

Review Article

Pulmonary Hypertension in Parenchymal Lung Disease

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Idiopathic pulmonary arterial hypertension (IPAH) has been extensively investigated, although it represents a less common form of the pulmonary hypertension (PH) family, as shown by international registries. Interestingly, in types of PH that are encountered in parenchymal lung diseases such as interstitial lung diseases (ILDs), chronic obstructive pulmonary disease (COPD), and many other diffuse parenchymal lung diseases, some of which are very common, the available data is limited. In this paper, we try to browse in the latest available data regarding the occurrence, pathogenesis, and treatment of PH in chronic parenchymal lung diseases.

1. Introduction

Pulmonary arterial hypertension (PAH) is defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest, with a mean pulmonary capillary wedge pressure (PCWP), left atrial pressure or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg validated by right heart catheterization (RHC) [1]. These values are being used by all PAH registries and in all randomized controlled trials (RCTs) [2–7]. Pressure measurements during exercise are no longer recommended or supported by data for pulmonary hypertension (PH) diagnosis. As of 2009, based on the latest Dana Point Classification [1], PH due to underlying parenchymal diseases, such as COPD and interstitial lung disease (ILD), remains in group 3. Other diseases with multisystemic, and more importantly pulmonary, manifestations such as connective tissue diseases (CTDs), or sarcoidosis are categorized separately (groups 1.4.1 and 5.2, resp.).

In patients with parenchymal lung disease, PH is reported likely modest (mPAP = 25 to 35 mmHg), although in some subjects PAP can be markedly increased (mPAP = 35 to 50 mmHg) [8, 9]. In such patients, especially in those who have mild-to-moderate impaired lung mechanics, this pressure increase is considered as “out-of-proportion” PH. As an example, in a retrospective study regarding RHC measurements in COPD patients, moderate-to-severe PH

(mPAP > 40 mmHg) has been found in only 1% of the study population [9].

Recently, the German consensus group attempted to define severe PH in patients with chronic lung disease according to the following criteria (at least two out of three have to meet): (a) mPAP > 35 mmHg, (b) mPAP ≥ 25 mmHg with limited cardiac index (CI < 2.0 L/min/m²), and (c) PVR > 480 dyn/s/cm⁻⁵ [10]. This definition describes less than 5% of patients with lung disease and gives a quantitative dimension to the “out-of-proportion” approach.

Epidemiological input on the prevalence of “out-of-proportion” PH is not available, except for few scattered data from subgroup analyses out of large studies. In a survey by a cardiac echo laboratory, the prevalence of all-cause PH (determined as systolic PAP > 40 mmHg) was 10.5% [11]. Among those subjects, only 9.7% had underlying lung diseases and hypoxia. In general, there is limited, albeit adding up data (Figure 1) regarding “out-of-proportion” PH due to chronic lung disease.

2. Pathophysiology

The pathophysiological mechanism in “out-of-proportion” PH due to parenchymal lung disease is multifactorial and depending on the underlying type of lung parenchymal

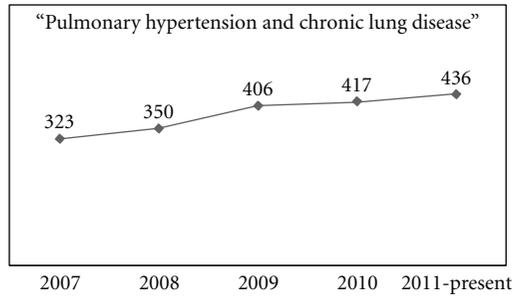


FIGURE 1: Distribution of PubMed search results within the last 5 years, per calendar year, with the search terms “Pulmonary hypertension and chronic lung disease.” Results contain original research articles, experimental articles, reviews, and case reports.

involvement. In general, mechanisms include chronic hypoxic vasoconstriction (which is a major factor), mechanical lung stress, capillary loss, smoking habit effects, and inflammation. The acute hypoxic effect in systemic circulation is vasodilation, whereas in pulmonary circulation it triggers an acute vasoconstrictive process regulated by endothelin, serotonin, and other compounds and mediated by ion-channel activity in pulmonary arterial smooth muscle cells (SMCs) [12]. Additionally, pulmonary vascular endothelial cells appear to exhibit a paracrine-like activity, metabolizing and uptaking vasoactive compounds that act on the pulmonary vascular tone under hypoxic state, probably contributing to hypoxic vasoconstriction [13].

On the other hand, in chronic hypoxia, which is the case in parenchymal lung disease, it seems that multiple pathological changes may occur in pulmonary vasculature, such as fibrous remodeling and an increase in both the number and mass of SMCs in the arterial wall, resulting in higher PVR over time and development of PH [14, 15]. In animal models, acute and chronic hypoxia appears to share causative intercessors in the disease cascade [16]; therefore, hypoxia may not only start the PH process but also encumber the disease, if not reversed.

