Chapter 2

Pulmonary Hypertension in Chronic Lung Diseases and/or Hypoxia

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1. Introduction

Pulmonary hypertension is a common complication in lung disease. In the most recent revised classification of pulmonary hypertension (PH), chronic lung diseases or conditions with alveolar hypoxia are included in WHO Group III of PH-related diseases (Table 1) [1,2]. In this classification the structure of this group was for the most part unchanged. The heading has been recently modified to denote cause and effect on PH development. The primary modification was to add a new category of chronic lung disease of a mixed obstructive and restrictive pattern, which includes chronic bronchiectasis, cystic fibrosis and a syndrome characterized by the combination of pulmonary fibrosis (mainly of the lower zones of the lung) and emphysema (mainly of the upper zones of the lung), in which the prevalence of PH is almost 50%.

Alveolar hypoxia and thereby PH may occur in distinct conditions including: parenchymal lung disease, chronic airway diseases, ventilatory control abnormalities, residence at high altitude, progressive neuromuscular diseases and mixed obstructive and restrictive lung diseases [1,3,4]. As both the primary respiratory condition and PH may be associated with dyspnoea, the latter often goes unrecognised. Therefore, data on PH prevalence in each of these conditions is limited [5].

Prevalence of COPD-related PH is influenced by COPD progression, its heterogeneity, comorbidities and methods of measurement. In a retrospective cohort study of over 4000 patients with advanced COPD awaiting lung transplant, a 30.4% prevalence of PH has been reported [6]. Elevated pulmonary artery pressure (PAP) is common in severe emphysema, although it may be independent of hypoxia [7]. However, the gold standard of measuring PAP by right heart catheterization to define PH has not been applied in the majority of prevalence studies.

In end-stage cystic fibrosis, PH prevalence, defined as mean PAP ≥25 mmHg, has been reported as high as 63% [8].

1. PAH

- 1.1 Idiopathic PAH (IPAH)
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK-1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2. Pulmonary hypertension due to left heart disease

- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension

5. PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

BMPR2: bone morphogenetic protein receptor, type 2; ALK-1: activin receptor-like kinase 1 gene; APAH: associated pulmonary arterial hypertension; PAH: pulmonary arterial hypertension.
From : Simonneau G et al, JACC 2009 [1].

Table 1. Classification of Pulmonary Hypertension

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In high altitude residents, PH prevalence is between 8-18% [9,10]. A geographical variation in altitude-related PH prevalence may suggest differences in genetic susceptibility to development of PH in people living above 2000 m [11,12]. Variations have been observed in PAP changes among individuals living in the same regions, with some familial clustering and ethnic differences, although no definite gene polymorphism affecting PAP has been isolated [13].

Until recently there was disagreement whether intermittent hypoxia, such as occurs in obstructive sleep apnoea (OSA), without primary lung or cardiovascular disease can cause sustained PH. Recent studies have resolved this controversy by demonstrating that OSA is associated with PH, with co-prevalence rates varying between 20-40% [14-16]. However, no large population-based studies of PH prevalence in OSA have been reported and management of PH in patients with OSA has been mainly directed to managing the primary condition.

2. Pathophysiology

Alveolar hypoxia is a potent stimulus for pulmonary vasoconstriction. It operates at the endothelial level and is one of the most important pathways leading to PH development in chronic lung diseases. Alveolar hypoventilation precipitates acute pulmonary vasoconstriction in some regions of the lungs, and vasodilation in others, causing physiological shunt. Hypoxia causes pulmonary vasoconstriction leading to an increase in pulmonary vascular resistance. Two mechanisms are postulated to underpin this phenomenon. Vasoconstriction is achieved either through activation of a vasoconstrictor pathway or inactivation of a vasodilator pathway, or alternatively via the effects of hypoxia on the vascular smooth muscle [17]. Studies in rats exposed to hypoxia suggest that hypoxia-exposed arterioles develop smooth muscle in the walls of non-muscular pre-capillary blood vessels, which persists after removal of the stimulus and contributes to ongoing PH [9].

Hypoxic insults can be sustained or intermittent. In sleep-disordered breathing, the presence of intermittent hypoxia has been linked to the development of systemic hypertension with changes in the vasculature similar to the changes in PH. It remains undetermined whether sustained or intermittent hypoxia elicits these changes through similar mechanisms [18]. Studies in mice and rats exposed to intermittent hypoxia, mimicking sleep disordered breathing, showed development of sustained PH and right ventricular hypertrophy [17]. Treatment with CPAP in sleep-disordered breathing results in the reversal of PH, supporting a role for acute hypoxic pulmonary vasoconstriction and endothelial dysfunction in these patients [17,19].

