Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis: A Review

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive diffuse parenchymal disease with a poor prognosis. Pulmonary hypertension (PH) often complicates the course of IPF and may even be found in patients with preserved lung function. Possible pathogenetic mechanisms of PH in IPF include vascular destruction, pulmonary hypoxic vasoconstriction and vascular remodeling due to overexpression of cytokines and growth factors. PH in IPF patients is associated with decreased exercise capacity and a worse prognosis. Due to its prognostic significance, it seems important to investigate for PH in these patients. As the symptoms of PH in IPF are non-specific, the development of PH in a patient with known IPF can be easily overlooked. Noninvasive methods provide clues for the diagnosis, but their sensitivity is limited. Doppler echocardiography is a useful tool for the detection of PH which also provides additional information regarding associated cardiac abnormalities. However, right heart catheterization remains the gold standard diagnostic test. Therapeutic options for PH in IPF are limited. Long-term oxygen administration for the correction of hypoxemia should be recommended. The availability of new pharmacological agents in the treatment of PH has raised the possibility of

therapy in patients with IPF and associated PH. Whether these PH-targeted therapies may be of benefit in this patient group, in terms of improving functional outcomes and survival, remains uncertain.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing and progressive parenchymal lung disease of unknown etiology limited to the lung [1, 2]. IPF is the most common idiopathic interstitial pneumonia with a remarkable diversity of prevalence by country, ranging from 14 to 20 per 100,000 inhabitants [3–5]. It is a fatal disorder with a median survival of 2.5–5 years, as no effective treatment exists to date. Poor prognosis has been associated with older age, male gender, lower forced vital capacity, lower diffusing capacity, desaturation during exercise and the extent of fibrosis on imaging studies [6–8]. Pulmonary hypertension (PH) is recognized as a severe complication of IPF [6, 9]. The development of PH during the course of the disease has a negative impact on the functional status and quality of life of IPF patients and is associated with poor survival [10–13]. The approval of new drugs for the treatment of pulmonary arterial hypertension (PAH) has renewed interest in IPF and associated PH and raised the possibility of therapeutic intervention for these patients.

The present review attempts to explore the role of PH in IPF and summarizes the current knowledge about the epidemiology, pathogenesis, diagnosis, prognostic significance and possible treatment for this condition.

Definition and Epidemiology

The recent guidelines for the diagnosis and treatment of PH [14] classifies PH in IPF in the third group of 'PH due to lung diseases and/or hypoxia', differentiating this from the other clinical conditions causing PH. Based on the same guidelines, PH has been defined as an increase in mean pulmonary arterial pressure (mPAP) of ≥ 25 mm Hg at rest as assessed by right heart catheterization (RHC). At the present time, the definition for PH upon exercise as assessed by RHC is not supported by the guidelines due to the lack of published data. Another point concerning PH associated with lung disease is the definition of 'out of proportion' PH. The current guidelines use the criterion of mPAP ≥ 40 –45 mm Hg for the definition of 'out of proportion' PH in chronic lung diseases, but whether this threshold value is suitable for patients with IPF is not clear [14].

Despite its critical role, the epidemiology of PH in IPF has not been extensively studied, and the reported incidence is wide, ranging from 32 to 84% [10, 11]. Several factors account for this wide range in the prevalence of PH in IPF. First is the inclusion of both incident and prevalent cases in the studies. Patients in whom the diagnosis has been made several months or years ago are more likely to have advanced disease and theoretically more likely to have PH. Second is the method used for the diagnosis. RHC remains the gold standard for hemodynamic evaluation of pulmonary circulation, but it is an invasive procedure and impractical to perform in a serial fashion. On the other hand, transthoracic echocardiography (TTE) is a useful modality for the detection of PH; it is noninvasive, repeatable and convenient to perform in daily clinical practice, but its accuracy for the assessment of PH in IPF patients has been seriously questioned [15, 16]. Furthermore, when evaluated at an earlier stage of the disease, IPF patients may show normal hemodynamics at rest and develop significant PH only during exercise [17, 18]. Finally, the majority of data regarding the incidence of PH in IPF comes from selected cohorts of patients, mostly with advanced disease, undergoing evaluation for lung transplantation for whom RHC data are usually available.

