Pulmonary hypertension (PH) can be triggered by any number of disease processes that result in increased pulmonary vascular resistance. Although historically associated with idiopathic pulmonary arterial hypertension (PAH), most patients with PH do not have the idiopathic subtype, but rather PH associated with another underlying diagnosis, such as left heart or lung disease. The World Health Organization (WHO) classification of PH helps conceptualize the different categories based on presumed etiology. WHO group 3 is PH associated with lung disease. This review focuses on PH in diffuse parenchymal lung diseases (DPLDs), such as the idiopathic interstitial pneumonias and other more rare forms of DPLD. Although there are clear associations of PH with DPLD, the exact pathophysiologic mechanisms and full clinical significance remain uncertain. Treatment of PH related to DPLD remains investigational, but an area of great interest given the negative prognostic implications and the growing number of available pulmonary vasoactive agents.
DPLDs. Sarcoidosis, PLCH, and LAM are included under group 5 because of their more complex pathophysiology. The most recent WHO update on PH proposed differentiating DPLD with PH (defined as mPAP ≥ 25 mm Hg) from DPLD with severe PH (defined as mPAP ≥ 35 mm Hg or mPAP ≥ 25 mm Hg with a low cardiac index [< 2.0 L/min/m²]).

It is well-established that when PH supervenes in DPLD, it is associated with impaired function and poor outcome. With the increasing array of therapeutic options for group 1 PH, there is burgeoning interest in applying these therapies to patients with DPLD, especially given the poor prognosis and paucity of other effective therapeutic options for patients with more advanced disease. This review will focus on PH caused by DPLDs, which has therefore become a hot topic for research, including clinical drug trials.

Epidemiology

The prevalence of PH in all patients with DPLD is not well characterized and is likely lower than the reported range because most published studies are biased by the inclusion of more severe patients who are undergoing treatment at tertiary care centers.

The highest prevalence and severity of PH appears to be in PLCH, a smoking-related ILD characterized by the proliferation and infiltration of the lungs by Langerhans cells, with the overall incidence of PH varying from 62% to 100%. Although PH seems to be more severe in advanced forms of PLCH, it can occur at any stage with a noted lack of correlation between the mPAP and spirometry.

Most data on the prevalence, severity, and impact of PH in DPLD emanates from the IPF literature. Patients with mild to moderate IPF, defined by a forced vital capacity > 50% of predicted and < 5% honeycombing on high-resolution CT scan, were reported to have a prevalence of hemodynamically confirmed PH in approximately 15% of cases. Of the 488 study patients with IPF, 5% (n = 25) had an elevated pulmonary arterial wedge pressure consistent with group 2 PH, whereas 14% (n = 68) had group 3 PH. On repeat right heart catheterization at 48 weeks, only an additional 4.7% of the patients developed PH, therefore attesting to the relatively low incidence of PH in early disease. Patients with more advanced disease, on the other hand, have a higher incidence and prevalence of PH. At the initial evaluation of a cohort of patients who underwent transplantation, only 38.6% had PH, whereas 86.4% of the same cohort had PH at the time of lung transplant. The serial development of PH in most of the cohort attests to the progressive nature of the pulmonary vasculopathy in patients with more advanced disease.

Using echocardiogram (ECHO) as a screening tool, Nadrous et al found evidence of PH in 84% of patients with advanced IPF. In patients with IPF listed for lung transplantation, PH was reported in 31% to 45% of cases, with 9% having an mPAP > 40 mm Hg in one series. There are less data available in other DPLDs, with studies attesting to prevalence rates of approximately 36% in nonspecific interstitial pneumonitis and approximately 50% in patients with chronic hypersensitivity pneumonitis.

The prevalence of PH in sarcoidosis has been evaluated in several studies. In a prospective ECHO-based study of a general sarcoidosis population, only 5.7% of 212 patients had PH based on an estimated systolic pressure > 40 mm Hg. However, in a cohort of 363 patients with advanced sarcoidosis awaiting lung transplantation, 74% had hemodynamically diagnosed PH.

There is a paucity of data on PH complicating LAM. It is thought to be rare, with a prevalence of 7% reported across a wide spectrum of disease severity in a series from France. In more advanced disease, specifically patients evaluated for lung transplantation, the prevalence ranges between 45% and 100%.