In idiopathic pulmonary arterial hypertension (IPAH) and other forms of PH, it is widely accepted that a key histological finding is the plexiform lesion seen in the vast majority of patients [17, 18]. The plexiform lesion develops when capillary formations produce a network that spans in the lumens of dilated thin-walled, small pulmonary arteries. Medial hypertrophy also can be present in smaller arterioles, caused by intimal thickening attributable to the accumulation of one or more layers of myofibroblasts and fibrous matrix proteins within the neointimal space between the endothelium (tunica intima) and the internal elastic lamina. In more advanced stages, small pre- and intra-acinar arterioles predominantly exhibit complex lesions, that cause occlusion of the vessel’s lumen, including concentric laminar intimal proliferation, called “onion skin” or concentric-obliterative lesions, and glomeruloid-like plexiform lesions [19]. Interestingly, this lesion was found to be similar in histological appearance with those occurring in limited cutaneous systemic sclerosis (lc-SSc) [20]. However, almost a decade

later, it was reported that lc-SSc lesions were all polyclonal, in contrast with plexiform lesions in IPAH which were mainly monoclonal (80%) [21].

3. Diagnostic Approach

Due to the limitations of the invasive, albeit consistent, and accurate RHC, transthoracic tissue Doppler echocardiography (TTE) has emerged to fill the diagnostic gap and noninvasively assess the systolic pulmonary artery pressure (sPAP) in order to detect PH at an earlier stage. This technique, when applied by well-trained experts, can be very useful as a “sentinel” study prior to RHC. On the other hand, there is a possibility of misinterpretation which may lead to PH misdiagnosis and devastating consequences [38]. It should be emphasized that TTE can provide only estimates of pulmonary arterial pressures and that RHC is needed in order to establish PH diagnosis. The technique of TTE has been used widely not only as the study of choice in PH screening, but also as the “gold standard” frequent follow-up study in patients under treatment [39]. In a recent prospective trial assessing TTE and RHC measurements in 155 PH patients, there was a significant correlation between RHC and TTE [40]. More specifically, single TTE parameters performed well in predicting final PH diagnosis in this cohort, such as sPAP (area under the curve (AUC) 0.63, $P = 0.025$), the lateral apical RV longitudinal strain (RVaSI) (AUC 0.76, $P = 0.001$), and the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/E’) (AUC 0.84, $P < 0.001$). In addition, TTE showed a sensitivity of 33.33% and specificity of 100% in all-type precapillary PH identification, as well as 84.72% negative predictive value (NPV) to rule out the disease. However, in a recent analysis of subjects from the REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) study by Farber et al. [41], in 1883 patients that underwent both RHC and TTE, with the reservation that there were cases where several months have passed in between the tests, there was little association between serial TTE and RHC values. Additionally, repeat TTE measurements alone have shown to be insufficient to accurately monitor changes in PAP or disease progression.

Nowadays, TTE remains unable to replace RHC in establishing PH diagnosis, although it is very reliable for screening, following up, and providing indices of disease severity [42]; furthermore, TTE may distinguish pre- from postcapillary PH in certain cases.

4. Pulmonary Arterial Hypertension Associated with Connective Tissue Diseases That Affect Lung Parenchyma

Pulmonary hypertension is an increasingly recognizable complication and a major cause of death in patients with connective tissue diseases (CTDs), notably occurring in systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and mixed CTD (MCTD), overall affecting 3% to 13% of such patients [43–46]; these

pathologies may develop solely or in association with ILD [47, 48].

Originally, pulmonary hypertension in IPAH and CTD was thought to share similar histologic and pathophysiologic characteristics [49, 50]. However, there is growing clinical evidence regarding differences in the disease process between CTD-PH and IPAH, in terms of endothelial and metabolic functions, as well as histological trails [51, 52]. In a study regarding the expression and activity of pulmonary endothelial angiotensin-converting enzyme (ACE), endothelial metabolic dysfunction was noticed in CTD-PH, compared to a group of IPAH patients. There was also functional evidence that a reduced DLCO value in patients with PAH-CTD was related to the degree of functional capillary surface area (FCSA) loss [53]. It is of interest that pulmonary endothelial dysfunction, based on the aforementioned techniques, was seen in patients with limited and diffuse systemic sclerosis at early disease stages, prior to PH development [54]. These findings could at least partly justify the worse prognosis in such patients, despite their hemodynamic semblance with IPAH [55, 56].

Beside direct involvement of pulmonary vasculature (i.e., group 1), pulmonary hypertension in CTDs may be due to left heart disease, lung parenchyma involvement, chronic thromboembolism (related to groups 2, 3, and 4 resp.), or even venoocclusive disease, often presenting a difficult diagnostic challenge.

4.1. Polymyositis/Dermatomyositis and Pulmonary Hypertension. These myopathies are part of the idiopathic inflammatory myopathies family, characterized by proximal muscle weakness, elevated serum creatine kinase, abnormal appearance in electromyography, and inflammatory cell infiltration in muscles. In polymyositis and dermatomyositis (PM/DM), involvement of multiple organs is common [57–59]. The most common affected site, apart from muscles, is the lung, with the general pulmonary complications reaching 40% in such patients, resulting in significantly high mortality rates [60].

