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PH and ILD

Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

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Hello to all! This summer proved again to be challenging, however, hope is everywhere for a brighter fall and winter of 2021. The resilience of our healthcare teams around the country has been incredible. I would like to thank everyone involved in *Advances in Pulmonary Hypertension,* who over the 20 months, have worked day and night to get the issues out during the pandemic. The guest editors, editorial board, authors and everyone at PHA have been truly phenomenal. Every issue and article published has been outstanding. Thank you and congratulations. All of these issues are state of the art resources that will be the backbone of each topic for years to come.

Our current issue is no different. The issue is focused on PH-ILD, a topic that has fascinated our field forever. This issue delves into the pathophysiology, etiology and management of this difficult disease state. Congratulations to all involved in this work which is so timely to our field.

In the first article of this issue, Drs. Farbod and Franck Rahaghi introduce the topic discussing the pathogenesis, identification, evaluation, and monitoring of PH-ILD. The authors reveal what is known about the clinical impact of PH in ILD. They move on from there to the actual evaluation and considerations in management of the disease.

In the next article, Drs. Denise Gabrielle Sese and Kristin Highland discuss the difficult topic of Connective Tissue Disease, Interstitial Lung Disease, and Pulmonary Hypertension (CTD PH-ILD). They review the differences (both in terms of severity and management) between CTD PH-ILD and PH-ILD. It is a topic that is so important for us all to recognize while caring for these patients.

In our third article, Dr. Eileen Harder and Dr. Aaron Waxman take us through the management strategies from the past, present and what we can look forward to in the future for PH-ILD. Discussions of therapies, transplant evaluation and future clinical trials are all discussed in detail.

Our PHPN article for this issue discusses the care of the infant with bronchopulmonary dysplasia and PH. Claire Parker, Natalie Villafranco, Nidhy Varghese and Elise Whalen give us a thorough overview of the comprehensive approach to care with consideration for multiple organ systems and with an interdisciplinary team of experts for these infants.

And lastly, but certainly not least, Dr. Jeff Edelman leads an extraordinary round table on the conundrums and controversies in PH-ILD discussing when and how to treat patients. The roundtable included world-class experts discussing their experience, opinions and the published literature on this topic. I would like to thank Drs. Jean Elwing, MD, Anjali Vaidya, MD and Steve Mathai, MD, for this up to date and incredibly important discussion.

Thank you to all of the authors, and everyone at PHA and Allen Press who have worked so hard to bring this outstanding issue to all of us.

Thank you again for joining us for this issue.

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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

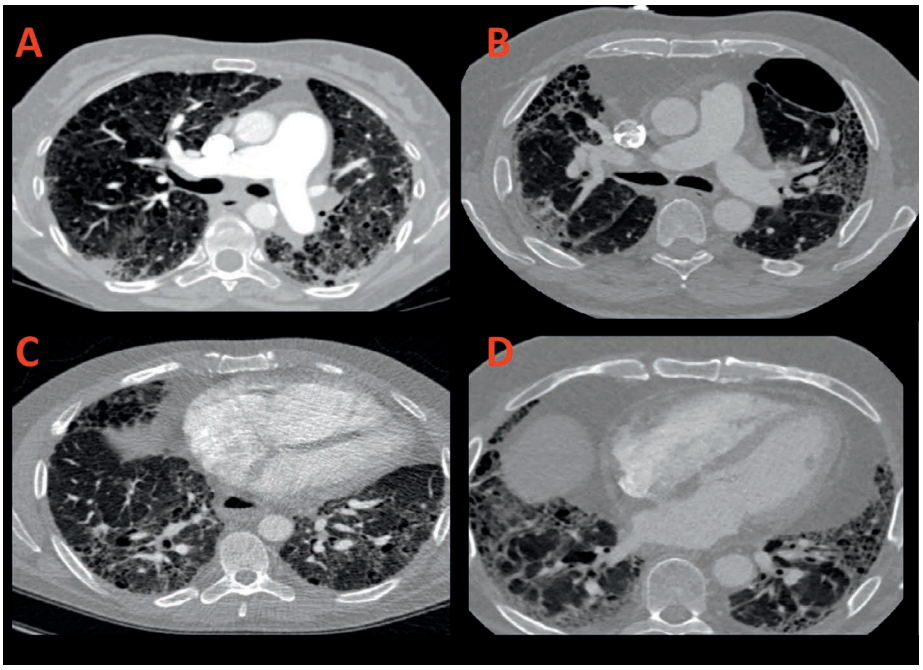

Figure: Axial computed tomography sections of patients with interstitial lung disease and right heart catheterization contemporary to computed tomography imaging. Patient in A with precapillary pulmonary hypertension (PH) has a significantly dilated pulmonary artery as compared to patient in B with pulmonary 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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REGULAR ARTICLE

Connective Tissue Disease, Interstitial Lung Disease, and Pulmonary Hypertension (CTD PH-ILD): A Distinct Entity and Potential Opportunity

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Connective tissue diseases are a multisystem disorder that can cause impairments in quality of life, shorten life expectancy, and increase the risk of mortality at a younger age. These patients have an increased risk for the development of pulmonary hypertension through several mechanisms including pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease. This review aims to discuss the various presentations of connective tissue disease associated with pulmonary hypertension associated with interstitial lung disease, demographics, and survival. It gives an overview of accepted mechanisms of disease pathogenesis, discusses advances in diagnostics, and treatment options. Despite a deeper understanding of disease pathogenesis, treatment for this remains limited to prevention of disease progression. The identification of the primary disease driver requires careful evaluation of the disease phenotype and is a potential target for treatment and prevention of death.

INTRODUCTION

Lung involvement in connective tissue disease (CTD) most commonly occurs as interstitial lung disease (ILD), pulmonary hypertension (PH), or a combination of both (PH-ILD). In most CTDs, including rheumatoid arthritis, systemic lupus erythematosus, polymyositis or dermatomyositis, Sjogren syndrome, mixed connective tissue disease, and systemic sclerosis (SSc), ILD is often early in the disease course and can be a presenting manifestation.[1] PH, on the other hand, can result from processes that affect organs other than the pulmonary vessels, such as left heart disease, liver fibrosis, and kidney dysfunction. CTD can also increase the risk of pulmonary emboli causing vascular remodeling due to endothelial damage without explicit venous thromboemboli.[2] More commonly, ILD causing hypoxic vasoconstriction and pulmonary arterial hypertension (PAH) due to a small vessel vasculopathy are the predominant causes of PH in CTD.[3] CTD-PH may therefore develop either as a consequence of progressive ILD or as an unfortunate complication of the autoimmune disease process itself. On a molecular level, this setting is a fraught with inflammatory cells including granulomas, myofibroblast, and extracellular matrix populations.[4] Altogether, this leads to a chronic inflammatory process that destroys functional lung parenchyma, encourages collagen deposition, and ultimately leads to fibrosis and an increased risk for morbidity and mortality.[5] The focus of this review is to understand the recent changes in defining CTD-PH-ILD, understand the pathophysiologic mechanisms involved, provide an approach to diagnosing the underlying phenotype, and offer new insights in considering treatment in the proper context.

DEFINITION, EPIDEMIOLOGY, AND PREVALENCE

The 6th World Symposium for PH revised the definition of group 3 PH in 2018. It requires a chronic a lung disease (CLD) accompanied by hemodynamic measurements via right heart catheterization (RHC). Hemodynamics must demonstrate a resting mean pulmonary artery pressure (mPAP) ≥ 20 mm Hg, PVR ≥ 3 Wood units, and a pulmonary artery occlusion pressure ≤15 mm Hg.[6] It is considered severe at mPAP ≥ 35 or at mPAP ≥ 25 mm Hg with cardiac index ≤ 2.0 L/min/m^2. Two studies in scleroderma patients demonstrated the importance of including what was previously thought of as *borderline PH*. They noted that a third of scleroderma patients with mPAP > 20 progressed to mPAP ≥ 25 in 3 years[7] with a mortality of 18%.[8] (Table 1)

Prevalence of ILD and PH-ILD in Connective Tissue Diseases (World Health Organization Group 3 PH)

The most common CTDs that present with group 3 PH-ILD are SSc, mixed CTD, sarcoidosis, and idiopathic inflammatory myositis.[4,9] The widespread variation in prevalence is because of the diagnostic techniques used to define PH and/or ILD. Furthermore, there are concomitant and multifactorial mechanisms leading to PH, and many of the studies diagnosed PH patients without RHC and through doppler echocar-

Key Words—pulmonary hypertension, interstitial lung disease, connective tissue disorders, vasodilators, immunosuppressants, detection of PH-ILD
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Table 1. PH in the Context of CLD PH[6]: (6th WSPH)

1. CLD without PH: mPAP < 21 mm Hg, or mPAP 21-24 mm Hg with PVR < 3 WU
2. CLD with PH: mPAP 21-24 mm Hg with PVR ≥ 3 WU, or mPAP 25-34 mm Hg
3. CLD with severe PH: mPAP ≥ 35 mm Hg, or mPAP ≥ 25 mm Hg with low cardiac index (<2.0 $L \cdot min^{-1} \cdot m^{-2}$)

Abbreviations: CLD, chronic lung disease; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WSPH, World Symposium for Pulmonary Hypertension; WU, Wood units.

diography with the exception of SSc. (Table 2)

Sarcoidosis is a granulomatous disease that appears with CTD and can present with multiple mechanisms leading to PH. Prevalence of PH in sarcoidosis ranges from 5.7% to 74% with a 5-year survival of 50% to 60%.[20] It is important to note that in studies with PH-ILD, sarcoidosis is often excluded and assigned to World Health Organization (WHO) group 5. Despite extensive fibrosis seen in 20% of sarcoidosis patients,[21] the PH in sarcoidosis is multifactorial (extrinsic pulmonary artery [PA] compression from lymphadenopathy, mediastinal fibrosis, pulmonary vascular arterial and venous granulomas, fibrosis-associated remodeling and obliteration of pulmonary vessels hypoxia, heart disease from granulomatous infiltration/cardiomyopathy from ectopy, and portopulmonary hypertension). Clinicians applying outcomes in trials with sarcoidosis-associated PH should be mindful of this fact.[22]

SURVIVAL: PH-ILD WITH THE WORST PROGNOSIS

Despite seemingly similar presentations, CTD-ILD differs in both response to treatment and prognosis from other forms of ILD such as idiopathic pulmonary fibrosis (IPF).[1] Furthermore, with PH onset regardless of cause of the PH, there is a trend toward increasing mortality in CTD with an estimated 3-year survival rate of 56%.[15] PH and/or ILD account for 60% of deaths in SSc.[23]

In the PHAROS registry (PH Assessment and Recognition of Outcomes in Scleroderma), SSc-PAH populations are found to have poorer long-term survival despite access to vasodilator therapy.[24] These worsen once CTD patients with ILD develop PH (CTD-PH-ILD). Data coming from SSc cohorts by Mathai and colleagues revealed that SSc patients with PH-ILD had an increased risk of death (hazard ratio 2.87) with 1-year, 2-year, and 3-year survival rates of 82%, 46%, and 39%. This is 5 times worse than survival in SSc or PH alone.[25] A lower diffusing capacity for carbon monoxide (Dlco) was associated with increased mortality, and there existed a trend toward decreased survival with higher PVRs.[25]

When authors explored the subsets of hemodynamics, they found that a low cardiac index was a marker for mortality in SSc-PAH patients while it was an increased mPAP for PH-ILD. This suggests that SSc-PH-ILD patients have increased risk of mortality earlier in the course of their disease when their mPAP starts to rise. This is echoed in studies looking at other CTDs with PH-ILD (rheumatoid arthritis, primary Sjogren, dermatomyositis/polymyositis, SSc) where patients with a higher mPAP at the initial evaluation had a worse survival regardless of the type of CTD.[26]

The French Network for PAH and the French Network for Rare Pulmonary Diseases (OrphaLung) reviewed 128 patients from 15 centers and found that at less severe hemodynamics, PVR ≈ 5 vs 8 Wood units ($P = .0005$) and lower Dlco (median 25% [interquartile range (IQR) 18%, 35%] versus 40% [IQR 31%, 51%]; $P = .0005$), mortality and WHO functional class was worse in those with SSc-PH-ILD than PAH.[27] Also, SSc-PH-ILD patients were younger and more regularly required continuous oxygen therapy.

Interestingly, the investigators found no difference in the initiation of oxygen therapy between SSc-PAH and SSc PH-ILD on PAH-specific therapy, although this study was not designed to distinguish between effects observed because of PAH-specific treatment versus worsening ILD.

Approach to Understanding the Spectrum of PH-ILD in Connective Tissue Disease

CTD-related PH (CTD-PH) occurs as a result of simultaneous mechanisms.[20] Lung predominant CTD with PH (CTD-PH-ILD) is therefore challenging to treat but presents a unique opportunity as these patients have a chance at responding to PH-targeted therapies.

Many believe that there are clear distinct phenotypes that drive the responsiveness to pulmonary vasodilator therapies in both PH-ILD and CTD-PH-ILD. In the group 3 phenotype, one is distinctly driven by hypoxic pulmo-

Table 2. Prevalence of PH-ILD and ILD in CTD

CTD	PH-ILD prevalence (%)	ILD prevalence (%)
SSc-ILD[a,b,c,d]	24[10]	70-90[11] (only 30-40 will develop clinically significant disease[12])
MCTD-ILD[a,b]	2-24[13]	20-78[2]
SLE-ILD[a,b]	<5[14]	1-15[15]
IIM[b]	7,9[16]	20-40[17]
RA-ILD[b]	<10[4]	6.5-33[18]
Sjogren	-	28-61[19]

Abbreviations: CTD, connective tissue disease; IIM, idiopathic inflammatory myositis (includes antisynthetase syndromes); ILD, interstitial lung disease; MCTD-ILD, mixed connective tissue disease associated with ILD; RA-ILD, rheumatoid arthritis associated with ILD; SLE-ILD, systemic lupus erythematosus associated with ILD; SSc-ILD, systemic sclerosis associated with ILD.