Studies in mouse models of emphysema have suggested alternative mechanisms to the vascular changes associated with PH in COPD patients, as the mice developed pulmonary vascular changes independent of hypoxia indicative of a much more complex mechanism than hypoxia alone [5,20].

The development of PH as a result of hypoxic insults, both intermittent and chronic, is subject to ongoing investigations, with several pathways implicated in hypoxic pulmonary vasocon-

striction (HPV). However, neither the oxygen sensing process nor the exact HPV pathways are fully understood [21]. The effector pathway is suggested to include L-type calcium channels, non-specific cation channels and voltage-dependent potassium channels, whereas mitochondria and nicotinamide adenine dinucleotide phosphate oxidases have been described as oxygen sensors (Figure 1). Reactive oxygen species (ROS), redox couples and adenosine monophosphate-activated kinases are also under investigation as mediators of HPV. Moreover, the role of calcium sensitisation, intracellular calcium stores and direction of change of reactive oxygen species is still under debate. Other pathways, such as the endothelin-1 pathway, nitric oxide pathway and ROS may also explain development of sustained PH. Endothelin-1 is an important mediator of systemic hypertension in intermittent hypoxic states [18,22] and ongoing studies suggest a role for endothelin in acute HPV. ROS are highly reactive and unstable free radicals. Intermittent hypoxia stimulates the synthesis and release of ROS through the tyrosine hydroxylase system, leading to the development of systemic hypertension. ROS have also been implicated in the induction of endothelin-1 and in angiotensinogen synthesis with all these agents believed to contribute to the development of PH induced by intermittent hypoxia [18,21,23].

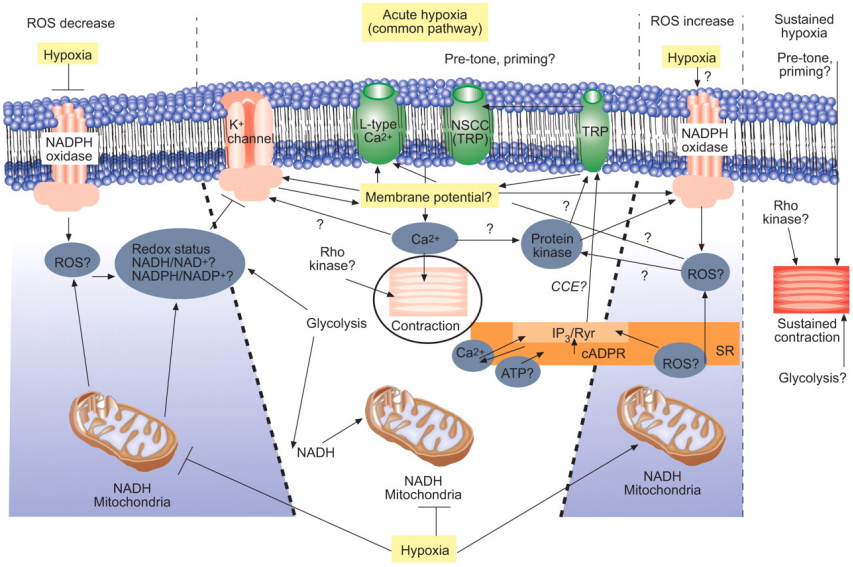

Figure 1. Pathways involved in hypoxic pulmonary vasoconstriction. Acute hypoxia results in an increase of intracellular calcium in pulmonary arterial smooth muscle cells and thus contraction. This increase in calcium is achieved by inflow of extracellular calcium through plasmalemnal calcium channels and release of intracellularly stored calcium. Hypoxic effects could be mediated or modulated by a decrease (left side) or increase (right side) of reactive oxygen species (ROS). NADPH: reduced nicotinamide adenine dinucleotide phosphate; NSCC: nonspecific cation channels; TRP: transient receptor potential; NADH: reduced nicotinamide adenine dinucleotide; NAD: nicotinamide adenine dinulceotide; NADP: nicotinamide adenine dinucleotide phosphate; CCE: capacitative calcium entry; ATP: adenosine triphosphate; IP_3: inositol triphosphate; cADPR: cyclic ADP-ribose; SR: sarcoplasmatic reticulum; *Sommer N et al. Eur Respir J 2008 [21], Reproduced with permission of the European Respiratory Society*