Pathogenesis is incompletely understood, with the obvious factor being the autoimmunity as PM/DM commonly presents along with other autoimmune diseases. Recent data suggest a genetic base of the disease that might predispose to autoimmunity [61–63]. In PM specifically, the muscle fiber seems to be the main target. On the other hand, DM is characterized by deposition of membrane attack complex in muscle capillaries. Interestingly, antinuclear and anticytoplasmic autoantibodies are found in up to 90% of patients with PM and DM, allowing clinicians to define homogenous cohorts of PM/DM patients [64].

Pulmonary hypertension occurrence in PM/DM is not thoroughly designated, with available data only in a case report basis. The majority of patients present with breathlessness in effort and pulmonary function test restriction or DLCO decrease. It is of interest that PH in PM/DM affects mainly females [65, 66]. In one autopsy series, 20% of patients with PM had pulmonary arterial medial and intimal hypertrophy, a clue that could be linked to PH pathogenesis

in such patients [67]. Another major factor in the PM/DM-PH pathogenesis could be the presence of ILD, that is quite common in the disease (5% to 65%) [68, 69]. True prevalence of PM/DM-PH is still not known, underlining the need for earlier referral of patients and RHC diagnosis confirmation.

4.2. Systemic Sclerosis and Pulmonary Hypertension. Systemic sclerosis (SSc) is a chronic systemic autoimmune disease characterized by fibrosis, vascular alterations, and autoantibodies. It is mainly expressed in two forms, (i) the limited systemic sclerosis-scleroderma with cutaneous manifestations such as CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) syndrome, a term recently quite abandoned, and (ii) the diffuse systemic sclerosis-scleroderma, which is rapidly progressive and is characterized by multiple internal organ involvement usually including interstitial lung disease of progressive severity [70].

The prevalence of PH in patients suffering from SSc is reported to be 7% to 35%, depending on the cohort studied [46, 71, 72]. Unfortunately, at the time of SSc-PH diagnosis, the plurality of these patients has been reported to be already in New York Heart Association (NYHA) functional class (FC) III or IV, which is of poorer survival compared to NYHA-FC II patients [1, 73–75].

Interestingly, in recent data reported by the French PAH-SSc Network [76], a considerable number of patients in NYHA-FC II with mild symptoms at the time of diagnosis had already severely impaired hemodynamic profile (mPAP > 35 mmHg, cardiac index of less than 3 L/min/m²). In the same study, the 3-year survival in NYHA-FC II patients was 80%, higher than previously reported (>66%) by the UK PH research group [74].

In a recent subgroup analysis of the largest known to date US cohort of RHC-confirmed PH patients [77] (REVEAL study), SSc-PH patients did not differ in hemodynamics at the initial diagnostic RHC compared to other CTDs, with an exception in the right atrial pressure (RAP) (SSc-PH group RAP was 9.1 ± 5.9 versus 8.1 ± 5.0 mmHg, $P = 0.05$). In addition, a higher percentage of patients with SSc-PH were in NYHA-FC IV at the time of enrollment, compared with patients suffering from other CTDs ($P = 0.04$), but the 6-minute walking distance test (6MWD) was not significantly different. In relation to pulmonary arterial pressure estimates by TTE at the time of enrollment, SSc-PH patients were significantly better than in other CTDs, with a lower percentage of RV enlargement and LV systolic dysfunction. The 1-year survival for SSc-PH patients was 87%, comparing to 93% of IPAH. In a 3-year survival followup, rates dropped to 47% for SSc-PH. Having in mind that these patients were treated under the current guidelines, their high 3-year mortality raises questions about the effectiveness of their current management. It should be noted that systemic sclerosis associated PH may be multifactorial: true PAH, left heart disease associated PH, and ILD-associated PH might sometimes overlap in the same patient.

4.3. Systemic Lupus Erythematosus and Pulmonary Hypertension. Systemic lupus erythematosus (SLE) is a complicated autoimmune disease of unclear pathogenesis, affecting multiple organs [78]. The pulmonary involvement, which results in SLE-PH, appears commonly in adult patients.

The theory of vasculitis, *in situ* thrombosis, and SMCs proliferation also applies in SLE-PH pathophysiology, with the exact causal relationship being still under investigation [79–82]. Several factors are incriminated for the induction of SLE-PH, such as hypoxic vasoconstriction, pulmonary venous hypertension resulting from left heart disease, antiphospholipid antibody-induced chronic or acute thrombosis, and pulmonary venoocclusive disease (PVOD) [83–88]. There are several pathological similarities in SLE-PH and IPAH, including SMCs hypertrophy, hyperactivation of transcription factors like hypoxia inducible factor-1 alpha and nuclear factor of activated T-lymphocytes, decreased expression of certain voltage-gated potassium channels, and *de novo* expression of antiapoptotic proteins [89]. Interestingly, immunoglobulin and complement deposition has been found in the pulmonary arterial wall of SLE patients [90]. In addition, mitral and aortic valve damage (also known as Libman-Sacks endocarditis) might occur in SLE patients, cause regurgitation, and subsequently provoke pulmonary venous hypertension. The exact incidence of this complication has not been effectively determined.