PH in DPLD: Associations and Implications

There is a notable lack of correlation between the prevalence and severity of PH with the degree of restriction as measured by the forced vital capacity percent predicted in IPF, a disease in which a lack of correlation between the degree of fibrosis on CT scan and PH has also been reported. There is, however, a clear association between the diffusion capacity for carbon dioxide (DLCO) and need for supplemental oxygen with the mPAP in IPF. In sarcoidosis, the correlation between lung function parameters and PH is a little less clear with an association and a lack of association previously reported. Similar to IPF, the need for supplemental oxygen is an independent predictor of underlying PH in sarcoidosis. In the French LAM series, subjects with PH had more pronounced airflow obstruction, a lower DLCO, and a shorter walk distance with greater desaturation on 6-min walk testing (6MWT).

However, PH was also seen in patients with preserved lung volumes. PH complicating LAM appears to be mild to moderate.
PH is associated with worse functional capacity as measured by the 6MWT in both IPF and sarcoidosis.\textsuperscript{11,17,22,23} PH complicating other forms of DPLD likely has similar consequences. In patients with LAM the presence of PH has similarly been associated with increased dyspnea, more day-to-day limitations, and a higher prevalence of NYHA functional class 3 or 4 symptoms.\textsuperscript{19} In IPF, there has been one report suggesting an association between PH and acute exacerbations.\textsuperscript{24} This awaits additional validation, and whether such an association exists for other forms of DPLD requires further investigation.

PH is associated with reduced survival in all forms of DPLD studied; however, most data attesting to this are derived from IPF and sarcoidosis cohorts.\textsuperscript{12,17-19} In a recently published analysis from the European Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Arterial Hypertension (COMPERA) registry,\textsuperscript{25} the 3-year survival was 34\% for patients with PH in association with interstitial idiopathic pneumonias (n = 151) in comparison with 68.6\% in patients with idiopathic PAH (n = 798) (P < .001). Likewise, the presence of PH has significant clinical implications for patients with LAM: almost one-fourth of the patients died or underwent lung transplantation within 2 years of PH diagnosis.\textsuperscript{18,19}

Pathogenesis

It used to be commonly believed that PH in DPLD was a consequence of and therefore directly related to the degree of fibrosis and associated vascular ablation. However, the lack of correlation between the degree of restriction and fibrosis with hemodynamics highlights the importance and contribution of other factors. Although there are likely etiologic commonalities between idiopathic PAH and PH in DPLDs, the pathophysiological processes of PH in DPLDs are likely more complex (Fig 1). There are probably certain shared features among the various DPLDs, whereas other factors might be unique to specific pathologic processes. Such unique factors include local compression of pulmonary arteries by hilar lymph nodes in sarcoidosis\textsuperscript{26} and pulmonary veno-occlusive disease described in PLCH, IPF, and sarcoidosis.\textsuperscript{5,27,28} Other unique mechanisms include a proliferative vasculopathy that contributes to the development of PH in PLCH,\textsuperscript{7} involvement of the pulmonary artery (PA) walls by characteristic HMB-45+ cells in LAM,\textsuperscript{29} and a granulomatous vasculopathy with sarcoidosis.\textsuperscript{26}

Possible shared contributory factors among the various DPLDs include regional hypoxic vasoconstriction, vascular remodeling, in situ thrombosis (thrombotic angiopathy), a deranged cytokine milieu, and vascular bed obliteration with vessel distortion caused by parenchymal destruction by ongoing interstitial inflammation and fibrosis.\textsuperscript{26,28,29} The latter can lead to turbulent flow with increased shear stress, which in turn can perpetuate the vasculopathy.

Pathologically, vasculopathic changes similar to PAH, including adventitial changes, smooth muscle cell hypertrophy, and intimal remodeling, can all be seen amidst the typical parenchymal remodeling that characterize the various diseases (Fig 2). Vasculocentric fibrosis can affect the capacitance and the ability of the vasculature to accommodate the increased blood flow that invariably accompanies activity and exercise. It has been demonstrated in group 1 PAH that a low vascular capacitance portends a worse prognosis.\textsuperscript{31} If the same holds true for the PH of DPLD, this might help explain the profound mortality implications of even mild elevations in PA pressures complicating parenchymal diseases.

