Pulmonary hypertension related to interstitial lung disease

Introduction

Patients with WHO group III pulmonary hypertension (PH) related to interstitial lung disease (ILD) are at an increased risk of mortality and morbidity including higher supplemental O2 requirements, reduced functional capacity and health related quality of life compared to those with ILD alone (Nikkho et al., 2022; Klinger, 2016). Median survival among patients with PH-ILD may be as low as 0.7 years among those with severe PH (Hassan, 2005). This highlights the importance of appropriate screening, early diagnosis, and safe and effective treatment for patients with PH-ILD. Notwithstanding, until recently there have been no effective or approved treatments for these patients.

The Pulmonary Fibrosis Foundation & Pulmonary Hypertension Association have partnered together by establishing a working group of experts in ILD, PH, PH-ILD and patient representatives to address gaps in screening, diagnosis, and treatment of patients living with PH-ILD.

Summary of Positions:

- The interplay of fibrosis, hypoxemia, and vascular remodeling in PH-ILD is not fully understood and needs further research. These studies should also consider the genetic factors, occupational/environmental exposures, geographic factors and, if present, comorbidities such as sleep apnea and left heart disease that may contribute to disease development and variability in presentation of PH in ILD.
- Epidemiologic studies for PH-ILD should define PH consistent with current recommendations from the World Symposium on Pulmonary Hypertension (WSPH) task force.
- All health-care providers should have a high index of suspicion for the development of PH, especially when patients with ILD develop worsening symptoms or start exhibiting signs concerning for PH. No single variable or scoring system uniformly predicts the presence of PH in the ILD population. Changes in symptoms and clinical measurements, such as diffusion capacity for carbon monoxide (DLCO), 6MWD, pulmonary artery (PA) diameter on CT, and BNP (or NT-proBNP) should raise suspicion for presence of PH.
- Although trans-thoracic echocardiogram (TTE) is regarded as the best non-invasive tool to assess right heart size and function and screen for PH, the performance characteristics of TTE are unreliable in ILD, and it should not be solely relied upon for screening or diagnosis of PH.
- Right heart catheterization (RHC) is essential for making the diagnosis of PH-ILD and in distinguishing between pre- and post-capillary pulmonary hypertension. RHC should be performed when the underlying parenchymal lung disease is stable and is generally well tolerated even among patients with advanced ILD, including those who require supplemental O2.
- When considering treatment of PH-ILD, one should also consider treatment of the underlying

ILD (both initiating and continuing treatment for underlying parenchymal lung disease). Comorbid conditions such as sleep disordered breathing and chronic thromboembolic disease that may also be associated with PH should be diagnosed and treated.

- Non-pharmacological treatments such as supplemental oxygen and pulmonary rehabilitation should be utilized when appropriate. We recommend supplemental oxygen in patients with PH-ILD who have exertional desaturation or resting hypoxemia.   Although further research is necessary, pulmonary rehabilitation likely has a positive impact on functional capacity and quality of life in patients with PH-ILD.
- Inhaled treprostinil (Tyvaso), a prostacyclin analogue, is the only FDA approved medication for WHO group III PH-ILD and should be considered in appropriate patients (mean PA pressure >=25 mmHg, pulmonary capillary wedge pressure (PCWP) < 15mmHg, pulmonary vascular resistance (PVR) >=3 Wood units).
- Data on phosphodiesterase type 5 (PDE5) inhibitors has been variable. If PDE5 inhibitors are being considered, this is best done at an expert center given potential for adverse effects in certain groups. Future studies should assess the efficacy of PDE5 inhibitors for this indication.
- Endothelin receptor antagonists (ERA) and riociguat (Adempas) should not be used in PH-ILD due to lack of efficacy and evidence for harm in the case of ambrisentan (Letairis) and riociguat.
- Diagnosis of PH in a patient with ILD should prompt consideration of lung transplant referral in patients without absolute contraindications.

Pathophysiology

The mechanisms that explain the exact interaction of parenchymal and vascular remodeling in patients with PH-ILD are not completely understood but are thought to be secondary to the following processes: 1) fibrotic distortion of pulmonary architecture and vasculature; 2) chronic or recurrent hypoxemic pulmonary vasoconstriction; 3) abnormal expression of inflammatory and vasoactive mediators.