The prevalence of SLE-PH is largely unknown, with unconfirmed data reporting it from 0.5% to 14% in adults, in whom it is commonly associated with Raynaud's phenomenon [91, 92], and in childhood-onset SLE approximately 4%–8% using TTE assessment [93]. In a study by Prabu et al. [94] in SLE patients assessed by TTE, the prevalence of PH was lower than it usually appears (4.2%), and only 3 of the 12 study patients were found to have high sPAP (>40 mmHg). Although the study sample was very small, these results are worth noting because of the study population, which, in contrast to other studies, had a community nontertiary background and therefore might be considered as vicarious of the general SLE population.

4.4. Rheumatoid Arthritis and Pulmonary Hypertension. Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease, affecting 1% of the general population and over 5% in ages >65 years. Besides its articular manifestations, RA can cause severe disability, with multiple extra-articular insults in over 40% of all RA patients, including the lung, with ILD being the most common manifestation in this organ [95–98].

Incidence of RA-PH is rather unknown, and the largest up-to-date study by Dawson et al. ($n = 146$) reported that 21% of the cohort had mild-to-moderate PH as assessed by TTE, while 19% of all patients enrolled had sPAP values within the 30–35 mmHg range. Major limitation in this study was the low cut-off point selection for sPAP (30 mmHg), which might have resulted in overestimating a considerable number of RA patients that were in the “grey zone” and might have led to precarious results [95].

4.5. Sjögren Syndrome and Pulmonary Hypertension. This is a chronic inflammatory disorder characterized by diminished lacrimal and salivary gland function and associated with lymphocytic infiltration of exocrine glands, especially the lacrimal and salivary glands. Sjögren syndrome (SS) also affects extraglandular systems such as skin, lung, heart, kidney, neural, and hematopoietic system. It can be seen in a sole form as a primary disorder (primary SS) or in the onset of an associated rheumatic disease (RA, SLE, SSc) with a peak among women >50 years of age [99]. The major complaints are skin dryness, xerostomia (mouth dryness), and keratoconjunctivitis sicca (dry eyes). In primary SS, there is a subclinical lung inflammatory process in more than 50% of patients, but interestingly, only 1 in 5 develops clinically significant pulmonary disease. Lung insult can be multiple, with a variety of manifestations such as xerotrachea and bronchial sicca (dryness in the tracheobronchial tree), obstructive small airway disease, ILD, lymphocytic interstitial pneumonitis (LIP), pleural effusions, lung cysts, thromboembolic disease, and PH [100].

Pathogenesis of PH in SS remains a clinical enigma. Drawing on data from a small number of reported cases (45 overall, since 1982; PubMed search June 27, 2012), patients with SS-associated PH (SSPH) have Reynaud's, cutaneous vasculitis, and ILD more frequently, compared to SS patients without PH. In addition, they seem to have quite frequent detectable antinuclear, anti-Ro/SSA, and anti-RNP autoantibodies, as well as positive rheumatoid factor and hypergammaglobulinemia. In summarized data available from 32 out of the 45 overall reported cases, patients' functional status was found to be markedly impaired (NYHA-FC III and IV in most cases), and so were their hemodynamics (mPAP = 44 ± 11 mmHg, CI 2.91 ± 0.72 L/min/m²) [101]. These findings, although punctuating the data insufficiency in this field, might suggest that systemic vasculopathy, activation of B-cells, and autoimmunity could be factors in the SSPH disease process.

5. Sarcoidosis and Pulmonary Hypertension

Sarcoidosis is a chronic, systemic granulomatous inflammatory disease that can affect any organ [102]. Although there is massive progress during the past decade, the pure pathogenesis of sarcoidosis is still undistinguished.

Sarcoidosis-associated PH (SA-PH) is one of the trickiest to define and lies in group 5.2 (PH with unclear and/or multifactorial mechanisms/systemic disorders) in current Dana Point PH classification, mainly because of its heterogeneity and lack of data, although this specific categorization has been criticized [103]. The main criticism is that sarcoidosis should be included in group 3 (PH owing to lung disease and/or hypoxia), along with pulmonary Langerhans cells histiocytosis (PLCH) and lymphangioleiomyomatosis (LAM), which are currently also classified in group 5.2, based on the fact that PH in such cases mainly occurs due to massive lung involvement and profound hypoxia [104, 105].

