Diagnosis and Management of Pulmonary Hypertension Associated With Pulmonary Fibrosis

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Pulmonary fibrosis is a term often used to refer to a group of interstitial lung diseases (ILD) that are characterized by the inappropriate deposition of collagen, fibrocytes, and inflammatory cells in the lung interstitium. Fibrotic scarring of lung tissue is a normal response to traumatic injury, toxins, or chronic irritation due to environmental exposure, recurrent infection, or drug reaction. However, in some patients, a progressive fibrosis of the lung interstitium occurs in the absence of any identifiable irritation and is referred to as idiopathic pulmonary fibrosis (IPF). This is the most common of the 7 listed interstitial pneumonias in the American Thoracic Society/European Respiratory Society consensus statement, with a prevalence of 14.0 to 42.7 cases per 100,000 population, depending on how the diagnosis is made (**Figure 1**).[1,2] Idiopathic pulmonary fibrosis is a progressive fibrotic lung disorder that does not normally respond well to any known treatment. Although the course of the disease is variable with periods of relative stability, the average survival is only about 3-5 years,[3-5] and in one study 10-year survival was only 27%.[6] Morphologically, the disease is characterized by abnormal parenchymal tissue remodeling with re-epithelialization of the alveolar surface, increased collagen deposition in the interstitium, and angiogenesis of terminal vessels. Radiographic changes demonstrate a fine reticular pattern at the lung periphery and bases with relative sparring of the alveolar space and the lack of ground glass appearance on chest computed tomography (CT). As the disease progresses, the formation of numerous small fibrotic cysts give the lung the appearance of a "honeycomb" pattern on chest CT. Loss of alveolar volume caused by the fibrotic process places laterally directed tension on adjacent airways causing "traction" bronchiectasis. Pulmonary function tests show a restrictive pattern with reduced diffusion capacity for carbon monoxide (DLCO). Progressive loss of functional gas exchanging units leads to dyspnea, hypoxia, and decreased functional capacity.

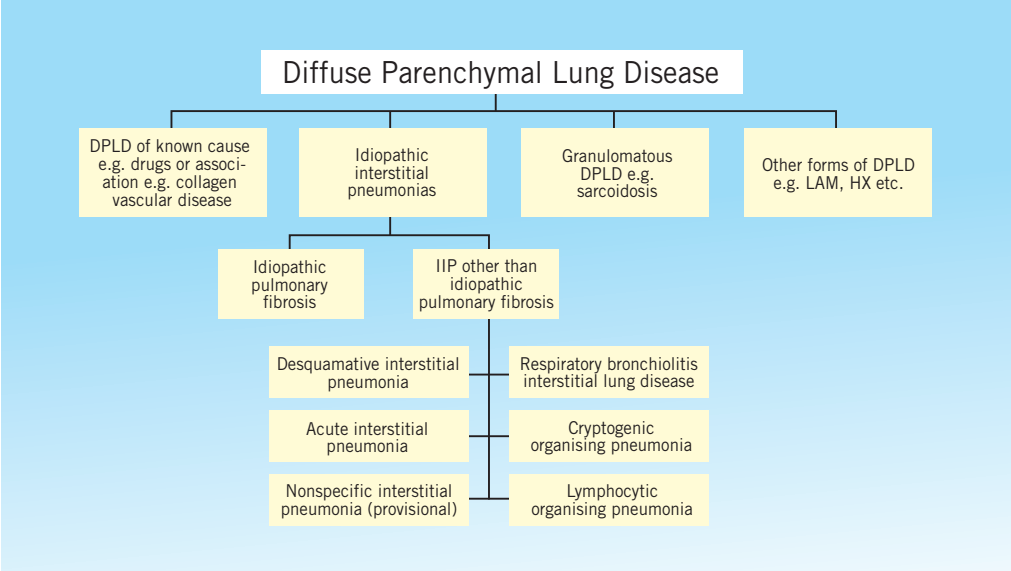

Figure 1. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias (from reference 1).