3. Pulmonary vascular remodelling

Studies of the vasculature in hypoxic PH have demonstrated changes including intimal thickening, medial hypertrophy and muscularization of the small arterioles [5]. When the balance between apoptosis and proliferation of endothelial cells in the pre-capillary pulmonary blood vessels, in particular, is altered in favour of proliferation, the overall resistance pattern is increased [24]. As shown in neonatal calves and rodent models, chronic hypoxia triggers endothelial cell proliferation [24,25]. Acute hypoxia triggers adventitial fibroblast proliferation within hours of exposure while medial hypertrophy and hyperplasia takes longer to develop [24,26,27]. Fibroblasts stimulated by chronic hypoxia can transform into smooth muscle cells. Hyperplasia is more prevalent in the less muscular arterioles, while hypertrophy is more common in the muscular arterioles. Chronic hypoxia in rat models results in a doubling of muscular arteries with proliferation into non-muscularized vessels [24]. The response of pulmonary vascular smooth muscle cells to acute hypoxia is still debatable with some studies indicating reduction in proliferation [24,28].

4. Role of systemic inflammation

Inflammation associated with underlying lung disease may be partly responsible for the development of PH in hypoxic states. Inflammatory cells have been detected in local vascular structures in COPD patients, in addition to the evidence of systemic inflammation with raised inflammatory markers, such as CRP and TNF–α [29,30]. In rats exposed to hypoxia, alveolar macrophages play a critical role in the inflammatory process, with inflammation occurring in the presence of reduced alveolar PaO_2 [31]. In alveolar macrophage-depleted conditions, systemic inflammation was not observed [32].

5. COPD and PH

There is a growing body of evidence supporting different phenotypes among patients with COPD. These COPD phenotypes may be useful in defining patients who may benefit from particular therapies or interventions more than others. Potential phenotypes may be defined by symptoms, physiology, radiology and exacerbation history, although the relevant clinical outcomes have not been defined [33].

A PH phenotype in COPD is potentially defined by perceivable effects on functional performance status and mortality [5]. PH is an independent prognostic factor in COPD [34-36]. The current accepted definition of PH in COPD is a mean PAP ≥ 25mmHg with underlying hypoxia. PH ideally should be measured by right heart catheterization, which may not be feasible in many cases. As an alternative, Doppler echocardiographic measurements have been used in a number of studies, although Doppler can be technically challenging due to body habitus and poor acoustic windows, precluding detection of a significant left heart pathology, which may

also contribute to elevated pulmonary pressures [37]. Scharf et al. in a study of patients with severe COPD, reported over 60% of subjects had elevated pulmonary capillary wedge pressures [7]. The impact of PH on mortality in COPD is independent of age, lung function and blood gas derangements [5].

PH has been associated with exercise limitation in patients with COPD. In a study of 362 pre-transplant patients with COPD, PH (mean PAP ≥25mmHg) was associated with shorter 6-minute walking distance (6MWD) after adjustments for demographics and lung function [38]. In a large retrospective study of COPD patients studied with right heart catheterization, PAP had an inverse relationship with 6MWD [6]. A much smaller study of 29 COPD patients assessed with Doppler echocardiography could not detect statistically significant differences in cardiopulmonary exercise test parameters and 6MWD in patients with or without PH. However, the authors acknowledged that the small sample size and lack of invasive measures could restrict the generalisation of the results [39].

In patients with parenchymal lung disease PH is generally modest (mean PAP 25-35 mmHg). While PAP at rest varies from normal to moderately elevated, it increases significantly during exercise, sleep and acute infective exacerbations. Hilde et al. in a study of 98 patients with COPD undergoing right heart catheterization reported a 27% prevalence of PH. Hemodynamic response to exercise, including mean PAP, was abnormal and similar between the PH and non-PH COPD patients [40].