On a cellular level, pulmonary endothelial dysfunction has been emphasized in multiple studies. Mediators known to be important in the genesis of idiopathic PAH are also upregulated in some of the DPLDs, including platelet-derived growth factor, transforming growth factor beta, endothelin-1, and tumor necrosis factor alpha.\textsuperscript{32-35} Therefore, there may be a spillover effect of these mediators on the pulmonary vasculature.

The potential role of comorbid conditions in the development of PH in DPLDs cannot be understated because most of these require distinct diagnostic and therapeutic approaches. Heart failure with preserved ejection fraction has been described in approximately 9\% to 28\% of patients with IPF\textsuperscript{9,36} and sarcoidosis.\textsuperscript{37} Pulmonary embolism may also contribute to elevated PA pressures in these conditions, especially given the increased prevalence of thromboembolic events in many of the DPLDs.\textsuperscript{38,39} In fact, pulmonary embolism has been described as the cause of death in 3.4\% of patients with IPF,\textsuperscript{40} and IPF lung transplant recipients are noted to be more prone to pulmonary embolism than other lung recipients.\textsuperscript{41} Procoagulant and antifibrinolytic pathways are thought to be important in the fibrotic...
process; therefore, local imbalances in coagulation factors could contribute to microscopic in situ thrombosis.\textsuperscript{39,42,43}

Concomitant emphysema has been described in approximately one-third of patients with IPF.\textsuperscript{44,45} There have been conflicting reports regarding the prognostic implications of combined pulmonary fibrosis and emphysema, but certainly this subgroup of patients have a higher prevalence of PH, which when it occurs, portends a worse prognosis. Sleep disordered breathing

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{pathogenesis_flowchart.png}
\caption{Pathogenesis flowchart. The chart highlights complex nature of pulmonary hypertension in parenchymal lung diseases. CF = cystic fibrosis; IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis; PLCH = pulmonary Langerhans cell histiocytosis; PVH = pulmonary venous hypertension; PVOD = pulmonary venous occlusive disease.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{histopathology.png}
\caption{A, B, Histopathology collage. Both histographs show significant medial hypertrophy of the pulmonary artery branches (the diameters of the lumina are only approximately one-third of the vessel wall diameter as indicated by black arrows) and underlying interstitial changes (A) Nonspecific interstitial pneumonitis. (B) End-stage fibrosis.}
\end{figure}
has been described to occur commonly in overweight patients with IPF, with nocturnal hypoxemia, increased sleep fragmentation, and impaired sleep quality.\textsuperscript{46} In sarcoidosis, the prevalence of OSA is reported to be 17\%, which is much higher than what might be expected in a matched healthy patient population.\textsuperscript{47} Finally, untreated hypoxia, at rest, during sleep, or with exercise represents an important reversible contributor to development of PH.

In summary, it appears that the factors contributing to the development of PH in DPLDs are complex and interrelated. Why some patients with DPLD might be more predisposed to the development of PH is unknown, and whether there are specific triggers or a genetic predisposition remain to be defined,\textsuperscript{48} as do the time course and the rate of progression.

**Diagnosis**

There are no current guidelines on whether, when, or how to screen for PH in patients with DPLD. Therefore, this remains an individualized decision based on each patient’s clinical circumstance. Suggestive physical examination findings are uncommon apart from a prominent P\textsubscript{2} heart sound, but evidence of right heart failure is unusual and only seen in cases with more moderate to severe PH.