Pulmonary Hypertension Associated With Pulmonary Fibrosis

Pulmonary hypertension (PH) occurs when mean pulmonary arterial pressure (PAP) is elevated more than 20-25 mm Hg at rest. Elevation of PAP can be caused by any process that impedes blood flow through the pulmonary circulation, including elevation of pulmonary venous pressure from left-sided heart disease. A modern classification of the pulmonary hypertensive diseases was proposed at the World Health Organization (WHO) conference on PH in Evian, France, in 1998, and has been revised in 2003 and 2008.[7] Using this classification system, PH associated with ILD is a subgroup of WHO Group III (**Table 1**).

The prevalence of PH in IPF is not well defined. Only a handful of studies have specifically tried to address how often PH oc-

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Table 1. WHO Classification of Pulmonary Hypertensive Diseases

Group I.	Pulmonary Arterial Hypertension
Group II.	Pulmonary Venous Hypertension
Group III.	Pulmonary Hypertension Associated With Chronic Lung Disease
Group IV.	Pulmonary Embolic Hypertension
Group V.	Miscellaneous

WHO Group III

1 Pulmonary Hypertension Associated With COPD

2 Pulmonary Hypertension Associated With Obstructive Sleep Apnea

3 Pulmonary Hypertension Associated With Interstitial Lung Disease

4 Pulmonary Hypertension Associated With High Altitude

curs, and prevalence has varied considerably depending on the study design and how PH is defined. For example, Nadrous et al[8] performed a retrospective review of 487 patients referred for evaluation of IPF and found 88 who had echocardiographic assessment of PAP without evidence of left ventricular dysfunction or valvular heart disease. The prevalence of PH was 89% when defined as right ventricular systolic pressure (RVSP) >36 mm Hg, but only 31% when defined as RVSP >50 mm Hg. More recently, in a retrospective review of 110 patients who had both transthoracic echocardiography (TTE) and right heart catheterization (RHC) as part of the evaluation of IPF, the prevalence of PH defined as a mean PAP at rest of >25 mm Hg was 34.5%.[9] However, the majority of these patients had advanced disease and were being evaluated for lung transplantation at the time of their catheterization. In an earlier prospective analysis of 78 consecutive patients undergoing evaluation for IPF, RHC was performed on 61 and only 6 (9.8%) had mean PAP >25 mm Hg.[10] Another confounding variable is at which point during the time course of the patients' disease they are assessed for the presence of PH. In one study[11] of 44 patients who underwent repeat RHC, the prevalence of PH increased markedly from 38.6% at the time of the initial catheterization to 86.4% at the time of repeat study. Of the 27 patients who did not have PH at initial evaluation, 77.8% had developed PH by the time of their second catheterization. Hence, PH is fairly common in patients with IPF and likely to occur in most patients who do not have PH on initial evaluation.

Pathophyiosology

Several factors contribute to the elevation of pulmonary vascular resistance (PVR) in chronic lung disease. Normally, the pulmonary circulation is a low-pressure system with little basal vascular tone, and most of the resistance to flow is caused by the normal narrowing and branching of the pulmonary vascular bed. When cardiac output (CO) increases, such as during vigorous exercise, the increase in blood flow is accommodated by dilatation of pulmonary vessels and recruitment of underperfused vessels. As a result, the PVR falls and PAP rises little despite a 3-4–fold increase in CO. Chronic lung disease commonly increases PVR by destruction of normal gas exchanging units and loss of the pulmonary vascular bed. In addition, most lung diseases result in chronic or intermittent periods of hypoxia. A fall in alveolar or arterial oxygen tension causes acute pulmonary vasoconstriction. Although hypoxic pulmonary vasoconstriction is rapidly reversed following re-exposure to normoxia, sustained or repeated exposure to hypoxia results in increased muscularization of the pulmonary vascular bed and the development of hypoxic PH that is only partially reversed upon correction of hypoxia. Pulmonary vascular resistance may also be affected by changes in lung volume. In general, extra-alveolar vessels are mildly distended by the negative pressure of the interstitium and dilate as the lung is inflated, while intra-alveolar vessels are compressed between alveoli during inflation and increase resistance. These forces act in opposite directions and offset each other most at functional residual capacity. As such, changes in lung volume above or below functional residual capacity usually increase PVR.