Three studies have reviewed data from lung transplant registries. In a large retrospective analysis of RHC data

from the lung transplant registry of the US, PH was common in IPF patients awaiting lung transplantation; 46.1% of the subjects presented PH, defined as mPAP ≥ 25 mm Hg, and almost 9% had severe PH, defined as mPAP ≥ 40 mm Hg [19]. Variables independently associated with the presence of PH were the need for supplemental oxygen and the presence of elevated wedge pressure and forced expiratory volume in 1 s. In another analysis of data from the United Network for Organ Sharing between 2004 and 2005, 454 patients with IPF listed for lung transplantation were retrospectively studied. PH, defined as mPAP ≥ 25 mm Hg, was detected in 36% of the 376 patients who underwent RHC [20]. Finally, in a recent retrospective review of data of 626 lung-transplanted patients, PH confirmed with RHC was found in 43% of patients with a diagnosis of IPF (mPAP 33 ± 8 mm Hg, range 26–57 mm Hg) [21].

Other studies also report variable estimates of the frequency of PH in IPF patients. Nadrous et al. [11] used TTE to diagnose PH, defined as estimated right ventricular systolic pressure (RVSP) > 35 mm Hg at rest, in 84% of IPF patients who were evaluated at initial admission to a tertiary care referral medical center. Similarly, in a previous study we performed, we used TTE to screen for PH in a large cohort of 127 IPF patients at their initial admission to referral centers. Although the patients presented with varying impairment of functional status, increased estimated RVSP was present in more than half (55%) of our patients [22].

Other studies have used invasive hemodynamics for the estimation of the prevalence of PH in IPF patients. Lettieri et al. [10] retrospectively reviewed data from a cohort of patients with IPF who underwent RHC as part of an evaluation for lung transplantation. From a total of 79 patients, PH, defined as mPAP > 25 mm Hg, was present in 25 patients (31.6%). The presence of PH was associated with a lower diffusing capacity of the lung for carbon monoxide (D_{LCO}) and the use of supplemental oxygen therapy. Moreover, in a retrospective review of the RHC and pulmonary function test (PFT) data of 118 IPF patients seen at a tertiary referral center over an 8-year period, PH was noted in 48 patients (40.7%) [23]. Cardiac dysfunction might have played a role in this estimation, since 16.1% of the patients had an associated elevated pulmonary capillary wedge pressure. Finally, Nathan et al. [24], analyzing serial RHC data, showed progressive development of PH in patients with advanced IPF who were transplant candidates. PH was found in 38.6% of the patients at baseline, while at the time of transplant, 86.4% of the patients demonstrated PH.

Pathogenesis

The pathogenesis of PH in IPF is incompletely understood. Multiple diverse mechanisms are implicated in the development of PH such as vascular obstruction or destruction from progressive parenchymal fibrosis, pulmonary hypoxic vasoconstriction and vascular remodeling due to overexpression of cytokines and growth factors [25, 26].

The destruction of the pulmonary capillary bed by fibrotic tissue is an initial mechanism. Vessel ablation in areas of dense fibrosis and within fibroblastic foci contributes to overall reduction of vessel density and elevated pulmonary vascular resistance [27]. However, lack of close association between restrictive physiology and PH supports the hypothesis that factors other than fibrosis and progressive reduction in vasculature are involved in the development of PH in IPF [10–12]. A recent study demonstrated that iron deposition and alveolar septal capillary density, histologic features associated with post-capillary remodeling, were associated with RVSP, suggesting that these features are possible morphologic predictors of PH in IPF [28].

Furthermore, an imbalance between angiogenesis and angiostasis may underlie the pathogenesis of IPF-associated PH [25]. The existence of neovascularization in IPF was first described in 1963 by Turner-Warwick [29]. Other studies reported increased capillary density and angiogenesis in nonfibrotic lung tissues [27, 30–32]. However, the new vessels formed in fibrotic areas are abnormal and are characterized by the absence of an elastin layer, which may contribute further to the development of PH [27]. The role of capillary regression and proliferation and the resultant effect on PH is still unclear and needs to be further clarified.