In some patients with COPD PAP elevations can be more substantial (mean PAP ≥35mmHg). In patients with only moderate pulmonary mechanical impairment, this is considered "out-of-proportion" PH. A subset of COPD patients has been identified where progressive PH has prognostic implications. The term “PH out-of-proportion to COPD” has been applied to this group of patients. An unusual pattern of cardiopulmonary abnormalities has been described in the patients with more severe PH, including mild to moderate airway obstruction, severe hypoxemia, hypocapnia, and a very low diffusing capacity for carbon monoxide. The characteristics of this subset include the presence of obstructive airways disease and presence of fibrosis. A relative preservation of lung function and severe PH in COPD is believed to define this “vascular phenotype” [5]. Thabut et al. in a cluster analysis identified a subgroup of COPD patients with out-of-proportion PH associated with severe hypoxia [41]. Chaouat et al. also identified a similar cluster [42]. The challenge remains, however, to have uniformly applied definition of PH in COPD. As with PH out-of-proportion to left heart disease, large randomized, controlled, studies of medications approved for PAH are not available for PH out-of-proportion for parenchymal lung disease.

6. Treatment of PH in COPD

Although treatment of PH in COPD is conceptually appealing, there are no clear guidelines and no medications currently registered for the treatment of PH secondary to COPD. The primary focus of treatment, therefore, even in the vascular phenotype of COPD involves standard therapy with smoking cessation, bronchodilators, inhaled steroids, long-term oxygen

therapy (LTOT) and pulmonary rehabilitation [43]. Symptomatic (non-disease modifying) therapy for COPD-related PH includes LTOT, peripherally-acting calcium channel blockers and non-pharmacological interventions such as activity pacing and relaxation therapies.

6.1. Long-term home oxygen therapy

The only therapy that has demonstrated a survival advantage in people with COPD and co-existent PH is LTOT. Indications for LTOT include patients with severe hypoxemia or those with moderate hypoxemia and cor pulmonale [44-46], as it reduces pulmonary artery pressure [44,47].

LTOT is, however, relatively cumbersome and intrusive, with variable patient adherence. Patients with the most severe COPD have the least reduction in PH with LTOT [44,46]. Patients will often be concerned about the imposition of being physically reliant on a machine [48]. LTOT is also expensive, and may be associated with a small number of very serious adverse events across the community, such as CO_2 retention or burns, particularly where patients continue to smoke [49-51]. Actual adherence rates to LTOT are not precisely known and reports vary between 45 - 70% [52,53].

6.2. Evidence from pulmonary arterial hypertension

PAH includes idiopathic disease and disease secondary to connective tissue disorders such as scleroderma and systemic lupus erythematosus. Current evidence points to the benefits of prostanoids, endothelin antagonists and phosphodiasterase-5 (PDE-5) inhibitors as disease modifying in these people [2].

Given the evidence from PAH, it is plausible that in PH secondary to COPD pulmonary vasodilatation may improve the subjective sensation of dyspnoea and extend exercise endurance. Pulmonary vasodilator treatment (alone or as an adjunct to oxygen supplementation) might be useful to reduce dyspnoea and improve quality of life (QOL) in people with COPD and secondary pulmonary hypertension. Potentially, if these interventions were of benefit, improved physical independence, symptomatic control of dyspnoea and potentially even extended survival could be achieved.

6.3. Prostanoids

Epoprostenol sodium is indicated for patients with idiopathic, heritable or connective tissue disease related PAH (Group 1) as a continuous infusion [54]. Iloprost is a prostacyclin analogue that can be administered orally, intravenously or as an aerosolised formulation [55]. These have been shown to improve exercise tolerance and haemodynamic parameters in patients with PAH.

However, evidence for the use of prostacyclin analogues in COPD-related PH is very limited and current practice does not favour routine use of these medications. The primary concern in using pulmonary vasodilators is related to worsening gas exchange due to ventilation/perfusion (V/Q) inequality [5].

6.4. Endothelin receptor antagonists (ERA)

Bosentan, an oral endothelin-1 receptor antagonist is registered for use in patients with PAH in World Health Organisation (WHO) functional classes (FC) II-IV. It has been shown to reduce pulmonary vascular resistance and moderately improve exercise tolerance in people with mildly symptomatic disease. Hepatotoxicity and teratogenicity are potential toxicities [56]. Ambrisentan has been approved for PAH in WHO FC II-IV and has been shown to delay disease progression and improve exercise tolerance in patients with PAH with lower levels of hepatotoxicity [57].

Trials with endothelin receptor antagonists in patients with COPD and PH have suffered from poor study design and the general trend was worsening gas exchange without improvement in functional capacity.

