Pulmonary hypertension associated with chronic lung diseases

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Introduction

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest measured during right heart catheterisation [1]. According to its aetiology, PH is classified into five diagnostic groups [1]. Pulmonary arterial hypertension (PAH, group 1) describes patients with precapillary PH, documented by a pulmonary artery wedge pressure (PAWP) ≤15 mm Hg, a pulmonary vascular resistance (PVR) >3 Wood units (WU) and the absence of other causes of pre-capillary PH, e.g. hypoxemia or chronic parenchymal lung diseases (group 3) or chronic thromboembolic disease (group 4) [1]. Chronic lung diseases induce PH and, because they are very prevalent, may also occur occasionally concomitant with PAH [1]. Group 3 PH includes chronic obstructive pulmonary disease (COPD) (group 3.1), interstitial lung disease (ILD, group 3.2) (e.g. idiopathic pulmonary fibrosis [IPF]), other lung diseases with mixed restrictive and obstructive pattern (group 3.3, e.g. combined pulmonary fibrosis with emphysema [CPFE]), sleep-disordered breathing (group 3.4), alveolar hypoventilation syndromes, where hypercapnic pulmonary vasoconstriction might have a role (group 3.5),...
chonic exposure to high altitude (group 3.6), and developmental abnormalities (group 3.7) [1]. Rare diseases involving the lung, like sarcoidosis or pulmonary Langerhans cell histiocytosis or lymphangioleiomyomatosis, are included in group 5.2 with unclear or multifactorial mechanisms [1]. In the following review we will focus on PH associated with the lung diseases COPD with or without emphysema, interstitial lung diseases, ILD (as an example IPF) and CPFE: PH group 3.1 to 3.3.

Pathophysiology of pulmonary hypertension in parenchymal lung diseases

Depending on the underlying lung disease, rarefaction of vessels (for example in emphysematous areas), parenchymal or vascular remodelling (for example in IPF), cytokine release, hypoxaemia, and to some extent pulmonary vascular abnormalities and thrombosis may contribute to the development of PH. In contrast, in PH due to sleep-disordered breathing (3.4), alveolar hypventilation disorders (3.5) and chronic exposure to high altitude (3.6) hypoxaemia is present although lung parenchymal structure is preserved.

Physiologically, the entire cardiac output flows through the pulmonary circulation and for a given cardiac output, pulmonary resistance decreases by pulmonary arterial dilatation or recruitment of under-recruited pulmonary vessels [2]. While pulmonary arteries regulate their diameters and are orchestrated by vasconstrictive signalling, including hypoxaemia-induced, resistance of alveolar capillaries is mainly dependent on alveolar pressure and volume [2]. The hypoxic regulation (HPV or Euler-Liljestrand mechanism) is relevant for pulmonary vasoconstriction in acute or chronic pulmonary diseases such as pneumonia, COPD or pulmonary embolism, which may all consecutively develop into acute or chronic PH. This pathophysiological consideration is particularly important to look at if vasoconstricting therapy targeting pulmonary arteries is considered in patients with PH due to heterogeneous lung diseases. Vasodilating therapy may recruit areas with worse oxygenation and may lead to worsening of hypoxia.

Hypoxaemia

Hypoxaemia, and on a cellular level hypoxia, is found in advanced stages of all diseases of group 3 PH, although in parenchymal diseases, destruction of lung tissue and reduction of total number of alveoli and vessels might additionally increase pulmonary arterial pressure. On one hand, destroyed lung parenchyma has reduced blood flow and to some extent increased pulmonary resistance; on the other hand, hypoxia induces release of cytokines and mediators which itself may lead to pulmonary vasoconstriction. The physiological response to alveolar hypoxia helps to regulate blood flow to alveolar areas with high oxygen partial pressure and is referred to as hypoxaemia-induced vasoconstriction (HPV or Euler-Liljestrand mechanism). Although the precise mechanisms of the regulation of vascular tone by hypoxaemia is still unknown, hypoxic effects are thought to be mediated through reactive oxygen species (ROS), redox couples and adenosine monophosphate-activated kinases [3]. L-type calcium channels, nonspecific cation channels and voltage-dependent potassium channels are effectors of the hypoxia induced pulmonary vasoconstriction [3].