It may not be surprising that PH is not uncommon in a group of diseases like IPF that affect the lung diffusely and severely enough to alter gas exchange and lung volume. The question arises, however, as to whether PH associated with ILD is an unavoidable consequence of the underlying damage that is done to the lung as the disease progresses or whether ILD is capable of inciting a pulmonary vascular disease that is separate from or out of proportion to the underlying lung injury. Several lines of evidence suggest that the latter may be correct. First, neither the prevalence nor the severity of PH that is seen in patients with IPF correlate well with measures of pulmonary function.[12] In fact, one study found a trend toward a higher prevalence and severity of PH in IPF patients with preserved function than in those with severe restrictive defect on pulmonary function tests.[12] Although some studies have found an inverse correlation between low DLCO and PAP in IPF,[12] it is not clear to what degree the fall in DLCO in these patients is due to their pulmonary fibrosis as opposed to their PH. That is to say, the reduction in DLCO in these patients may be caused by their pulmonary hypertensive disease and not by their ILD.

The second line of evidence is that histopathologic examination of patients with IPF shows evidence of vascular remodeling in areas of normal lung. In one study[13] of lungs obtained from IPF patients who were transplanted, 65% of patients had evidence of pulmonary arterial thickening and occlusion of small pulmonary veins and venules in areas of preserved lung architecture (**Figure 2**). Although the greater degree of pulmonary vascular wall thickness and luminal narrowing was seen in areas of dense fibrosis, these findings suggest that patients with IPF have pulmonary vascular remodeling in areas that are remote from the site of lung injury.

Finally, many of the inflammatory mediators and abnormal expression of growth factors that have been implicated in the pathogenesis of IPF are felt to play substantial roles in the pathogenesis of idiopathic pulmonary arterial hypertension (IPAH) as well. For example, genetic overexpression of endothelin-1 (ET-1) causes pulmonary fibrosis in mice.[14] Increased expression of endothelin converting enzyme colocalized with ET-1 and its precursor big endothelin have been observed in type II pneumocytes of patients with IPF.[15] Increased expression of ET-1 has also been demonstrated in the plexiform lesions of patients with IPAH.[16] Furthermore, plasma ET-1 levels correlate with the severity of disease in IPAH[17] and have been shown to correlate with PAP at rest and