Endothelial dysfunction may represent another mechanism accounting for the development of PH in IPF. Gagermeier et al. [33] suggested an abnormal vascular phenotype in a subgroup of IPF patients presenting moderate to severe PH. Using gene microarray analysis, a subset of differentially expressed genes was identified. A decrease in angiogenic factors such as vascular endothelial growth factor and platelet endothelial cell adhesion molecule as well as an increase in inflammatory and remodeling genes such as the phospholipase A₂ gene was observed. This fact suggests an alteration in the vascular cell phenotype in IPF patients that may contribute to the development of PH [33].

Hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy is a well-recognized mechanism

of PH in chronic lung disease [34]. Pulmonary vascular remodeling is more than just medial hypertrophy from long-lasting hypoxic vasoconstriction; all layers of the vessel wall appear to be involved, with intimal changes being the most prominent [34]. Undoubtedly, this mechanism plays a role, but it is unlikely to account for all cases of PH, for example the presence of PH in normoxemic IPF patients. Furthermore, intermittent nocturnal hypoxia and also exercise-induced desaturation, which are often present in IPF patients [8, 35], might represent important factors in the development of disproportionate PH in these patients and need to be appropriately evaluated [36]. Interestingly, Pouwels-Fry et al. [37] demonstrated that oxygen did not improve an exercise-induced increase in pulmonary artery pressure in IPF patients, suggesting that hypoxic vasoconstriction is not the only mechanism contributing to the acute increase in pulmonary pressure during exercise.

Several mediators have been implicated in the pathogenesis of both IPF and idiopathic PAH [25, 38]. This fact suggests possible common mechanistic pathways in the two disorders but also provides possible therapeutic targets. Profibrogenic leukotrienes are overproduced in both diseases due to upregulation of 5-lipoxygenase [39, 40]. Leukotrienes, in turn, may upregulate mediators such as tumor necrosis factor- α , platelet-derived growth factor and fibroblast growth factor, all of which are involved in both pulmonary vascular remodeling and lung fibrosis. Furthermore, prostaglandin E₂ levels have been reported to be reduced in bronchoalveolar lavage fluid of IPF patients [39], while there is evidence of decreased prostacyclin synthase expression in pulmonary vessels of patients with idiopathic PAH [41]. Decreased levels of prostaglandin E₂ may lead to increased expression of tumor necrosis factor- α and transforming growth factor- β , both of which are involved in interstitial collagen deposition and pulmonary artery remodeling [25].

Endothelin-1 (ET-1) is a powerful vasoconstrictor and also a mitogen that stimulates the proliferation of smooth muscle cells [42]. ET-1 may also participate in the pathogenesis of lung fibrosis through its effects on cellular apoptosis and the oxidant/antioxidant imbalance [43]. The molecule exerts its effects by binding to 2 distinct receptor isoforms in pulmonary vascular smooth muscle cells, i.e. endothelin A and endothelin B receptors. In patients with idiopathic PAH, enhanced expression of ET-1 was detected in plexiform lesions [44]. Elevated serum levels of ET-1 have been detected in patients with IPF as well [45]. Increased concentrations of ET-1 in bronchoalveolar lavage fluid and secretion of ET-1 from alveolar

macrophages have been reported in IPF and other pulmonary diseases [46]. Moreover, IPF lung tissue shows increased expression of the enzyme responsible for converting ET-1 [47], while arterial ET-1 levels were shown to correlate inversely with arterial oxygen and directly with mPAP in IPF patients [35].

Diagnosis

The symptoms of PH in IPF are nonspecific and include breathlessness, fatigue, weakness, palpitations and chest discomfort or syncope [14, 48]. Exercise limitation is one of the first manifestations at earlier stages. Physical signs such as an accentuated pulmonary component of the second heart sound, pansystolic murmur of tricuspid regurgitation, fixed split of the second heart sound and murmur of pulmonary insufficiency may be present. Signs such as jugular vein distension, hepatomegaly and peripheral edema characterize more advanced cases as right ventricular dysfunction worsens.