Another mediator of hypoxia induced vasoconstriction, the transcription factor hypoxia-inducible factor 1-alpha (HIF-1α), contributes to hypoxia-mediated pulmonary vascular remodelling and hypertension [4] and has been linked to pulmonary hypertension in chronic fibrotic lung disease [5]. Interestingly, vasoconstricting effects of hypoxaemia are not linear: if hypoxaemia is very severe, hypoxaemic pulmonary vasodilation will be observed [6].

Proliferative mediators in PH overlapping with fibrotic pathways

In addition to hypoxia-induced signalling, increased cytokines potentially promote vascular remodelling and pulmonary (arterial) hypertension [7]. Similar to pulmonary hypertension, fibrotic lung disease typically is characterised by increased cell proliferation and impaired apoptosis. Lung fibroblasts differentiate into myofibroblasts and destroy normal lung tissue by accumulation and extracellular matrix production. In pulmonary hypertension typically smooth muscle cells of pulmonary arterial vessels show increased proliferation and accumulation. Cytokines and other signalling mediators orchestrate cell migration, proliferation and survival, and can overlap between PH and fibrotic lung disease. One important cytokine is endothelin, a potent vasoconstrictor, which contributes to vascular remodelling in PH but also fibroblast accumulation in pulmonary fibrosis [8].

Endothelin is a vasoactive peptide, with three subtypes, ET-1, ET-2 and ET-3. It is expressed in several cell types such as endothelial cells, epithelial cells, smooth muscle cells and many more [5]. Endothelin binds to two G-protein coupled receptors, endothelin receptor A and B [8]. Endothelin receptor B (specifically B1) is found on endothelial cells, which are known to stimulate release of nitric oxide and prostacyclin and thus vasodilation. Endothelin receptor B (B2) mediates also vasoconstrictive effects. Endothelin A and B receptors are found on fibroblasts and smooth muscle cells [8]. Endothelin receptor A is mainly responsible for vasoconstriction [8]. Unselective or selective endothelin receptor antagonism is a well-established treatment option for patients with PAH [9]. For fibrotic diseases, the role of endothelin has been extensively studied in different models, and increased levels of endothelin have been found in patients with IPF [8]. This double signalling role of endothelin contributing to pulmonary hypertension and fibrosis has led to several clinical trials investigating endothelin antagonism in IPF or other idiopathic interstitial pneumonia (IIP) patients, although none of them found positive results so far [10–14].

Platelet derived growth factor (PDGF) has been associated with pulmonary hypertension and lung fibrosis. PDGF is found in several cell types including epithelial cells and smooth muscle cells and acts via its two receptors PDGFα and PDGFβ, with an intracellular tyrosine kinase domain which can be inhibited by specific tyrosine kinase inhibitors [7, 15]. PDGF activation promotes proliferation, migration and survival of smooth muscle cells in PAH and tar-
Pulmonary hypertension associated with interstitial lung disease

In comparison to COPD and emphysema, chronic fibrosing interstitial lung diseases (ILD) are less common. Idiopathic pulmonary fibrosis (IPF) is the most prevalent idiopathic form of ILD, with prevalence estimates below 5000 cases for Switzerland [31]. PH in IPF is also associated with advanced disease stages, (i.e. the severity of the underlying IPF) and ranges from 8–15% [32, 33] at the time of diagnosis to 35–45% [34, 35] for patients before lung transplantation [23]. In IPF patients with mild-to-moderate restriction, who were recruited for a study of ambrisentan in IPF patients (ARTEMIS-IPF), PH could be found in 14% [36]. In patients with advanced or end-stage IPF, pulmonary hypertension occurs in 30-50% or >60% respectively [23]. However, in a cohort of patients awaiting lung transplantation, only 9% had an mPAP of >40 mm Hg [37]. Lung functional or radiological impairment (high resolution computed tomography; HRCT) do not correlate well with severity of PH [23, 25, 37]. The evolution of PH-ILD is characterised by a progressive increase in mPAP of 0.17–3.8 mm Hg/month over time [34, 36]. PH represents an independent predictor of survival for IPF [33].

Pulmonary hypertension associated with combined pulmonary fibrosis and emphysema (CPFE) is a characteristic combination of basal fibrotic and apical emphysematous lung lesions affecting elderly male smokers, but the prevalence of the disease is rather low. CPFE has a typical appearance on chest computed tomography and is characterised by a severely impaired diffusion capacity but preserved lung volumes in functional testing. PH-CPFE is found in up to 50% of patients, and 60% of PH-CPFE patients had mPAP >35 mm Hg [23, 38]. Presence of PH in these patients is associated with worse outcome, with a median survival of less than 1 year in the subgroup of patients with a PVR of >485 dyn·s·cm⁻⁵ [39].