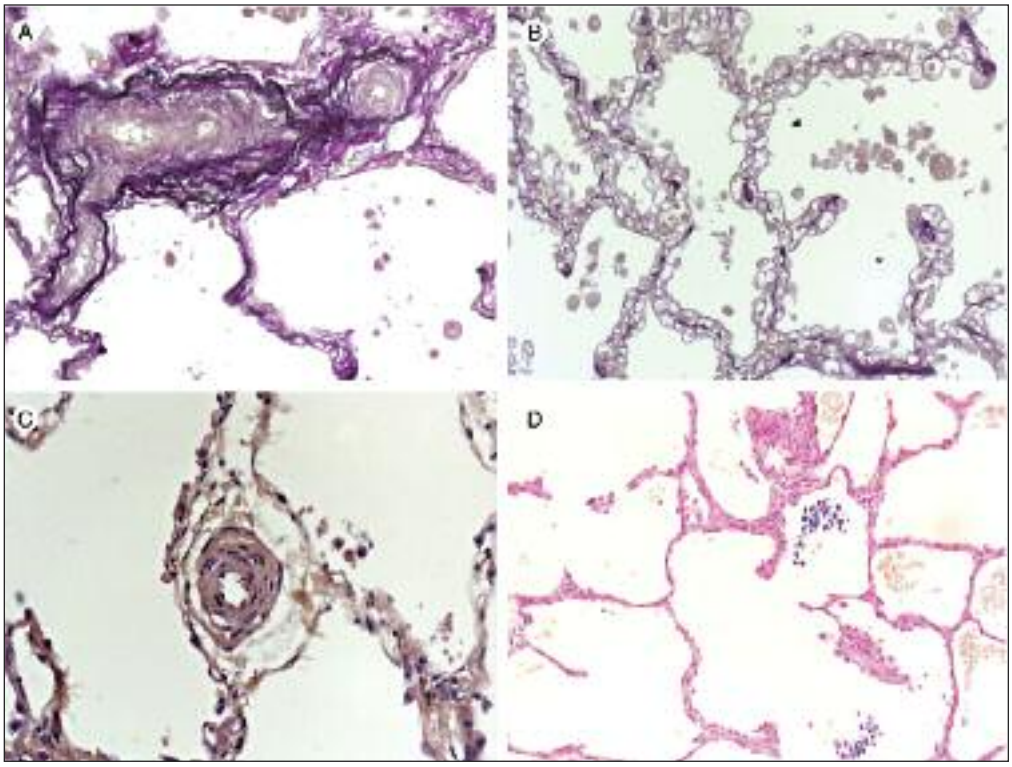

Figure 2. Lung sections taken from a patient with pulmonary hypertension and pulmonary fibrosis. Note panel C showing pulmonary vascular remodeling with medial hyperplasia in a vessel distant from areas of fibrosis (see reference 13).

during exercise in patients with ILD.[18] Similarly, bronchioalveolar lavage fluid levels of Interleukin-6 are elevated in patients with IPF[19] and overexpression of Interleukin-6 induces PH in mice.[20] Transforming growth factor beta (TGF-β) is a member of a superfamily of growth factors and receptors that are intimately involved in the development of normal pulmonary vascular and alveolar architecture. Overexpression of TGF-β has been well demonstrated in the lungs of patients with IPF [21] and while its role in the pathogenesis of IPAH is unclear, it is interesting that TGF-β has been shown to inhibit serum-induced proliferation in pulmonary artery smooth muscle cells (PASMCs) isolated from healthy lung donors, but to stimulate proliferation of PASMCs isolated from patients with IPAH.[22] Although the pathogeneses of PAH and IPF have not yet been linked, considerable overlap exists between the mediators of both disease processes, raising the possibility that IPF creates an environment that allows the induction of a pulmonary vascular disease similar to that seen in PAH. Thus, it is possible that chronic lung disease may increase the risk of developing a true pulmonary vasculopathy similar to that seen in IPAH. If so, treating the patient's pulmonary vascular disease may result in improvement in cardiopulmonary performance and possibly survival.

Diagnosis

The diagnosis of PH in IPF can be extremely challenging, as the symptoms of PH are nearly identical to those of IPF. Patients with both diseases are usually comfortable at rest but complain of dyspnea with exertion, decreased functional capacity, and increasing fatigue. Strenuous activity can result in chest heaviness, chest pain, lightheadedness, or syncope. The primary pathophysiologic difference between symptoms caused by IPF and those caused by PAH is that in the former, the patient is limited primarily by impairment in gas exchange and in the latter by both impaired gas exchange plus limited cardiac output. Oxygen delivery (DO_2) to systemic tissues is the product of the oxygen content of arterial blood (CaO_2) and CO:

$DO_2 = CaO_2 \times CO$, where:
$CaO_2 = 1.34$ (Hgb gm/dl) (% $HgbO_2$ Saturation) + 0.003 (PaO_2 mm Hg).

Patients with IPF have significant impairments in oxygenation and often demonstrate hypoxia at rest or a fall in oxygenation with exercise. The etiology of hypoxia in IPF is multifactorial and includes ventilation/perfusion (V/Q) mismatch, decreased pulmonary capillary blood transit time, and diffusion impairment due to disease at the alveolar, pulmonary capillary interface. As O_2 demands increase with exercise, these impairments in gas exchange lead to inadequate oxygenation and exercise-induced hypoxemia. The fall in oxygen saturation results in a lower CaO_2 and reduces DO_2. If PVR remains normal, the patient can attempt to compensate for the decrease in CaO_2 by increasing CO. However, if PVR is elevated at baseline or increases significantly with exercise, the patient's ability to increase CO becomes limited. In addition to decreasing DO_2, a fall in CO (or insufficient rise) results in greater extraction of O_2 from arterial blood in the systemic tissue and thus a fall in mixed venous oxygen saturation (VmO_2 Sat), thereby worsening whatever limitation in oxygenation already exists. A lower VmO_2 also increases the adverse effect of any right-to-left shunt on arterial oxygenation. Thus, the combination of impaired gas exchange from pulmonary fibrosis and limited CO from PH can greatly reduce arterial oxygenation during exercise, leading to severe dyspnea and reduced functional capacity.