As symptoms in both IPF and PH overlap widely, the development of PH in a patient with known IPF can be easily overlooked. A high index of clinical suspicion is thus required for the diagnosis. Clinicians should pursue further diagnostic testing for PH when the patient presents symptoms which are disproportionate to the severity of parenchymal lung disease.

Besides, several comorbidities such as obstructive sleep apnea, coronary artery disease with left ventricular dysfunction and pulmonary embolism, which are common in IPF patients, may contribute to the development of PH in this patient population [49, 50]. Diagnostic testing is indicated not only for the establishment of a diagnosis of PH but also for differential diagnosis and for the exclusion of other causes of PH in patients with IPF.

Imaging

Findings of central pulmonary arterial dilatation, loss of the peripheral blood vessels and right ventricular enlargement on chest X-ray suggest the presence of PH. In general, the degree of PH does not correlate with the extent of radiographic abnormalities [14]. On computed tomography (CT), enlargement of the main pulmonary artery (>29 mm), right ventricular dilatation and an increased diameter of the pulmonary artery as compared with the aorta are indicative of the development of PH [51]. However, in a recent study, high-resolution chest CT findings failed to predict the presence of PH in advanced IPF [52]. High-resolution CT may also provide clues as to

alternative etiologies of PH such as pulmonary venoocclusive disease, which can be mistaken for IPF complicated by PH [53].

Electrocardiogram

An electrocardiogram (ECG) may provide supportive evidence of PH by demonstrating right ventricular hypertrophy and strain and right atrial dilatation. The ECG has insufficient sensitivity (55%) and specificity (70%) to be a screening tool for detecting significant PH [14]. Consequently, absence of the above ECG findings does not exclude the presence of PH.

Pulmonary Function Tests

PFTs and arterial blood gases are necessary to identify the contribution of parenchymal lung disease. Interestingly, a poor association between PH and pulmonary function has been found in several studies [10–12, 23, 54]. Lettieri et al. [10] did not find a significant difference in lung function indexes, except for D_{LCO} , between IPF patients with and without PH. The combination of a D_{LCO} of $<40\%$ predicted and the need for supplemental oxygen determined in subjects with a resting $SpO_2 <88\%$ identified the presence of PH with a sensitivity and specificity of 65 and 94.1%, respectively. Similarly, in the study of Nadrous et al. [11], none of the lung function tests correlated with estimated RVSP, with the exception of D_{LCO} , to which RVSP was inversely related. More recently, Nathan et al. [23] failed to demonstrate a significant relationship between measures of lung volumes with underlying PH, whereas a modest association was found between D_{LCO} and PH, with $D_{LCO} <30\%$ predicted associated with a twofold higher prevalence of PH.

Zisman et al. [55, 56] developed a method to screen for PH based on a formula to predict mPAP from standard lung function tests. In this equation, resting room air pulse oximetry (SpO_2) together with percentage forced vital capacity and $D_{LCO}\%$ predicted were found to be important indices for the calculation of pulmonary pressure. Although the formula has a low positive predictive value of only 51%, it provides a high negative predictive value of 96%, thus identifying patients with IPF that have a low risk of PH. A recent evaluation of this formula showed that it is a useful tool which can be used like TTE to screen for PH in IPF patients [57].

The development of PH is common in combined pulmonary fibrosis and emphysema syndrome [58–60]. This could be considered a distinct entity with a characteristic functional profile, with preserved lung volumes, strongly impaired D_{LCO} and hypoxemia upon exercise [61]. The

severe impairment of diffusion capacity probably represents the additive or synergistic effects of emphysema, fibrosis and pulmonary vascular disease and is one of the hallmarks of the syndrome [62]. The associated high prevalence of PH is a critical determinant of poor prognosis [58–60].

