REGULAR ARTICLE

PH-ILD: Identification, Evaluation, and Monitoring: A Diagnostic View From Both Sides

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INTRODUCTION

Pulmonary hypertension (PH) has long been recognized as a complication of interstitial lung disease (ILD). It contributes significantly to morbidity and mortality and thus is of key importance in prognostication and deciding the timing of referral for lung transplant. There is increasing evidence of the complexity of its pathogenesis beyond simple fibrosis and hypoxemic vasoconstriction. The pathophysiologic overlap with pulmonary arterial hypertension (PAH) has led to trials of pulmonary vasodilatory therapy in PH-ILD. While prior trials of pulmonary vasodilatory therapy in ILD have presented mixed results, a recent trial of inhaled pulmonary vasodilator therapy in this group has shown positive effect.[1] As a result, the early recognition of the development of PH in ILD may have a greater implication for patients than just prognostication and assessment during considerations for transplant, and may contribute to better outcomes.

In this paper we review the current understanding of the pathogenesis of PH in patients with ILD and what is known about the clinical impact of PH in the context of ILD. We then review the importance of hemodynamic assessment to the diagnosis of PH in ILD. Lastly, we review different symptoms, physical exam findings and studies that raise the index of suspicion for the presence of PH in ILD and considerations for incorporating these into initial and subsequent evaluations for patients with ILD.

DEFINING PH-ILD

While PH can occur in many different contexts in a patient who also has ILD, the implications of labeling an individual as having PH-ILD suggests that ILD is the primary driver of the presence of PH. This can be a subtle distinction: many patients with group 1 PH (PAH), and in particular those with connective tissue disease (CTD), may have a mild form of ILD while also having PAH. Similarly, patients with sarcoidosis may have both ILD and PH while still not being considered as group 3 PH. The understanding of these distinctions is crucial for interpretation of results of clinical studies, which often use such definitions for inclusion or exclusion.

Significant history exists in classification of patients with ILD into group 3 PH (PH associated with chronic lung disease) using a combination of hemodynamics and the degree of lung disease. The hemodynamic definition of PH, in the context of chronic lung disease (group 3 PH) was updated in the 6th World Symposium on Pulmonary Hypertension to include a resting mean pulmonary artery pressure of >20 mm Hg, a pulmonary artery occlusion pressure ≤15 mm Hg, and a pulmonary vascular resistance of >3 Wood units.[2] It is important, however, to note hemodynamic definitions do not create a distinction between group 3 and group 1 PH, rather the distinction relies on defining chronic lung disease as the primary driver of precapillary PH.[2,3] This is done through a combination of pulmonary function testing and imaging—evidence of significant decrement in lung volumes or evidence of significant ILD burden on imaging moves the patient from group 1 to a group 3 designation. The challenge then becomes to define "significant ILD burden". This is particularly difficult in conditions such as CTD where PH can exist with and without the presence of ILD. If we look at most PAH trials, a lower limit of forced vital capacity (FVC) of close to 70% or total lung capacity (TLC) of 60% is used as a hard cutoff, suggesting that of the patient with higher ILD burden should be classified as group 3.

Special note must be made about sarcoidosis, which leads to the development of both ILD and PH through multiple mechanisms. Currently PH due to sarcoidosis remains categorized as group 5 disease and is excluded from many studies and discussions of PH-ILD.[3]

PATHOPHYSIOLOGY OF PH-ILD

Direct hypoxic vasoconstriction and tissue fibrosis have been long been postulated to underlie the development of PH in ILD.[4] While these mechanisms are an important driver of pulmonary vascular disease in ILD, there is increasing appreciation of the complex combined tissue and vascular remodeling leading to PH in ILD.[3-6]

In areas of fibrosis, there is significant narrowing of the lumen of the arteries,[7] which is associated with a degree of fibrosis in the surrounding tissue.[8] On the other hand, that direct fibrosis is not solely responsible for PH-ILD. This is supported by the presence