[a]World Health Organization Group 1.
[b]World Health Organization Group 2.
[c]World Health Organization Group 4.
[d]World Health Organization Group 5.

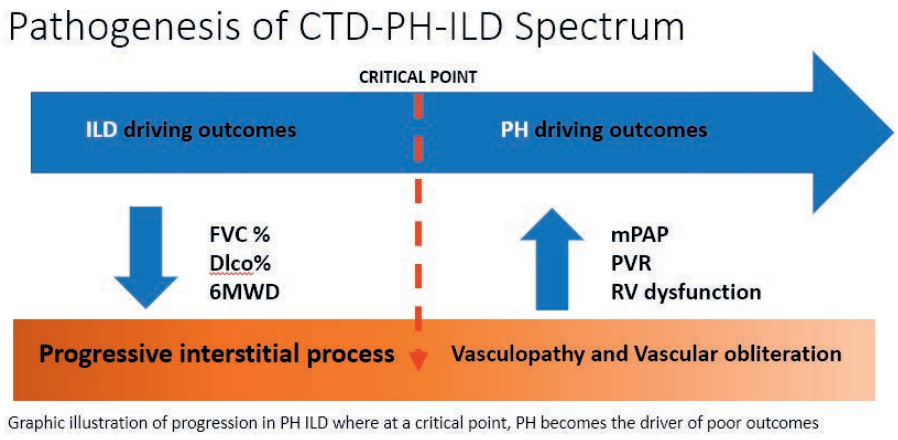

Figure: Pathogenesis of connective tissue disease and pulmonary hypertension associated with interstitial lung disease spectrum. Graphic illustration of progression in pulmonary hypertension associated with interstitial lung disease where at a critical point, pulmonary hypertension becomes the driver of poor outcomes. Adapted from King and Nathan.[20]

nary vasoconstriction versus a more hemodynamically/right ventricle (RV) failure group 1 phenotype.[20] There develops a critical point at which PH becomes the larger driver of outcomes, and this is probably more true and possibly earlier realized in CTD patients. King and Shlobin[28] offers a therapeutic approach to PH-ILD where one can view PH as a surrogate marker of disease progression in advanced fibrotic lung disease versus a maladaptive phenotype where PH is the driver of pathophysiologic derangements that is out of proportion to the degree of ILD. This maladaptive or out-of-proportion PH-ILD is thus more likely to benefit from the initiation of vasodilator therapy. (See Figure)

NONINVASIVE CLUES SUGGESTING PULMONARY VASCULAR DISEASE IN CTD-ILD

Clinical History and Examination

Patients with CTD-ILD-PH are more likely to be younger, female, and nonsmokers. Patients with preexisting ILD will endorse worsening exertional dyspnea or poor exercise capacity despite mild lung disease or severe lung disease that has been stable for several years. Patients will start to complain of symptoms suggestive of right heart dysfunction such as lower extremity, ascites, and weight gain. They often have rapid desaturations on activity with movement or mild exercise. Clinical high-risk features include syncope and presyncope, lightheadedness, dizziness, and kidney or liver dysfunction, which are suggestive of worsening cardiac output.

BNP or NT-proBNP

An elevated BNP (brain natriuretic peptide) or NT-proBNP (N-terminal-pro hormone BNP) are released in response to myocardial stretch, and serial levels can be used to prognosticate as they correlate with PVR and inversely correlate with 6-minute walk distance (6MWD). CTD patients with NT-proBNP levels of 395 pg/mL predicted PH with a 56% sensitivity 95% specificity.[1]

Pulmonary Function Testing

A 6-minute walk test has several variables that may help predict PH. A sudden decrease in walk distance and pronounced desaturation (distance-desaturation product) are both associated with PH and reduced survival.[29]

The DIBOSA is a composite score that includes 3 variables obtained from a 6-minute walk (DIstance walked in 6 min, BOrg dyspnea index, and SAturation of oxygen at 6 min). This was validated in cohort of more than 200 SSc patients diagnosed with a RHC. A score of 0 had a negative predictive value (NPV) of 100% and a score of 3 had a positive predictive value (PPV) of 86.58%. The DIBOSA score was devised as is a noninvasive way of predicting mPAP as measured by RHC and right ventricular systolic pressure (RVSP) as estimated by echocardiogram. It is a good predictor of disease severity and mortality and can be used to prognosticate SSc patients who are at risk for developing PH though could not distinguish between PAH (WHO group 1) and PH-ILD (WHO group 3).[30]

Other clues that patients are developing worsening cardiac dysfunction in the setting of CTD-ILD include a failure of the heart rate to fall after cessation of exertion (abnormal heart rate recovery) of >13 b/min.[31]

Pulmonary hemodynamics have not been demonstrated to correlate with pulmonary function, although DLCO and FVC (forced vital capacity) are pulmonary function tests that can be used to predict the probability of PH. A DLCO < 55% predicted and FVC % predicted / DLCO % predicted > 1.4 was strongly associated with PH in a set of 815 SSc patients.[32]

Finally, Zisman and colleagues also validated a prediction formula for mPAP using standard lung function tests that can be used to screen for PH in IPF patients. This can similarly be applied in CTD-PH-ILD patients, however it has not been validated in this population.

$$\begin{aligned}\text{mPAP} &= -11.9 + 0.272 \times \text{SpO}_2 \\ &\quad + 0.0659 \times (100 - \text{SpO}_2)^2 \\ &\quad + 3.06 \times \left(\frac{\text{percentage of predicted FVC}}{\text{percentage of predicted DLCO}} \right).\end{aligned}$$

DETECT and Australian Scleroderma Interest Group Tools in SSc

Because greater prevalence of PAH is seen in SSc patients, screening guidelines and tools have been validated in SSc. Strategies using composite screening instruments such as the DETECT or Australian Scleroderma Interest Group (ASIG) tools identify patients with SSc-PAH using a composite index. The DETECT algorithm assigns numerical scores to clinical variables and, using a web-based calculator, the score determines need for an echocardiogram and subsequently RHC. The ASIG algorithm uses PFT and NT-proBNP as an indication for RHC. (Table 3)

Table 3. When to Order an Echocardiogram Looking for PH in CTD-ILD

History and exam
• Low oxygenation evidenced by decreased Spo_2 or Pao_2, increasing need for oxygen supplementation
• Rapid desaturation of oxygen with mild exercise or movement
• Worsening dyspnea with stable PFTs and or chest CT
• Preserved lung volumes but worsening exertional dyspnea
• Signs and/or symptoms of right heart failure (edema, JVD, hepatomegaly)
Imaging
• A PA-aorta ratio of >1.0 correlated with mPAP > 20 mm Hg on CT chest
• PA diameter and PA-aorta ratio cutoff values >34 mm and >1.1 on MRI
PFTs and CPET
• Low DLCO and low KCO
• Hyperventilation (low $Paco_2$) to maintain oxygenation (especially during exercise)
• CPET: Low Vo_2-co_2 ratio, Low o_2 pulse
• Ratio of FVC % to DLCO % >1.8 (based on DETECT)
• FVC <55% and ratio of FVC to DLCO (% predicted) >1.4
• Heart rate recovery after 6MWT of >13 b/min
• Declining DLCO without evidence of visually worsening fibrosis (absolute DLCO or change)
Labs
• Elevated NT-proBNP/BNP

Abbreviations: 6MWT, 6-minute walk test; BNP, brain natriuretic peptide; CPET, cardiopulmonary exercise testing; co_2, carbon dioxide; CT, computed tomography; CTD-ILD, connective tissue disease associated with interstitial lung disease; DLCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity; JVD, jugular venous distension; KCO, transfer coefficient of the lung for carbon monoxide; MRI, magnetic resonance imaging; NT-proBNP, N-terminal (NT)-pro hormone BNP; PA, pulmonary artery; PFT, pulmonary function test; PH, pulmonary hypertension.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing can also help distinguish the limiting physiology in patients with group 1 and group 3 PH. A ventilatory limitation is a typical feature in patients with ILD but can also occur in PAH. Often, patients with PAH will have resting and peak exercise hypocapnia with low $Petco_2$ versus those with ILD have a more ventilatory limitation. The $P(a\text{-}et)co_2$ gradient, which is the difference between the partial pressure of carbon dioxide on an arterial blood gas ($Paco_2$) minus the end tidal co_2 on capnography, fails to decline or rather, increases in patients with PAH that are exercising.[34]

In patients with severe ILD with severe PH (mPAP ≥ 40 mm Hg), there is a lower Vo_2 peak, higher Ve/Vco_2 slope, and lower peak exercise $Petco_2$ compared to ILD patients without PH.[35]

Imaging

High Resolution Computerized Tomography Findings in PH-ILD: The Goh criteria identifies mild ILD in CTD as <20% involvement on high resolution computerized tomography and <5 % of emphysema. Patients with FVC > 70% are classified as indeterminate despite extent of ILD. Finally, in patients with combined fibrosis and emphysema, a DLCO <40% leads to severe group 3 PH even if fibrosis is modest (10% to 20% on high resolution computerized tomography). In SSc patients, emphysema can occur regardless of smoking status.[3]

Based on the results of the Framingham study, a PA ≥ 29 mm in males and ≥ 27 mm in females is considered to represent abnormal dilation.[36] This is not as sensitive in patients with ILD or CTD that have other reasons for dilated pulmonary arteries. A ratio of PA to aorta of >1.0 correlated with mPAP > 20 mm Hg, with a specificity of 92% and positive predictive value of 96%.[36] The measurement of the main PA and ascending aorta diameters should be done at the level where the PA bifurcates (when both the right and left PA appear to be of similar size) using electronic calipers.[37]

Magnetic Resonance Imaging: Magnetic resonance imaging is more accurate than a computed tomography chest scan. PA diameter and PA-aorta ratio cutoff values >34 mm and >1.1 yielded specificities of 98% and 100%, with corresponding sensitivities of 65% and 50% and positive predictive values of 98% and 100%. Serial magnetic resonance imaging machines have the advantage of demonstrating longitudinal and circumferential RV strain, PA stiffness, and reduced RV and PA coupling.[38]

Echocardiography: The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of PH recommend screening patients with suspicion for PH using a transthoracic echocardiogram. These guidelines recommend yearly echocardiographic screening for all patients with SSc. These guidelines are specific to SSc and not other CTDs because of higher prevalence and mortality in this population.

In other disorders where PH is suspected, a screening echocardiogram is ordered when clinical and noninvasive testing parameters suggest PH. In patients with PH-ILD however, the tricuspid regurgitation velocity jet may be difficult to visualize and may lead to inaccurate estimations of the RV systolic pressure when compared with diagnostic RHC.[28] It is important for the PH provider to review the echocardiograms and interpret other markers of RV dysfunction within the clinical context.[39] (Table 4 and Table 5)

INVASIVE CLUES SUGGESTING PULMONARY VASCULAR DISEASE IN CTD-ILD

RHC remains the gold standard in diagnosis of PH. Left heart abnormalities and PH-ILD can coexist with vasculopathy in many CTDs, hence it is important to clearly determine the hemodynamic phenotype. Diastolic dysfunction is common in CTD because of cardiac fibrosis seen in SSc, idiopathic inflammatory myositis, and mixed CTD. It is also seen more commonly in older patients who have left heart disease risk factors and have CTD. Therefore, we recommend free fluids before the procedure or withholding diuretics for 48 hours. In patients where pulmonary capillary wedge pressure ≤15 mm Hg,

Table 4. Clinical Criteria Favoring Group 1 versus Group 3 PH[a]

Favoring PAH	Testing	Favoring PH-ILD
Extent of lung involvement		
Mildly impaired: FEV 1 > 60% pred FVC > 70% pred Low DLCO relative to obstruction/restriction	PFT	Moderate to very severely impaired: FEV 1 < 60% pred FVC < 70% pred DLCO corresponds to obstructive/restrictive changes
Hemodynamic phenotype		
Moderate to severe PH	RHC Echo	Mild to moderate PH
Ancillary testing		
Present	Group 1 risk factors: BMPR2 mutation, HIV, drug use, schistosomiasis, etc	Absent
CPET		
Exhausted cardiac reserve Low O_2 pulse Lower mixed venous oxygen saturation No change in $Paco_2$ during exercise Low CO/Vo_2 slope		Exhausted ventilatory reserve Reduced breathing reserve Normal O_2 pulse Mixed venous oxygen higher limit Increase in $Paco_2$ during exercise Normal CO/Vo_2 slope

Abbreviations: CO, cardiac output; CPET, cardiopulmonary exercise testing; DLCO, diffusing capacity of lung for carbon monoxide; FEV, forced expiratory volume; FVC, forced vital capacity; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; pred, predicted; RHC, right heart catheterization.

[a]Adapted from: Nathan et al[6]

we recommend a rapid saline bolus to unmask diastolic dysfunction. It is ideal to obtain a wedge saturation >90% to ensure accuracy.[9] Finally, in patients with significant pulmonary disease and PH, pressure measurements during a RHC can be affected by changes in intrathoracic pressures during a breathing cycle. The 6th World Symposium for PH recommends that clinicians use the average mPAP and pulmonary capillary wedge pressure after several breaths (without a breath hold).[40] Reviewing waveforms is therefore of utmost importance.