Assessment and diagnosis

Patients with COPD (with or without emphysema), ILD or CPFE and suspected PH require careful staging of the parenchymal lung disease. Lung disease assessment includes lung functional testing by body plethysmography, diffusion capacity measurements, arterial blood gas analysis, HRCT of the chest and eventually bronchoscopy with bronchoalveolar lavage and lung biopsy (if possible) to evaluate lung parenchymal structure. Functional exercise tests including cardiopulmonary exercise testing (CPET) and the 6 minutes walking test or sit-to-stand test [40] are part of the assessment to diagnose and define disease stages accurately. Non-invasive screening for PH-COPD, PH-ILD and PH-CPFE is performed with echocardiography [1]. The combination of the clinical and functional assessment with brain natriuretic peptide measurements has been shown to be useful to predict the presence of PH [41]. Nevertheless, echocardiographic measurements might be inaccurate, especially in COPD patients [42]. However, while echocardiography and referral to an expert centre is recommended if echocardiographic signs of severe PH are present (class I, level C) in the recently updated European guidelines [1], right heart catheterisation is discouraged for suspected PH in patients with lung diseases (class III, level C).
unless therapeutic consequences are to be expected (e.g. lung transplantation, alternative diagnosis such as PAH or chronic thromboembolic pulmonary hypertension). Contributing factors with an impact on treatment decisions are to be searched for, including full night polysomnography in the search for obstructive sleep apnoea or nocturnal hypoxemia, left heart catheterisation and coronary angiography in suspected coronary or left heart disease and ventilation-perfusion scintigraphy to evaluate for venous thromboembolism [1].

Sometimes it is difficult to differentiate whether lung disease and PH are coincidental or related. In suspected PH-COPD or PH-ILD, previously proposed criteria [23] favouring PAH, with FEV1 >60% or forced vital capacity (FVC) >70%, the absence of parenchymal abnormalities on chest computed tomography and preserved breathing reserve with reduced oxygen pulse and a low cardiac output / oxygen consumption ratio (CO/VO₂ slope) are uncommon. Most of the time patients show additional signs of parenchymal disease which complicates differentiation between PAH or group 3 PH [23]. If PH is disproportionate to parenchymal lung disease the term “out of proportion” has been previously used [43], but it has been suggested that this term be abandoned because only a loss >80% of normal lung structure will provoke PH [23]. However, a recent study showed that differentiation into mild and severe lung disease as previously suggested [23] and illustrated in table 1 has no impact on survival, but only severe PH-ILD showed poor survival similar to the overall reduced survival of the ILD cohort (fig. 1 and fig. 2) [44]. The current guidelines now categorise patients with parenchymal lung diseases into three groups: lung disease without PH (mPAP <25 mm Hg), lung disease with PH (mPAP ≥35 mm Hg) and lung disease with severe PH (mPAP ≥35 mm Hg or ≥25 mm Hg in the presence of low cardiac output (<2.5 l/min/m²), not explained by other causes (table 2) [1, 23]. PH-ILD patients have an overall worse survival when compared with other PH groups as observed in our national Swiss registry for pulmonary hypertension [45].

Management

For PH-COPD, PH-ILD and PH-CPFE, recommendations aim at optimal treatment of the underlying lung disease for symptomatic improvement, improvement in quality of life and in survival (class I, evidence level C) [1, 23]. The mainstays for treatment recommendations for lung diseases associated with PH have been listed previously [46].

Management of PH-COPD

For PH-COPD, smoking cessation, anti-obstructive treatment and pulmonary rehabilitation are the most important recommendations in all disease stages. As for exercise training, it has recently been shown in a prospective randomised controlled trial in patients with severe PH related

![Image](359x454 to 562x594)

**Figure 1**

Survival for patients with pulmonary arterial hypertension, pulmonary hypertension associated with CPFE, COPD, emphysema and ILD. Survival for PH-ILD was significantly lower compared with PAH (p <0.0001), PH-COPD (p = 0.0026) and PH-CPFE (p = 0.05), while survival for other lung phenotypes did not differ significantly. CPFE = combined pulmonary fibrosis and emphysema; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension. (Reproduced with permission of the European Respiratory Society © Eur Respir J. 2015;46(5):1378–89; DOI: 10.1183/13993003.02307-2014)