Exercise Capacity

Assessment of exercise capacity is a key part of the evaluation of PH. The most commonly used exercise tests are the 6-min walk test (6MWT) and cardiopulmonary exercise testing. Impaired gas exchange which worsens with exercise is a common feature in the pathophysiology of IPF and appears to have prognostic value as well [7, 8, 63]. When PH is present in the setting of IPF, common physiological abnormalities during exercise include decreased maximal oxygen consumption, increased dead space with progressive exercise and a low anaerobic threshold [64, 65]. Importantly, left ventricular dysfunction, which is often present in these patients, could be an additional factor that may further impair exercise performance [66].

Exercise limitation disproportionate to lung volume abnormalities and prominent arterial oxygen desaturation during exercise should raise suspicion of the development of PH in IPF patients. This negative impact of PH on the exercise capacity of IPF patients has been shown in several studies; in a cohort of patients with interstitial lung diseases evaluated for lung transplantation with RHC, patients with PH differed from those without PH in terms of distance walked and also minimal SpO₂ upon exercise [67]. In the study by Lettieri et al. [10], both the distance walked and SpO₂ at the end of the 6MWT were significantly lower in IPF patients with PH. Finally, in a study evaluating exercise intolerance in patients with pulmonary fibrosis via cardiopulmonary exercise testing, patients suffering from PH showed a significantly lower exercise capacity and worsened dyspnea, being more hypoxic both at rest and during exercise [13].

Gas exchange parameters and exercise desaturation seem to represent better indices than PFTs in characterizing PH in patients with IPF; in a recent study by Nathan et al. [16], the parameter from the 6MWT that best predicted PH was exercise desaturation. Specifically, desaturation to <85% presented 100% sensitivity and 61.9% specificity for detecting underlying PH. Furthermore, in another study, in a consecutive population of 81 patients with IPF who underwent cardiopulmonary exercise testing, resting RVSP was found to correlate significantly with exercise parameters indicative of gas exchange and

circulatory impairment but not with defective lung mechanics [68].

Transthoracic Echocardiography

TTE is a useful, noninvasive tool for the detection of PH. The estimation of pulmonary pressure is based on the peak velocity of the jet of tricuspid regurgitation using the simplified Bernoulli equation [69]. Tricuspid regurgitation velocity of 2.9–3.4 m/s, which corresponds to an estimated RVSP of 37–50 mm Hg, assuming a right atrial pressure of 5 mm Hg, is considered suggestive of PH [14]. Other echocardiographic variables that might raise suspicion of PH include a short acceleration time of right ventricular ejection, increased dimensions of right heart chambers, abnormal shape and function of the interventricular septum, increased right ventricular wall thickness and a dilated main pulmonary artery [14]. TTE can also provide additional information for associated abnormalities such as left ventricular systolic and diastolic dysfunction, valvular disease and pericardial effusion. Most studies report a strong correlation between Doppler echocardiography and pulmonary artery pressure assessed by RHC in IPF patients [15, 70]. The reported sensitivity of TTE-estimated RVSP for detecting PH ranges from 0.79 to 1.00 and specificity from 0.60 to 0.98 [48]. However, there are significant limitations in the performance of TTE in patients with chronic lung disease [15, 16]. In a cohort study of Arcasoy et al. [15] including 374 lung transplant candidates with advanced lung disease, estimation of RVSP by Doppler TTE was possible in less than one half (44%) of all patients. A discordance of greater than 10 mm Hg between estimated and measured RVSP was found in 52% of all patients. In addition, in the population with interstitial lung disease, the positive and negative predictive values of TTE were low when compared to RHC measures [15].

Right Heart Catheterization

RHC remains the gold standard method for the diagnosis of PH. It helps to establish the severity and etiology of PH and also to assess pulmonary vasoreactivity, thus giving useful information for guiding therapy and for prognosis [14]. When performed at experienced centers, RHC has low morbidity (1.1%) and mortality rates (0.055%) [71]. However, at this time, the indication to perform RHC in patients with PH associated with chronic lung disease is questionable since there is no clear indication for PH therapy [14]. RHC in advanced lung disease should be reserved for patients with suspected ‘out of proportion’ PH on TTE, for establishing a definite diagnosis