Poor survival outcomes in the CTD population are demonstrated especially in the SSc cohort. Studies have shown that SSc patients develop greater RV dysfunction independent of the pulmonary afterload. This was demonstrated by Tedford and colleagues[41] when they used invasive RV pressure-volume relations to show differences in RV contractile function. Despite finding no differences in afterload between SSc-PAH, SSc-PH-ILD, and idiopathic PAH, they saw that with increasing afterload, the RV in SSc-PAH patients had a greater inability to compensate.

Table 5. Echocardiographic Parameters that Increase Suspicion for Pulmonary Hypertension[a]

Peak tricuspid regurgitation velocity (m/s)	Presence of echo 'PH signs'	Echocardiographic probability of pulmonary hypertension	RHC Referral
≤2.8 or not measurable	absent	low	No
≤2.8 or not measurable	present	Intermediate	Consider
2.9-3.4	absent		
2.9-3.4	present	High	Yes
≥3.4	Not required		
Echo 'PH signs'			
Ventricles	**Pulmonary Artery**		**IVC and RA**
RV/LV basal diameter ratio >1.0	RV outflow doppler acceleration time <105 msec and/or mid-systolic notching Early diastolic pulmonary regurgitation velocity >2.2 m/sec		IVC diameter>21 mm with decreased inspiratory collapse <50% with a sniff or <20% with quiet inspiration
Flattening of the interventricular septum (LV eccentricity index >1 during systole/diastole	PA diameter>25 mm		Right atrial area (end-systole)>18 cm^2

Abbreviations: IVC, inferior vena cava; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

[a]Adapted from Galiè et al.[39]

This maladaptive response translates to poorer response to vasodilators in severe SSc-PAH patients and is thought to be the reason why there are less echocardiographic changes in SSc-PAH versus idiopathic PAH despite escalation of therapy.[42] It is important therefore to determine RV dysfunction or risk *earlier* in this group of patients. (Table 6)

Table 6. When to Confirm With a RHC

1. Abnormal right sided morphology or function on echocardiogram (see echo PH signs and tricuspid regurgitation velocity m/s)
2. PH will likely be influenced by RHC results
- Possible transplantation
- Inclusion in clinical trials or registries
3. Needing to unmask left heart dysfunction (those with group 2 risk factors such as metabolic syndrome, structural left heart disease, LBBB on ECG, dilated LA, hypertension, type 2 diabetes)
4. Consideration of compassionate use therapy

Abbreviations: ECG, electrocardiogram; LA, left atrium; PH, pulmonary hypertension; RHC, right heart catheterization.

TREATMENT: WHAT THE EVIDENCE CURRENTLY SUPPORTS

PH-Specific Therapy

There has long been controversy regarding the use of PAH-specific therapy in PH-ILD. Despite progressive strides in treatment options for PAH, a treatment approach to PH-ILD has largely been expert-led rather than evidence-based. The currently accepted treatment approach is to correct or prevent progressive hypoxemia by treating the underlying lung disease with immunosuppression and/or antifibrotics, preventing progression, and considering lung transplantation when not contraindicated.[43]

One of the barriers is the lack of consensus regarding the definition of disproportionate PH in chronic respiratory disease and the danger of causing worsening gas exchange through inhibition of hypoxic pulmonary vasoconstriction. Secondly, most trials enrolled patients using diffusion capacity or transthoracic echocardiogram criteria to diagnose PH rather than through invasive hemodynamics.[23] Finally, the prognosis is so grim that often life expectancy is short, making enrollment challenging. Clinicians are hesitant to enroll patients in a trial that might commit patients to placebo or worsen their already poor prognosis and quality of life.

Unfortunately, the pathogenesis of PH-ILD being multifactorial and the reversal of hypoxia rarely reverses PH in patients.[43]

Despite this, a survey looking at current practice patterns in PH providers reveal that PAH-specific therapies are still prescribed to patients with PH-ILD. Practitioners state that the factor influencing their decision to treat was usually RV dysfunction or RV failure.[44] Clinicians have long been treating what they believed was a predominantly circulatory rather than ventilatory dysfunction.

The data for group 3 PH-ILD is mostly from the idiopathic interstitial pneumonias, particularly IPF, and have shown little benefit[45] until the recent INCREASE study.[46]

And yet with SSc-ILD-PH, PH-specific therapy has demonstrated mixed results. At expert PH centers, patients with SSc-ILD-PH are often given a trial of pulmonary vasodilators with the hope of treating a responsive arteriopathy.[23]

Clinical trial data in CTD-PAH demonstrate that PH-specific therapies such as prostacyclins, endothelin receptor antagonists and phosphodiesterase type 5 inhibitors have been shown to improve exercise tolerance, health-related quality of life, and hemodynamic parameters.[15] Unfortunately, not the same can be said with trials that included populations that had ILD. Patients with ILD have been historically excluded, however, with the exception of a few trials in SSc.

Mathai and colleagues found a 3-year survival rate of 39% among patients with SSc-PH-ILD who were on PH-specific treatment. It is unclear if this was because of worsening disease progression and the known disease course of these patients versus the effects therapy.[25]

Sildenafil: Small observational studies in IPF and oral sildenafil and tadalafil (phosphodiesterase type 5 inhibitors) have demonstrated improved ventilation-perfusion matching with oxygenation.[45] Furthermore, incident patients in the COMPERA registry who were treated with phosphodiesterase type 5 inhibitors demonstrated a median improvement in 6MWD of 24.5 m, and close to a quarter of patients had improved functional class.[47] Importantly, many studies in this population demonstrated no gas exchange abnormalities[45] and rarely resulted in trea tment withdrawal. Reductions in oxygen delivery because of pulmonary vasodilation is thought to be compensated for by an increased cardiac output that may maintain or even improve tissue oxygen delivery most notably during exercise.[6] This is further supported by a post hoc subgroup analysis of the STEP-IF (Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis) trial where RV dysfunction by echocardiography was improved and they found a mean increase of 99.3 m (95% confidence interval, 22.3-176.2 m) in their 6MWD at 12 weeks compared with baseline.[48]

In CTD-PH-ILD patients, a small retrospective observational study of 13 CTD-PH-ILD patients who were treated with bosentan, sildenafil, or bosentan plus sildenafil revealed that despite no change in exercise tolerance, FVC, and 6MWD, treatment was tolerated with no untoward side effects.[49]

In another study of 10 patients with CTD and moderately elevated pulmonary pressures (mPAP ≥ 21 mm Hg), Reith et al found that sildenafil 20 mg 3 times daily for 90 days reduced the median total pulmonary resistance during exercise 6.22 mm Hg/min/L (IQR 4.61, 8.54) to 5.24 mm Hg/min/L (IQR 3.95, 6.96) ($P = .005$) and increased median pulmonary arterial capacitance during exercise 1.59 mL/mm Hg (IQR 0.93, 2.28) to 1.74 mL/mm Hg (IQR 1.12, 2.69) ($P = .005$).[50] This was independent of their mPAP, suggesting that vasodi-

lator therapy is beneficial in improving the hemodynamics response to exercise in CTD.

Interestingly, a small phase IIB/III trial of fibrotic ILD patients who have yet to develop PH but were on long-term oxygen treated with pulse inhaled nitric oxide demonstrated increased moderate vigorous activity on actigraphy.[51]

BUILD Trials: Despite smaller studies demonstrating efficacy of prostacyclins and endothelin receptor antagonists in SSc-ILD,[52,53] randomized controlled trials on the efficacy of bosentan and macitentan in IPF and SSc-ILD demonstrated no change in 6MWD.

RISE-IIP: The soluble guanylate stimulator riociguat in PH-ILD was used in a pilot trial to evaluate safety in idiopathic interstitial pneumonias (IIP) with RHC-confirmed PH and was terminated early for increased rates of serious adverse events and death in the treatment group both in the randomized trial and the crossover arm of the open-label extension. There was no improvement in 6MWD in patients treated with riociguat.[54]

INCREASE Study (Treprostinil): Treprostinil, a prostacyclin analogue, promotes vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. Data suggests that there is an added antifibrotic property in its ability to affect extracellular matrix remodeling and fibrosis in vivo by decreasing fibrocyte recruitment to sites of vascular remodeling.[55] This is the first trial to successfully address PH-ILD. CTD-ILD comprised 22% of the population. Compared with placebo, treprostinil improved exercise capacity as demonstrated by an increase in 6MWD from baseline at 16 weeks. Secondary endpoints that were met included a decrease in the NT-proBNP by 15% from baseline with inhaled treprostinil and increased 46% from baseline with placebo, decreased risk for clinical worsening, and less exacerbations in the treprostinil group.

Surprisingly, a subgroup analysis showed that in patients with a resistance of ≥5.275 Wood units there were also improvements in FVC at 16 weeks. This trial's success is met with caution, however, as the use of inhaled treprostinil requires thoughtful phenotyping of the PH and an understanding of hemodynamics. While there is excitement to use a medication in a disease that previously had no therapeutic options, we recommend that the decision to initiate inhaled treprostinil be done in conjunction with an expert PH center and that realistic expectations regarding benefit to quality of life should be discussed with patients. (Table 7 and Table 8)

Table 7. When to Consider Initiation of Inhaled Treprostinil (Tyvaso)[a]

PVR ≥ 3 WU, PCWP < 15 mm Hg Relative risk considerations: • Median PVR of patients in INCREASE was 6 WU • Subgroup analysis of participants that saw the most benefit was PVR ≥ 4
≤6 L of supplemental oxygen at rest unless being referred for transplantation Ambulatory distance of >300 feet Not a hospice or nursing home candidate

Abbreviations: PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; WU, Wood units.

[a]Other clinical trials using PH-specific therapy are summarized in Table 8.

ILD-Specific Treatment: Antifibrotics and Immunosuppression

A discussion on the prevention of progressive fibrosis in CTD-ILD requires separate discussion. We emphasize its importance in prevention of progression

Table 8. PH-Specific Therapies in CTD-PH-ILD

Author	N	Drug	Trial	Outcomes	CTD
Mittoo (2010)[15]	13	Bosentan/ sildenafil	Retrospective	No decrease in 6MWD or FVC in 24 months	CTD-ILD
Heresi and Minai (2008)[52]	19	Epoprostenol and bosentan	Retrospective	15/19 had improved 6MWD > 50 m	SSc-ILD
Ahmadi-Simab et al (2006)[53]	8	Bosentan	Open label, prospective	Improved 6MWD and WHO FC	SSc-ILD
BUILD 2 Seibold et al (2010)[56]	163	Bosentan	RCT	No change in 6MWD	SSc
Furuya and Kuwana (2011)[57]	9	Bosentan	Open label	No effect on lung function decline	SSc
RISE-IIP Nathan et al (2019)[54]	147	Riociguat	Double-blind, placebo-controlled RCT	no improvement in 6MWD ↑adverse events	IIP
Baughman et al (2014)[58]	39	Bosentan	Double-blind, placebo-controlled RCT	Change in mPAP	Sarcoidosis
INCREASE Nathan et al (2021)[55]	326	Inhaled treprostinil		Change in 6MWD FVC	IIP (20% had CTD)

Abbreviations: 6MWD, 6-minute walk distance; CTD, connective tissue disease; FC, functional class; FVC, forced vital capacity; IIP, idiopathic interstitial pneumonias; ILD, interstitial lung disease; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; RCT, randomized controlled trial; SSc, systemic sclerosis; WHO, World Health Organization.

to the CTD-PH-ILD phenotype in the model we previously discussed. If clinicians managing CTD-ILD are able to halt or slow progression, there may be improvement in this group with the worst prognosis.

More importantly, in vitro data on antifibrotics have not only demonstrated an ability to slow down the initiation and progression of lung fibrosis, including the release of proinflammatory and profibrotic mediators, but also to inhibit the vascular cell proliferation.[59] With the recent approval of antifibrotic medications for fibrosing ILDs such as IPF and SSc-ILD, we may potentially see a decrease in the incidence of PH-ILD and PAH in the future.

Supportive Care: We recommend supplemental oxygen to keep oxygen saturation ≥90%. Supplemental oxygen to treat lung disease is first line in patients with PH-ILD (supplemental oxygen). Additionally, because of the known increased incidence of sleep disordered breathing in PH, we recommend that patients be screened and treated for coexisting sleep apnea. Pulmonary rehab and consideration of early palliative care is key to preventing deterioration and focusing on patient-centered goals and health-related quality of life.

Considering Palliation and Hospice

Despite sound physiologic evidence for benefit, treatment of this high risk group will require a constant evaluation of clinical risk versus benefit. As most patients with CTD also have diastolic dysfunction, patients may demonstrate volume overload, recurrent hospitalizations and worsening symptoms that makes their overall quality of life worse rather than better. We recommend this guide for clinicians deciding to remove pulmonary hypertension specific therapy. The patient clinician relationship requires a clear communication of risk and mutual understanding of clinical benefit for patients to derive the most out of any attempted treatment. (Table 9)

Table 9. When to Stop Inhaled Treprostinil (Tyvaso)

• Not tolerating due to diastolic dysfunction • Volume overload • No added benefit to quality of life • Continuing to decline due to hospice trajectory
Clinical markers of worsening include weight gain >3 lbs, worsening hypoxia

SUMMARY

The development of PH in CTD-ILD is usually a consequence of worsening advanced lung disease, a primary result of vascular inflammation due to the CTD itself or a combination of both. Clinicians must be on the lookout for markers of disease progression such as early desaturation, impaired heart rate recovery, worsening gas exchange despite stable lung volumes, and imaging. The critical point at which the progression is mediated by a vasculopathic driver is when PH-specific therapies may be most useful at improving outcomes. Despite worsening ventilation-perfusion mismatch, augmenting cardiac output may eventually relieve hypoxia in some patients.