6.5. Phosphodiesterase-5 (PDE-5) inhibitors

Sildenafil is a selective inhibitor of PDE-5, an enzyme that is specific for both lung and penile vasculature. Although originally developed for treatment of erectile dysfunction, sildenafil is an effective pulmonary vasodilator [58-60]. PDE-5 is found throughout the muscularized pulmonary vascular tree, including in newly muscularized distal pulmonary arteries exposed to hypoxia.

Sildenafil may be preferred to other vasodilator agents, particularly in patients with severe COPD, PH and poor RV function, because hemodynamic effects are likely to be selective on the pulmonary circulation. PDE-5 inhibition with sildenafil attenuates the rise in PAP and vascular remodelling when given before chronic exposure to hypoxia and when administered as a treatment during ongoing hypoxia-induced PH [61].

Previous trials in patients with PAH (primary or associated with scleroderma) showed that sildenafil-induced pulmonary vasodilatation is well tolerated, increased exercise capacity, decreased Borg dyspnoea index and WHO functional class and improved haemodynamics [62,63]. Therefore, it has been proposed to consider the use of this medication in selected patients with COPD-related PH, although clinical trials in this group are limited.

A recent randomized trial in 20 patients with COPD-associated PH demonstrated that sildenafil improved pulmonary haemodynamics both at rest and during exercise, with mild to moderate worsening of gas exchange at rest due to worsening V/Q mismatch [64]. A longer duration of 3 months treatment with sildenafil did not significantly alter hemodynamic or functional capacity [65]. A more recent cross-over trial of sildenafil and placebo in COPD-related PH showed significant worsening of gas exchange at rest and quality of life indices with no beneficial effect on exercise capacity [66].

6.6. Calcium channel blockers

The administration of vasodilator drugs has been proposed as an alternative or adjunct to oxygen supplementation in the treatment of PH in COPD for a number of years. However, there remains considerable controversy regarding the likely benefits of non-selective vasodilators [67-69].

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Reports of worsening ventilation / perfusion (V/Q) inequality [70,71], a lack of long-term effectiveness (or development of tolerance) [72,73] and the high incidence of side effects [73] have raised doubts about the benefits of a non-selective vasodilator treatment in COPD.

Calcium channel blockers of the dihydropyridine group are the most extensively studied vasodilators in both PAH and PH secondary to COPD [70-85]. However, the non-selective vasodilator properties of these drugs give frequent systemic side effects (e.g. ankle oedema, headache, facial flushing), preventing their wider use in the COPD population. Their use is largely limited to patients who demonstrate acute vasoreactivity testing [73].

In an earlier study by our group, felodipine, a non-selective dihydropyridine calcium channel blocker, significantly improved pulmonary haemodynamics in patients with COPD and PH [83]. Pulmonary vasodilatation in these patients was sustained for 3 months of treatment, without development of tolerance or deterioration in gas exchange, although a high incidence of vasodilator side effects was observed. A subsequent study by our group showed that amlodipine was as effective as felodipine in improving pulmonary haemodynamics in patients with COPD, with fewer side effects than felodipine [84]. One small randomised placebo-controlled trial in patients with COPD and PH reported significant improvement of the dyspnoea score and preserved cardiac output with nifedipine for one year, although there was no significant survival benefit [85]. This supports the hypothesis that pulmonary vasodilatation in patients with severe COPD and PH may improve their functional performance, dyspnoea and QOL, particularly if systemic vasodilatation side effects can be avoided.

An important practice point is that alternative causes of PH in patients with COPD, such as concomitant sleep disordered breathing or chronic thromboembolic disease should be actively investigated, as there are important treatment alternatives in these patients.

7. Sleep disordered breathing and PH

True prevalence of PH in OSA is unknown and ranges from 17 - 52% [86]. In our study of 27 patients with OSA 11 (41%) had mildly elevated PA pressures, mean PAP = 26 mmHg, in the absence of cardiac or pulmonary disease [14].

OSA patients maintain normal daytime oxygenation but experience episodic hypoxic events during sleep. Acute rises in PAP with sleep-disordered breathing have an inverse relationship with the degree of oxygen desaturation. Pulmonary artery pressure is influenced by an obstructive sleep apnoea cycle associated with changes to intra-thoracic pressure with the changes most marked in REM sleep [87]. Three main mechanisms have been proposed including hypoxia, mechanical factors and reflex mechanisms [16]. However, there are conflicting data to support these proposed mechanisms. It has been observed that changes in PA pressure were inversely correlated with the degree of arterial hypoxia [88, 89] while in another study supplemental oxygen did not affect pulmonary artery pressures [90].