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<tr>
<th>Table 1: Typical findings for lung function, radiology and exercise testing in pulmonary hypertension due to chronic lung diseases and in pulmonary arterial hypertension.</th>
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<tr>
<td><strong>PH due to parenchymal lung diseases (Group 3)</strong></td>
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<tr>
<td>Lung function</td>
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<tr>
<td>FEV₁</td>
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<tr>
<td>FVC or TLC</td>
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<td>High resolution CT scan</td>
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<td>CPET</td>
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<td>Exercise limitation</td>
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<td>Breathing reserve</td>
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<td>Oxygen pulse</td>
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<td>CO/VO₂ slope</td>
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<tr>
<td>Oxygen saturation</td>
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<td>CO₂ during exercise</td>
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COPO = chronic obstructive pulmonary disease; CO/VO₂ slope = cardiac output / oxygen consumption ratio; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

**Table 2: Current haemodynamic classification of pulmonary hypertension due to lung diseases (adapted from [1]).**

<table>
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<tr>
<th>Right heart catheterisation</th>
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<td>COPD/ILD without PH</td>
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<td>COPD/ILD with PH</td>
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<td>COPD/ILD with severe PH</td>
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COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; PAP = pulmonary arterial pressure; PH = pulmonary hypertension |
to inoperable chronic thromboembolic disease that pulmonary resistance, that right ventricular function as well as CPET parameters and walking distance improved with rehabilitation [47]. Bronchodilators, in the form of long-acting muscarinic antagonists (LAMAs) and long-acting beta agonists (LABAs), often together with topical steroids, are indicated in advanced symptomatic COPD, newly defined GOLD class C (few symptoms, GOLD class 3–4 and/or 2 or more exacerbations per year) and D (more symptomatic, GOLD class 3–4 and/or 2 or more exacerbations per year). Interestingly, in COPD patients, it has been observed in a randomised trial that lung deflation is associated with consistent beneficial effects on cardiac function and pulmonary vasculature [48]. For advanced emphysematous COPD with PH, endoscopic lung volume reduction may be beneficial for both COPD and PH and is preferred over surgical interventions because of the associated perioperative risks in PH-COPD. As hypoxia triggers PH, supplemental oxygen at rest and upon exercise is recommended (class I, evidence level C) [1]. Even though long-term randomised controlled trials are not available, it has recently been shown in a double-blind cross-over trial that nocturnal oxygen was able to improve right ventricular function and walking distance after only 1 week of treatment in patients with precapillary PH and sleep-disturbed breathing [49]. Lung transplantation for PH-COPD is an option if other treatments fail, but post-transplant mortality seems to be increased [50].

PAH specific drugs for PH-COPD

Many trials to treat PH in patients with COPD by drugs targeting pulmonary vessel tone have been disappointing. Inhaled iloprost failed to improve exercise capacity in COPD patients with PH [51]. The endothelin receptor antagonist bosentan was not beneficial, but rather worsened arterial oxygen pressure and health-related quality of life in COPD patients without severe PH [52]. In contrast, sildenafil improved pulmonary haemodynamics in COPD patients with associated PH in a short term study, but long term investigations are lacking [53]. In a more recent study, patients with severe PH-COPD failed to improve functional class for dyspnoea or exercise performance [54]. In a pilot study, riociguat, a soluble guanylate cyclase stimulator, improved haemodynamics without impairing gas exchange in mild PH-COPD, but this needs to be confirmed in a larger study [55]. According to current knowledge and recommendations, specific drugs to induce vasodilatation of pulmonary arteries are thus not a successful treatment option for patients with PH-COPD with or without emphysema at this time [1]. Nevertheless, retrospective studies suggest that some COPD patients with relevant PH (mPAP >30 mm Hg) might profit from specific PH therapy, but additional studies need to be performed [56, 57].