A combination of antifibrotic, immunosuppressive and vasodilating agents may be the key to slowing progression toward this devastating disease. The recent success of inhaled prostacyclins in this subgroup[55,60] may be credited to the drug delivery mechanism as well as some inherent antifibrotic properties as well.[27]

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REGULAR ARTICLE

Management of PH-ILD: Past, Present, and Future

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Pulmonary hypertension associated with interstitial lung disease signifies worse outcomes. Given previous negative clinical trials, the use of pulmonary vasodilators in pulmonary hypertension associated with interstitial lung disease has traditionally been on a case-by-case basis; however, the recent INCREASE study has led to the first and milestone approval of inhaled treprostinil for this population. This review discusses the management of pulmonary hypertension associated with interstitial lung disease from the pulmonary vascular perspective, with an emphasis on clinical trials in this population.

INTRODUCTION

Pulmonary hypertension (PH) in interstitial lung disease (ILD) is a serious complication that heralds significant morbidity and mortality.[1,2] Apart from early referral for transplantation evaluation, management of PH associated with ILD (PH-ILD) focuses on treatment of the individual parenchymal and pulmonary vascular disorders. While the advent of multiple therapeutics for pulmonary arterial hypertension (PAH) has sparked much interest in their use in PH-ILD, the first Food and Drug Administration approval for such a medication was granted only recently. This review will focus on the management of PH-ILD, with particular reference to previous and current pharmacologic studies in this area.

CHALLENGES TO CLINICAL TRIALS

Clinical trials in PH-ILD have faced multiple unique challenges stemming from the complexity inherent in diagnosing and managing a combined cardiopulmonary disorder. Potential disruption of ventilation-perfusion matching led to the exclusion of this population from the original medication trials; instead, initial work largely consisted of small series in PH-ILD and subgroup analyses of ILD-only studies. From a diagnostic perspective, conclusions from these studies are limited: not only were many based on echocardiography, but those with invasive hemodynamics generally did not include the pulmonary vascular resistance (PVR), a now-required component of the 6th World Symposium on Pulmonary Hypertension (WSPH) definition of Group 3 disease.[2] Similar variations in the studied lung disease subtype and severity have also limited comparison between analyses.

Clinically, PH-ILD exists on a spectrum, and it may be difficult to untangle the contribution of each disease to symptom burden and functional limitation. From a trial perspective, this has created considerable difficulty in determining the most appropriate endpoint in PH-ILD: ideally, such a metric would accurately delineate parenchymal and pulmonary vascular limitations, reproducibly monitor treatment response, and carry prognostic significance. The 6-minute walk distance (6MWD)—the standard exercise assessment in PAH—is often used in PH-ILD; however, it is affected by each individual disease and cannot distinguish between them.[3] Going forward, composite endpoints that include separate PH-specific and ILD-specific parameters and overall functional measures will likely be helpful. Similarly, cardiopulmonary exercise testing to differentiate limitations or cardiac magnetic resonance imaging to evaluate right ventricular (RV) function may also be important tools.[3]

THE NITRIC OXIDE PATHWAY

Phosphodiesterase-5 Inhibitors

The earliest studies of PAH-specific therapy in PH-ILD focused on phosphodiesterase-5 inhibitors. Initial small studies noted phosphodiesterase-5 inhibitors positively impacted hemodynamics and exercise capacity in PH-ILD.[4-6] Compared to intravenous epoprostenol, sildenafil also enhanced ventilation-perfusion matching—at least partly because of reduced shunting—and ultimately improved oxygenation.[7] This phenomenon was attributed to preferential vasodilation of well-ventilated regions of lung, potentially from the effect of sildenafil on local vasoregulation including nitric oxide.[7]

The Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF) study was a double-blind randomized controlled trial (RCT) of sildenafil in advanced idiopathic pulmonary fibrosis (IPF), defined by a diffusing capacity for carbon monoxide (DLCO) <35%. There were small improvements in oxygenation, DLCO, dyspnea, and quality of life with sildenafil, although it was not associated with increased 6MWD.[8] While patients on background PAH therapy were excluded, a small number (18.6%) had RV

Key Words—pulmonary hypertension, interstitial lung disease, treatment, clinical trials
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hypertrophy or dysfunction on echocardiogram. While the entire population experienced a decrease in 6MWD, this finding was attenuated among patients with RV dysfunction treated with sildenafil.[9]

Based on these positive results, it was hypothesized that phosphodiesterase-5 inhibitors and antifibrotics may work synergistically in PH-IPF. INSTAGE, a double-blind RCT, evaluated the combination of sildenafil and nintedanib, a tyrosine kinase inhibitor with antifibrotic properties, in IPF with severely impaired gas exchange (DLCO ≤ 35%).[10] Compared to nintedanib alone, quality of life was not improved with nintedanib-plus-sildenafil. Among the subgroup with echocardiographic RV dysfunction (43%), there was a more pronounced stabilization of BNP—likely reflecting reduced RV stress—although this again did not translate to improved quality of life.[11]

Similar equivocal results were recently reported from a Phase 2b RCT of sildenafil and pirfenidone, an antifibrotic that blocks the proliferative effects of platelet-derived growth factor, in advanced IPF with DLCO ≤ 40%. Notably, this study enrolled only patients at risk of WSPH Group 3 disease, defined either by PH on right heart catheterization (mean pulmonary arterial pressure ≥20 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg) or intermediate-high probability on echocardiogram.[12] Pirfenidone-plus-sildenafil was not associated with a change in disease progression, exercise capacity, quality of life, or pulmonary function. The addition of sildenafil to antifibrotics is therefore not routinely recommended in IPF, although certain subpopulations may benefit from this treatment approach.

Riociguat

Initial open-label evaluation of the soluble guanylate cyclase stimulator riociguat in treatment-naive PH-ILD patients suggested it was both safe and well-tolerated.[13] RISE-IIP (Riociguat for Idiopathic Interstitial Pneumonia-Associated PH) was a subsequent RCT studying riociguat in PH associated with idiopathic interstitial pneumonias (IIPs) with forced vital capacity (FVC) ≥45%.[14] RISE-IIP was terminated early at 22 weeks: not only did riociguat fail to improve exercise capacity, but treated patients also had increased rates of adverse events including deaths. The reason for this clinical worsening is not clear but has been attributed to the wide variety of enrolled ILDs with different long-term prognoses or the possibility of a harmful hemodynamic response causing increased RV workload.[13] Regardless, the use of riociguat is not recommended in PH-IIP.

THE ENDOTHELIN-1 PATHWAY

While initially thought promising due to additional parenchymal antifibrotic effects, studies of the endothelin receptor antagonists have been largely underwhelming. Although an early case series suggested the dual endothelin receptor antagonist bosentan increased exercise capacity in PH-ILD, this finding did not persist at 1 year.[15] Negative results were also seen in B-PHIT, a placebo-controlled RCT of bosentan in fibrotic PH-IIP. Among 60 patients, this medication was not associated with improvements in indexed PVR, exercise capacity, dyspnea, or oxygenation.[16] In contrast, interim results from a small open-label study suggested bosentan improved hemodynamics and survival in patients with exercise or mild-moderate PH and IPF without parenchymal inflammation.[17] As the inclusion of only stable lung disease minimized confounding from respiratory exacerbations, it was suggested this may more accurately reflect the effect of bosentan on the pulmonary vasculature.

While studies of bosentan were mixed, evaluation of the selective endothelin receptor antagonist ambrisentan in PH-ILD has been disappointing. Within the small PH-ILD population (9.4%) in the open-label ARIES-3 study, 6MWD decreased at 24 weeks despite improved BNP, potentially related to progressive underlying lung disease.[18] The double-blind ARTEMIS-IPF RCT was subsequently initiated to evaluate ambrisentan in IPF with no-to-minimal honeycombing; however, it was terminated early at 75% enrollment because of poor efficacy and increased adverse events.[19] While those on background PAH treatment were excluded, 14% of the original cohort had WSPH Group 3 disease on preenrollment right heart catheterization.[20] After 48 weeks of randomized treatment, ambrisentan was not associated with hemodynamic improvements among those who underwent interval right heart catheterization. Moreover, there was a nonsignificant trend among ambrisentan-treated PH patients toward increased ILD progression. Endothelin receptor antagonists are therefore not routinely recommended for treatment of PH-ILD.

THE PROSTACYCLIN PATHWAY

Intravenous Prostacyclins

The most favorable results in PH-ILD treatment have centered on prostacyclins. In an early comparison study, inhaled iloprost was associated with decreased mean pulmonary arterial pressure and PVR, without adverse impact on oxygenation.[21] Hemodynamic improvements were largely similar with intravenous epoprostenol, although they occurred at the expense of systemic vasodilation. The use of parenteral treprostinil therapy in 15 patients awaiting lung transplantation with severe pulmonary fibrosis-associated PH was similarly promising. While most patients were on background PAH therapy—such that the study was enriched for a population that had already tolerated pulmonary vasodilators—hemodynamics significantly improved at 12 weeks, which correlated with better RV function on both echocardiographic and invasive assessment.[22] Exercise capacity, dyspnea, and quality of life also improved with stable oxygenation. Similar hemodynamic improvements have also been noted with parenteral treprostinil in an autoimmune disease-containing PH-ILD population.[23]

Inhaled Prostacyclins

Inhaled treprostinil is currently the most effective treatment for PH-ILD, leading to its recent approval by the Food and Drug Administration as the first therapeutic option for this population. In an initial retrospective review of 22 WSPH Group 3 PH patients—the majority of whom had ILD or combined pulmonary fibrosis and emphysema—inhaled tre-

prostinil was associated with improved functional class, exercise capacity, and oxygenation.[24]

The recent double-blind placebo-controlled INCREASE study was the first RCT of inhaled treprostinil in PH-ILD.[25] Inclusion criteria necessitated PH on right heart catheterization—notably with an elevated PVR > 3 Wood units—and diffuse parenchymal lung disease on computed tomography chest scan. The study met its primary endpoint: at 16 weeks, there was a significant difference between the treprostinil-treated and placebo-treated cohorts in the change in peak 6MWD from baseline (least-squares mean difference 31.1 m, $P < .001$). Notably, the largest increases occurred in the subgroups with PVR ≥ 4 WU or DLCO < 40%, suggesting that patients with the most severe—and likely disproportionate—pulmonary vascular remodeling benefited the most from treatment.

Importantly, inhaled treprostinil treatment was also associated with improved markers of clinical status and RV function. Time to clinical worsening—a composite of 6MWD decline, cardiopulmonary hospitalization, lung transplantation, and all-cause mortality—was significantly prolonged with treatment. NT-proBNP decreased with inhaled treprostinil but rose precipitously with placebo, without change in oxygenation. These results therefore suggest inhaled treprostinil ameliorated RV stress, likely through improved perfusion of only well-ventilated lung and preservation of ventilation-perfusion matching.

Interestingly, INCREASE revealed a number of unexpected findings with potential significance in ILD. Inhaled treprostinil was associated with a significantly reduced rate of ILD exacerbations. Furthermore, FVC rose with treatment (inhaled treprostinil vs placebo, absolute difference 44.4 mL [$P = .21$]; predicted change 1.8% [$P = .028$]).[26-28] Notably, this finding occurred despite the wide range of studied ILDs—including combined pulmonary fibrosis and emphysema—and was driven by a true FVC increase, not between-group rates of decline as observed in previous antifibrotic trials. This improvement was most prominent among the IPF subgroup, as well as those with increased pulmonary vascular remodeling and likely RV stress (PVR ≥ 5.275 WU; NT-proBNP >503.85 pg/mL). While the physiologic mechanism underpinning these findings is not yet clear, it may be related to antifibrotic effects of inhaled treprostinil, potential impact of pulmonary vascular stiffness on parenchymal compliance, or possible interactions between RV stress and respiratory muscle function.[26,29,30] A double-blind RCT studying the pulmonary effects of inhaled treprostinil in IPF is currently ongoing (ClinicalTrials.gov identifier NCT04708782).

NONPHARMACOLOGIC MANAGEMENT

General Principles

Study of the nonpharmacologic care of PH-ILD is limited. Screening with management of related comorbidities is encouraged, as are lifestyle modifications including smoking cessation. As oxygen in ILD is not a well-studied therapy, recommendations derive largely from chronic obstructive pulmonary disease, where long-term oxygen therapy (≥15 h daily) is recommended in severe hypoxemia (defined as (1) partial pressure of oxygen ≤55 mm Hg or oxygen saturation ≤88%, or (2) partial pressure of oxygen = 56 mm Hg to 59 mm Hg or oxygen saturation = 89% plus one of edema, hematocrit ≥55%, or P pulmonale on electrocardiogram).[31,32] While recent guidelines suggest application of the same criteria for long-term oxygen therapy in ILD, there are no recommendations for PH-ILD.[32] Until official guidelines are established, frequent evaluation for hypoxemia—with treatment when it is severe—is generally advised.[2]

Transplantation

Lung transplantation is an important management option in PH-ILD. Guidelines recommend referral for evaluation in ILD including for any patient with IPF, fibrotic nonspecific interstitial pneumonia, FVC <80%, DLCO < 40%, oxygen requirement, dyspnea, or functional limitation.[33] Furthermore, listing is recommended for any eligible patient with concurrent PH.[33] As the wait time may be extensive, artificial support may be employed as a *bridge* to transplantation in a select population.[2,33]

FUTURE DIRECTIONS

There is growing interest in the use of novel therapeutics in PH-ILD. Pulsed inhaled nitric oxide was associated with improved moderate-vigorous physical activity and oxygenation in a phase 2b trial in fibrotic PH-ILD, and a phase 3 trial is currently enrolling (Clinical Trials.gov identifier NCT03267108).[34] Furthermore, as efforts to better phenotype and understand PH-ILD continue through programs like PVODMICs, this will hopefully provide a future basis for the clearer delineation of study populations and endpoints reflective of individual disease burden.