**Pulmonary Testing**

Pulmonary function tests have been examined for their ability to predict the presence of PH in various DPLDs. D\textsubscript{LCO} < 30\% of predicted and supplemental oxygen requirements have been found to be independent predictors of PH in IPF.\textsuperscript{12,36} Similarly, reduced D\textsubscript{LCO} and hypoxia have been shown to be associated with PH in sarcoidosis\textsuperscript{49} and PLCH.\textsuperscript{49} There is no correlation between the degree of restriction and the presence or severity of PH in IPF.\textsuperscript{13,36,50} However, rather than having distinct cut points, these variables might be best scrutinized as a continuum with enhanced utility in combination with other tests. The 6MWT can provide important clues, with a short distance, lower oxygen saturation nadir, and low heart rate recovery (HRR), all found to be associated with underlying PH in patients with IPF.\textsuperscript{12,51} HRR is calculated by the difference in the pulse rate at the end of 6 minutes and after 1 minute of recovery. In a study of 82 patients with IPF with right heart catheterization data and contemporaneous 6MWT, 41\% of the cohort with an HRR < 13 beats per minute had PH, vs only 18\% with an HRR of >13 beats per minute.\textsuperscript{51} This HRR threshold provides a sensitivity, specificity, positive predictive value, and negative predictive value of 52\%, 74\%, 41\%, and 82\%, respectively, for the presence of PH in IPF.

**Serum Biomarkers**

The only serum biomarker evaluated as a predictor of PH in DPLD is the brain natriuretic peptide, which appears to have very good performance characteristics in detecting the presence of PH and discerning prognosis in chronic lung disease, specifically IPF.\textsuperscript{52} Leuchte et al\textsuperscript{53} showed that the brain natriuretic peptide levels were higher in patients with fibrotic lung disease and mPAP > 35 mm Hg than in patients with mPAP < 35 mm Hg. However, BNP does not discriminate between various etiologies of PH. Further studies across the spectrum of patients with DPLD are needed to confirm the diagnostic and prognostic value of this and other biomarkers.

**Chest Imaging**

Chest CT imaging may be a useful screening tool for PH in DPLD. Although the extent of parenchymal changes in patients with IPF does not correlate with the presence or severity of PH,\textsuperscript{21} there is conflicting data on the utility of the main PA diameter in relation to the aorta (PA to aorta ratio).\textsuperscript{54} A recent study of patients with IPF demonstrated that a PA to aorta ratio > 1 was associated with a higher risk of death or transplant compared with a PA to aorta ratio ≤ 1.\textsuperscript{55} Whether or not measurement of the PA diameter might be useful in other forms of DPLD remains to be determined (Fig 3).

**ECG**

There are limited data on the utility of ECG in the detection or screening of patients with DPLD for the presence of underlying PH. ECG is unlikely to be helpful.
in those patients with mild PH and no right ventricular dysfunction. The presence of right axis deviation or right ventricular hypertrophy on ECG is more likely to be seen in patients with severe PH. ECG is therefore probably an insensitive screening tool but one with greater specificity.

**Echocardiography**

ECHO is commonly used to screen patients with DPLD. It can also provide clues about other factors important in the etiology of PH, specifically heart failure with preserved ejection fraction. ECHO-derived measurement of the tricuspid regurgitant jet velocity with two-dimensional ECHO allows for the estimation of the right ventricular systolic pressure gradient which, when added to the estimated right atrial pressure, is synonymous with the systolic pulmonary artery pressure. However, these estimates may frequently be inaccurate, especially in patients with advanced lung disease. A higher right ventricular systolic pressure threshold is associated with increased specificity but reduced sensitivity for the presence of PH. In the absence of tricuspid regurgitation, the diagnosis of PH should still be suspected when signs of right ventricular dysfunction, including dilatation, hypertrophy, and flattening or bowing of the interventricular septum are present. In a study of 135 patients with DPLD, ECHO evidence of right ventricular dysfunction was associated with an increased risk of mortality.

**Combination Testing**

The diagnostic accuracy of ECHO and other noninvasive indicators may be enhanced if used in concert with each other. For example, the main pulmonary artery diameter to ascending aorta ratio together with echocardiography-derived right ventricular systolic pressure has been shown to result in improved accuracy for PH diagnosis. Similarly, DLCO percent, resting peripheral capillary oxygen saturation (SpO₂), exercise SpO₂ nadir, and brain natriuretic peptide levels have been shown to complement ECHO in the prediction of PH in both IPF and sarcoidosis.

**Right Heart Catheterization**

Noninvasive testing, including ECHO, should not be solely relied on to make the diagnosis of PH. Right heart catheterization is necessary to definitively diagnose PH.

