



The unmet medical need of pulmonary hypertension in idiopathic pulmonary fibrosis

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Prospective studies are needed for noninvasive detection of pulmonary hypertension in patients with IPF <http://ow.ly/Yydw30hoGqk>

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Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) greater or equal to 25 mmHg, and is a frequent complication in patients with idiopathic pulmonary fibrosis (IPF) [1], especially at an advanced stage of the disease, or when emphysema is associated, as in the syndrome of combined pulmonary fibrosis and emphysema [2]. At diagnosis, 8% to 15% of patients with IPF may already have precapillary PH [3], a proportion which rises up to 30% to 50% of patients at the time of evaluation for lung transplantation [4–7]. The frequency of PH further increases with comorbidities such as obstructive sleep apnoea, thromboembolism or cardiac diastolic dysfunction [8]. PH, when present, is associated with dramatic worsening of shortness of breath, greater oxygen requirements, more severe limitation to exercise capacity and increased mortality [4, 8–10]. PH in IPF (group 3 of the World Health Organization pulmonary hypertension classification [11]) is usually of mild or moderate haemodynamic severity, although 2–10% of patients have a mean PAP greater than 35–40 mmHg [3–5].

Given the relentless, progressive nature of IPF, despite the impact of antifibrotic drugs on disease course, and the impact of PH on morbidity and survival, it is not surprising that efforts are being made to detect PH as early as possible in patients with IPF, and that research is being conducted to treat precapillary PH when present. Unfortunately, there is no validated screening tool for PH in the setting of interstitial lung disease. Right heart catheterisation (RHC) is the gold standard for the diagnostic confirmation of PH, used in some studies at the time of diagnosis of IPF [3], but it is not appropriate as a routine screening tool because it is invasive. RHC is currently recommended in patients with lung disease if organ transplantation is considered, if pulmonary arterial hypertension or chronic thromboembolic PH is suspected, in case of episodes of right heart failure, of inconclusive echocardiographic findings with a high level of suspicion and potential therapeutic implications [12], and in selected cases with suspected diastolic

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left ventricular dysfunction [8] where certainty of assessment of pulmonary capillary wedge pressure is needed. Echocardiography is the most widely used noninvasive method to assess for PH; however, it has low accuracy in patients with advanced respiratory diseases [7, 13, 14], and possible over- or under-estimation of right ventricular systolic pressure by the systolic tricuspid regurgitation velocity at Doppler [13]. Pulmonary function parameters and novel echocardiography parameters have also been studied as noninvasive predictors of PH in IPF; however, they are not discriminant enough to be used alone [15, 16]. The combination of multiple echocardiographic signs of right heart dysfunction might increase predictive accuracy. Among other potential tools, the pulmonary artery diameter to ascending aorta diameter ratio (PA/Ao) on chest computed tomography may be useful [14], and is predictive of subsequent mortality [17].

Given the insufficient discrimination ability of the parameters studied alone, several groups have proposed scoring systems or a combination of parameters to screen for PH in patients with IPF. ZISMAN *et al.* [6] have created a formula to estimate mean PAP based on pulse oximetry (SpO_2), percent predicted forced vital capacity (FVC) and percent-predicted diffusing capacity ($DLCO$). The equation $mPAP = -11.9 + 0.272 \times SpO_2 + 0.0659 \times (100 - SpO_2) + 3.06 \times (\%FVC / \%DLCO)$ had a sensitivity of 71% and a specificity of 81% to predict PH in patients with IPF [6], and a sensitivity of 95% and a specificity of 58% in a different cohort [16]. ALKUKHUN *et al.* [14] found that a combination of worse right ventricular function at echocardiography, higher PA/Ao ratio, and a rightward QRS axis deviation at ECG independently predicted precapillary PH with a c-index of 0.86 (0.76–0.92). However, these tools have not been validated in prospective cohorts and may arguably not be easy to use routinely.

In this issue of the *European Respiratory Journal*, FURUKAWA *et al.* [18] in Japan have revisited this challenge with the aim of providing clinicians with a simple scoring system to predict elevated PAP in IPF. They select a cut-off of mean PAP ≥ 21 mmHg, which is in the realm of “borderline PH” (mean PAP 21–24 mmHg) at elevated levels of pressure that are above normal values, but below diagnostic PH criteria. Based on a retrospective single centre cohort of 273 treatment-free patients with IPF who had undergone RHC at initial evaluation, they have used logistic regression to create a screening tool for the prediction of elevated mean PAP at RHC. They have created a simple score based on three variables: $DLCO < 50\%$ of predicted value, PA/Ao ratio ≥ 0.9 , and $PaO_2 < 80$ mmHg. Inter-rater variability for PA/Ao ratio ≥ 0.9 was good, with an intraclass correlation coefficient of 0.706. A score of 3 (with the three criteria present) had a specificity of 95.8% and a negative predictive value of 85.1%.