Several pathogenic mechanisms are implicated in SA-PH development, with major causal factor the destruction of distal capillaries due to fibrosis that leads to chronic hypoxia,

increased PVR, and pulmonary arterial pressure [106–108]. Vascular involvement is quite established in pulmonary sarcoidosis, with a reported occurrence of 69% to 100% in pathological-histological case studies [109, 110]. However, it is of interest that SA-PH has already been stated as an early complication in the disease course. In addition, there is no reported correlation with the severity of SA-PH and the grade of lung fibrosis. These findings could suggest that other mechanisms might contribute to PH development in such patients, such as “outside” compression by mediastinal and hilar lymphadenopathy on main pulmonary arteries or their large branches [111], vascular granulomatous involvement [112] with the possibility of secondary PVOD development, and pulmonary vasoconstriction induced by vasoactive agents [113]. In certain cases, portal hypertension due to liver sarcoidosis can also cause PH mediated by increased circulating endothelin-1 (ET-1) levels [114].

The exact prevalence of SA-PH is not known, partly because of the population selection in several studies and their different diagnostic protocols. Recently, two separate single-center studies, concerning SA-PH development in consecutive patients suffering from sarcoidosis, reported an incidence of 5% to 15% [115, 116]. In other cohorts enrolling symptomatic-only sarcoidosis patients, the prevalence of SA-PH was higher than 50% [117, 118]. The highest prevalence documented by RHC has been reported in patients listed for lung transplantation (74%), with a concurrent increase in mortality rate, compared to listed patients without PH [111].

6. Idiopathic Pulmonary Fibrosis (IPF) and Pulmonary Hypertension

IPF is an idiopathic, fibrosing, interstitial, chronic lung disease with a characteristic appearance in histological findings currently known as usual interstitial pneumonia (UIP). It involves abnormal collagen deposition in the pulmonary interstitium (alveoli walls) with an associated inflammation. IPF has been linked to cigarette smoking and gastroesophageal reflux disease, but these factors are not present in all IPF patients. Genetic associations with the disease include pulmonary surfactant-associated proteins (SFTPA-1 and SFTPA-2), telomerase reverse transcriptase (TERT), and telomerase RNA component (TERC) [119, 120]. It is of interest that statistically significant association in survival has been reported between IPF patients with and without PH at the time of initial IPF diagnosis [121]; PH in IPF can develop either as consequence of the fibrotic process or disproportionate to the degree of fibrotic lung damage [122]. Although chronic hypoxia and its subsequent pulmonary arterial vasoconstriction are thought to have a major role in secondary IPF-PH, studies that showed the existence of PH in such patients even with arterial pO_2 levels within normal range (normoxic) led the investigators to partly relinquish this concept and redirect to other possible underlying mechanisms [123–125]. However, in one study of 70 IPF patients, there was a significant, but rather loose, correlation between mPAP and both PaO_2 and DLCO ($R = -0.47$, $P < 0.001$ and $R = -0.46$, $P < 0.001$, resp.) [126].

In “out-of-proportion” to the degree of fibrotic lung damage IPF-PH, there is a much more complex mechanism involved. Taking into account the extensive alveolar damage, the growth of connective tissue, and the ongoing inflammatory process in IPF, vascular remodeling of pulmonary arteries might be more important in the development of “out-of-proportion” IPF-PH than hypoxic vasoconstriction. In favor of this perspective, there is an inconsistency in PH severity and pathological findings; reduction in vessel density and vascular ablation in IPF patients have been reported, especially in “honeycombing” areas, along with simultaneous development of new vessels (neangiogenesis) [127–132].

Furthermore, there is data regarding the role of endothelial cell dysfunction in “out-of-proportion” IPF-PH, also justifying the bad correlation between the severity of lung fibrosis and PH development. A microarray gene study involving a subgroup of IPF-PH patients revealed an unexpected underexpression of genes such as the vascular endothelial growth factor (EGF), the platelet endothelial cell adhesion molecule (PECAM), as well as factors known to regulate vascular tone, such as ACE and ET-1 ($P < 0.05$) [133]. In contrast, an overexpression of the phospholipase A2 gene was noticed, which could be potentially causative in pulmonary vascular remodeling [133].

Interestingly, several mediators that are established in IPAH have been recently incriminated for “out-of-proportion” IPF-PH. Such mediators are tumor necrosis factor alpha (TNF- α), platelet-derived growth factor (PDGF), and fibroblast growth factor [134]. Additionally, studies on the role of eicosanoids both in IPF and PH suggest a potential role of supplementation of PGE2 or prostacyclin in IPF patients, particularly those with PH [134]. The basic postulant in “out-of-proportion” IPF-PH pathogenesis may be ET-1, as suggested by recent data revealing a profibrotic ability of ET-1 in patients with IPF but no clinical evidence of PH [135]. Levels of ET-1 have also been found elevated in airway epithelium, type-2 pneumocytes, and pulmonary vascular endothelial cells [136–138]. In currently published experimental data, PDGF is under investigation as a potential therapeutic target in IPF and it is of interest that it has been found upregulated in PH. Furthermore, tissue growth factor beta (TGF- β), which is a possible pathogenetic cytokine of interstitial fibrosis, showed impaired signaling in patients with IPAH and could be another underlying mediator in pulmonary vascular remodeling in “out-of-proportion” IPF-PH [139].