Three key questions need to be addressed when evaluating PH in patients with IPF. 1) Does the patient have elevated PAP? 2) Is the degree of PH more than can be explained by the patient's underlying lung disease? 3) Is treatment of the PH likely to impact the patient's symptoms, functional class, or survival? The first question is best addressed by a high index of suspicion for PH in patients with IPF. Most studies suggest that the prevalence of mild PH is high in patients with IPF and that the majority of IPF patients will develop PH at some point in their disease. As PH begins to affect the patient, most symptoms are often attributed to the patient's underlying lung disease and not viewed as a new disease process. The onset of worsening dyspnea or fatigue in a patient whose underlying lung disease has been stable should prompt consideration of PH, as should symptoms of exercise limitation that are greater than would be expected from the degree of IPF alone. New symptoms such as palpitations, exertional chest pain, or syncope should also warrant exploration of pulmonary vascular disease.

Physical signs of PH are usually subtle, even in patients without chronic lung disease. An increase in the pulmonic component

Table 2. Diagnostic Tests for Evaluating Pulmonary Hypertension in Pulmonary Fibrosis

Test	Findings Consistent With PH
PFTs	Decreased DLCO Decreased O_2 saturation
6-minute walk test	Decreased walking distance Fall in O_2 saturation
BNP	Plasma BNP level >18 pg/ml
TTE	Dilated RV or RA RVSP >40 Increased IVC pressure
HRCT	Increased PA diameter Increased RV size, septal bowing
Formula to predict mPAP*	mPAP >21 mm Hg

PFTs – pulmonary function tests, BNP – brain natriuretic peptide, TTE – transthoracic echocardiogram, HRCT – high resolution computed tomography, RVSP – right ventricular systolic pressure, IVC – inferior vena cava, mPAP – mean pulmonary artery pressure.

*mPAP = 11.9 + 0.272 x SpO_2 + 0.0659 x $(100\text{-}SpO_2)^2$ + 3.06 x (FVC%/DLCO%)

of the second heart sound, heard best over the left sternal border, may indicate that PAP is elevated. Elevation of RVSP may lead to the onset of a tricuspid regurgitant murmur, usually heard best over the right sternal border during systole. A fall in oxygen saturation, especially during exercise, may be another clue that PAP has risen to abnormal levels. Signs of elevated right heart pressure such as jugular venous distension, lower leg edema, or a right ventricular heave indicate a significant increase in right ventricular afterload. Signs of overt right heart failure may be uncommon in patients with PH associated with IPF, presumably because the adverse affect of mild to moderate PH on patient survival precludes the time needed to develop severe heart failure. Thus, the clinician must remain on the lookout for subtle changes in the patient's symptoms or signs that could herald the advent of significant PH.

Although noninvasive diagnostic tests have limited sensitivity and specificity for identifying PH, they are easier to obtain, more economical, and safer for the patient and should be used to help develop an index of suspicion for PH in patients with IPF (**Table 2**). As mentioned previously, neither the prevalence nor severity of PH in IPF correlates well with functional vital capacity or total lung capacity.[12] However, DLCO and other indices of impaired gas exchange have been shown to be lower in IPF patients with PH than in those with normal PAP.[12,23] In one study,[23] IPF patients with PH had significantly lower 6-minute walking distance (143.5 +/- 65.5 vs 365.9 +/- 81.8 m; $P<0.001$) and lower O_2 saturation nadir during 6-minute walk test (80.1 +/- 3.7% vs 88.0 +/- 3.5%, $P<0.001$) than those without PH. Interestingly, IPF patients with PH were nearly 4-fold more likely to require supplemental oxygen (66.7% vs 17.6%, $P<0.0001$) than those without. One method of trying to discern the contribution of parenchymal vs pulmonary vascular disease to a patient's lung disease has been to examine the ratio of forced vital capacity (FVC)/DLCO. In patients with scleroderma-related lung disease, some studies have found that PH is more common when the ratio of the percent predicted FVC/DLCO rises above 1.4.[24] The ability of this ratio or higher levels of FVC/DLCO to predict PH in IPF has not been confirmed in patients with PH associated with other ILDs.[12] However, one group of investigators recently developed a formula that utilizes both the O_2 saturation and FVC/DLCO to predict mean PAP in patients with IPF (see **Table 2**).[25] In a validation study of 60 patients with IPF from 2 centers, the sensitivity, specificity, and positive and negative predictive values were 95%, 58%, 51%, and 96%, respectively, for PH defined as mean PAP from RHC >25 mm Hg.[26]