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of vascular changes in patients with idiopathic pulmonary fibrosis (IPF) in areas without significant architectural distortion.[7] Furthermore, the presence of PH is not well associated with lung volume loss as measured by pulmonary function testing (PFT)[9] or the degree of fibrosis on imaging.[10] While low diffusing capacity for carbon monoxide (DLCO) and oxygenation are associated with PH-ILD, it is not clear whether this implicates hypoxemia as a causal pathway in the development of PH. Nevertheless, histologic studies of PH in the context of ILD do show significant vascular remodeling reminiscent of that found in PAH.[3,4] For example, in a study of explants from advanced fibrotic ILD undergoing transplantation, severe arterial vasculopathy, including plexiform lesions thought to be classically associated with PAH, were noted in 16 of the 38 subjects studied, regardless of the presence or severity of PH.[11]

Alterations in markers commonly indicative of PAH have been reported in patients with IPF. For example, the expression of endothelin, a well described peptide implicated in the pathology of PAH,[12] have been noted in ILD.[13,14] Additional data also supports that many inflammatory mediators known to be abnormally expressed in PAH are also altered in ILD.[15] For example, TGFβ is an inflammatory mediator that is heavily involved in both IPF[16] and PAH.[17] Alterations in VEGF levels,[18] IL-6,[19] as well tumor necrosis factor α[3] have also been reported. Thus it is likely that the emergence of PH in ILD is a complex interplay of tissue destruction, inflammation, and hypoxia, leading to pulmonary vascular remodeling through multiple pathways.

CLINICAL IMPACT

Prevalence of ILD is estimated to be between 0.0672%[20] (females)/0.0809% (males) and 0.071%[21] in 2 cohort studies. The estimation of the prevalence of PH-ILD is difficult given the variable admixture of causes of ILD, and the inherent bias of the presence of retrospective hemodynamic data only in those patients already suspected of having PH or undergoing transplant work-up. As a result, a wide range of estimates of prevalence of PH in ILD exist. For example, a review of 126 studies in IPF revealed a range of prevalence of PH between 3% and 86%.[22] Illustrating the temporal prevalence of PH-ILD, in a study of 44 IPF patients with serial right heart catheterization (RHC) at initial evaluation and prior to transplantation, 39% of the patients were found to have PH-ILD, whereas at the time of transplant evaluation, 86.4% of patients had PH-ILD.[23] A study of 340 ILD patients undergoing RHC showed 96 (28%) of patients with PH, of which 56 were considered to be severe.[24] In a study of 135 patients with IPF being evaluated for lung transplantation, 39 patients (29%) had PH-ILD.[25] Evaluation of 488 IPF patients with mild or moderate restrictive disease showed that 14% of subjects met the criteria for PH-ILD.[26]

CTD such as the systemic sclerosis/scleroderma spectrum are highly associated with development of progressive PH. As mentioned previously, many such patients are classified as having group 1 disease (PAH) based on the degree of ILD involvement, particularly in comparison to the degree of PH. Nonetheless, PH remains a major complication of CTDs in the presence of ILD. In one study of patients with systemic sclerosis with interstitial lung disease (SSc-ILD), 31% had PH while 16% met the definitions of group 3 PH.[27] In another study, the prevalence of PH-ILD in patients with idiopathic interstitial pneumonias was 29% vs 64% in those with CTD-ILD.[28]

While PH-ILD in the context of CTD-ILD and IPF have been the most thoroughly studied, PH has also been documented in the context of other forms of ILD including nonspecific interstitial pneumonias (NSIP) (31.4%)[29] and chronic hypersensitivity pneumonitis (44%).[30]

Of note, most of the data used in prior studies in this and other reviews have included a previous definition with a resting mean pulmonary artery pressure cutoff of 25 mm Hg. The impact of the new definition on the prevalence of PH-ILD in IPF was recently studied in 15 563 subjects undergoing RHC in the United Network for Organ Sharing database. This analysis revealed that that the threshold of 20 mm Hg increased the number of patients considered to have PH from 47.6% to 73.6%. However, the new hemodynamic definition also imposes a pulmonary vascular resistance limitation not present in the previous definitions, which together with the pulmonary artery occlusion pressure requirements leads to a prevalence of 36.8% for precapillary PH in this cohort.

