

Should We Screen for Pulmonary Hypertension at the Initial Evaluation of Idiopathic Pulmonary Fibrosis?

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Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease that leads to respiratory failure and death with a median survival of 2.5–3 years from the time of diagnosis [1]. Progress has been made recently in the diagnosis [2] and evaluation of prognosis [3, 4]. An accurate evaluation of the risk of death is essential to inform patients and help transplant decisions in subjects less than 60–65 years old who have limited comorbidities. Although pirfenidone and nintedanib have recently been shown to reduce the rate of decline in lung function in patients with mild-to-moderate IPF [5, 6], the management of advanced disease remains mostly supportive especially when lung transplant is contraindicated.

Pulmonary hypertension (PH) is relatively frequent in patients with advanced chronic respiratory disorders including IPF [7] and other chronic lung diseases including chronic obstructive pulmonary disease [8]. Because all these conditions create hypoxia, they are considered as separate entities according to the etiologic classification of PH (group 3) [9]. When present in the setting of IPF, PH is associated with increased dyspnea, decreased exercise capacity, greater oxygen requirements, lower diffu-

ing capacity of the lung for carbon monoxide (DLCO) and reduced survival [7, 10]. However, the prevalence of PH in IPF varies depending upon the procedures, diagnostic algorithm, definition used, and the severity of the underlying parenchymal impairment. Hemodynamic data are mainly available in the setting of patients with severe disease, who are referred for lung transplant and routinely undergo right-heart catheterization (RHC) – a mandatory procedure to diagnose precapillary PH. Precapillary PH (defined by a mean pulmonary artery pressure (mPAP) of 25 mm Hg or greater and a pulmonary artery wedge pressure of 15 mm Hg or less) is present in 32–46% of IPF patients evaluated or listed for lung transplant [10–13]. In addition, severe PH (mPAP \geq 40 mm Hg) is present in 2–10% of patients [10, 11].

In contrast, because no specific therapy for PH is recommended in chronic respiratory diseases, and because the practical consequences of detecting PH at an early stage are unclear, very few studies have focused on PH in IPF patients with moderate functional impairment. In a series of 61 patients with IPF [14] who underwent RHC at initial evaluation, a value of mPAP greater than 17 mm

Hg was associated with a higher relative risk of mortality within 5 years. Patients had mild-to-moderate IPF, with a mean value of forced vital capacity (FVC) of 76% of predicted and a mean DLCO of 45% of predicted. Interestingly, FVC did not differ between patients with an mPAP lower or greater than 17 mm Hg, suggesting that the development of PH may be related to remodeling of the pulmonary arteries independent of the severity of lung fibrosis or hypoxemia.

In the present issue of *Respiration*, Kimura et al. [15] report on the prevalence of PH as assessed by RHC at the initial evaluation of 101 patients with mild-to-moderate functional impairment (mean FVC: 70% of predicted; mean DLCO: 48% of predicted; mean 6-min walk distance: 527 m; mean PaO₂ at room air: 79 mm Hg). PH defined as mPAP greater than 25 mm Hg was present in 14.9% of patients (and >35 mm Hg in 5%), highlighting that PH can develop in IPF patients without chronic hypoxia and/or severe capillary destruction. It is likely that the pathophysiology of pulmonary vascular remodeling in patients with IPF is complex and multifactorial and not limited to vascular destruction in fibrotic areas [16–18], involving local and systemic inflammatory processes, environmental factors including tobacco smoking and probably still unknown genetic predisposition.

Furthermore, 19.8% of patients in this series had borderline values of mPAP (e.g. between 21 and 25 mm Hg) [15]. Further, receiver operating curve analysis demonstrated that a cutoff of 20 mm Hg for mPAP best predicted survival, with a median survival of 20.8 months in patients with mPAP greater than 20 mm Hg compared to 37.5 months in those with mPAP not greater than 20 mm Hg ($p = 0.001$). In contrast to previous work [14], the prognostic value of this cutoff was confirmed using multivariate analysis, with FVC being another independent predictor of prognosis (as demonstrated in numerous previous studies). Furthermore, mPAP greater than 20 mm Hg was associated with lower DLCO, lower PaO₂ and a 100-meter reduction in 6-min walk distance. This does not demonstrate that a threshold of 20 mm Hg should be used to define PH in IPF; however, the area under the curve was rather low (0.679) and a prospective evaluation in independent studies is definitely required. There is accumulating evidence that borderline mean pulmonary pressures may be clinically relevant in patients with systemic sclerosis; the study by Kimura et al. [15] indicates that the relevance of mildly elevated pulmonary pressures also warrants further scrutiny in the context of IPF.