Epidemiologically, both types of IPF-PH combined (secondary and “out-of-proportion”) affect a large number of patients with IPF, especially those who are listed for lung transplantation. The prevalence of PH in all IPF patients shows a wide range, being reported from 14.2% to 84% [124, 140].

This large variation in reported prevalence values might be related, at least in part, to the method of PAP measurement (estimated sPAP in TTE or exact mPAP in RHC), the difference in selected pressure cut-off value, and to the timing of measurement. In recently published data, it was suggested that a key point in such patient cohorts seems to be “how fast” PH progresses in time, and not “how severe”

PH is on a single time point of sPAP estimation by TTE or mPAP measurement by RHC [140–142]. The presence of PH confirmed by RHC in IPF lung transplanted patients preoperatively has a negative effect on survival and notably increases the risk for developing primary graft dysfunction (PGD) in the posttransplantation period; for every increase of 10 mmHg in mPAP, the odds of PGD increase by 1.64 (CI 95%, 1.18–2.26; $P = 0.003$) [141]. One study underlined a PH prevalence of 33% in the initial RHC measurements that jumped to 85% in the pretransplantation assessment. In another study, baseline prevalence was 41% and jumped to 90% in the follow-up RHC measurement [140, 142]. The question of whether the lung fibrotic process and the vascular alterations that lead to PH share common pathophysiologic pathways remains open.

It should be noted that possible treatment options in IPF-PH by means of PAH-specific agents have been tested; disappointingly, 3 large RCTs, where the dual endothelin receptor antagonist (ERA) bosentan and the phosphodiesterase-5 inhibitor sildenafil were used, gave negative results [26, 31, 32].

7. Lymphangiomyomatosis (LAM) and Pulmonary Hypertension

It is a multisystemic disease, affecting mostly young women and characterized by abnormal SMC deposition along lymphatics of the thorax and abdomen. As a result, there is a formation of lung cysts and abdominal tumors, predominantly renal angiomyolipomas [143–148]. As far as it concerns the lung, LAM decreases FEV₁ and DLCO, with the latter previously demonstrated as an independent predictor of mortality in patients listed for lung transplantation, and aggravates peak oxygen uptake (VO₂ max) [149, 150].

The pathogenesis of PH in LAM (LAM-PH) is quite complex and not completely clarified. As in other lung diseases, chronic hypoxia resulting from the damaged lung parenchyma (i.e., cyst formation) can cause pulmonary hypoxic vasoconstriction and increase PVR, trigger the vascular remodeling process, and establish PH. However, in LAM patients, there is a low reported observation of RV failure and high PAP at rest, suggestive of different pathway(s) [151]. Taveira-DaSilva et al. evaluated a cohort of LAM patients for PH, estimating resting and exercise PAP with TTE, under cardiopulmonary exercise testing (CPET). Overall, resting TTE-estimated sPAP was found to be 26 ± 0.7 mmHg, while exercise TTE-estimated sPAP was 40.5 ± 1.1 mmHg. Resting LAM-PH was present in less than 10% of the cohort (8 out of 95, sPAP = 43 ± 3 mmHg) [151]. In recently published data extracted from patients with severe disease, listed for lung transplantation and evaluated by RHC, morphological and clinical signs of PH were present in all subjects [152]. Similarly, another recent retrospective multicenter study reported data from RHC evaluations in LAM-PH patients. Severe PH (defined by the investigators as mPAP > 35 mmHg) was present in only 20% of patients. Interestingly, 6 patients received oral PAH specific therapy and improved hemodynamically (mPAP decreased from

33 ± 9 to 24 ± 10 mmHg and PVR from 481 ± 188 to 280 ± 79 dyn/s/cm⁻⁵). In this cohort of 20 female patients, the overall 2-year survival was 94% [153]. There is very few available data regarding LAM-PH, and the field needs more large-scale studies to extract more enlightening data regarding pathophysiology and prevalence of disease.

8. Chronic Obstructive Pulmonary Disease and Pulmonary Hypertension

The pathogenesis of “out-of-proportion” PH in COPD (COPD-PH) is quite complex and being continuously elucidated by ongoing research. Pulmonary vascular endothelial dysfunction, as well as the inflammatory effect, is roughly the outline of the disease mechanisms. A major inflammatory factor in COPD is thought to be tobacco smoke inhalation, with established vascular and parenchymal changes in human and experimental animal lungs, and could act additively in COPD-PH as a direct hit to pulmonary vasculature [154, 155]. There is a documented decrease of endothelial NO synthase (eNOS) expression and impaired vasodilation response in asymptomatic smokers, as well as in advanced COPD disease, delineating a potential role of eNOS in the disease [156–160]. Additionally, certain eNOS and ACE polymorphisms have been found to be associated with COPD-PH [161]. Interleukin-6 (IL-6) and the presence of its polymorphism were associated with higher PAP in COPD patients, adumbrating an involvement in COPD-PH pathogenesis [162, 163].