The presence of PH-ILD is generally believed to be a poor prognostic indicator in patients with ILD. Initially, this was thought to reflect the relationship between advanced disease and presence of PH. However, an alternate explanation is the impact of pulmonary vascular disease and right ventricular dysfunction on exercise capacity and eventual progression to heart failure. Supporting this explanation is data relating hemodynamics with exercise impairment and mortality. For example, in an analysis of 124 patients with IPF, resting mean pulmonary artery pressure was shown to be the best predictor of 6-minute walk distance (6MWD) in multivariable analysis including pulmonary function testing. Elevated resting mean pulmonary artery pressure has been shown to predict mortality in patients with IPF,[31] even when not meeting the criteria for PH-ILD.[31] Additionally, in a study of patients with IPF being evaluated for lung transplantation, increased pulmonary vascular resistance, evidence of right ventricle dilation and dysfunction were associated with increased mortality.[25] The importance of hemodynamics in predicting mortality in IPF has also been demonstrated using exercise hemodynamics in IPF.[33] Findings similar to those in IPF have been reproduced in more general ILD population with reduced 6MWD and survival noted in patients with PH-ILD.[24,34]

The severity of PH in the context of ILD is believed to generally be biased toward mild to moderate elevations in pulmonary arterial pressures.[3] In addition to fundamental pathophysiologic differences, other explanations for this include classification bias (patients with severe PH are classified as group 1) and survivorship bias (patients with advanced PH and ILD do not survive or are transplanted). Nonetheless, out-

comes in PH-ILD are fairly poor. In an analysis of the COMPERA registry, an international registry of PH patients on pulmonary vasodilatory therapy, significantly lower 3-year survival rates were noted in patients with PH associated with idiopathic interstitial pneumonias (34.0%) compared to idiopathic PAH (68.6%). In the analysis of the Giessen PH registry, 3-year survival rates in patients with PH-ILD were noted to be 40.3% compared to 72.2% in PAH.[35]

DIAGNOSIS, SCREENING, AND MONITORING

RHC is necessary for the diagnosis and the consideration of treatment of PH in patients with ILD, a statement supported by society and group recommendations.[2] The rationale for this requirement is many-fold. As discussed below, noninvasive methods to diagnose PH in the context of ILD have significant limitations and as a result, initiation of treatment requires hemodynamic confirmation. Additionally, postcapillary PH is not an uncommon finding in patients with ILD, requiring a very different approach to management. For example, in a study of 157 patients with ILD-PH, 20% were diagnosed with postcapillary PH.[36] In another study of 8991 patients undergoing transplant for IPF, 11.3% had postcapillary PH, of which 4% were combined precapillary and postcapillary disease. Lastly the hemodynamic severity and circulatory impact of ILD-PH can better be quantified by RHC, which then in turn is part of the critical decision making and application of clinical evidence in the decision to treat with pulmonary vasodilatory therapy.

Because RHC is needed for the diagnosis and assessment of PH prior to therapy, both screening at initial evaluation and subsequent monitoring rest on the index of suspicion for PH. Assessment of symptoms, physical examination, pulmonary function tests and computed tomography (CT) imaging are a part of the routine assessment and monitoring of patients with ILD and can provide information that can be used to risk-stratify patients.

In general, there are 2 groups of findings that signal the presence of pulmonary vascular disease in ILD: those related to out-of-proportion impairment of gas exchange resulting from increase in pulmonary vascular resistance, and those related to right ventricular dysfunction. Both these mechanisms then feed into increased shortness of breath and decreased exercise tolerance. Thus, increased dyspnea on exertion, worsening oxygenation, and decreased exercise tolerance in the context of stable disease markers of ILD should raise concerns for PH-ILD. Physical exam findings associated with PH-ILD are also related to increased PA pressure (pronounced P2) or related to right ventricle dysfunction: pulmonary edema, jugular venous distension and cardiac exam suggestive of right ventricle dysfunction (such as parasternal heave).

It is important to note that the traditional markers of disease severity in ILD such as reduction of lung volume on PFTs have not been associated the presence of PH-ILD.[4,9] On the other hand, multiple studies have demonstrated that low DLCO is a predictor of the presence of PH in ILD.[9,31,37-39] Steen and colleagues observed that an FVC:DLCO ratio of >1.4 was an excellent predictor of development of isolated PAH.[40] Seibold reported that an FVC:DLCO ratio of ≥1.8 was a good predictor of death in SSc, while Trad and colleagues found a ratio of ≥2 to predict survival.[41,42] Associated with this finding is the observation that hypoxemia itself may be a predictor of PH in ILD.[38,39]

