs interact with IP-receptors in the pulmonary and systemic vasculature, through which they induce vasodilation, and inhibit cell proliferation and in situ thrombosis.

Given the presence of IP-receptors in the systemic circulation, hypotension is a known adverse effect of the prostacyclins. Furthermore, similar to the PDE-5 inhibitors and ET-1 antagonists, systemic administration of prostacyclin holds the risk of vasodilation in poorly ventilated areas with a resultant intrapulmonary shunt and hypoxemia. IV infusion of prostacyclin has been compared to inhaled prostacyclin in patients with pulmonary fibrosis [122]. Administered by IV infusion, prostacyclin decreased the pulmonary pressure, but also the systemic pressure and the arterial oxygen level. Given by inhalation, however, a selective pulmonary pressure reduction without worsening of the V/Q mismatch was observed. In line with this, 10 males with COPD and echocardiographic indices of PH inhaled iloprost, and an increase in 6 minute walk test was observed afterwards, while arterial blood gases were unaltered [8]. However, the study was not blinded or placebo controlled. It is, though, logically plausible that inhaled delivery of pulmonary vasodilators may be better suited for PH in relation to lung disease, in order to direct the drugs to oxygenated lung sections.

8.4. Other potential pharmacological treatments for PH related to lung disease

In addition to inhaled formulations of existent pulmonary vasodilators, drugs targeting the abnormalities of angiogenesis in COPD and ILD such as VEGF are interesting. VEGF may, however, promote lung fibrosis [123], limiting its use. The peptide apelin modulates the response to ET-1 in isolated lung arteries [124] and it has some similarities with VEGF, which makes apelin interesting to investigate further in PH related to lung disease [68].

It may also be possible that other already existing drugs may have an effect in PH related to lung disease. The PDE-4 inhibitor roflumilast which is a relatively new agent used for COPD is interesting with regard to treating the vascular component of chronic lung disease. It is targeted against neutrophilic inflammation in COPD, but due to inhibition of PDE-4, the breakdown of cAMP in vascular smooth muscle is also to be expected. In line with this, roflumilast has been shown to attenuate both hypoxia induced PH, and bleomycin induced pulmonary fibrosis and right ventricular hypertrophy in rodents [125,126]. If roflumilast reduces pulmonary pressure in humans, this drug may be well suited for COPD patients with PH. Also, statins have been shown to reduce hypoxia-induced PH in animals [127], to increase exercise capacity in COPD patients [128] and a new epidemiological study has shown a decreased mortality in COPD patients using statins [129]. Studies of the effect of roflumilast and statins have been summarized together with the effects of the pulmonary vasodilators in Table 3.

9. Future trials

For future studies on existing PAH drugs or up-coming drugs, only randomized placebo-controlled studies on patients with ILD or COPD and a firm diagnosis of PH can determine whether specific treatment of PH is beneficial. As mentioned previously, patients with severe PH can be expected to have a better response to pulmonary vasodilators, which speaks in favor of their inclusion into clinical trials. Due to different pathophysiological factors and patient characteristics in COPD and ILD, least variation in responses may occur if trials were conducted separately within the two groups. The higher number of ILD patients with severe PH taken together with their survival, which seems to be the worst of all types of PH [93], suggests that this group of patients should be highly prioritized.

With regard to clinical trial end-points, mortality is obviously important, but surrogate markers such as the 6MWT has been used extensively as the primary end-point in trials in PAH patients. Apart from being simple, reproducible and inexpensive to perform [130], it correlates to prognosis and quality of life in patients with cardio-pulmonary disease

Table 1
Prevalence of PH in COPD patients.