Our understanding of the relationship between OSA and PH is evolving following recent studies. Twenty patients with OSA were treated for 4 months with CPAP and a decrease in

the mean PAP by 13.9 mmHg was observed for all patients although only five had PH [19]. This reduction of PAP and hypoxic pulmonary vascular reactivity in OSA following CPAP treatment was associated with improved pulmonary endothelial function due to the elimination of intermittent hypoxemia [19]. A randomised controlled cross-over trial using sham and effective CPAP in 23 patients with OSA (AHI = 44 ± 29.3/h) and 10 normal controls concluded that severe OSA was independently associated with PH [86]. The clinical impact of PH in sleep-disordered breathing remains under investigation. PH in OSA patients may lead to dyspnoea and reduction in 6MWD, suggesting functional impairment [91]. In a study of 296 OSA patients (AHI ≥ 20/hr) using nasal CPAP, pulmonary haemodynamics were not independently associated with mortality [42]. There are no consensus guidelines to recommend routine screening for PH in OSA. Although current data suggest improvement in PH when OSA is treated with CPAP therapy, the significance of this improvement in the clinical context remains unclear, particularly with mild to moderate PH observed in most patients with OSA.

8. High altitude PH

High altitude PH (HAPH) prevalence is between 5 and 18% in those living at ≥3000 metres and may be more common in children than adults [9,11,92]. As mentioned previously, the roles of the endothelin-1 and prostaglandin I2 pathways in the pathophysiology in high altitude associated PH have not been clearly defined [9]. Alteration in trans-membrane transport of K^+ and Ca^{2+} has been implicated in the process. Recent work by Beall et al. has suggested a role of free radical-mediated reduction in NO bioavailability [93, 94].

Migration to a lower altitude reverses HAPH. However, due to family, social and economic reasons, migration is not an option for some patients. As an alternative, sildenafil for 3 months has been shown to reduce PAP, improve 6MWD and cardiac index in patients with HAPH [95]. Reduction in mean PAP of up to -6.9 mmHg and improvement in walking distance of up to 45 m was observed and sildenafil was well tolerated [95].

The role of endothelin receptor antagonists in HAPH is yet to be determined. A small randomised cross-over study of 8 patients on bosentan did not improve pulmonary pressures or functional capacity when initiated prior to ascent during high intensity exercise [96]. Acetazolamide was successful in reducing pulmonary pressures and improving cardiac output at 6 months of therapy in patients with excessive erythrocytosis and HAPH [97]. Other drugs under evaluation include angiotensin inhibitors and results of the ongoing studies are pending.

9. PH in Cystic Fibrosis (CF)

PH prevalence in CF population remains uncertain with figures as high as 21-59%. A retrospective study of 179 pre-transplant CF patients revealed that 38.5% had PH with a RHC mean PAP of ≥ 25 mmHg [98]. In a recent series of 57 CF patients with advanced lung disease considered for lung transplant, 36 (63.2%) had PH [99]. Patients with PH were significantly

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more hypoxaemic than those without PH. A small number of patients (4) had more marked PH with mean PAP ≥40 mmHg [99].

PH develops as a consequence of alveolar hypoxemia and progressive destruction of the lung parenchyma and pulmonary vascular bed. However, other mechanisms may also be involved. An early study of the prevalence and impact of PH in adult patients with CF reported PH in 7 of 17 patients (41%) with stable but severe lung disease. PH correlated with declining FEV_1, diurnal and nocturnal oxygen saturation [4]. However, Doppler echocardiography, although used routinely as an initial screening test to estimate PAP, may frequently be inaccurate and some studies report poor correlation with right heart catheter measures [99]. The clinical impact of PH in most CF patients' management is unclear, although a trend towards worsening mortality has been observed in some small studies.

No properly conducted studies of PH management in CF have been reported.

10. PH in non-CF Bronchiectasis

There are no systematic studies to determine true prevalence of PH in bronchiectasis, which is defined as a progressive and permanent dilatation of predominantly medium and small airways. Bronchiectasis is often accompanied with significant airway obstruction and airflow limitation, and is associated with considerable morbidity but low mortality.

In a recent study of 94 patients with bronchiectasis, 31 patients (32.9%) had PH, defined as systolic PAP of ≥40 mmHg on Doppler echocardiography [100]. Significant correlation was observed between right ventricular dimensions and systolic PAP (r = 0.74) while RV dimensions were inversely related to PaO_2 values (r = - 0.37) suggesting a role for hypoxemia in the development of PH [100].