At first, as in other parenchymal lung disease-associated PH subtypes, acute hypoxia-induced vasoconstriction was thought to be the initializing factor in vascular remodeling. In fact, chronic hypoxia induces the neomuscularization of pulmonary arterioles, resulting in intimal thickening by SMC assemblage and extracellular deposition of plenteous collagen and elastin, a phenomenon widely referred as “intimal fibroelastosis.” Of great interest is that these changes have also been described in normoxemic (pO₂ within normal range) COPD patients without pulmonary hypertension and also in asymptomatic smokers [159]. In addition, in an experimental animal study, pCO₂ as well as pH was found to have an amplifying effect on acute hypoxia-induced vasoconstriction [164].

Recent data proposes an important role for serotonin (5-HT) and its transporter (5-HTT) in intimal fibroelastosis. The 5-HTT LL genotype, which is linked with greater 5-HTT expression, was found to be associated with considerably high PAP in COPD, compared to other polymorphisms [165]. A pathological examination of postpneumectomy lungs demonstrated mass attraction of mostly CD8+ lymphocytes infiltrating the vascular adventitia [166].

An adaptive response to hypoxemia is polycythemia (increased total erythrocyte number), which is also incriminated for alterations in pulmonary vasculature. It has been shown experimentally that a sole hematocrit increment in dogs can notably increase PVR by 112% ($P < 0.01$). Moreover, there was a combined augmentation effect of polycythemia and hypoxia, increasing PVR by 308% ($P < 0.005$)

TABLE 1: Representative randomized control trials and studies on non-PAH pulmonary hypertension related to parenchymal lung diseases.

| Treatment | Lung disease | Study/reference | Comments |
|-----------------|---|---|---|
| Sildenafil | Lung fibrosis including an IPF subgroup | Ghofrani et al., 2002, [22] | Improvement in hemodynamics and gas exchange |
| Sildenafil | IPF | Collard et al., 2007, [23] | Improvement in 6MWD in 57% of patients |
| Sildenafil | IPF | Jackson et al., 2010, [24] | No improvement in 6MWD |
| Sildenafil | IPF | Madden et al., 2006, [25] | Only 3 patients treated for 3 months and showed improvement in 6MWD and TTE parameters |
| Sildenafil | IPF | The IPF Clinical Research Network, 2010, [26] | There was no difference in 6MWD between the two groups, as a primary outcome measure |
| Sildenafil | COPD | Rietema et al., 2008, [27] | No improvement in stroke volume or exercise capacity |
| Sildenafil | Sarcoidosis | Barnett et al., 2009, [28] | In 9 patients treated with sildenafil out of 22 total, there was slight improvement in hemodynamics, 6MWD, and NYHA-FC |
| Sildenafil | Sarcoidosis | Milman et al., 2008, [29] | In 12 patients treated, who were listed for transplantation, there was a significant decrease in mPAP. No improvement found in 6MWD |
| Sildenafil | COPD | Blanco et al., 2010, [30] | In a RCT of 20 patients with COPD-associated PH, sildenafil improved acute pulmonary hemodynamics at rest and during exercise and deteriorated oxygenation |
| Bosentan | IPF | BUILD-1 study, King et al., 2008, [31] | Bosentan treatment in patients with IPF did not show superiority over placebo on 6MWD |
| Bosentan | IPF | BUILD-3 study, King et al., 2011, [32] | No treatment effects were observed on health-related quality of life or dyspnea. The primary objective was not met |
| Bosentan | COPD | Stolz et al., 2008, [33] | 30 patients with COPD were randomly assigned in a 2:1 ratio to receive either bosentan or placebo for 12 weeks. Bosentan did not improve 6MWD and deteriorated hypoxemia and functional class |
| Bosentan | COPD | Valerio et al., 2009, [34] | In a quite small sample size ($n = 16$), there was benefit in PAP, PVR, and 6MWD. No improvement in GOLD IV patients |
| Riociguat | COPD | Ghofrani et al., 2011, [35] | In a quite small sample size ($n = 22$), there was a trend of improvement in hemodynamics (abstract) |
| IV epoprostenol | Sarcoidosis | Fisher et al., 2006, [36] | In 5 patients treated with parenteral epoprostenol, there was improvement of NYHA-FC by one or two stages within 29 months |
| IV prostacyclin | COPD | Archer et al., 1996, [37] | Treatment of 7 mechanically ventilated patients for COPD exacerbation caused worsening of hypoxemia |

6MWD: 6-minute walking distance test; COPD: chronic obstructive pulmonary disease; INH: inhaled; IPF: idiopathic pulmonary fibrosis; IV: intravenous; mPAP: mean pulmonary artery pressure; NYHA-FC: New York Heart Association functional class; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; TTE: transthoracic tissue Doppler echocardiography.