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**TABLE 1** Summary of Studies in Sarcoidosis-Associated Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Study Design</th>
<th>Therapy (No. Treated)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preston et al⁶⁶/2001</td>
<td>Prospective observational (8)</td>
<td>IH NO (5), IH NO with EPO (1), CCBs (2)</td>
<td>Short-term 20% ↓ in PVR and mPAP; long-term ↑ in 6MWT&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Culver et al⁶⁷/2005</td>
<td>Retrospective chart review (7)</td>
<td>Bosentan (3), bosentan and EPO (4)</td>
<td>↓ in mPAP at 6 to 18 mo in approximately 50% of patients&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fisher et al⁶⁸/2006</td>
<td>Retrospective case series (7)</td>
<td>EPO (6), SQ trep (1)</td>
<td>Improved NYHA class&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Milman et al⁶⁹/2008</td>
<td>Retrospective chart review (12)</td>
<td>Sildenafil (12)</td>
<td>↓ in mPAP and PVR, ↑ in CO, no change in 6MWT&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Barnett et al⁷⁰/2009</td>
<td>Retrospective case series (22)</td>
<td>EPO (1), bosentan (12), sildenafil (9)</td>
<td>↑ 6MWT and NYHA class, ↓ in mPAP and PVR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Baughman et al⁷¹/2009</td>
<td>Prospective open label 16 wk (15)</td>
<td>IH iloprost (15)</td>
<td>↓ in mPAP/PVR in 6 of 15 and ↑ in 6MWT in 3 of 15 patients&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Baughman et al⁷²/2010</td>
<td>Retrospective chart review (5)</td>
<td>Bosentan (5)</td>
<td>↓ in mPAP in 3 of 5 patients at 4 mo&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Judson et al⁷³/2011</td>
<td>Prospective placebo-controlled 12 wk (25)</td>
<td>Ambrisentan (21)</td>
<td>No change in 6MWT, 11 discontinued drug at 12 wk&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Baughman et al⁷⁴/2014</td>
<td>Prospective placebo-controlled 16 wk (35)</td>
<td>Bosentan (23 on drug, 12 on placebo)</td>
<td>↓ in mPAP and PVR but no change in 6MWT&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bonham et al⁷⁵/2015</td>
<td>Retrospective case series (26)</td>
<td>EPO 7, treprostinil 6, ERAs (12), PDE5i (20), CCB (1)</td>
<td>↑ CI/CO, ↓ PVR, ↑ NYHA, ↓ NT-pro-BNP, NO ↑ in oxygen requirements&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>6MWT = 6-min walking test; CCB = calcium channel blocker; CI = cardiac index; CO = cardiac output; EPO = epoprostenol; ERAs = endothelin receptor blockers; IH = inhaled; mPAP = mean pulmonary artery pressure; NO = nitric oxide; NYHA = New York Heart Association; PDE5i = phosphodiesterase 5 inhibitor; PVR = pulmonary vascular resistance; SQ = subcutaneous.</sup>

<sup>aPositive findings.</sup>

<sup>bNegative findings.</sup>
catheterization with direct measurement of the pulmonary artery pressure and pulmonary capillary wedge pressure remains the gold standard.\textsuperscript{59,62} Although there are currently no approved medications for the treatment of PH associated with parenchymal lung disease, these data can be useful for prognostication purposes, therapeutic trial enrollment, and calculation of the lung allocation score in those patients listed for lung transplantation.