Clinical observations demonstrate that the extent of fibrosis does not correlate with PH severity, therefore other mechanisms likely play a large role in the development of PH in patients with ILD. Chronic hypoxemic pulmonary vascular vasoconstriction leads to distal arteriolar hypertrophy and luminal narrowing which increases the pulmonary vascular resistance. However, the core pathophysiologic process likely results from dysregulated inflammatory mediators (e.g., interleukin-6, tumor necrosis factor-alpha) and vascular growth factors (e.g., fibroblast growth factor, platelet-derived growth factor, transforming growth factor-beta) causing endothelial injury and vascular remodeling. Future studies are needed to better understand the interplay of these mechanisms.

Epidemiologic Landscape

The reported prevalence of PH among patients with ILD varies widely and is likely a result of multiple factors, including the baseline cohort characteristics, the etiology of ILD, and the severity of the fibrosis and hypoxemia. Additionally, studies in specific patient populations used varied methods and parameters for diagnosing and defining PH, including echocardiographic measurements rather than gold standard right heart catheterization measurements contributing to potential classification bias. RHC is required to accurately determine the presence, and therefore true prevalence, of PH among ILD patients. This may be challenging in poor or remote communities that may not be well represented in past and future studies due to lack of access. Nonetheless, these are significant challenges that must be overcome to accurately determine the true prevalence and impact of PH-ILD. Retrospective studies have demonstrated that the finding of PH in patients with ILD is not uncommon. When present, PH portends a worse prognosis and an increased risk of mortality regardless of ILD etiology. All health-care providers should therefore have a high index of suspicion

for the development of PH especially if patients with ILD start to have worsening symptoms or start exhibiting signs concerning for PH. Even mild pulmonary hypertension can negatively impact symptoms, survival and increase hospitalization (Lettieri et al., 2006).

Among the idiopathic interstitial pneumonias, idiopathic pulmonary fibrosis (IPF), is the best studied for PH prevalence with an estimated prevalence between 17-50%; the highest prevalence has been described in pre-transplant cohorts and likely reflects their greater disease severity and more advanced disease. The prevalence of PH in hypersensitivity pneumonitis appears similar to IPF with reports ranging from 19-44% and has been associated with significantly lower forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO). The prevalence in pulmonary sarcoidosis was lower in retrospective studies, ranging from 13-23%, however in advanced pulmonary sarcoidosis undergoing transplant evaluation this is over 70%. Presence of PH appeared to be higher among patients with pneumoconiosis with progressive fibrosis (~40%) however these estimates are from small studies and may not be accurate.

The reported prevalence of PH in connective tissue disease related ILD (CTD-ILD) varies with each disease entity, complicated by the fact that CTD can also predispose to PH irrespective of the degree of parenchymal involvement. Among patient with scleroderma related ILD, the prevalence ranged from 11 to 55%. Smaller single center studies reported overall prevalence of around 21-23% among patients with ILD related to rheumatoid arthritis, scleroderma, autoimmune myositis/anti-synthetase syndrome, lupus, Sjogren, mixed connective tissue disease, Sjogren's syndrome and lung dominant-CTD.

Screening and diagnosis

There is a significant overlap in symptomatology between ILD and PH, which may lead to delays in the diagnosis of the latter. Although there is currently no standard algorithm for the screening and work up of PH in the setting of underlying ILD, there are expert recommendations in this regard. Understanding that patients who develop PH-ILD have increased symptom burden and worse outcomes, it is important to consider PH at the time of diagnosis of ILD and subsequently based on a patient's clinical course and symptoms.

Any symptoms of right heart failure or progression of cardiorespiratory symptoms in the face of stable results of pulmonary function testing (PFT) and imaging assessments should raise suspicion for PH-ILD.