CONCLUSIONS

The development of PH in ILD portends a poor prognosis. Given the many negative clinical trials, PAH-targeted medications have historically been used on a case-by-case basis. The recent INCREASE trial of inhaled treprostinil represents a milestone in PH-ILD, such that this is the first medication approved by the Food and Drug Administration for treatment of this group. As understanding of PH-ILD grows, this will hopefully drive the emergence of novel agents, selection of specific trial populations, and definition of accurate endpoints to promote additional therapeutic options for this cohort.

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360-degree Care for the Bronchopulmonary Dysplasia Infant with Pulmonary Hypertension: A Comprehensive Review

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Premature infants are at risk of developing bronchopulmonary dysplasia and associated pulmonary hypertension. These infants make up a complex group of patients with unique considerations regarding development of lung and vascular disease, comorbidities, and care plans. They are high risk for many complications and poor outcomes due to the severity and complexity of disease. Because of this, a comprehensive approach to care with consideration for multiple organ systems and with an interdisciplinary team of experts is the preferred approach. Here we describe in detail the major considerations in care for these infants.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) following preterm birth is an increasingly common diagnosis in modern medicine. Many different definitions have been used and modified over the years, with various iterations to work toward the improved ability to predict later outcomes. The most recent definitions rely on an evaluation of respiratory support at 36 weeks postmenstrual age (PMA), have incorporated the most current respiratory support modalities, and can reliably predict respiratory, late death, and neurodevelopmental impairment outcomes.[1-3] BPD is defined as the continued need for respiratory support at 36 weeks PMA, in an infant born at ≤32 weeks of gestation and is stratified to reflect severity (Table 1).[1] The actual incidence of BPD is difficult to state with certainty because of differences in clinical practice and reporting, and it has been cited as 10% to 60%. However, incidence has generally been estimated at 40%, a figure which has remained stable despite advances in medical care.[4-6] Notwithstanding, the absolute number of affected infants has steadily increased, reflecting the increased number of preterm births and survival of these infants.[7]

Table 1. Stratification of BPD Severity by Oxygen Requirement and Age[a]

Severity	Definition
No BPD	Breathing room air at 36 wk PMA or discharge home, if earlier
Grade 1	Nasal cannula at less than or equal to 2 liters per minute at 36 wk PMA or discharge home, if earlier
Grade 2	Nasal cannula at greater than 2 L/min, "high flow" nasal cannula, CPAP, NIPPV at 36 wk PMA
Grade 3	Invasive PPV at 36 wk PMA

Abbreviations: BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; NIPPV, non invasive positive pressure ventilation; PMA, postmenstrual age; PPV, poitive pressure ventilation.

[a] Adapted from Jensen et al.[1]

Although the definition of BPD is rooted in respiratory disease burden, the infant with BPD often suffers from associated comorbidities that contribute significantly to the child's clinical course and affect therapy and prognosis. Prematurely born infants are at particularly increased risk for neurologic sequelae, feeding difficulties, and developmental delays, all of which pose significant threat to overall stability and ultimately the child's respiratory prognosis. Therefore, it is of utmost importance that the pulmonary hyper-

Key Words—bronchopulmonary dysplasia, pulmonary hypertension, tracheostomy, newborn, congenital heart disease, chronic lung disease of prematurity, pulmonary vascular disease, care coordination
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tension (PH) clinician assess the BPD infant in a comprehensive manner to minimize perturbation of PH-BPD and to ensure a robust outcome for the BPD survivor.

Respiratory Embryology

Embryologically, the developing fetus goes through 4 periods of lung growth: embryonic, pseudoglandular, canalicular, and saccular. A fifth stage, alveolar, begins near term and continues through birth and childhood. Most premature infants are born during the canalicular and saccular stages of lung development, rendering significant disruption to respiratory development. And since the airways act as a template for pulmonary vascular growth, vascular development is abnormal by association and angiogenesis is therefore significantly impaired in the preterm infant.[8] Postnatally, this abnormal lung is now subject to mechanical ventilation, oxygen toxicity, and altered fluid mechanics, creating a complex inflammatory environment that further impairs alveologenesis and angiogenesis.

Respiratory Burden of Bronchopulmonary Disease

The clinical pulmonary features of BPD include abnormalities in the lung parenchyma, small airways, large airways, and pulmonary vasculature. The most severe forms of the disease exhibit parenchymal heterogeneity with areas of air trapping, hyperinflation, atelectasis, and thickened septa, and can be complicated by severe tracheobronchomalacia, small airway obstruction, and PH.

The diagnosis of BPD is not an acute event. Rather, it reflects a chronic series of exposures in the prenatal, perinatal, and postnatal periods.[9] Prenatal exposures such as preeclampsia, placental insufficiency, and growth restriction all modify and contribute to abnormal alveolarization and therefore angiogenesis in the developing fetus. However, gestational age and weight of the fetus at the time of birth have been cited as the greatest predictors of BPD development.[7] In the postnatal period, the preterm infant requires significant support, which negatively impact the developing lungs. Surfactant dysfunction, oxygen toxicity, barotrauma, nutritional failure, infection, and inflammation pose recurring challenges to the preterm infant, prevent normal pulmonary growth and repair, and result in a loss of alveolar surface area.[10] These challenges extend well beyond the postnatal period and/or discharge from the neonatal intensive care unit since the lungs continue to develop until early adulthood and remain at continual risk for insult and injury.

While the field of neonatology continues to push forward with advances in medical therapy and clinical approaches, the aging BPD population at any moment reflects the care of decades earlier.[6,11] Nevertheless, the study of current adult BPD populations may shed insight into continued lung development and therefore inform present-day strategies to minimize BPD development. Examination of lung disease in prematurely born adults reveals significant deficits in percent predicted values for forced expiratory volume in the first second and distorted architecture. However, these deficits are magnified when preterm birth is accompanied by severe BPD diagnosis.[6,12,13] Although serial evaluations of lung function in preterm infants, specifically forced expiratory volume in the first second, demonstrate catch-up growth, the metrics remain below matched subjects born at term. Children with BPD are more likely to present with asthma-like symptoms of wheezing, airway hyperreactivity, and exercise symptoms and are often treated with inhaled corticosteroid therapies.[12,14] The reversible airway obstruction may be related to a combination of abnormal airway tone, heterogeneity in inflation, and air trapping, reflecting the significant complexities of assessing the BPD infant with continued respiratory complaints.[7]

CARDIORESPIRATORY ASSESSMENT OF THE INFANT WITH BPD

Comprehensive cardiac assessments are crucial in the BPD infant because of the high risk of clinical complications associated with abnormal morphology.

The most widely employed tool for cardiac assessment is echocardiography, a valuable screening and diagnostic modality that should be part of every BPD clinician's toolkit. Echocardiography is seminal to verify cardiac anatomy, to assess for the presence of intracardiac and extracardiac shunts, and to confirm pulmonary venous drainage.

Shunt Lesions in the BPD Infant

Shunts are particularly problematic in the BPD infant as they increase volume load to simplified and stressed alveolovascular units and therefore when judged to be significant, they must be addressed. Patent ductus arteriosus and ventricular septal defects are typically accepted as potentially problematic in the BPD infant, especially if left atrial dilation is noted, and therefore discussion of closure has not typically been controversial. However, atrial septal defect (ASD) closure has been a particularly controversial topic among neonatologists, pulmonologists, and cardiologists.

Classically, the ASD is not considered to significantly increase pulmonary blood flow and therefore the risk of pulmonary overcirculation is judged to be low. However, there is now a growing understanding that for a child with developmental lung disease, the pulmonary vascular bed is typically reduced, simplified, and often abnormal. Therefore, any additional pulmonary blood flow is unlikely to be tolerated and can result in significant pulmonary vascular strain. This has been recognized in the BPD medical literature, with numerous case reports and case series about the morbidity associated with ASD and the improvement in the BPD infant after closure.[15-21] Persistent left-to-right atrial level shunts have been linked to failure to wean from respiratory support (oxygen, positive airway pressure), poor growth, and lack of clinical progress. In fact, in a large multicenter observational study, the presence of an ASD was associated with increased odds of BPD development in premature infants.[22] The mechanism for ASD-associated injury is not well-known but is thought to be related to the impaired capacitance of a maldeveloped pulmonary vascular bed. In the child who suffers ASD-associated morbidity, the positive pressure support, oxygen supplementation, and

use of diuretics may be significant and therefore contribute to the development of BPD. Therefore, in the BPD infant with an atrial level shunt, closure should be considered if the shunt is persistently left-to-right and the infant has significant associated respiratory morbidity.

Pulmonary Vein Stenosis

Pulmonary vein stenosis (PVS) may be congenital or acquired, and is often progressive, leading to recurrent pulmonary edema, failure to thrive, secondary PH, and right heart failure.[23] Unfortunately, PVS requires frequent intervention by cardiac catheterization because of recurrence and progression. Although PH is frequently noted on echocardiography and its development imparts a worse prognosis, the use of targeted pulmonary vasodilator therapy frequently results in exacerbation of the PVS disease and the child develops pulmonary edema. Therefore, these treatments are used sparingly in PVS, if at all. Therapies aimed at the mechanistic development of venous occlusion have been trialed in PVS with varying success: sirolimus, imatinib, bevacizumab, methotrexate, and vincristine.[23,24] The etiology of PVS in the preterm infant is not clear. The postnatal positive pressure used in the premature infant has been thought to create back pressure on the left heart that then induces pulmonary venous changes. Once the pulmonary veins are affected, pulmonary edema is a common development, which prompts use of increased positive pressure support, fostering a vicious cycle. The BPD infant with PVS is unfortunately at higher risk of death than the BPD infant without PVS, so the BPD clinician has the responsibility to be acutely aware of this condition, maintain a high index of suspicion, and support screening and intervention.[25,26]

Pulmonary Hypertension

In the modern era, one of the biggest threats to the survival of the BPD population is the development of PH.[27] PH is a condition of elevated pulmonary artery pressure, secondary to elevated pulmonary vascular resistance. In the BPD infant, it's further characterized by elevated abnormal vasoreactivity to even mild episodes of hypoxemia.[28,29] The development of PH in this vulnerable population is multifactorial and reflects derangements in alveolarization and the additive effect of prenatal and postnatal injuries on a delicate pulmonary vascular bed. The resulting vascular disorder in conjunction with abnormal respiratory units results in pulmonary vascular disease, which in its severe form can cause PH with right ventricular dysfunction.[4,7] This highly comorbid diagnosis is associated with a significant risk for adverse clinical outcome, with mortality rates cited as high as 14% to 38%.[4,30] Interestingly, while there is a steep mortality risk in the first 6 months after diagnosis, the cumulative mortality over the first 2 years of life suggests that these children remain at increased risk of death following discharge from the neonatal intensive care unit.[31]

A modifier of prognosis is early identification to help direct therapy.[32] Therefore, infants who acutely require increased support or have worsening hypoxemia should be evaluated for PH, even if it is before the 36 weeks PMA time point, as worsening pulmonary disease is often the harbinger of PH.[33] Unfortunately, PH-BPD screening criteria and methods of screening are inconsistent in the published literature, inconsistent at the bedside, and therefore inconsistent for diagnosis. These irregularities are reflected in the reported prevalence of PH-BPD.[34] PH guidelines released by the American Heart Association in conjunction with the American Thoracic Society recommend echocardiography screening of all PH-BPD infants with moderate to severe BPD at 36 weeks gestational age, and the Pediatric Pulmonary Hypertension Network expanded on this recommendation with clinical specifics.[33,35,36] Despite these consensus statements, implementation remains variable. Echocardiography is often done in response to clinical change.

Although cardiac catheterization is the gold standard for PH diagnosis, PH-BPD is usually diagnosed by echocardiography because of concerns for transport stability of the critically ill BPD infant and hemodynamic stability with anesthesia and catheterization procedure. The identification of PH by echocardiogram can be hampered by the hyperinflation, expansion of the thoracic cage, and alteration of the heart position, obscuring important measurements such as that of the tricuspid regurgitation jet velocity.[37] For these reasons, careful consideration for right heart catheterization may still be considered for the diagnosis of PH, while also allowing interrogation of important potential cardiac comorbidities.[38]

The echocardiogram must be reviewed carefully to exclude other causes of elevated right ventricular pressure, such as left heart disease, PVS, left-to-right shunts, and intrinsic cardiac conditions. A direct estimate of the systolic function of the right ventricle (RV) may not be possible because of inadequate tricuspid jet velocity. However, other indicators of RV pressure include the position of the interventricular septum, the appearance and function of the RV, changes in RV ejection time to pulmonary artery acceleration time ratio, and changes in direction of shunt flow. A useful calculation is the ratio of the estimated RV systolic pressure in relation to the systemic systolic pressure. An RV-systemic ratio > 1:2 is consistent with at least mild PH in the PH-BPD infant.[34,39] Cardiac catheterization should be considered in the PH-BPD infant with recurrent pulmonary edema to assess for concomitant PVS, the infant who has persistently elevated RV pressure estimate on echo, or the infant with shunt lesions.