### TABLE 2: Summary of Studies in ILD-Associated Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Study/Year</th>
<th>Study Design (No. of Subjects)</th>
<th>Therapy</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILD</td>
<td>Olschewski et al\textsuperscript{73}/1999</td>
<td>Open label (8)</td>
<td>IH NO and EPO IV EPO</td>
<td>IH prostanoids ↑ gas exchange\textsuperscript{a}</td>
</tr>
<tr>
<td>ILD</td>
<td>Ghofrani et al\textsuperscript{74}/2002</td>
<td>Open label (16)</td>
<td>Sildenafil or EPO</td>
<td>Sildenafil ↑ V/Q and ↑ O₂, EPO worsened V/Q\textsuperscript{a}</td>
</tr>
<tr>
<td>IPF</td>
<td>Krowka et al\textsuperscript{75}/2007</td>
<td>RCT (51)</td>
<td>IH iloprost</td>
<td>No differences 6MWT, NYHA FC, dyspnea score, exercise O₂ percent\textsuperscript{b}</td>
</tr>
<tr>
<td>IPF</td>
<td>Gunther et al\textsuperscript{76}/2007</td>
<td>Open label (12)</td>
<td>Bosentan</td>
<td>No worsening of gas exchange\textsuperscript{c}</td>
</tr>
<tr>
<td>IPF</td>
<td>Collard et al\textsuperscript{77}/2007</td>
<td>Open label (14)</td>
<td>Sildenafil</td>
<td>57% ↑ 6MWT by ≥ 20%\textsuperscript{a}</td>
</tr>
<tr>
<td>ILD</td>
<td>Minai et al\textsuperscript{78}/2008</td>
<td>Retrospective (19)</td>
<td>EPO (10) Bosentan (9)</td>
<td>79% with ↑ 6MWT &gt; 50 m\textsuperscript{a}</td>
</tr>
<tr>
<td>ILD</td>
<td>Chapman et al\textsuperscript{79}/2009</td>
<td>Retrospective (5)</td>
<td>Sildenafil</td>
<td>↑ 6MWT; ↓ mPAP\textsuperscript{b}</td>
</tr>
<tr>
<td>IPF</td>
<td>Zisman et al\textsuperscript{80}/2010</td>
<td>RCT (180)</td>
<td>Sildenafil</td>
<td>Failed to ↑ 6MWT by ≥ 20% but ↑ QOL and O₂\textsuperscript{c}</td>
</tr>
<tr>
<td>IPF</td>
<td>Jackson et al\textsuperscript{81}/2010</td>
<td>RCT (29)</td>
<td>Sildenafil</td>
<td>No difference in 6MWT or Borg\textsuperscript{b}</td>
</tr>
<tr>
<td>ILD</td>
<td>Corte et al\textsuperscript{82}/2010</td>
<td>Retrospective (15)</td>
<td>Sildenafil</td>
<td>↑ 6MWT and ↓ BNP\textsuperscript{a}</td>
</tr>
<tr>
<td>ILD</td>
<td>Badesch et al\textsuperscript{83}/2012</td>
<td>Open label (21)</td>
<td>Ambrisentan</td>
<td>↓ 6MWT\textsuperscript{b}</td>
</tr>
<tr>
<td>IPF</td>
<td>Raghu et al\textsuperscript{84}/2013</td>
<td>RCT (492)</td>
<td>Ambrisentan</td>
<td>Terminated early: lack of efficacy in TTCW\textsuperscript{b}</td>
</tr>
<tr>
<td>ILD</td>
<td>Hoeper et al\textsuperscript{85}/2013</td>
<td>Open label (22)</td>
<td>Riociguat</td>
<td>↑ CO and ↓ PVR but not mPAP\textsuperscript{a}</td>
</tr>
<tr>
<td>ILD</td>
<td>Zimmerman et al\textsuperscript{86}/2014</td>
<td>Open label, observational (10)</td>
<td>Sildenafil (5) Tadalafil (5)</td>
<td>↑ CO and ↓ PVR, no change in 6MWT and BNP\textsuperscript{c}</td>
</tr>
<tr>
<td>ILD</td>
<td>Corte et al\textsuperscript{87}/2014</td>
<td>RCT (60)</td>
<td>Bosentan</td>
<td>Unchanged hemos, symptoms, NYHA FC\textsuperscript{b}</td>
</tr>
<tr>
<td>ILD</td>
<td>Saggar et al\textsuperscript{88}/2014</td>
<td>Open label (15)</td>
<td>Treprostinil</td>
<td>Improved hemos without hypoxemia\textsuperscript{a}</td>
</tr>
<tr>
<td>IPF</td>
<td>Raghu et al\textsuperscript{89}/2015</td>
<td>RCT (117)</td>
<td>Ambrisentan</td>
<td>Unchanged hemos\textsuperscript{b}</td>
</tr>
<tr>
<td>ILD</td>
<td>Brewis et al\textsuperscript{90}/2015</td>
<td>Retrospective (118)</td>
<td>PDE5i</td>
<td>↓ BNP, unchanged 6MWT\textsuperscript{c}</td>
</tr>
<tr>
<td>ILD</td>
<td>Bayer\textsuperscript{91}/2014</td>
<td>Prospective</td>
<td>Riociguat</td>
<td>Stopped because of increased mortality in drug group at interim analysis\textsuperscript{b}</td>
</tr>
</tbody>
</table>

BNP = brain natriuretic peptide; FC = functional class; hemos = hemodynamics; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; QOL = quality of life; RCT = randomized controlled trial; TTCW = time to clinical worsening; V/Q = ventilation/perfusion. See Table 1 legend for expansion of other abbreviations.