Brain natriuretic peptide (BNP) is a cardiac hormone that is normally present in very low concentration in peripheral blood but rises in patients with chronic right or left heart failure. Plasma BNP levels correlate with PAP and can be useful as a screening tool for patients at high risk of developing elevated PAP. In a study by Leuchte et al,[27] mean PAP in 12 IPF patients with elevated plasma BNP levels was nearly twice that of 16 patients with normal BNP levels (22.88 ± 1.65 vs 39.83 ± 4.45 mm Hg, $P=0.001$) and CO was significantly lower (5.85 ± 0.24 vs 4.4 ± 0.34 L/min; $P<0.05$). Using a cutoff level of 18 pg/ml, plasma BNP was able to predict the presence of PH in patients with ILD with a sensitivity of 100% and specificity of 89%. Further studies are needed to confirm these findings, but BNP may be a helpful test in screening patients with IPF and signs of PH.

Transthoracic echocardiography remains the most convenient method of estimating PAP and right heart function. Dilation of the right atrium or ventricle, particularly with normal size left sided heart chambers, strongly suggests increased RV afterload. In particular, bowing of the intraventricular septum toward the left ventricle during diastole suggests RV overload. The RVSP can be estimated by using Doppler ultrasound to measure the speed of the regurgitant tricuspid jet. In patients free of parenchymal lung disease, estimates of peak PAP obtained by TTE have been shown to correlate well with PAP measured during RHC. Unfortunately, the accuracy of TTE in estimating PAP in patients with IPF has not been as good. Arcasoy et al[28] examined the ability of TTE to measure PAP in a large cohort of patients being evaluated for lung transplant over a 10-year period. They identified 374 patients who had TTE and RHC within 72 hours, 106 of whom had ILD. Only 54% of the ILD patients had an adequate tricuspid regurgitant jet to assess peak PAP. Although peak PAP estimated by TTE correlated with that measured by RHC, the difference in measurements was less than 10 mm Hg in only 37%. In their study, the sensitivity and specificity of TTE for predicting the presence of PH in ILD was 85 and 17% and the negative predictive value was only 44%. Thus, patients diagnosed with PH by TTE were often found to have normal PAP at RHC and over half of the patients without PH on TTE were found to have PH at RHC. These findings demonstrate the marked limitation of TTE to screen for or exclude the presence of meaningful PH in patients with IPF. As such, the physician must depend on his or her level of suspicion to determine which patients should proceed to RHC.

Computed tomography of the chest is another imaging technique that has been used to predict the presence of PH. Patients with chronic elevation of PAP often display enlarged proximal pulmonary arteries and signs of RV enlargement and leftward shifting of the intraventricular septum may be seen as well. Unfortunately, this modality has not been successful in identify-

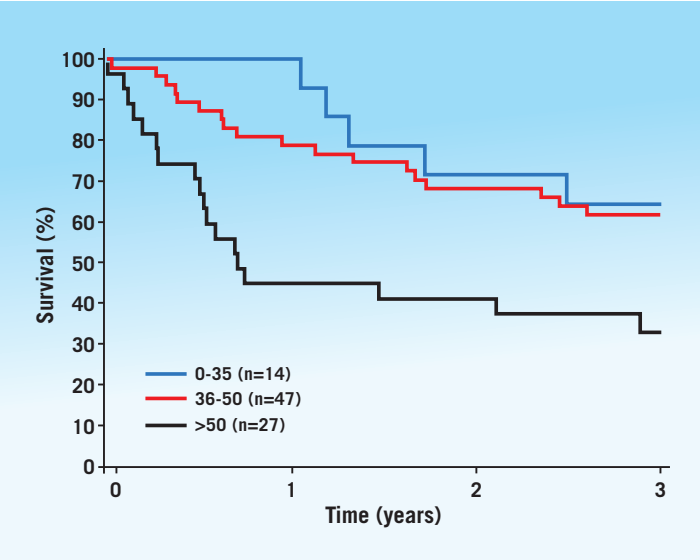

Figure 3. Effect of systolic pulmonary arterial pressure on 3-year survival as estimated by Kaplan-Meier survival curve for 88 patients with IPF (see reference 8).