Upon diagnosis of PH, the crux of PH-BPD treatment rests in the optimization of the infant's respiratory status as the single most impactful therapy that can be offered.[27] Modifiers of pulmonary vascular resistance include hypoxemia, acidosis, hypercarbia, hyperinflation, and atelectasis. Therefore, use of advanced imaging such as a chest computed tomography scan, VQ scan, dynamic airway computed tomography scan, or even newer modalities of magnetic resonance imaging may be useful in characterizing extent of pulmonary disease as targets for optimization.[33,35,37,40] Interventions include adjusting mechanical support to minimize extremes of inflation (hyper- and hypo-), titrating oxygen supplementation to reach appropriate targets for age and disease, judicious use of diuretics, and encouragement of growth

Table 2. Medications Used to Treat PH-BPD

Class	Action	Side effects	Generic names (USA)
Phosphdiesterase-5 inhibitor (PDE-5i)	Nitric oxide potentiators	Reflux, systemic hypotension, worsening hypoxemia	Sildenafil: can be given orally[41-47] or intravenously[48] Tadalafil: oral use only[49]
Soluble guanylyl cyclase stimulator	Enzyme in nitric oxide pathway	Hypotension, cannot be combined with PDE-5i class.	Riociguat[a]
Endothelin receptor antagonist (ERA)	Block binding of endothelin-1	Dose-related liver dysfunction (bosentan), teratogenicity, anemia (ambrisentan)	Bosentan: oral administration[46,50,51] Ambrisentan: oral administration*
Synthetic prostacyclins and prostacyclin receptor agonists	Increases levels of circulating prostacyclins	Systemic hypotension, nausea, vomiting, diarrhea Platelet dysfunction Infectious risks with indwelling central line Pain at subcutaneous site Cough, bronchospasm with inhalation	Treprostinil: can be given orally, by inhalation,[b] continuous subcutaneous infusion,[46] continuous intravenous infusion.[52] Iloprost: inhalation[46,53,54] Epoprostenol: inhalation, continuous intravenous infusion[46,52,55]

[a] Use has not been described in pulmonary hypertension associated with bronchopulmonary dysplasia.

[b] Inhaled treprostinil requires breath actuation by patient.

with adequate nutrition. Impact of these interventions should be characterized and closely monitored in a serial way with diagnostics such as blood gases and radiographs.[28] With close management of ventilation and respiratory mechanics, PH in severe BPD may even be adequately managed without PH-directed pharmacotherapy in cases. To achieve this, infants with severe lung disease and resultant PH may require chronic supplemental oxygen or chronic mechanical ventilation. For the infant with significant PH, PH-targeted therapies have been used in PH-BPD with good results and tolerance (Table 2).

MANAGEMENT OF PULMONARY DISEASE

Respiratory Support Strategies

Infants with severe BPD and associated PH benefit from the optimization of oxygenation, ventilation, atelectasis, and hyperinflation, as physical factors and inflammatory factors increase pulmonary vascular resistance in response to perturbations in these physiologic parameters.[56] For infants who are oxygen dependent, it is essential to ensure that the oxygen support is adequate to maintain oxygen saturations above 92% and that the infant can achieve somatic growth with no signs of PH worsening.[35]

Ventilation of the BPD infant is challenging. In the first few weeks of life, a premature infant's lung disease is characterized by low compliance and relatively homogeneous lung involvement. However, as BPD develops, bedside clinicians will note more pronounced evidence of the abnormal parenchyma that hallmarks this disease: heterogeneous lung disease with air trapping, interspersed with atelectatic segments and high airways resistance. As the lung disease evolves over the course of the infant's life, the mechanical support strategy must also evolve to minimize hyperinflation and atelectasis, worsening gas exchange, and increased work of breathing with ventilator asynchrony. The currently recommended model of ventilation includes high tidal volume, long inspiratory time, and low respiratory rate to adequately ventilate the lung unit with heterogenous time constants.[57,58] Optimization of ventilation is the cornerstone of BPD-PH management and must be taken seriously to prevent further PH exacerbation.

Tracheostomy

With severe BPD, tracheostomy is often considered to facilitate long-term mechanical ventilation. These infants are overall a small proportion of total BPD patients, but they are a high-risk population with high morbidity and mortality, requires specialized care, and has grown in recent years.[59] An interdisciplinary team including neonatology, otolaryngology, pulmonology, respiratory therapy, and palliative care may be helpful in determining which patients would benefit from tracheostomy placement and best determine the timing for this intervention.

There is often more than one indication for tracheostomy.[60] Indications include neurologic impairment, secretion management, upper airway obstruction, and abnormal ventilatory drive. Chronic respiratory failure or respiratory insufficiency, especially with associated PH should be considered as an indication for tracheostomy for chronic long-term ventilation.[35] This may manifest as a failure of extubation, increased work of breathing, or carbon dioxide retention with invasive or noninvasive ventilator support once at term.[57] Importantly, tracheobronchomalacia increases the likelihood that tracheostomy will be necessary for infants with respiratory failure and PH.[61]

The decision to place a tracheostomy should not be taken lightly, as there are risks associated with tracheostomy placement that must be weighed with the benefit of long-term respiratory support. Risks include complications such as mucus plug, accidental decannulation, tracheostomy-associated

infections, and bleeding, any of which can lead to neurologic devastation and death.[60] While the decision to pursue tracheostomy may begin around term gestation, the timing of surgery is still debated in the literature and there are no established criteria or guidelines. Reports of surgical placement range from 40 to 51 weeks PMA, and timing of this has not been shown to impact mortality, time to liberation from ventilator, or time to decannulation.[62,63] Tracheostomy placement, however, has been associated with improved proportional growth, improved participation in developmental therapies, and developmental progress, which may be a consideration in earlier trach placement.[64] While chronic mechanical ventilation via tracheostomy is initially an overwhelming idea for many families, the natural history of ventilator-dependent severe BPD infants (even those whose courses are complicated by PH) is that most patients are able to reach liberation from the ventilator and decannulation between 3 and 5 years of age.[65] Risk of neurodevelopmental impairment in this population is high, however, and neurologic disorder increases the likelihood that decannulation is delayed.[66]

Neurodevelopmental Concerns

Neurodevelopmental outcomes (cognitive, language, and motor) are important considerations for the BPD infant as there is considerable risk for significant deficits compared to non-BPD infants: cerebral palsy, neurosensory deficits, changes in academic performance, language delays, and disorders of visuospatial perception.[67] Conditions that favor hypoxic brain injury (recurrent hypoxemic events, chronic hypercapnia, and respiratory acidosis) set the infant up for impaired oxygen delivery to the cerebral tissues. The use of postnatal corticosteroids has also been implicated as a risk factor for neurodevelopmental deficits in this population, a treatment that is commonly used in this population to facilitate extubation. The exact mechanism by which glucocorticoids affect neuromotor impairments is not clear but may have to do with abnormal growth and maturation of the brain (decreased gray matter, brain-cell hypoxic division, differentiation, myelination, and electrophysiological reactions.)[68]

Unfortunately, the PH-BPD infant is at particularly increased risk for developmental delays compared to the BPD infant without PH.[69,70] This underscores the critical illness of these children and associated interventions that are required for support, the considerable histologic derangements of the alveolovascular units, and the ultimate effects on oxygen delivery to a vulnerable neurologic system.

BPD is an independent predictor of motor delays above that of prematurity alone.[71] Motor delays in particular can be difficult for infants with severe BPD, as they rely on musculoskeletal strength to power the respiratory system that is at a mechanical disadvantage compared to healthy children, limiting their ability to participate in effective therapies and tolerate interactions with the ventilator. The length and severity of critical illness in these infants often necessitates significant time with sedation and neuromuscular blockade to maintain stability in the setting of severe lung disease and frequent ventilator asynchrony, which contributes to the motor delay.[72] In addition, the nutritional deficiencies noted to be associated in infants with BPD and associated PH impacts the growth of the skeletal muscle.[69] This impact on skeletal muscle strength can last through childhood and into adulthood with weakness of peripheral muscle groups and posture reported to be affected.[73] Careful assessment and early detection and treatment of neurologic impairment can improve quality of life for children and families.[71]

Nutritional and Gastrointestinal Concerns

Nutrition is a key contributor to the overall health of the infant with BPD. The approach to nutrition should be multifaceted, with input from experienced speech therapists, dieticians, and gastrointestinal specialists as needed to optimize growth and safe feeding options.[3,28] Unfortunately, BPD infants often begin life at a nutritional disadvantage. Small size at birth (small for gestational age) and inadequate perinatal somatic growth impact the risk of BPD development and confer higher mortality in comparison to appropriate-for-gestational-age counterparts.[74,75] The effect of poor nutrition has been noted to affect neurodevelopmental and pulmonary outcomes, reflected in postnatal growth failure at 36 weeks and inadequate linear growth as risk factors for negative outcome.[75-76] The importance of caloric and protein intake despite critical illness in this at-risk population therefore cannot be overstated and must be a focus of the BPD clinician.

Infants with BPD have higher energy needs than infants without BPD, impacted by work of breathing, stress, inflammation, and the need for catch-up growth. Estimates show that the energy needs of infants with BPD are 15% to 25% higher than healthy controls.[78] Optimal nutrition, and particularly protein intake, is necessary for lung growth, repair, and recovery over time.[28] Achieving optimal lung growth is often difficult in the setting of fluid restriction, diuretic use, and avoidance of excessive mineral intake, all of which need to be accounted for in planning feeds for these infants.[79]

In addition to careful consideration of growth parameters in the impact of lung health, safe feeding is of utmost concern. BPD is strongly associated with oral feeding problems such as oral aversion, disturbed suck-swallow-breathing coordination, aspiration, and gastroesophageal reflux disease, which all contribute to poor oral feeding and dependence on tube feeding.[80] Reflux and aspiration are risks for ongoing lung injury in patients with BPD and are associated with episodic worsening of respiratory status, so there should be a low threshold to proceed with diagnostic studies such as an upper gastrointestinal series, pH probe, impedance probe, and videofluoroscopic swallow studies to assess the infant's reflux and/or aspiration risk.[28,81,82] To manage these symptoms and ensure a reliable feeding method, many infants with severe BPD require an alternate enteral feeding option such as gastrostomy tube, anti-reflux surgery, or a gastrojejunal tube.[83] Infants with severe BPD-PH are more likely to have anti-reflux surgery than those without PH, and there seems to be an improvement in respiratory status in many of these infants after surgery.[84]

DISCHARGE OF THE COMPLEX BPD PATIENT

Children diagnosed with BPD remain at increased risk for hospital readmissions particularly in the first several years of life, and it is estimated that nearly 50% of infants born prematurely are readmitted during their first years of life.[85] Reducing hospital readmissions in this patient population can significantly improve patient and family stressors, health care costs, and reduce the use of community and hospital resources.

The severity of the child's BPD determines the type of respiratory support and therapy the child may need as they go home.[86] Discharge planning should be individualized to the specific needs of the child and family. Adoption of a smooth discharge process in institutions caring for these children can reduce the risk of hospital readmissions. This process can help ensure that all necessary tasks are completed and that follow-ups are arranged before discharge.

Discharge Checklist

Discharge planning for these children usually begins weeks to months in advance of the actual discharge. Families progress in proficiency in administration of oxygen supplementation, medical therapies, and airway treatments, if appropriate for the child. They may also start classes to learn the care needed for a technology-dependent child (ie, for a tracheostomy, ventilator, and/or gastrostomy) and work with home health agencies for care arrangements at home. One potential approach to more successful discharge management is the creation of a discharge checklist to ensure all appropriate aspects for care management are completed before the child's discharge. While the outpatient clinical care of the child varies from child to child, a discharge checklist can ensure that necessary tasks such as specific ventilator training for parents and/or appropriate vaccinations are given before going home.

Checklist Components

Pharmacotherapy Management: Before discharge, the timing of medications should be adjusted to ensure that the schedule is reasonable for families and the child's schedule at home (for example, to coincide with scheduled feedings.) Children who are discharged home with PH medications should understand the appropriate timing of these medications and how to refill them. When educating families before discharge, it is imperative to understand the caregivers' best learning style, if they can read, and their preferred language. Neglecting to identify this can create misunderstanding and confusion once the child is discharged home.

Immunizations: Every BPD-PH child should receive routine pediatric vaccinations as recommended by the Centers for Disease Control and Prevention based on their chronological age and immunological state.[87] For those who are at least 6 months or over, the influenza vaccine should be given before discharge with the second vaccine given by the primary care provider about 1 month after the initial dose. The palivizumab vaccine is recommended for the child's first respiratory syncytial virus season by the American Academy of Pediatrics for preterm infants younger than 32 weeks gestational age and required oxygen supplementation for the first 28 days of life.[88] Often, the first dose is given before discharge as well. The American Academy of Pediatrics extended recommendations for the 23-valent pneumococcal polysaccharide vaccine beginning at age 2 years and could be considered for those with BPD given their chronic lung disease status once they reach that age mark.[89]

Outpatient Medical Care: Infants with BPD require ongoing outpatient medical care depending on their severity of BPD as well as other associated comorbidities with prematurity. Consultants may include specialists from neurology, cardiology, pulmonology, developmental pediatrics, gastroenterology, and nutrition. Some BPD centers may offer collaborative clinics to facilitate a comprehensive care plan and minimize burden of care for families. Outpatient efforts should be focused on making continued global progress, with the primary goals of care being the development of a well-developed child with good growth parameters and minimal burden of comorbid disease. The discharge checklist should ensure these appropriate follow-ups are made before discharge and that families know how to contact these teams should issues arise at home.