Unfortunately, this study suffers from a number of limitations [19], including its retrospective design with a

large number of missing data (101 out of 172 patients could be evaluated) [15] and possible selection and evaluation bias. Pulmonary artery wedge pressure was significantly more elevated in patients with mPAP greater than 20 mm Hg, suggesting that coexisting left heart disease (a frequent finding in the context of IPF) may have contributed to PH. Further, the lack of a review of chest imaging precluded the appropriate evaluation of the proportion of patients who may have had significant emphysema at computed tomography of the chest, as suggested by the imbalance in the proportion of smokers and the preservation of lung volumes together with decreased DLCO in some patients. Indeed, the syndrome of combined pulmonary fibrosis and emphysema is associated with a high risk of PH carrying a dismal prognosis [20–22], and must be taken into account whenever assessing PH in the setting of IPF.

Beyond the important findings that PH is frequent and clinically relevant in IPF, the study by Kimura et al. [15] raises the question of systematic screening for PH at the initial evaluation of IPF. As RHC cannot be performed routinely in all patients diagnosed with IPF and during follow-up, an appropriate method remains to be found to screen for PH. Indications for RHC in the setting of IPF have been proposed [7] and remain to be evaluated. Currently, RHC may be reserved for patients who exhibit signs and symptoms of right-heart dysfunction, including clinical worsening disproportionate to ventilatory impairment (especially in the context of DLCO lower than 40% predicted and/or combined emphysema). RHC may also be warranted in patients being evaluated for lung transplantation, when an accurate prognostic assessment is critical, when off-label treatment is considered due to severe PH at echocardiography, and in selected cases with suspected diastolic dysfunction. Transthoracic echocardiography is generally performed prior to RHC although the measurement of tricuspid regurgitation velocity might be difficult and imprecise [23]. Beside the prognostic impact, would the early diagnosis of PH influence the management of patients recently diagnosed with IPF, e.g. would it lead to changes in therapy that may improve their functional status or survival? If PH contributes to poor prognosis in IPF even with mild restrictive physiology, it would be reasonable to expect that therapies targeting vascular remodeling would offer a viable approach. PH-specific therapy in this indication, however, has not demonstrated a clear benefit in prospective studies using phosphodiesterase-4 inhibitors [24–26], endothelin-1 receptor antagonists [27], and the recently developed stimulator of soluble guanylate cyclase riociguat [28]. It is also impor-

tant to emphasize that vasodilators used in the treatment of PH can have deleterious effects on gas exchange. In addition, the endothelin receptor antagonist ambrisentan has proven deleterious in patients with IPF [27] and must be avoided in this setting. Further trials are necessary in PH associated with IPF, and it may prove necessary in the future to better characterize the subgroup of patients who could benefit from PH-specific therapies, presumably among subjects with disproportionate elevation of pulmonary vascular resistance as compared to the severity of pulmonary fibrosis and restrictive physiology.

Notwithstanding the limitations, this observational study sheds new light on the prognostic impact of early pulmonary vascular remodeling in patients with IPF. PH is an essential part of the assessment of disease severity, and a mild elevation of mPAP (borderline PH) may be associated with a shorter survival. Prospective studies are needed to determine the best methods to screen for PH in

IPF, and the potential efficacy of PH therapy to improve the functional status and prognosis of patients must be carefully evaluated by randomized, controlled studies. Both conditions are necessary before the routine screening for PH may be considered in all patients with IPF.

Financial Disclosure and Conflicts of Interest

Dr. L. Savale has relationships with the drug companies Actelion, Bayer, GSK and Pfizer. In addition, he has been an investigator in trials of these companies; his relationships have also included consultancy services.

Dr. L. Bertoletti has received fees for speaking from Actelion, GSK and Pfizer (in the field of pulmonary hypertension).

Dr. V. Cottin has received fees for speaking from Actelion, Bayer, Boehringer Ingelheim, GSK, Intermune, Lilly, Novartis and Pfizer; he has been an investigator in clinical trials of these companies and has served on their advisory boards.

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