\textsuperscript{a}Positive findings.

\textsuperscript{b}Negative findings.

\textsuperscript{c}Equivocal findings.
Treatment

PH complicating DPLD may be a direct contributor to morbidity and mortality, but it may also be a proxy for other upstream determinants of outcomes. Although the concept of therapy makes intuitive sense and certainly has appeal, the role of PAH medications in the treatment of PH in DPLD requires further investigation in the context of well-designed, prospective randomized controlled trials.
The current literature attesting to the benefits of vasodilator therapy for PH in DPLD is confined mostly to retrospective series, registry data, and open-label studies in IPF and sarcoidosis (Tables 1, 2).8,9,62-88 The few prospective, randomized controlled trials have thus far mostly been negative.63,65,88 However, some of these have generated positive signals for efficacy.63,64 Taken in total, it does appear that there are subgroups of patients with PH in DPLD who may benefit from pulmonary vasoactive therapy.4 How best to identify this phenotype of patients with DPLD and PH and subject this hypothesis to appropriate randomized controlled trial validation is open to conjecture. Issues pertaining to study design for PH in DPLD are highlighted in Table 3.

Given the lack of robust evidence for use of vasodilator therapy for PH in DPLD at this time, clinical attention should be focused on the assessment and treatment of comorbidities that may be contributory. Indeed, therapies directed at these contributing factors may ameliorate the PH and improve patient functional status and quality of life. Specific entities to consider include OSA, congestive heart failure, concomitant COPD, hypoxia, and, in select cases, where there is a high index of suspicion, thromboembolic disease.89,90 Certainly, the importance of CPAP therapy, oxygen therapy, diuresis, and anticoagulation, where clinically appropriate, cannot be overemphasized.

Are there patients who can or should be considered for off-label PAH therapy? Although this cannot be endorsed at this time, there are certainly some patients whose hemodynamics resemble those of patients with PAH. Can or should these patients be regarded as having group 1 PH and comorbid DPLD and therefore warrant therapy under the guise of having PAH? Indeed, some of these patients have hemodynamic compromise with evidence of a low output state or right heart failure. The option to treat such cases can be difficult to ignore in the clinical trenches, even with a lack of supportive randomized controlled trial evidence. Arguably, this is where clinical judgment and the art of medicine resurface to trump the paradigm of only practicing within the constraints of evidence-based medicine.91 If treatment is to be considered, then it should only be undertaken in PH centers with expertise in this area, where the priority should be to first populate any available clinical trials.

The potential for harm with pulmonary vasoactive agents is important to recognize and may occur through several potential mechanisms. Despite a theoretical concern that PH-specific treatments may result in worsened oxygenation caused by increased ventilation perfusion mismatch, this phenomenon has not been borne out in the literature. Even if there is an element of reduced oxygenation, it may be compensated for by a concomitant increase in cardiac output resulting in a net improvement in tissue oxygen delivery. The presence of occult left-sided heart failure and/or pulmonary veno-occlusive disease are the other scenarios in which treatment with pulmonary vasodilators could result in increased venous congestion.

**Conclusions**

PH complicating DPLD is not uncommon and is clearly associated with worse outcomes. Whether and when supervening PH is an adaptive vs maladaptive phenomenon remains unclear. There is a paucity of prospective randomized, placebo-controlled studies of pulmonary vasoactive agents for PH in DPLD. Encouraging signals from some of the studies reinforce the critical need for robust clinical trials to assess the impact of therapies for this deadly pathophysiologic combination. More attention to this evolving field is crucial as we seek to better understand the mechanisms, clinical impact, and potential role of treatment in patients with PH in the context of DPLD.

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