Authors	Patients	N	Lung function	Design	Definition of PH	Prevalence
Evers et al., 1992 [27]	Stable male COPD patients	315		Cross-sectional	MPAP > 20 mm Hg by RHC	33%
Keller et al., 1986 [70]	Stable COPD patients	89	FEV1 48/33% FVC 64/53% (no PH/PH)	Cross-sectional	MPAP > 20 mm Hg by RHC	35%
Oswald mammosser et al., 1991 [71]	Stable COPD patients with emphysema	151	FEV1 1.2 l RV 2.66 l	Retrospective	MPAP ≥ 20 mm Hg by RHC	20%
Scharf et al., 2002 [72]	patients with severe emphysema	120	FEV1 27% RV 225% Tlco 27%		MPAP >20/>35/>45 mm Hg by RHC (mild/moderate/severe)	Mild 86% Moderate 5%
Thabut et al., 2005 [73]	Candidates for Lung Volume Reduction Surgery or Lung Transplantation	215	FEV1 24% TLC 128% RV 260%	Retrospective	MPAP >25/>35/> 45 mm Hg by RHC (mild/moderate/severe)	Mild 37% moderate 10% Severe 4%
Cuttica et al., 2010 [74]	COPD lung transplant candidates	4930	FEV1 22% FVC ~ 54%	Retrospective	MPAP ≥25 mm Hg by RHC	30.4%
Sims et al., 2009 [75]	COPD lung transplant candidates	362	FEV ~ 21%	Cross-sectional	MPAP >25 mm Hg by RHC	23%
Andersen KH et al., 2012 [28]	COPD lung transplant candidates	409	FEV 23% TLC 126%	Retrospective	MPAP ≥ 25 mm Hg by RHC	36%
Mykland Hilde et al., 2012 [76]	Stable COPD out-patients	98	FEV1 46/32% FVC 76/61% Dlco 57/36% (no PH/PH)	Cross-sectional	MPAP ≥ 25 mm Hg by RHC	5/27/53% GOLD stages II/III/IV
Fayngersh et al., 2011 [77]	Stable COPD out-patients	105	FEV1 63/52% RV 127/150% Dlco 72/60% (No PH/PH)	Cross-sectional	SPAP >/= 36 mm Hg by echo	60%
Andersen CU et al. [51]	Stable COPD out-patients	117	FEV1 42% FVC 72%	Cross-sectional	TR >40 mm Hg, TAPSE < 1.8 cm, or right ventricular dilatation	<12%
Chaouat et al., 2005 [26]	COPD and chronic respiratory failure	998		Retrospective Case–control	MPAP > 40 mm Hg	1%

Table 1: Summary of studies investigating the prevalence of pulmonary hypertension in COPD. Echo; echocardiography, Dlco: Diffusion capacity, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, MPAP: Mean pulmonary artery pressure, PH: pulmonary hypertension, RHC: right heart catheterization, RV: residual volume, SPAP: systolic pulmonary artery pressure, TLC: total lung capacity, TR: tricuspid pressure gradient, TAPSE: tricuspid annular plane systolic excursion, %: % of predicted value.

[130]. While the endurance shuttle walk test (ESWT) and cycle endurance test (CET) have been shown to be more sensitive than the 6MWT in COPD patients [131], the 6MWT has been shown to be more sensitive to treatment-induced clinical improvements than ESWT and CET in PAH patients [131], which speaks in favor of this exercise test in COPD and ILD patients with PH. 6MWT should preferably be supplemented by hemodynamic measurements by RHC to clarify the mechanism of action of the drug tested. Furthermore, in the light of

Table 2
Prevalence of PH in ILD.

Authors	Patients	N	Lung function	Design	Definition of PH	Prevalence
Nathan et al. 2007 [32]	IPF Lung transplant candidates	118	TLC 54/59% DLco 36/33% (No PH/PH)	Retrospective	MPAP > 25 mm Hg by RHC	41%
Lettieri et al., 2006 [79]	IPF Lung transplant candidates	79	TLC 55/58% Dlco 38/31% (No PH/PH)	Retrospective	MPAP > 25 mm Hg by RHC	31%
Shorr et al., 2007 [80]	IPF Lung transplant candidates	2525	FVC ~ 50% FEV1 ~ 50%	Retrospective Analysis of the lung transplant registry for the USA 1995–2004	MPAP ≥ 25 mm Hg by RHC	41% (9% MPAP > 40 mm Hg)
Hamada et al., 2007 [92]	IPF	61	VC 76% Dlco 45%	Five year follow-up from initial work up with RHC	MPAP > 25 mm Hg by RHC	8%
Andersen et al., 2012 [29]	ILD population at tertiary referral center	212	Dlco 45% TLC 69% FVC 71% FEV1 67%	Cross-sectional study	TR > 40 mm Hg by echo Confirmation by RHC	14% (6%MPAP ≥ 35 mm Hg)
Handa et al., 2007 [81]	IIP	78	TLC ~ 70% Dlco 63/37% (no PH/PH)	Retrospective	SPAP ≥ 40 mm Hg by echo	28%
Handa et al., 2007 [81]	CVD-IP	85	TLC ~ 80% Dlco ~ 50%	Retrospective	SPAP ≥ 40 mm Hg by echo	21%
Launay et al., 2007 [83]	ILD related to scleroderma	110		Retrospective	TR > 40 mm Hg by echo Confirmation by RHC	22%
Shorr et al., 2005 [82]	Lung transplant candidates with sarcoidosis	363	FVC: 45/46/49% FEV1:39/40/44% (no PH/PH/severe PH)	Retrospective	MPAP > 25 mm Hg by RHC	74% (9% MPAP ≥40 mm Hg)