Management of PH-ILD

For PH-COPD, smoking cessation, pulmonary rehabilitation and supplemental oxygen to maintain saturations above 90% at rest and upon exercise are recommended. In patients with nonspecific interstitial lung diseases, a trial of immunosuppressive therapy may be indicated. Anti-fibrotic treatment with pirfenidone and nintedanib have recently been approved for the treatment of IPF in Switzerland. These drugs may potentially stabilise PH in fibrotic lung disease by reduction of fibrosis progression. In addition, novel anti-fibrotic treatments, specifically tyrosine kinase inhibitors, target several of the overlapping signalling pathways between IPF and PH. Nintedanib inhibits VEGF and PDGF tyrosine kinases [58]. Unclear are the effects of VEGF inhibition by nintedanib in PH-IPF, as VEGF is beneficial for PH but might have pro-fibrotic effects [15]. Interestingly, tyrosine kinase inhibitors have previously shown to be promising in PAH treatment [59]. However, long-term safety data on treatment of PAH with imatinib showed severe adverse events and imatinib is no longer approved for PAH treatment [60]. Whether novel anti-fibrotic treatment impacts PH-IPF merits future investigation. Although anti-fibrotic treatments are now able to slow down disease progression in IPF, lung transplantation remains the ultimate treatment for respiratory failure in selected PH-IPF patients. A recent large retrospective analysis of a transplant registry showed no difference in post-transplant survival for IPF patients with or without associated PH [61].

PAH specific drugs in IPF and PH-IPF

In fibrotic lung disease, several studies have investigated the effects of specific PH treatment on PH and also on anti-fibrotic effects of the underlying parenchymal lung disease. For both aspects results have been disappointing. Some very interesting preliminary studies with encouraging results led to the hypothesis that inhaled vasodilators for fibrotic pulmonary disease may reach only well-ventilated areas [62, 63], but until today, these observations have not been published in larger studies. Bosentan, a dual endothelin receptor antagonist, was well tolerated in patients with IPF [10, 64], but failed to reduce progression of lung fibrosis in a phase III trial [11, 23]. Ambrisentan, a selective endothelin A antagonist, was investigated in a randomised clinical trial (ARTEMIS-IPF) for patients with IPF. The study was stopped early for lack of benefit and high likelihood of harm [12]. International guidelines recom-
mend against the use of ambrisentan in IPF-associated PH [65].

Recent data from a large prospective registry (COMPERA) suggested short-term functional improvement in idiopathic ILD patients with PH treated with any vasodilating therapy, although impact on survival remains unclear [66]. Many of the included patients were treated with a phosphodiesterase-5 inhibitor (PDE5i), probably because a recent study of IPF patients with low diffusion capacity (STEP-IPF) suggested that ILD patients with PH might benefit from treatment with sildenafil [67]. In a small study with selected lung fibrosis patients responding to NO vasodilating treatment, in the acute setting sildenafil did not worsen gas exchange due to dilatation of areas with increased hypoxic pulmonary vasoconstriction [68]. Retrospective studies found possible survival benefits of patients with chronic lung disease and severe PH under PDE5i therapy [69]. However, these results need to be confirmed in large prospective controlled trials before this treatment may be recommended. In one recent phase II clinical study on the effects of riociguat in patients with PH associated with IIP (RISE-IIP), riociguat was associated with a possible increased risk for death and other serious adverse events as compared with patients in the placebo group, and the study was terminated by the independent drug monitoring committee [70].

Conclusion and current recommendations

In COPD, ILD (IPF) and CPFE, PH is more prevalent in advanced disease stages and is associated with more symptoms and worse prognosis. Current guidelines recommend that patients with suspected PH-COPD, PH-ILD and PH-CPFE are referred to expert centres with experience in assessment and management of both diseases [23]. Echocardiography is recommended for the non-invasive diagnostic assessment of suspected PH in patients with lung disease. For clarification of the differential diagnosis, lung function tests, chest HRCT, CPET and ventilation-perfusion scans may be helpful. The optimal treatment of the underlying lung disease including long-term oxygen therapy in patients with chronic hypoxaemia at rest or upon exertion is recommended in patients with PH due to lung diseases. Right heart catheterisation is not routinely recommended for suspected PH-COPD and PH-ILD, unless therapeutic consequences are to be expected. In summary, the use of drugs approved for PAH is not recommended in patients with PH due to chronic parenchymal lung diseases [1]. Further studies focusing on novel therapeutic approaches are therefore urgently needed.

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Survival by severity of lung disease. For patients fulfilling the definition of severe PH (mPAP >35 mm Hg or CI <2.0 l/min/m²) and mild/moderate lung disease (FEV1 >60%), there was no difference in survival observed compared to severe PH/severe lung disease (Panel A). On the contrary, in patients with severe PH, the underlying lung disease had a significant impact on survival (Panel B).

CPFE = combined pulmonary fibrosis and emphysema; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; LD = lung disease; PH = pulmonary hypertension. (Reproduced with permission of the European Respiratory Society © Eur Respir J. 2015;46(5):1378–89; DOI: 10.1183/13993003.02307-2014).