Other Discharge Elements: Other discharge elements to be considered for a thorough checklist include home supplies, developmental therapy referrals (early childhood intervention), and car seat testing. Additional elements will vary for each neonatal intensive care unit, reflecting local culture and practice. While these elements are not specific to the BPD infant, failure to complete these routine discharge tasks could also be significant risk factors for readmissions.

CONCLUSION

Infants with BPD-PH are a particularly vulnerable group of patients with multiple comorbidities, increased risk of mortality, and are often technology dependent. A comprehensive view of their care in the setting of a multidisciplinary team is necessary to meet the varied needs that these patients present. The complex nature of their care unfortunately leaves these patients at high risk for recurrent hospitalizations, poor neurologic and developmental outcomes, and serious or life-threatening events in the many transitions that they face between inpatient and outpatient services. Therefore, these infants should be cared for by a team who has special knowledge of medically complex children and PH to best support them in a global and comprehensive manner.

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Conundrums and Controversies in PH-ILD: To Treat or Not to Treat—Identifying Optimal Treatment Candidates

This fall, Jeffrey Edelman, MD, Associate Professor of Medicine at the University of Washington and at the VA Medical Center in Seattle, Washington, gathered with Jean Elwing, MD, Professor of Medicine and the Director of the Pulmonary Hypertension Program at the University of Cincinnati; Anjali Vaidya, MD, Associate Professor of Medicine and Co-Director of the Pulmonary Hypertension, Right Heart Failure & CTEPH Program at Temple University in Philadelphia; and Steve Mathai, MD, Associate Professor of Medicine at Johns Hopkins School of Medicine and Co-Director of the Ann Dana Kusch Multidisciplinary Research Program for Pulmonary Hypertension and Interstitial Lung Disease, to discuss pulmonary hypertension (PH) in World Health Organization (WHO) Group 3 patients with interstitial lung disease (ILD).

Dr Edelman: Good morning. I'd like to start with discussing some general concepts, and how we approach these patients. Pulmonary hypertension is certainly common in patients with interstitial lung disease. There's been an increasing awareness of the prevalence of interstitial lung disease accompanied by increased identification of interstitial lung disease patients with associated pulmonary hypertension.

We have a burgeoning population of patients that we are seeing and it's important to discuss how we approach these patients in our clinics. It might be prudent to start with discussing the evaluation of these patients, and how it may be different than what we do with other PH patients. Are there different things that we should focus on in this population?

Dr Mathai: I think, in general, the approach is very similar to any patient in whom we suspect pulmonary hypertension. The recommended algorithm should be undertaken, including history physical examination, pulmonary function testing, imaging, echocardiography, etc. Determining whether or not a right heart catheterization is indicated I think is something that is important to consider as the evaluation progresses.

Some of the motivation and indication for right heart catheterization may vary based upon the individual patient who is in front of you. If the patient has severe interstitial lung disease and is really headed towards a lung transplant, catheterization may be absolutely indicated to understand whether or not pulmonary hypertension is complicating that patient's current situation and thus would increase the urgency for evaluation and potentially receiving a lung transplant.

Other clinical scenarios exist, perhaps someone at the extreme of age or with significant other comorbidities that preclude their candidacy for lung transplantation, a right heart catheterization may not be indicated because of the likelihood of other forms of pulmonary hypertension being present and/or limited utility of available therapies for pulmonary hypertension in that setting. I'm curious if others have a similar approach or if there are different approaches that Anjali or Jean might adopt.

Dr Elwing: I echo what you've just said, Steve. We take the approach, as you've mentioned, to go through the routine algorithm to work up a patient with pulmonary hypertension because we really want to know all the factors that might be contributing. The thing that's really changed is that, in the past, we when we diagnosed Group 3 disease, we would concentrate on symptom management and potentially discuss transplant evaluation. We would discuss PH and make the patient aware that we previously didn't have any approved therapies that were shown to benefit patients with hypoxic PH in large clinical trials, but now we can look at that differently.

As Steve has said, we focus on looking towards transplant, assessing goals of care, and then deciding if we need to go onto more invasive testing to prove the presence and severity of pulmonary hypertension. What about you, Anjali?

Dr Vaidya: Yes, I agree with all of that. Certainly, the thorough and comprehensive approach in the evaluation and diagnosis for all of the reasons that both of you just nicely described is very important.

I think, because we know these patients are what we would call "mixed physiology pulmonary hypertension" with underlying lung disease, my mind goes to the actual clinical phenotype of the patient—is it somebody with pulmonary heart disease Type 1, which is predominantly that of lung disease with a relatively mild phenotype of pulmonary vascular disease and right heart failure, or is it more of what we would call Type 2 pulmonary heart disease, where, yes, they have parenchymal lung disease but also a really strong phenotype of PH and right heart failure? I think we have to think about those patients very differently.

You're right. While we now have on-label treatment options that have opened up an opportunity for more discussion of treatment with our lung disease PH patients, I think, at least for the last 8 to 10 years, we've been having physiologic and phenotype-based discussions and categorizations of these patients to determine if we need to think about targeting the PH. We take into account, not just the severity of PH and right heart failure but their baseline oxygenation requirements, the severity of their [pulmonary function test] PFT and [computed tomography] CT scan abnormalities, and the risk of wors-

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ening oxygenation if we were to consider treating them. It's certainly another layer of complexity in the evaluation of these patients.

Dr Edelman: I think it's also important to consider some of the comorbidities that come along with these patients, particularly in the group of patients with idiopathic interstitial lung disease that tend to be older. We need to think about not only the severity of lung disease and the severity of hypoxia, but also other conditions such as sleep-disordered breathing.

Also, I always like to make sure that we've looked for chronic thromboembolic disease because that is an entity for which we may also have other treatment changes. Granted, these patients are less likely to be candidates for surgical treatment, but at least we can consider medical treatment and hopefully prevent disease progression and recurrence with reference to thromboembolic disease.

Dr Mathai: Just to add to that important discussion about comorbidities, I think coronary disease is also something that would be perhaps at a higher prevalence in the age group that might be affected by [idiopathic pulmonary fibrosis] IPF. There's some literature suggesting that there's at least an increased risk of coronary disease manifesting after the diagnosis of IPF. That's something that also should be considered, particularly given the potential complications of giving patients pulmonary vasodilators with coronary disease.

Dr Edelman: I fully agree. I think coronary disease can be quite sneaky in this population because the symptoms can certainly fly under the radar screen. Manifestations such as worsening dyspnea can be attributed to interstitial lung disease. Then, lo and behold, you find coronary disease perhaps in evaluation for transplant. When that's treated, some of those symptoms get better. Yes, I do think that coronary disease is certainly a common comorbidity and something that we need to be aware of.

Dr Elwing: I think we all are saying the very same thing. These patients deserve that full workup and really a global approach to their care because, oftentimes, they are a very different group of patients than our younger idiopathic patients who frequently have no other comorbidities. The only way to help these people feel better is really to not only address their pulmonary hypertension and ILD and assess what they want out of treatment, but also make sure we're not undertreating any other comorbidities. It seems we're all thinking about this patient population and approaching their care similarly.

Dr Vaidya: Jean, it's interesting how you mentioned how they're feeling and helping them feel better, which I think is an important point in this complicated population because sometimes I think, as the physician, we feel limited knowing that this patient has multiple contributions to their dyspnea, and it can feel very discouraging. We might treat one or another but overall might not improve their symptoms.

Sometimes that can feel limiting in what we should do or what we can do, and sometimes I have to remind myself that, if we choose the right patients, we may be able to at least minimize the comorbidity of the heart failure syndrome, which can help support that patient in the grand scheme of getting what they really need, which is often lung transplant, as Steve was saying.

Sometimes I have to remind myself and tell the patients, "Look, we might consider you for treatment, and while it might not help you be able to walk a mile around the track, it might stabilize you and get you out of heart failure, which will improve your nutrition, your renal function, and your overall wellness to be able to safely undergo lung transplant." I wonder if other people think about that in a similar way.

Dr Edelman: Certainly in the absence of other significant comorbidities, transplant remains a definitive therapy in this setting, particularly if they have ILD with significant pulmonary hypertension. I think that lung transplant is a very important part of the discussion and an important part of the goals of care. Several of the comments have touched on other issues such as symptom relief. I think it's important also to think about palliation and goals of care for patients who may not be able to get to transplant and who have significant progressive disease.

Dr Mathai: I think, with any chronic progressive disease, and in this scenario, we're actually dealing with 2 of them—pulmonary hypertension and interstitial lung disease—discussions about management of symptoms and goals of care are integral to overall patient management and satisfaction.

What is a goal for the patient in terms of interventions and whether the patient wants to consider additional therapy for either interstitial lung disease or pulmonary hypertension or both, or whether he or she would prefer more of a symptom-based approach with palliation? I think these are fundamental things to discuss with the patient to understand his or her perspective and to inform your treatment plan going forward. I think those are really important things, particularly since these diseases are progressive and portend a poor prognosis.

Dr Elwing: I agree 100% with that. I think sometimes, in this population, we are surprised by what people really want from our care. Patients with advanced lung disease and pulmonary hypertension may not anticipate that we are going to change things dramatically. They just want some relief of this daily dyspnea that is occurring with routine tasks like walking to the bathroom or the disappointment they have that they can't do certain things like going out shopping or spending time with family and friends.

Echoing what Steve just said, this patient population's goals may be very different than our idiopathic or pulmonary arterial hypertension patients. I think we have to ask detailed questions, understand what they want and what they are expecting out of what we can offer them so we can really modify our treatment plan to fit that.

Dr Vaidya: I agree with that as well. That's such an important discussion, not necessarily for hospice transitions, but to

really help with those goals of care conversations and to alleviate the suffering. It's a whole other level compared to, like you said, Jean, our idiopathic patients.

Dr Edelman: How liberally do you use pulmonary rehab in this population? I think pulmonary rehab can benefit some patients, but it can also be quite complicated for patients requiring high amounts of oxygen, not only complicated with reference to actually participating in rehab, but also the added care burden of having to go to pulmonary rehab. This may not be as much of an issue over the last year as a lot of our rehab programs have been inactive, but I'm wondering how people utilize pulmonary rehab in this population.

Dr Elwing: I've been taking a little bit different approach for these individuals that have significant ILD and more advanced pulmonary hypertension. If they are homebound when I meet them, I've been offering home physical therapy and then working up to outpatient physical therapy for core strengthening when they are ready.

The physical therapy teams I've been working with have been very helpful and are communicating when the patient is ready to progress to cardiopulmonary rehab. Then when the patient goes to cardiopulmonary rehab, I've been really trying to communicate clearly about saturation goals in addition to choosing exercises that they derive benefit from but don't cause as much hypoxia. It has been by experience that some types of exercise machines seem to be better tolerated for ILD-PH patients than others. I'm not sure if anyone else has had that experience, but that's been my approach for the PH-ILD patients with significant deconditioning.

Dr Vaidya: I haven't had that experience, but it sounds great, Jean.

Dr Mathai: Yes, I was about to say the same thing. It sounds like a really important protocol you have there. Starting with focused physical therapy and then moving towards pulmonary rehabilitation is something that I haven't done consistently without some obvious indication for physical therapy prior to pulmonary rehabilitation. I think that's a really great approach and something that I will adopt from your guidance, Jean.

Dr Elwing: Thank you. It's been working for some, so I'd love to hear your feedback if it works for you also.

Dr Vaidya: I think that's so smart because we tend to sometimes undervalue the degree of musculoskeletal deconditioning that happens with all of our patients that have such chronic cardiopulmonary disease, and so it can be very challenging for them to participate in rehab effectively. I think this is such a smart approach. It's a great idea.

Dr Edelman: I'd add that there is a nascent field in pulmonary rehab which is home-based pulmonary rehab where it's not necessarily that there's a therapist coming to the patient but that there's a video link, and the patient is doing their exercise at home under the supervision of a rehab therapist who may be remote. That may be a very good intermediate compromise that includes some of the ideas that Jean mentioned where the patient stays at home. They can exercise, they're supervised, and care can be efficiently administered via remote approach.

Dr Elwing: That is very interesting. I've never tried that. Has anyone else?

Dr Mathai: We've used it for our [chronic obstructive pulmonary disease] COPD patients who may be more familiar overall with pulmonary rehab. For many of our patients who have already completed pulmonary rehab to reengage them, particularly during the time of COVID, we've done that. I've not done it yet for any of my pulmonary hypertension patients, but we have discussed it. I don't think anyone's taken me up on it yet.

Dr Elwing: I'm going to check into it.

Dr Edelman: I think it's another potential tool that we may have going forward in treatment of these patients. We're about halfway through and it's a good point to shift gears and talk a little bit about drugs and pharmacotherapy and to talk about not only PH treatment but also to recognize that these patients have ILD and that treatment may also include use of antifibrotic drugs.

For patients who are candidates for the anti-fibrotic drugs and able to tolerate them, these should be considered as part of the approach to treatment. It's not PH directed, but certainly there's evidence that that treatment at least slows progression. Would everyone agree?

Dr Elwing: I actually have a question. I am wondering, when you are considering an antifibrotic therapy for your ILD-PH patients, do you initiate that before you initiate pulmonary vasodilator therapy, or do you start the pulmonary vasodilator therapy first?