Table 2: Summary of studies investigating the prevalence of pulmonary hypertension in ILD-populations. CVD-IP: ILD related to collagen vascular disease, echo; echocardiography Dlco: Diffusion capacity, FEV1: forced experatory volume in one second, FVC: forced vital capacity, IIP: idiopathic pulmonary pneumonia, IPF: idiopathic pulmonary fibrosis, MPAP: Mean pulmonary artery pressure, PH: pulmonary hypertension, RHC: right heart catheterization, RV: residual volume, SPAP: systolic pulmonary artery pressure, TLC: total lung capacity, TR: tricuspid pressure gradient, %: % of predicted value.

Table 3
Effects of registered drugs with potential effects in PH related to lung disease.

Evidence of drug effect in lung disease related PH from	Sildenafil	Bosentan	Prostacyclins	Roflumilast	Statins
In vitro studies	Reduces smoke-induced endothelial cell damage [108]	Reduces smoke-induced vasoconstriction [108]			
Animal studies	Attenuates hypoxia and bleomycin induced PH [22,105–107]	Attenuates hypoxia and bleomycin induced PH [115,116]		Attenuates hypoxia and bleomycin induced PH [125,126]	Attenuates hypoxia-induced PH [127]
Studies of acute effect in patients with PH	Decreases pulmonary pressure in COPD [7] and ILD patients with PH [109]. In COPD, PaO_2 was decreased [7]		IV prostacyclin reduces pulmonary pressure and PaO_2. Inhaled prostacyclin reduces pulmonary pressure and does not affect PaO_2 in ILD [8,122]. Inhaled iloprost reduces pulmonary pressure in COPD and does not affect PaO_2		
Randomized studies of Long-term treatment in patients not selected based on the presence of PH	No effect on stroke volume or exercise capacity in COPD [112]	No effect on 6MWT or pulmonary pressure. PaO_2 decreased [120]			Pravastatin increases exercise capacity and reduces SPAP [128]
Open label studies or case reports of long term treatment in patients with a firm diagnosis of PH	Improves 6MWT in COPD and ILD [110,111]. Well-tolerated [110,111]. Not proven to improve mortality in COPD patients, but comparative group had less severe PH [31]	Improves 6MWt in ILD [118,119]			
Randomized Studies of long term treatment in patients with a firm diagnosis of PH		Improves 6MWT in randomized, but non-blinded study [121]			

Table 3: Effects of pulmonary vasodilators (sildenafil, bosentan and prostacyclin analogs), the new COPD-antiinflammatory agent roflumilast, and statins in in vitro, animal and human studies of PH related to COPD or ILD. COPD: chronic obstructive lung disease, ILD: interstitial lung disease, PaO_2: arterial oxygen pressure, SPAP: systolic pulmonary pressure.

the importance of the RV, BNPs are informative, but magnetic resonance imaging is considered gold standard for assessing changes in RV mass and volume [132], and would thus be a better tool to address an effect of treatment on the right ventricle.

10. Conclusions

PH in lung disease probably has the worst prognosis of all types of PH, and conversely, PH worsens the prognosis of the underlying disease. PH should be suspected in patients with a lower Dlco than expected from the degree of derangement in other lung function parameters. Furthermore, the risk is high in patients with combined fibrosis and emphysema. The screening tool of choice for PH in COPD and ILD patients is echocardiography. RHC is necessary to finally establish the diagnosis, and should be supplemented by V/Q scan and HR-CT to classify PH correctly. NT-proBNP may be useful as a rule-out test, but lung derived biomarkers for detection of early changes in pulmonary arteries are still needed.

The prevalence is unclear, but the total of patients with lung disease related PH is large, due to the high prevalence of ILD and especially COPD. It seems that mild PH does not impair exercise capacity per se, while severe PH arbitrarily defined as MPAP >35–40 mm Hg exhaust circulatory reserve, speaking in favor of specific treatment of this condition. There is currently no evidence based recommendations for treatment of COPD or ILD related PH with drugs targeting PH per se. Systemic administration of pulmonary vasodilators implies the risk of worsening V/Q mismatch. However, animal studies, acute studies and a small randomized but non-double blinded study suggest a beneficial effect. But so far, no randomized, placebo controlled double blinded study in patients with a firm diagnosis of PH have been published. However, improving treatment for PH in patients with lung disease could have a great impact on the general knowledge about this condition and improve quality of life and survival for the patients.

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