CT scan-derived measurements of the pulmonary artery have been shown to correlate favourably with the mean PAP derived from right heart catheterization [101-104]. In a study of 91 patients with bronchiectasis, increasing PH as characterised by CT measurements of PA dimensions was found to be an important prognostic marker [104].

As with CF patients, there is lack of data in managing PH in this group of patients.

11. PH in interstitial lung diseases

Interstitial lung diseases (ILD) are characterized by restrictive lung physiology with progressive impairment of gas exchange resulting in alveolar hypoxemia and PH. Mortality in these conditions is predicted by the degree of hypoxemia, spirometry and functional capacity as defined by 6MWD and presence of PH [105-108].

The prevalence of PH in IPF is high and varies between 32 - 85%. PH is mostly of moderate severity although in a few patients pulmonary pressures may approximate systemic levels

[109-111]. In one study of 212 patients with ILD screened by echocardiography and/or right heart catheter 29 (14%) had PH and 13 (6%) had severe PH defined as PAP ≥ 35mmHg [112]. To clinically diagnose PH in ILD is a challenge due to the overlap of symptoms of breathlessness and functional impairment in both conditions.

The pathophysiology of PH due to chronic lung fibrosis is under active investigation (Figure 2). Mechanisms other than alveolar hypoxemia and loss of parenchymal tissue may lead to development of PH in this condition [113-115]. The development of pulmonary fibrosis was closely linked in experimental studies to elevated pulmonary artery pressures [116]. Vascular remodelling in ILDs is heterogeneous with fibrotic areas being less vascularised and normal tissue being hyper-vascularised with the creation of anastomoses between capillaries and pulmonary veins [108]. An imbalance has been observed between pro-angiogenic and anti-angiogeneic factors with reduction of vascular endothelial growth factor (VEGF) and up-regulation of epithelium-derived growth factor (EDGF). In animal models, reduction in VEGF has been linked to endothelial apoptosis and PH [108,117]. Vascular smooth muscle cell growth factors are thought to be released from apoptotic endothelial cells which in turn lead to muscularization of the vasculature which augments PH [116,117]. In addition, endothelial dysfunction with reduced levels nitric oxide and prostacyclins and increased presence of vasoconstrictive mediators, such as endothelin-1 and thromboxanes may contribute to the development of PH [108,116,117].

Recent experimental work focused on the role of adenosine in development of PH in chronic lung disease [118]. Adenosine through G protein linked pathways has been associated with progression of fibrotic lung disease and PH through the adenosine receptor, A2bR [118,119]. Karmouty-Quintana et al. were able to demonstrate that inhibition of the A2bR, by inhibition or genetic removal of the receptor, slowed the progression of the fibrotic process and associated PH in rodents [120].

Vascular remodelling has been observed in other forms of interstitial lung diseases. In systemic sclerosis an autoimmune disorder involving skin fibrosis, respiratory complications are the commonest causes of death [121]. The prevalence of PH in systemic sclerosis is as high as 45% [115]. Autoantibodies, including anti-fibrillin and anti-EC antibodies, have been implicated in endothelial apoptosis and endothelial injury with the resultant inflammatory reaction. Advanced systemic sclerosis is associated with reduced capillary density which could contribute to PH [108,122,123].

In sarcoid, granulomatous involvement of the pulmonary arteries with occlusion and peri-vascular inflammation, invasion of pulmonary veins with inflammatory cells, and direct compression of the arteries by lymph nodes are thought to contribute to the development of PH. Endothelin-1 has an important role in PH in sarcoid with high levels reported in the broncho-alveolar fluid of affected patients [124]. Currently there is no clear evidence to suggest a role for angiogenesis or endothelial injury in sarcoid-related PH [107,125].

Few small studies have suggested a possible role of vasodilators in attenuating the progression of PH in ILD [126,127]. The development of PH in ILD is associated with high mortality, hazard ratio for death of 8.5 (95%CI: 4-17) [128]. However, most guidelines do not recommend use of PAH-specific treatments in patients with ILD [2,129].