Table 1. Key diagnostic symptoms and tests for diagnosis and differential diagnosis of PH in patients with IPF

History	dyspnea disproportionate to ventilatory restriction, palpitations, chest pain
Physical examination	accentuated pulmonary component of S2, jugular vein distension, hepatomegaly, peripheral edema
Chest X-ray	central pulmonary arterial dilatation, cardiomegaly
CT chest angiography	main PA >29 mm, diameter of PA/aorta >1, exclusion of pulmonary embolism
ECG	right ventricular hypertrophy and strain
PFTs	reduction of D_{LCO} disproportionate to lung volumes
Arterial blood gases	low resting oxygen saturation, need for supplemental oxygen
Overnight oximetry	assessment of oxygenation during sleep; exclusion of obstructive sleep apnea
6MWT	low distance walked, significant exercise desaturation
TTE	tricuspid regurgitation, increased dimensions of right heart chambers
RHC	increased mPAP (≥ 25 mm Hg) with a low PWP (≤ 15 mm Hg)
BNP, NT-proBNP	elevated levels
Immunological markers	exclusion of connective tissue disease
PA = Pulmonary artery; PWP = pulmonary wedge pressure; NT-proBNP = N-terminal prohormone BNP.	

of PH in candidates for lung transplantation and also for patients presenting frequent episodes of right ventricular failure [14]. RHC might also be considered in IPF subjects with dyspnea insufficiently explained by lung mechanical disturbances, patients with low resting SpO_2 who need supplemental oxygen therapy or present significant exercise desaturation and even in patients demonstrating a reduction of D_{LCO} disproportionate to lung volumes [38, 72].

Natriuretic Peptides

Another approach to the diagnosis of PH in IPF patients is based on the measurement of natriuretic peptides. These are peptide hormones that are released from cardiac myocytes in response to cardiac pressure and volume overload [73]. Both B-type natriuretic peptide (BNP) and N-terminal prohormone BNP can serve as prognostic markers and screening parameters for PH [74–78]. In the study of Leuchte et al. [75], elevated BNP concentrations identified significant PH with a sensitivity of 0.85 and a specificity of 0.88 and predicted mortality in patients with PH and chronic lung disease. Conversely, a normal plasma BNP concentration is associated with a very low probability of PH and prolonged survival [74,

75]. In a retrospective review of 131 patients with IPF, Song et al. [78] found that BNP performed better than estimated RVSP as a marker of prognosis. Similarly, in a population of patients with interstitial lung disease, an increased serum BNP concentration was shown to be the strongest predictor of overall mortality [79].

Moreover, BNP can serve as a noninvasive marker that reflects the severity of PH; BNP concentration was shown to correlate significantly to hemodynamic measures, functional class and 6MWT distance [74]. However, BNP levels do not allow early diagnosis of mild or latent PH, and elevated plasma levels seem to normalize in completely compensated disease despite the presence of PH [72]. Moreover, the diagnostic accuracy of N-terminal prohormone BNP is diminished by renal function since renal excretion is the main route of clearance for the molecule [76]. Finally, further studies focusing exclusively on patients with IPF are needed to validate this marker in this patient population [75].

Table 1 summarizes the key diagnostic factors from patient history and physical examination and also the tests for diagnosis and differential diagnosis of PH in patients with IPF.

Prognostic Significance

The development of PH in IPF patients is associated with worse survival [6, 10–12, 78, 80, 81]. In an earlier prospective study in a cohort of 238 IPF patients, King et al. [6] showed that the presence of PH as estimated by the size of the pulmonary artery on chest X-ray correlated with mortality. More recently, in the study of Nadrous et al. [11], RVSP estimated by TTE had a significant adverse impact on survival; when patients were divided into 3 subgroups, i.e. RVSP ≤ 35 mm Hg, 36–50 mm Hg and >50 mm Hg, the median survival rates for these 3 groups were 4.8, 4.1 and 0.7 years, respectively. Thus, those patients with RVSP >50 mm Hg had significantly worse survival compared to the other subgroups [11]. In the study of Lettieri et al. [10], in which RHC data were retrospectively analyzed, increasing mPAP was shown to be a significant predictor of death; 1-year mortality rates were higher among those subjects with PH (28.0 vs. 5.5%, respectively; $p = 0.002$), while the presence of PH predicted mortality with a sensitivity and specificity of 57.1 and 79.3%, respectively. Furthermore, Hamada et al. [12] prospectively analyzed data of 78 IPF patients undergoing initial workup with RHC and PFTs. Although the cut-off value of mPAP of 17 mm Hg which was used does not fulfill the criterion for PH, the authors demonstrated a significant difference in the 5-year survival rate between the groups with normal (62.2%) and high mPAP (16.7%) [12]. In the same study, D_{LCO} was the only significant parameter to predict survival time [12].