Various PFT parameters have been evaluated as screening tools for PH-ILD. A DLCO <40% Is known to be a strong predictor for the presence of PH. A decrease in the DLCO with a stable FVC should raise suspicion for PH, especially with a reduction by ≥15%. A high FVC/DLCO ratio is associated with an increased risk of PH in ILD. The threshold of a %pred FVC/%pred DLCO ratio > 1.6 and TLC/DLCO index >1.67 have been suggested as predictors of PH in scleroderma and ILD. Reduced distance on a six-minute-walk test (6MWT) is proposed as a trigger for suspicion of PH, however a specific absolute cut-off is yet to be identified. An abnormal heart rate recovery <13 bpm at one minute post 6MWT is associated with PH in IPF. Decreasing 6MWT distance, in the absence of worsening FVC should also increase the index of suspicion for PH.

On CT scan, a pulmonary artery diameter (dPA) >29 mm and the ratio of the pulmonary artery diameter to the aorta diameter (dPA:dAorta) >0.9 correlates with presence of PH.

A BNP >50 pg/ml in patients with ILD has a reported sensitivity of 75% and specificity of 80% for PH. N-Terminal Pro BNP can similarly be used as a screen, but with both biomarkers it should be borne in

mind that they can be confounded by left ventricular dysfunction, left ventricular hypertrophy, acute pulmonary embolism ad acute coronary syndrome.

Although TTE is regarded as the best non-invasive tool to assess right heart size and function and screen for PH, the performance characteristics of TTE are unreliable in ILD due to poor acoustic windows, altered location of the heart, and overlying lung tissue. Changes of the right ventricle combined with elevated estimates of pulmonary pressures improve performance characteristic of TTE, however TTE cannot be reliably used to rule out the presence of PH. Nonetheless, an estimated right ventricular systolic pressure (RVSP) ≥45 mmHg, in conjunction with hypertrophy, dilatation, or systolic dysfunction of right ventricle correlate well with PH but right heart catheterization is always essential for the diagnosis. Evaluation of the right heart (by TTE) is at least as important as the estimate of the RVSP which is most often reported. Various TTE screening algorithms have been proposed, incorporating the RVSP, right atrial area, early diastolic pulmonary regurgitation velocity, fractional area % change, ratio of the right to left ventricular diameter, and the eccentricity index. Although these perform relatively well in predicting PH, not all are readily available or evaluable. Multi-modal screening scoring systems incorporated many of the variables mentioned above including:

- Age, 6MWT distance, total lung capacity to DLCO ratio
- DLCO<50% predicted, dPA/dA ratio on CT ≥0.9, PaO2 <80 mmHg
- History, exam, 6MWT distance, DLCO, chest imaging, and BNP
- Gas exchange-derived pulmonary vascular capacitance measured during exercise tests and delta end-tidal carbon dioxide.

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This is an area of ongoing study, and no single variable or scoring system uniformly predicts the presence of PH in the ILD population. Right heart catheterization is therefore always necessary to distinguish between the pre-capillary and post-capillary phenotypes of the disease, rule out left heart disease, and confirm the diagnosis of PH-ILD.

Management/Treatment
Some of the early studies of pulmonary vasodilators in ILD evaluated these therapies regardless of the presence or absence of PH. These studies were driven by the concept that properties independent of their known vasodilatory effects may impact pathophysiologic mechanisms of fibroproliferation leading to fibrotic lung disease. However, RCTs results with bosentan, ambrisentan, and macitentan were all disappointing (Raghu, Behr, Brown, et al., 2013; King et al., 2011; Raghu, Million-Rousseau, Morganti, et al., 2013). Another conceptual framework had been studies in subjects with low DLco, as a surrogate for the presence of PH. The STEP-IPF trial was a pivotal RCT in patients with IPF and a DLCO < 35% predicted (Zisman et al., 2010). The study did not meet the primary end point of a 20% increase in the 6MWT distance but did show small yet significant positive effects on DLCO, arterial oxygenation, dyspnea and quality of life (Zisman et al., 2010). However, later studies of patients with IPF and DLCO < 35% showed no change in quality of life at 12 weeks among patients treated with nintedanib plus sildenafil vs nintedanib plus placebo. Yet, the trial did show a trend toward a reduced rate of decline in FVC and stabilization of BNP in the sildenafil arm (Kolb et al., 2018; Behr et al., 2019). A longer-term study in patients on pirfenidone also failed to show a difference in outcomes between those randomized to sildenafil versus those on placebo.