ing patients with PH associated with IPF. In one study of 65 patients with IPF who underwent high-resolution chest CT within 1 month of RHC, neither the diameter of the main pulmonary artery nor the ratio of pulmonary artery to aorta diameter differed between IPF patients with PH and those without.[29] Although correlation between pulmonary artery diameter on chest CT and PAP pressure measured at RHC has not been good,[29] the routine use of high-resolution chest CT to evaluate parenchymal lung disease in patients with IPF provides a readily available assessment of pulmonary vascular structures. Whereas findings of normal pulmonary artery caliber do not exclude the presence of PH, enlarged pulmonary artery or a progressive increase in pulmonary artery diameter on serial scans can alert the clinician to the possibility of concomitant PH. High-resolution chest CT may also reveal alternative diagnoses that are associated with PH such as sarcoidosis or pulmonary veno-occlusive disease.

Right heart catheterization remains the gold standard for evaluating PH in patients with IPF. In addition to providing an accurate measurement of PAP, RHC allows determination of CO and calculation of PVR. Right atrial pressure (RAP) and right ventricular end diastolic pressure (RVEDP) can also be measured and are essential for proper interpretation of PAP in pulmonary vascular disease.[30] For example, even a moderate elevation in PAP can indicate severe PH if it occurs in the setting of increased RAP, RVEDP, and decreased cardiac output. Right heart catheterization also allows measurement of pulmonary venous pressure, which is important in the evaluation of PH associated with IPF as up to 16% of patients with IPF had elevated pulmonary artery occlusion pressure in one study.[12]

Management of Pulmonary Hypertension in Patients With Pulmonary Fibrosis

The presence of PH in IPF has a significant adverse affect on patient outcome, with a median survival as short as 1-2 years (**Figure 3**).[8,23] Thus, considerable interest has been generated over the idea of treating PH associated with IPF with pulmonary antihypertensive medications. The development of numerous drugs targeting 3 different pathways that modulate abnormal pulmonary vascular remodeling over the last 15 years has provided clinicians with a large number of weapons to attack this disease. Many of the clinical trials that validated the effectiveness of these medications in PAH included some patients with mild or moderate pulmonary fibrosis. However, virtually all of these trials sought to exclude PH associated with IPF and excluded patients with evidence of moderate to severe reductions in lung volumes. As such, the effectiveness of any of the presently approved therapies for PAH in the management of PH associated with IPF is not known. Additional studies that address the efficacy of these agents in PH associated with pulmonary fibrosis are badly needed. In the meantime, findings from a handful of small studies have begun to suggest that some pulmonary antihypertensive drugs may have beneficial effects.[31]

Ghofrani et al[32] randomized 16 patients with PH associated with pulmonary fibrosis to receive either 50 mg oral sildenafil or intravenous epoprostenol at the maximum tolerated dose. They found that the PVR index was reduced to a similar degree by both agents (-32.5% and 36.9%, respectively) but that the ratio of pulmonary to systemic vascular resistance decreased only in those patients given sildenafil. Alterations in V/Q matching are a potential concern with the use of pulmonary arterial vasodilators in the setting of chronic lung disease, and in this study, prostacyclin increased right-to-left shunt from 4.8% to 16.8% and perfusion to low V/Q areas from 0.1% to 3.8%, resulting in a decrease in arterial oxygenation. However, treatment with sildenafil was associated with a decrease in right-to-left shunt (4.8%-3.3%) without affecting V/Q matching and raised PaO_2 by an average of 14.3 mm Hg (range -1.7 to 31.3 mm Hg). The effect of long-term sildenafil administration on PH associated with chronic lung disease was examined in a small study of 7 patients (4 with COPD and 3 with IPF) who had TTE, RHC, and 6-minute walk test before and after 8 weeks of sildenafil 50 mg 3 times daily.[33] The PVR decreased in all 3 patients with IPF and their 6-minute walking distance increased. The beneficial effect of sildenafil on 6-minute walking distance was observed again in a later, open-label study of 14 patients with IPF and PH determined by RHC (10 patients) or TTE (4 patients).[34] Eleven of the 14 patients completed 6-minute walk tests before and after 3 months of therapy. The mean improvement in 6-minute walk distance was 49.0 m (90% confidence interval, 17.5 to 84.0 m), and 8 of the 14 increased their 6-minute walk distance more than 20% from baseline. Although the efficacy of sildenafil or other phosphodiesterase type 5 inhibitors in treating PH associated with IPF has not been demonstrated in randomized controlled trials, encouraging results from these studies have created a moderate level of enthusiasm for their potential use in these patients.[35]