Novel echocardiographic indices might prove useful for risk stratification in these patients before severe PH is established; in a study we performed in a small cohort of IPF patients with mild to moderate PH, tissue Doppler parameters of right ventricular function were found to be strongly associated with the severity of PH and correlated better with survival than conventional TTE parameters [82]. Lastly, Swigris et al. [80] showed that heart rate recovery after the 6MWT predicts survival in IPF patients. In a multivariate model, the presence of estimated RVSP >35 mm Hg was a predictor of heart rate recovery 1 min after the 6MWT [80].

The impact of preoperative PH on the outcome of patients with advanced lung disease after lung transplantation is controversial [83–87]. However, in a cohort study of 830 IPF patients in the International Society for Heart and Lung Transplant Registry, elevated pulmonary artery pressure proved to be a risk factor for 90-day mortality after single-lung transplantation [87].

Treatment

Currently, there is no specific therapy for PH associated with IPF. The association of PH with reduced exercise capacity and excess mortality in IPF patients has suggested that specific PH therapies may be of benefit in this patient group [88]. However, published experience with specific PH drug therapy is limited. The current guidelines discourage the use of targeted PH therapies in PH associated with chronic lung disease since there are no systematic data regarding their safety or efficacy [14].

As hypoxemia is a potent pulmonary vasoconstrictor, correction of hypoxemia is a first priority. Long-term oxygen administration should be recommended to maintain arterial oxygen saturation above 90%; however, the role of long-term oxygen therapy in the progression of PH in this patient group is less clear than in chronic obstructive pulmonary disease patients. Detection and correction of exertion-related oxygen desaturation should be performed as part of standard care, although in a small study, oxygen administration did not improve the exercise-induced increase in pulmonary artery pressure in IPF patients [37]. Screening for nocturnal hypoxemia may prove beneficial since nocturnal desaturation is a common finding in these patients [35, 49]. As an adjunct to conventional treatment, diuretics are indicated to manage volume overload due to right ventricular failure. Patients with right ventricular failure or low cardiac output may also benefit from digitalis.

There are 3 classes of PH-targeted therapies approved for other groups of PH and in particular for PAH patients: prostacyclins, endothelin receptor antagonists and phosphodiesterase-5 inhibitors [14, 89, 90]. However, treatment with vasoactive agents in patients with lung fibrosis carries the risk of worsening hypoxemia due to the inhibition of hypoxic vasoconstriction in low-ventilation/perfusion lung units [91–93].

Prostacyclin induces relaxation of vascular smooth muscle, inhibits the growth of smooth muscle cells and is also a powerful inhibitor of platelet aggregation with favorable effects in patients with PAH [14, 89]. However, in patients with diffuse parenchymal lung disease, the use of intravenous prostacyclin has not proven beneficial because it lacks selectivity for the pulmonary vasculature [91, 93]. Ghofrani et al. [93] compared the acute effects of epoprostenol, sildenafil and nitric oxide in 16 patients with PH secondary to lung fibrosis. All 3 agents reduced pulmonary vascular resistance, but in contrast to the others, prostacyclin increased the ventilation/perfusion mismatch and worsened gas exchange.