The third category of studies include PH-specific treatment targeting PH. There have been small prospective observational studies of PDE5 inhibitors demonstrating improvement in 6MWT distance among patients with IPF and an increase in the cardiac index with a reduction in PVR in patients with PH-ILD (Collard et al., 2007; Zimmermann et al., 2014). Another small prospective observational study

with parenteral treprostinil showed improved right heart hemodynamics and echocardiographic findings among patients with pulmonary fibrosis and advanced PH (13). However, other RCTs targeting PH-ILD patients did not show benefit. These include trials of bosentan (no effect on hemodynamics at 16 weeks) and riociguat (terminated early for increased hospitalization and mortality in the treatment group) (Corte, Keir, Dimopoulos, et al., 2014; Nathan, Behr, Collard, et al., 2019). Similarly, subgroup analyses of ARTEMIS-IPF trial have shown increased risk of disease progression and respiratory hospitalization in PH-IPF patients treated with ambrisentan (Raghu, Nathan, Behr, et al., 2015).

The recent completion of the INCREASE trial of inhaled treprostinil in patients with WHO Group III PH-ILD has heralded a new avenue of treatment in ILD patients once PH develops (Waxman et al., 2021). In this trial, 326 patients were randomized to either inhaled treprostinil (n=163) or placebo (n=163). Patients were titrated up to a target dose of 9-12 breaths four times daily. Enrolled subjects had a variety of fibrotic lung diseases including idiopathic interstitial pneumonia (44.8%), combined pulmonary fibrosis and emphysema (25.2%), CTD-ILD (22.1%) and chronic hypersensitivity pneumonitis (5.8%). Of note, subjects with CTD-ILD were required to have a baseline FVC less than 70% predicted to exclude patients with possible group 1 PAH. All patients had precapillary PH with a mean PA pressure of ≥25 mm Hg, a PVR of ≥3 Wood units and a PCWP of ≤15 mm Hg. Patients in the treatment arm demonstrated a significant placebo-corrected improvement in the 6MWT distance at week 16 (31.12 m, 95% CI, 16.85-45.39; $p < 0.001$). A number of secondary endpoints showed improvement at 16 weeks as well, including the composite endpoint of time to clinical worsening and the NT-proBNP, commonly regarded as a surrogate of right ventricular strain. The treatment was overall well tolerated with similar incidence of serious adverse events (23.3% treprostinil versus 25.8% placebo) and study discontinuation (24.5% treprostinil and 23.3% placebo). The positive results of this study led to inhaled treprostinil being the first FDA approved therapy for PH-ILD. It is hoped that the positive results of the INCREASE study will be followed by further advances in the field leading to more therapeutic options.

There are a number of additional interventions which should not be overlooked. First and foremost, clinicians should ensure that appropriate treatment of the underlying ILD is instituted. Antifibrotic therapy can slow progression of lung function decline, may decrease mortality and the risk of acute exacerbations in those with IPF (Flaherty et al., 2019; Petnak et al., 2021). Data on the effects of antifibrotic therapy on WHO Group III PH in ILD are inconclusive (Tahara et al., 2019), however, slowing the progression of the underlying fibrotic lung disease may improve outcomes. Use of immunosuppression in more inflammatory forms ILD also holds similar potential benefit. Smoking cessation should be recommended to patients who continue to smoke (Rigotti et al., 2022). Supplemental oxygen is recommended for patients with ILD with chronic resting as well as exertional hypoxemia (Jacobs et al., 2020; Visca et al., 2018). Chronic hypoxemia induces hypoxemic pulmonary vasoconstriction and pulmonary arterial remodeling, contributing to an increased PVR (Nathan, Barbera, Harari, et al., 2019). Sleep-disordered breathing is common in patients with ILD and may worsen PH and should therefore be addressed (Jacobs et al., 2020). Fluid and salt restriction, as well as diuretic therapy, is essential to prevent RV volume overload and failure. Although further research is necessary, pulmonary rehabilitation likely has a positive impact on functional capacity and quality of life in patients with PH-ILD. Finally, PH-ILD is an indication for lung transplantation per the 2021 Consensus document of the ISHLT (Leard et al., 2021), and thus timely referral for transplant evaluation should be initiated in appropriate candidates.

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