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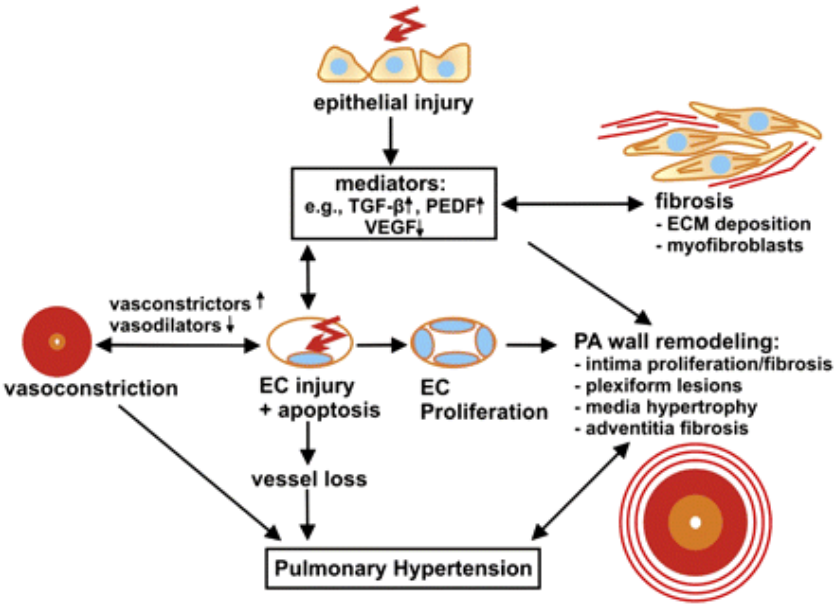

Figure 2. Concept for the development of pulmonary hypertension (PH) in IPF/UIP. Epithelial injury with subsequent production of different mediators is the hallmark of fibrosis induction. These mediators induce fibroblast activation with extracellular matrix (ECM) deposition, which leads to fibrosis. Some of these mediators (e.g., TGF-β) also activate ECs and, as a result of a shift in favor of increased angiostatic (e.g., pigment epithelium–derived factor [PEDF]) and reduced angiogenic factors (e.g., vascular endothelial growth factor [VEGF]), EC apoptosis results. Apoptotic ECs produce less vasodilators, but more vasoconstrictors, which leads to augmented vasoconstriction of smooth muscle cells (SMCs). At the same time, EC apoptosis gives rise to a reduction in vascular density, but also to enhanced production of vascular SMC (VSMC) growth factors, which is important for remodeling of mesenchymal cells in the PA wall. However, EC apoptosis also results in proliferation of apoptosis-resistant ECs or endothelial progenitors, with the consequence of angioproliferative lesions, including plexiform lesions. Another component of PA wall remodeling is the release of additional factors generated in the fibrotic tissue, which contribute to PA wall remodeling from the outside of the vessel; *Farkas L et al., AJRCMB 2011 [107], Reprinted with permission of the American Thoracic Society.*

12. Developmental abnormalities and PH

In the largest registry to date, 42 (12%) of 362 children (<18 years) with confirmed PH (defined as mean PAP of ≥25mmHg) had associated respiratory diseases or hypoxemia [130]. Bronchopulmonary dysplasia (BPD) was the commonest condition; other disorders included congenital diaphragmatic hernia, congenital pulmonary hypoplasia and kyphoscoliosis [130]. BPD traditionally was defined by the presence of persistent respiratory distress, abnormal chest radiography and requirement for oxygen supplementation [131]. With improvements in neonatal care, persistent lung disease after prematurity is no longer characterised by florid fibro-proliferative lung disease, but reduced vascular development and enlargement of distal airspaces associated with impaired gas exchange and development of PH [132]. Congenital diaphragmatic hernia presents similarly and is associated with variable lung growth leading to persistent PH [133]. Specific drug treatments for PH in this group of disorders have not been studied.

13. Conclusions

Pulmonary hypertension in chronic lung disease and/or hypoxia is a relatively common complication caused by complex pathophysiologic processes. Alveolar hypoxia, either sustained or repetitively intermittent, triggers the development of PH, although other mechanisms are also important. Development of PH is associated with worsening dyspnoea with the long-term prognosis dependant on the underlying disease process. Treatment of PH is largely defined by the underlying lung pathology. Therefore, etiological diagnosis and assessment of PH by WHO functional class is critical for management. Different classes of drug therapies have been developed as a result of our current understanding of the pathophysiology of PH. Although the treatments have had some impact on the progression of PH, further research is required to more fully understand the condition and develop better therapeutic approaches.

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