Selective pulmonary vasodilatation by inhalation of a vasoactive agent is an appealing concept to circumvent the risk of a worsening ventilation/perfusion mismatch, which appears with systemic vasodilatory therapy. In a pilot study, Olschewski et al. compared the effects of intravenous prostacyclin, inhaled nitric oxide and aerosolized prostacyclin in 8 patients with lung fibrosis and associated PH [91]. Aerosolization of prostacyclin or its stable analog iloprost caused marked pulmonary vasodilatation with maintenance of gas exchange and systemic arterial pressure. In contrast, intravenous prostacyclin resulted in a significant drop in arterial pressure and worsening of hypoxemia [91].

Nevertheless, there are case reports of successful use of intravenous treprostinil, a prostacyclin analog, and inhaled nitric oxide as well as a bridge to lung transplantation in patients with IPF [94, 95].

Sildenafil is a potent and highly specific phosphodiesterase-5 inhibitor with vasodilatory and antiproliferative effects approved for patients with PAH [96]. In the study by Ghofrani et al. [93], a single dose of sildenafil exerted its pulmonary vasodilatory effect while improving ventilation/perfusion matching. In contrast to infused prostacyclin, sildenafil showed selectivity for well-ventilated areas of the lung, resulting in an improvement rather than a deterioration in gas exchange [93]. In a preliminary report by Collard et al. [97], sildenafil improved 6MWT distance in a 3-month, open-label study which included 14 IPF patients with PH. Small uncontrolled studies have also reported sustained benefit with sildenafil in patients with secondary PH [98, 99]. However, in the Sildenafil Trial of Exercise Performance in IPF study, a placebo-controlled trial which included 180 patients with advanced IPF, the therapeutic efficacy of sildenafil was not established [100]. The study failed to show a benefit with sildenafil with regard to improvement of the 6MWT distance, which was the primary outcome. Nevertheless, sildenafil was associated with symptomatic improvement with regard to the degree of dyspnea and quality of life [100]. A certain limitation is that the study does not provide RHC data, which could have suggested the presence of a subgroup of patients with more severe pulmonary vascular disease.

Bosentan, an oral active dual endothelin A and endothelin B receptor antagonist, has been evaluated in PAH and has been shown to improve exercise capacity, functional class and hemodynamics in this patient group [101, 102]. In a small open-label study exploring the safety and tolerability of bosentan in 12 IPF patients, bosentan administration did not induce clinically relevant gas ex-

change abnormalities as estimated by the multiple inert gas elimination technique [103]. Bosentan Use in Interstitial Lung Disease-1, a recent randomized placebo-controlled trial, investigated the role of bosentan in IPF [104]. The primary endpoint of improvement in 6-minute walk distance was not reached. There were trends towards delaying time to death or disease progression and improving quality of life. Observations from an exploratory analysis suggested benefits of bosentan with regard to quality of life and dyspnea in a subset of patients who had a diagnosis of IPF confirmed by surgical lung biopsy [105]. A prospective study is ongoing to assess the efficacy of bosentan in prolonging survival and time to disease progression in patients with biopsy-proven IPF.

Finally, lung transplantation should be considered in patients with severe or progressive disease despite medical therapy [106]. For patients with secondary PH, no clear advantage was shown regarding the type of transplantation which should be performed, i.e. single versus double lung transplantation [107]. However, in the new Registry of the International Society for Heart and Lung Transplantation, double lung transplantation presents a higher relative risk for 1-year mortality compared to single lung transplantation for IPF patients [108].

Conclusion

In conclusion, PH is a common severe complication of IPF and is usually correlated with poor disease outcome and adverse impact on survival. As symptoms in IPF and PH overlap widely, the development of PH in a patient with known IPF can be easily overlooked. Clinicians should suspect PH and pursue further diagnostic testing for this condition when the patient's symptoms are disproportionate to the severity of the parenchymal lung disease and also when exercise limitation is disproportionate to lung volume abnormalities and prominent arterial oxygen desaturation occurs during exercise. RHC is the gold standard method for the diagnosis of PH. Currently, there is no specific therapy for PH associated with IPF. As multiple diverse mechanisms not completely elucidated are implicated in the pathogenesis of PH in IPF, further understanding of pathogenetic pathways could probably optimize management of these patients.

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