As mentioned earlier, patients with PH-ILD have decreased exercise tolerance as measured by 6MWD.[34] Though 6MWD is not routinely part of the ILD follow-up protocols, when performed, a decrease in exercise capacity, particularly if not associated with progression of the underlying ILD, can be a signal of progression of pulmonary vascular disease. Other measurements obtained during 6MWT may also be telling: abnormal heart rate recovery at 1 minute has also been found to be predictive of both the presence of PH and survival in patients with IPF.[43] Oxygenation measured in the context of exercise is also predictive of PH in ILD.[44]

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP), well-known markers of heart failure, have been investigated as a tool for screening for PH in ILD. In 2 studies, a low NT-proBNP (<95 ng/L) in ILD patients had a negative predictive value of >94% for the presence of PH.[45,46] These studies used echocardiography as a gold standard of diagnosis.[45]

Echocardiography and specifically findings suggestive of elevated pulmonary circulatory pressures, volume overload, and right ventricular dysfunction are commonly used as a final touchstone before the decision to proceed to RHC. While many different advanced metrics have been proposed and shown to be promising as markers of PH in ILD, standardization particularly across performing sites remains a challenge in broad acceptance. The tricuspid regurgitant velocity, which is often used to estimate a right ventricular systolic pressure (RVSP) or pulmonary arterial systolic pressure, is the most well studied and employed method of screening for PH on PAH as well as PH-ILD. Unfortunately, this measure in isolation has significant limitations. For example, in a study of 265 ILD patients being investigated for PH, 86% of patients with a tricuspid regurgitant velocity >3.4 m/s were found to have to have PH on RHC, whereas only 40% of those with a tricuspid regurgitant velocity <2.8 m/s were found to have PH.[47] Similarly, a cross-sectional study of 110 IPF patients found that while higher RVSP was associated with increased likelihood of PH in ILD, without consideration of additional testing such as PFT and 6MWT, no clear optimal cutoff for classification was present.[48] Other smaller or more focused studies have confirmed the conclusion that while elevated tricuspid regurgitant velocity or derived measures such as RVSP are helpful in risk stratification, they cannot be used in isolation.[49,50]

CT imaging is widely available on presentation and for monitoring of progression in patients with ILD. As pressures in the pulmonary circulation increase, the main pulmonary artery dilates. The pulmonary artery diameter can be used as a marker of PH either on its own or normalized by the diameter of aorta in the same CT slice. One study