Dr Mathai: Well, I think, in part, that would depend upon the individual patient and the relative contribution of parenchymal disease versus pulmonary vascular disease to the clinical picture. For example, in a patient with progressive interstitial disease with severe restrictive physiology and severe hypoxemia with mild pulmonary vascular disease, as determined by heart catheterization, I think I'd be more inclined to focus on the ILD. If the reverse were true, more significant contribution of PH relative to parenchymal disease, I might think about targeting the PH. I think, in general, we're talking about medications that have a lot of side effects as well, so tolerability becomes an issue. Quite frankly, I've not had many patients on the combination of the inhaled treprostinil and either of the antifibrotic medication[s]. I'm curious whether others have had issues with tolerability in combining these medications.

Dr Elwing: That is exactly why I asked the question and hoping to gain more insight in this challenging situation. It has been my experience that people do have difficulty tolerating both therapies, and like you had mentioned, trying to figure out which sequence to introduce therapy so that they can adjust to one medication before we add another. I very much like your approach of looking at the biggest driver of their symptoms

from their assessment and then target that first and then followed by targeting the other part of their disease process.

Dr Vaidya: I would agree with that approach as well because, very often, it's not going to be a mystery, which is the driving factor. Certainly, some patients have severe phenotypes of both PH and lung disease, but there are certainly many patients where it's clear they're suffering predominantly from heart failure from PH with their neck veins up to their ears, peripheral edema, and an echo-Doppler study with an [right ventricle] RV that's bigger than their [left ventricle] LV and evidence of a double-digit [pulmonary vascular resistance] PVR and low cardiac index.

I would argue in those patients, as Steve was suggesting, to opt for the PH medical therapy first, try to alleviate their degree of severe heart failure, then perhaps in short sequence, adding on the ILD therapy.

Dr Mathai: I think, in addition, we've been talking a lot about IPF, but other patient phenotypes may also dictate or at least contribute to our decision making regarding treatment of pulmonary vascular versus parenchymal disease. Those patients with connective tissue diseases, scleroderma, as an example, where the combination of pulmonary vascular disease and interstitial lung disease is very common might warrant targeting both the interstitial disease and pulmonary vascular disease.

Dr Vaidya: I agree. I think, those patients, that brings up an important distinction between classifying patients versus characterizing patients. Then I think it's much easier in that scenario because connective tissue disease patients are characterized and phenotyped in the same way that they're classified (as Group 1 [pulmonary arterial hypertension] PAH). We have a much lower threshold and a green light, so to speak, to go forward early with their PH medical therapy while treating their lung disease.

I would argue that there are some patients with WHO Group 3 that don't have connective tissue disease that, from a pure PH perspective, behave in the exact same way in terms of severity and acuity of PH and heart failure presentation. They may warrant a similar consideration for approach.

Dr Edelman: I think it's reassuring when you have an associated WHO Group 1 diagnosis such as scleroderma or [rheumatoid arthritis] RA to know that you're using treatments that have at least been studied and shown to be effective in those groups. I do tell people that even though they have a WHO Group 1 diagnosis but also have significant interstitial lung disease, their expectations for a significant response to therapy may be lower. The other thing I would add is that the lines get even more blurred when we start to think about where our knowledge has evolved with reference to the autoimmune conditions associated with ILD.

There are a lot of patients who don't fall under the typical autoimmune diagnoses that we think of in PH, but do have interstitial lung disease. I'm referring to the group of patients with anti-synthetase syndromes. I think we've seen a growth in that population, and I'm not sure where to classify that specific group of patients. I think it's probably good to have some discussions about the approach to the use of vasodilators in this population. I'd like to hear from the group. What your thoughts are on this topic?

Dr Vaidya: There was a really nice paper. I want to give credit to Rajeev and Rajan Saggar, who had published in *Thorax* about 7 years ago right on the topic. I found it helpful, or if anyone's interested, they talked about changes in hemodynamics and echo function in an advanced PH pulmonary fibrosis population where they used parenteral prostacyclin therapy.

It was a study of patients with relatively advanced lung disease. I think their percent predicted [forced vital capacity] FVC and [forced expiratory volume in 1 second] FEV1s were in the teens and 20s and diffusion capacity about 13, but what was really interesting was that they picked a population that had at baseline a phenotype of really significant PH. Their right atrial pressures were nearly 10, cardiac index was 2.3, and PVR, I think, was in the double digits. When treated with parenteral prostacyclin therapy, they suffered no change in oxygenation requirements or lung function on PFT.

This was over 12 weeks, with dramatic improvements in 6-minute walk distance, [brain natriuretic peptide], PVR, cardiac index. I just want to give them credit for looking at this very challenging population and describing a phenotype that might guide us in this discussion and how we approach patients. It directly applies to what we're talking about here. It's similar to what Marco Guazzi did years ago when he took a severe PH/right heart failure phenotype within the heart failure with preserved ejection fraction patient population and published on benefits with sildenafil use.

Dr Elwing: I personally find these patients extremely challenging because of the unpredictability of their response to therapies. I'm not sure if anyone else has had that experience, but because of that, I always am very cautious about what I talk to the patient about in terms of their expectations from therapy. I divide them out in terms of, do they have risk factors for Group 1 disease, or are they truly an interstitial lung disease patient or a combined emphysema fibrosis patient?

This information helps me choose best therapy options. For those that have ILD or combined emphysema and fibrosis as etiology of their pulmonary hypertension, I would take the approach of what we learned from the INCREASE trial that they may have benefit from inhaled prostacyclin therapy. In contrast, those that have the risk for Group 1 in addition to coexisting interstitial lung disease would be approached differently. The best example of this group would be our PH patients that are associated with connective tissue disease and also have some degree of ILD. I often open up many more options for PAH therapy to this subgroup of patients. I'm wondering if everyone else is having a similar approach or they're approaching it differently.

Dr Mathai: I agree with that approach, Jean, and it's similar to what I employ. I will try to temper expectations with patients, and in general, I'd say it's a rule of thirds: a third of the people may get better, a third of people will have no significant change, and a third of people may get worse. I'll tell patients that, "I don't know into which you're going to fall with a trial of therapy."

I also consistently use that term "trial of therapy" and tell patients we're going to reassess in 1 month and 3 months after you start therapy. This is to see if you're feeling better or having significant side effects that make it intolerable for you to continue on the therapy before deciding whether there's been a treatment response or not. I do think that tempering expectations is important because of the heterogeneity of the phenotypes of patients that we're seeing, if it's really hard to know exactly who is going to benefit and who isn't.

Dr Elwing: Despite being Food and Drug Administration (FDA) approved, payors may not be ready. That's the really challenging part for us because we have a therapy that we've shown to be effective in a randomized controlled trial. We can prescribe but not uncommonly having issues with cost. We are oftentimes utilizing assistance programs to help patients with expense of therapy.

Dr Mathai: Yes, that's been my experience. Although I've had some success recently with insurance approval.

Dr Elwing: That is wonderful news.

Dr Vaidya: I agree with the prior comments of really managing expectations of the patients if we do embark on treatment. I would only add that I think, if you take all patients with this combination of PH and ILD, there are certainly patients that I think we do know that they would have no chance of a meaningful symptomatic or clinical benefit with PH medical therapy based on the imbalance of lung disease versus PH. Then there's the opposite extreme of patients with severe PH and right heart failure versus more mild ILD, where we actually do know with certainty that they are likely to benefit. There certainly are some patients in that in-between where it is a bit uncertain, and setting those expectations is really key.

Dr Edelman: How important do people think that the inhaled route of therapy is? The rationale applied has been V̇Q̇ matching with the inhaled route because obviously the drug is being selectively delivered to presumably less affected areas.

Dr Mathai: I think that's a tough question to answer. As you point out, the theoretical advantage of an inhaled therapy would be targeting functioning lung units with therapies directed to the pulmonary vasculature, as opposed to targeting the lung as a whole, in which dilating the pulmonary vasculature in areas of the lung not participating in gas exchange might worsen systemic hypoxemia. I think that, while this mechanism is theoretically appealing, whether that happens in reality or not is a little bit challenging to determine.

There are older studies using multiple inert gas elimination or MIGET techniques in patient populations with underlying lung disease, both COPD complicated by pulmonary hypertension and interstitial lung disease without pulmonary hypertension, that demonstrate differences in ventilation-perfusion matching at rest and exercise when patients are exposed to oral pulmonary vasodilator therapy. This type of investigation would be interesting in our PH-ILD patients in particular to see if what we suspect is happening theoretically is happening in reality.

I think it's important to point out that, in the INCREASE study, there was no significant worsening of oxygenation, either at rest or at the end of the 6-minute walk test, which was the major safety concern about the study. I think there's some reassurances there, but the exact mechanisms that explain why inhaled therapy is potentially superior to other delivery mechanisms of pulmonary therapy remains uncertain.

Dr Edelman: The reason I brought that up was the recognition that treprostinil does have a relatively long half-life, and it is systemically absorbed. Granted, obviously, there will be preferential higher concentrations at the site of delivery, but there also will be a systemic effect of the drug. I would hope that maybe there is some future consideration to studying the oral route of delivery for treprostinil as well in this group because I am not sure how important the inhaled route would ultimately be for this drug. I think you outlined the uncertainties very nicely, Steve.

Dr Mathai: I think the other interesting finding from the INCREASE study was born out of the safety data looking at pulmonary function, in particular FVC, that demonstrated some possible improvement in FVC in patients receiving the study drug. This finding has prompted a larger prospective randomized study of inhaled treprostinil in isolated interstitial lung disease. I think that's an interesting observation, and it might explain some of the improvement in functional capacity as well if there was improvement not only in pulmonary hemodynamics but also in lung function.

Dr Elwing: I agree with that also. I thought that it was very reassuring to see that lung function did not decline with the inhaled therapy in this population with parenchymal lung disease. We've never studied inhaled prostacyclin in this patient population before in a randomized placebo-controlled trial. I was also happy to see that we're going to look at the potential of positive effect on lung function further with a randomized trial.

The other thing I thought was very interesting was an abstract that was presented at American Thoracic Society (ATS) by Dr Steve Nathan, looking at the worsening events in these patients that were treated with the inhaled treprostinil versus placebo. Dr Nathan presented a waterfall plot showing that patients who received therapy with inhaled treprostinil had a delay to the first event of worsening and the second event to worsening.

This information made me think hard about how we treat ILD-PH patients. This patient population frequently experiences exacerbations. They fre-

quently have worsening. We should not think about giving up on our treatment strategy with inhaled treprostinil when they do present with that episode of exacerbation because with this data, we learned that a large percentage of PH-ILD patients are going to have worsening events, but they are delayed in those treated with inhaled prostacyclin in the INCREASE trial. I don't know if anyone else found that interesting or that information helpful in their treatment.

Dr Vaidya: I think that's a great point, and it's very important not to react to those ILD decompensations in a way that makes us then withdraw or withhold some of the PH therapy that might have actually been helping them.

Steve had mentioned earlier about assessing oxygenation at rest, after the 6-minute walk. I think carefully assessing this, when we do choose to treat, when they presumably are not having an ILD exacerbation, is really helpful. It guides us in the future when they present with dyspnea and hypoxia not to jump to the conclusion that it's related to their PH medical therapy. This is another angle of thinking about it that can be helpful.

Dr Mathai: I guess I'll add to that and bring up another interesting result from the study, which I found important: the lack of response in patient-reported outcomes. Despite improvement in 6-minute walk distance, lack of worsening oxygenation, and improvement in the secondary analysis of time to clinical worsening, there was no improvement in symptoms as assessed by the St. George's respiratory questionnaire (SGRQ). I'm curious about the other panelists' impression of that and whether my bias that the SGRQ might not have been the best tool to assess the quality of life in a combined population such as this with PH and ILD is shared by the other panelists.

Dr Vaidya: One of the possible contributions that is worth noting is that the patient population in INCREASE was a somewhat modest phenotype of PH compared with what we've all been talking about and are used to seeing. Their average PVR was only 6 Wood units, which is of course abnormal but not as severe as is commonly seen in clinical practice and some of the other published data in this area.

You would potentially expect to see and have the patients report a more dramatic subjective improvement when they're going into treatment with a worsening PH hemodynamic profile. That may have been part of it. It was a positive study and certainly met its primary endpoint, but they may have had a greater opportunity for symptom and other clinical improvement with a more severe hemodynamic abnormality going into the study.

Dr Elwing: I think it also circles back to us talking through our goals for these therapies with each patient. Quality of life impact measured by SGRQ wasn't a positive finding in the study; however, as Steve mentioned, this may not have been the optimal questionnaire for this patient group. Maybe something more targeted towards this type of patient would have been more helpful. Hopefully, when we study more patients with PH-ILD in the future, we will assess with additional quality of life questionnaires to help us better understand this complex patient population.

Dr Edelman: I think, going forward, it will also be interesting to see if we can parse out which groups of patients have a greater degree of response to treatment overall because there certainly were some signals in INCREASE that there was a variation in response based on different patient groups.

Dr Elwing: Group 3 pulmonary hypertension is a heterogeneous patient population. We have a lot more to learn from this group. Over time, we may learn that there would be benefit from taking a different approach to the various subsets of PH-ILD patients. For example, we may find our IPF-PH patients, combined emphysema fibrosis patients, and CT-ILD patients benefit from different management. Additional study is needed, but I was happy to see we at least saw a signal in the positive direction for this group in the recently published INCREASE trial.

Dr Edelman: I think we can perhaps summarize by saying that this is a heterogeneous group. I think we've also discussed taking a very broad and global approach to the evaluation of these patients with careful attention to addressing and identifying comorbidities, thinking about goals and expectations of care, and now understanding that we do have at least one PH treatment option that may modify disease course and progression and lead to improvement in 6-minute walk and perhaps even lung function. I want to thank everyone for a very thoughtful discussion.

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