[167]. Recently, it was demonstrated that the presence of excessive erythrocytosis in mice increased the sPAP *in vivo* [168]. Additive data shows that there is definitely a role of polycythemia in the COPD-PH mechanism, but in humans is yet to be investigated.

The true incidence of clinically significant resting “out-of-proportion” PH is difficult to be estimated in COPD patients, as most data comes from reports that include COPD patients with advanced disease, resulting in a notably wide reported range varying from 5% to 70% [169–171]. This is confounded by several limitations. Firstly, there are no large-scale studies assessing the true prevalence of COPD-PH by means of RHC. Commonly, the test selected for PH documentation in such patients is TTE. As already emphasized elsewhere in this paper, TTE can only estimate sPAP and mPAP values, and only the invasive RHC can establish the presence of elevated PAP. This must be kept in mind by the clinician when evaluating the reported incidence for COPD-PH, because in many settings PH diagnosis relies only on TTE. There is additive data for this statement, showing TTE inaccuracy in PAP and cardiac output (CO) estimation, when compared to RHC, in several PH subtypes [172]. Secondly, most available studies are of retrospective nature and include mostly patients with severe disease ($FEV_1 < 30\%$ predicted). As an example, studies on severe COPD patients report an incidence of 91%, with the majority suffering from mild-to-moderate PH (mPAP = 20–35 mmHg) and 1% to 5% suffering from severe disease (mPAP > 35–40 mmHg) [8, 169, 173]. However, in some COPD patients, the hemodynamic impairment might be more severe than expected from the related progress of parenchymal disease. This group of patients is characterized in anecdotal basis as “PH out-of-proportion to degree of respiratory compromise.” This is of significant interest, because such patients have been viewed as potential beneficiaries of PAH-specific therapeutic agents, although, as of now, there is neither consensus on the best candidates for studying such management, nor RCTs running.

It seems that there is a strong negative impact on survival from the occurrence of PH in COPD patients, even though the hemodynamic impairment is rather mild in terms of pressure values *per se*. The 5-year survival regarding severely affected COPD patients with PH (mPAP ≥ 25 mmHg) has been reported as low as 36%, compared to 62% in COPD patients without PH [174]. Although several studies demonstrate high mortality rates in COPD patients with pulmonary hypertension, it is still under discussion if the occurrence of pulmonary hypertension is an independent cause of death or just a sign of disease worsening.

9. Treatment Suggestions for Pulmonary Hypertension in Lung Disease

It should be emphasized that specific treatment for PAH has been approved by regulatory authorities for group 1 (PAH) only [1]. Drug-related information provided herein (text and Table 1) is based on case reports and small case series, provided to roughly inform the reader about current

anecdotal use of PAH-specific agents in selected cases. This results in minimum strength of evidence, and the need for large-scale randomized controlled trials is profound.

Patients with underlying parenchymal lung diseases who develop PH are always an intriguing subset regarding their management and treatment, as the occurrence of PH is associated with mortality; whether this association has a causal relation with mortality or simply represents a marker of disease severity is not clear.

There is no clear consensus on how or when to treat severe PH in parenchymal lung diseases. PAH-specific treatment in this setting does not ensure improvement of pulmonary vascular hemodynamics or exercise capacity while on the other hand might worsen ventilation/perfusion (V/Q) mismatch and subsequently lead to shunting and further hypoxia [27, 33, 37].

As of today, the European guidelines regarding “out-of-proportion” PH (PH owing to lung disease and/or hypoxia) recommend performance of TTE for screening (Class of recommendation-Level of evidence, I-C) and RHC for a definite diagnosis of PH due to lung disease (I-C). Again, the use of PAH-specific therapeutic agents is not recommended in this group (III-C). Additionally, optimal treatment of the underlying lung disease and the use of supplemental O₂ are the recommended therapeutic measures in such patients. In PAH associated with CTDs, the recommendation is for the same treatment algorithm as in IPAH (I-A); *terra incognita* remains the group of CTD patients with significant ILD, since such patients have usually been excluded from performed related RCTs. The performance of TTE is strongly recommended in all symptomatic patients with scleroderma for PAH screening (I-C) and RHC is recommended in all patients with the clinical question of starting a PAH-specific treatment (I-C). In nonsymptomatic patients with scleroderma, a screening study (TTE) may be considered (IIb-C) [1].

In conclusion, we emphasize again that the use of PAH-specific therapeutic agents is not approved for patients belonging to groups 3 and 5 by the Dana Point classification [1], which is the case of all the diseases analyzed in this review with the exception of CTDs. Clinical studies and RCTs should be performed in such nongroup 1 patients, in an effort to clearly designate subcategories of subjects that might benefit from specific treatments.

Authors' Contribution

I. Tsangaris and S. E. Orfanos had the main concept idea and critically reviewed and edited the paper, G. Tsaknis wrote, drafted the paper and performed the literature search, and A. Anthi critically reviewed the paper. All authors have read and approved the paper.

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