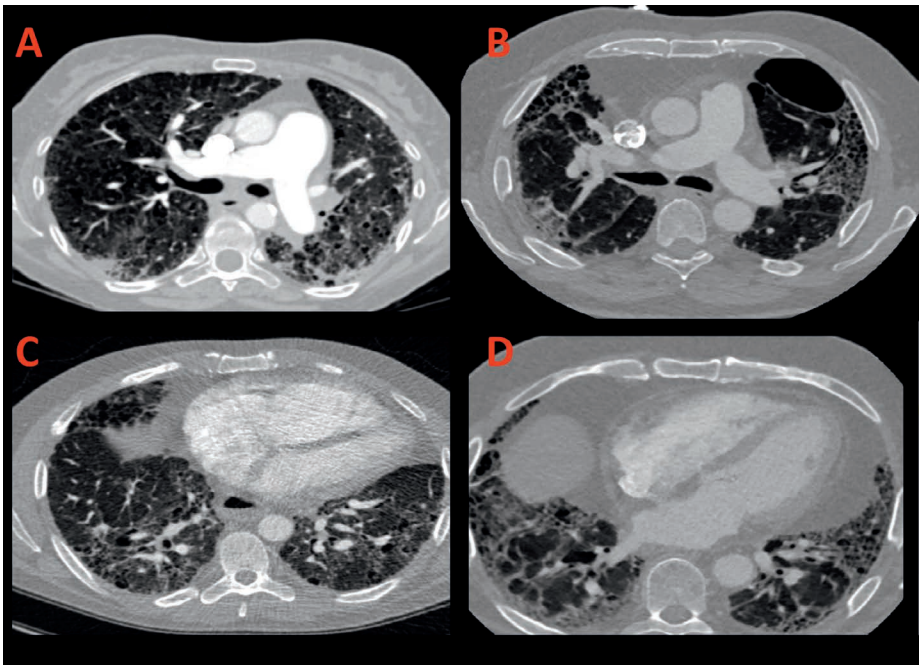

Figure: Axial computed tomography sections of patients with interstitial lung disease and right heart catheterization contemporary to computed tomography imaging. Patient in A with precapillary pulmonary hypertension (PH) has a significantly dilated pulmonary artery as compared to patient in B with pulmonary artery to aorta diameter ratio of slightly <1 and no PH. Patient in C shows a right ventricle to left ventricle diameter ratio of >1 and has precapillary PH, whereas patient in D has a right ventricle to left ventricle diameter ratio of <1 and does not have precapillary PH. It is important to note that these measurements are optimally used in the context of other findings to suggest PH.

Table. Symptoms and Findings That Likely Indicate Pulmonary Hypertension and Thus Lead to the Decision to Pursue Invasive Diagnosis

Symptoms	Physical Exam	Pulmonary Function	Imaging
Dizziness	Loud S2 or P2	Low DLCO <40%	**CT**
Pre- Syncope or Syncope	Jugular Venous Distension	Large Decrease in DLCO Decline >15%*	PA Dilation PA/Aorta > 1.0
Palpitations	Peripheral Edema	↑FVC%/DLCO% > 1.6	↑RV/LV Ratio
Swelling	Ascites	**Exercise Testing**	**Echo**
Decreased Exercise Tolerance*	**Labs and Biomarkers**	Low/Decreased Exercise Tolerance*	↑Estimated PASP/RVSP/ TR Jet Velocity
Oxygen	NT-proBNP > 395 pg/ml	Low/Decreased O_2Sat% with Exercise*	RV Dilation
Significant Oxygen Requirement*	BNP >200 pg/ml	Elevated O_2 Sat% Recovery Time*	RV Dysfunction
Worsening Oxygen Saturations*		Elevated Heart Rate Recovery Time	

O2 Sat%: Oxygen Saturation By pulse oximeter or blood gas; PASP: Pulmonary Artery Systolic Pressure; RVSP: Right Ventricular Systolic Pressure; TR : Tricuspid Regurgitant;
***These measures are particularly relevant in the context of low burden of ILD relative to the finding, or stable burden of ILD in case of longitudinal changes.**

found that a pulmonary artery diameter of >25 mm in patients with ILD had a sensitivity of 86.4% but only a specificity of 41.2% in identifying RHC-proven PH in ILD patients. When using pulmonary artery diameters of >29 mm as compared to echocardiography evidence of PH, this criteria had a 63% sensitivity and 41.5% specificity in identifying high pulmonary artery pressure on echocardiograms.[51] Additionally, pulmonary arterial size is a predictor for mortality in IPF.[52] While most CT imaging in ILD is not cardiac gated, the size of the right ventricle as compared to the left ventricle, particularly visible in contrast imaging, is also suggestive of PH (See Figure). CT imaging may also be used for the detection of the presence of both fibrosis and emphysema on CT imaging has been proposed a distinct entity, which has been associated with increased prevalence of PH.[53,54]

The results of the studies reviewed above and others have led to the general agreement that no single noninvasive diagnostic modality should be used in isolation in the screening and monitoring of patients with ILD for PH-ILD. In particular, multivariable analysis has generally led to the verification of this observation and to multiple algorithms incorporating a selected set of measurements (BNP, DLCO, echocardiography),[55] (Ratio of FVC/DLCO, PAA, RVSP)[56] (TLC/DLCO index, age, 6MWD, room air oxygen saturation at 6MW).[57] In absence of established research, a combination of these methods could be used to lead clinicians from routine history, examinations, and laboratory findings to a primary workup for PH with echocardiography, 6MWD measurements, and BNP/NT-proBNP, with a low threshold for RHC in the right clinical setting. (See Table)

CONCLUSION

The appearance of increased pulmonary pressures is uniformly a harbinger of poor outcomes, and so is the case in PH-ILD. Advances in therapeutic options has led to an urgency to look for PH in our ILD patients. Certain symptoms, physical exam signs, and laboratory and imaging findings in the routine care of ILD patients can suggest

the need for a deeper dive with further testing including echocardiography. Presence of elevated RVSP and a clinical picture consistent with PH should result in a low threshold to obtain a RHC. Further research in years to come should help better identify the patients that need to be screened and then sent for confirmation with a RHC.

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