Encouraging results have also been reported with iloprost in patients with pulmonary fibrosis. Olchewski et al[36] compared the acute effects of inhaled nitric oxide and inhaled iloprost to intravenous epoprostenol or oral calcium channel antagonists in 8 patients with PH associated with IPF. Iloprost decreased mean PAP from 44.1 +/- 4.2 to 31.6 +/- 3.1 mm Hg, and PVR from 810 +/- 226 to 386 +/- 69 dyn. s. cm(-)(5) ($P<0.05$, respectively) without affecting systemic arterial pressure, arterial oxygen saturation, or intrapulmonary shunt fraction. Similar results were seen in response to inhaled nitric oxide, but both intravenous prostacyclins and calcium channel antagonists caused a fall in systemic arterial pressure and prostacyclin infusion increased intrapulmonary shunt. Long-term treatment with inhaled iloprost was given to one patient and resulted in marked clinical improvement.

Considerable enthusiasm for the use of endothelin receptor

antagonists to treat PH associated with IPF was generated by the idea that overexpression of ET-1 may mediate the pathogenesis of both diseases. Initial findings from the **B**osentan **U**se in **I**nterstitial **L**ung **D**isease (BUILD) trials suggest a favorable effect of bosentan in slowing disease progression. In the first trial, BUILD-1, 158 patients were randomly assigned to receive bosentan (n=74) or placebo (n=84).[37] The primary efficacy endpoint was change in 6-minute walking distance. No difference was seen compared to placebo up to Month 12, but there was a trend toward increased time to death or disease progression in favor of bosentan that was more pronounced in a subgroup of patients diagnosed by open lung biopsy. There were also trends toward improvement in dyspnea and quality of life that favored bosentan. Similar results were seen in the BUILD-2 study that examined the effect of bosentan on pulmonary fibrosis associated with scleroderma. The BUILD-3 study is a larger 2:1 (bosentan to placebo) randomized controlled trial with a primary endpoint of time to disease worsening or death that enrolled 616 patients with IPF. Enrollment was completed in November 2008, and final results are expected by the end of 2009. Although neither of these trials was designed to look specifically at IPF patients with PH, it is likely that PH will be present in many of the patients enrolled. If bosentan is able to delay time to occurrence of disease worsening, it may have a role in the treatment of IPF-associated PH.

Lung transplantation remains an important option for the patient with progressive IPF whether or not PH is also present. Indeed, biopsy-proven usual interstitial pneumonitis is an indication for referral to a lung transplant center.[38] The presence of PH does not preclude lung transplantation in patients with pulmonary fibrosis, although it may result in double rather than single lung transplant approach. Patients with PH and IPF should be considered for transplant at an earlier stage than IPF patients with normal PAP, as the prognosis of the former is worse and time to clinical worsening shorter.

Conclusion

In summary, PH is commonly associated with IPF and its presence adversely affects functional capacity and survival. Whether PH occurs in this setting as an unavoidable complication of progressive lung injury or as a separate disease process, perhaps incited by the chronic inflammatory state, is unknown and continues to be an area of active research. Diagnosis of PH in IPF is complicated by the similarity of symptoms and physical findings in both diseases and hampered by the lack of an accurate, readily accessible, noninvasive test. Clinicians caring for patients with IPF should have a high level of suspicion for PH, especially in patients whose dyspnea or exercise intolerance appears to be out of proportion to their underlying lung disease or in those who deteriorate with no evidence of progression of their pulmonary fibrosis. Presently available treatments for PH have not been well studied in patients with IPF, but phosphodiesterase inhibitors and inhaled prostacyclins have shown acute beneficial effects on hemodynamics and oxygenation. The judicious use of these agents in the appropriate patient with careful follow-up of exercise capacity and gas exchange seems prudent until larger studies have been completed.

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