TABLE 1 Main randomised controlled clinical trials using drugs approved for pulmonary arterial hypertension (PAH) in idiopathic pulmonary fibrosis (IPF) and IPF associated with pulmonary hypertension (PH)

	Drug tested	Primary outcome	Result
Trials targeting IPF with drugs approved in PAH			
STEP-IPF [22]	Sildenafil	Proportion of patients with >20% increase in 6-min walk distance	Negative on primary outcome, some positive effect on secondary and exploratory end-points
ARTEMIS-IPF [23]	Ambrisentan	Time to disease progression, defined as death, respiratory hospitalisation, or a categorical decrease in lung function	Deleterious effect
BUILD-1 [24]	Bosentan	6-min walk distance	Negative
BUILD-3 [25]	Bosentan	Time to IPF worsening (a confirmed decrease from baseline in FVC $\geq 10\%$ and $DLCO \geq 15\%$, or acute exacerbation of IPF) or death	Negative
MUSIC [26]	Macitentan	FVC	Negative
Trials targeting IPF-PH with drugs approved in PAH			
ARTEMIS-PH (NCT00879229)	Ambrisentan	6-min walk distance	Terminated early
RISE-IIP [27] (results unpublished)	Riociguat	6-min walk distance	Terminated early
BPHIT [28]	Bosentan	Indexed pulmonary vascular resistance	Negative

FVC: forced vital capacity; $DLCO$: diffusing capacity of the lung for carbon monoxide.

This novel tool contributes to the better noninvasive detection of PH in IPF. Unfortunately, the study suffers from limitations, including its retrospective design, and the absence of external validation, although some internal validation was assessed using a bootstrap method. It is debatable whether the proposed score really is easier to perform for the clinician than previous ones [6, 14]. More importantly, the score was designed to predict a mean PAP ≥ 21 mmHg, and not a threshold of ≥ 25 mmHg, which defines PH as per international guidelines [12]. Although the same group has previously demonstrated that a mean PAP ≥ 21 mmHg predicts mortality in patients with IPF [3], the choice of 21 mmHg as a threshold is highly controversial, since it is unlikely that the findings would therefore translate into management decisions. It is unknown whether the finding of a mPAP > 21 mmHg might predict the future development of more severe PH, and, indeed, whether pre-emptive use of PH therapies may even prevent this. There were very few patients in this cohort with confirmed PH, and especially with severe PH, and the findings may not apply to a population of patients with more advanced IPF and higher prevalence of PH. As the indication to perform RHC was not mentioned in the manuscript, other than being part of their “initial evaluation” protocol, the applicability of the findings based on the study population may be limited.

Although the specificity of the score was relatively good when all three parameters were present, the scoring system had remarkably low sensitivity to detect PH, with a sensitivity varying from 13.2% to 32.1% for a score of 0 to 3, challenging the usefulness of the tool to screen for PH. Similarly, the positive predictive value was not more than 65.4% for a score of 3, suggesting that in a significant proportion of cases elevated mean PAP would not be confirmed by RHC.

The main limitation of detecting PH in IPF, however, is that so far the approaches taken to tackle vasculopathy in IPF have been deceptive. Indeed, several randomised controlled clinical trials have been conducted to target either the progression of IPF, or haemodynamic or clinical parameters in patients with IPF or IPF-PH, respectively (table 1). Of particular concern, no haemodynamic improvement was found as compared to placebo in subjects with IPF-PH who received a drug approved for pulmonary arterial hypertension; this suggests that PH drugs might not improve the vasculopathy in IPF, which would explain the absence of clinical improvement. In patients with PH due to chronic lung diseases, guidelines recommend optimal treatment of the underlying lung disease, including supplemental long-term oxygen therapy [12].

Despite negative results of trials, a glimpse of hope has come from registries demonstrating haemodynamic improvement in a proportion of patients with IPF-PH [19] and possibly survival with sildenafil [20], suggesting that we may not yet have used the right drug in the right target population and with the right study endpoint. Importantly, no trials have been performed in the subgroup of patients with severe PH associated with IPF or combined pulmonary fibrosis and emphysema, defined by a mean PAP > 35 mmHg, or ≥ 25 mmHg in the presence of low cardiac output (cardiac index < 2.5 L·min⁻¹, not explained by other causes) [12]. It remains to be explored whether PH drugs may provide some benefit in subgroups of patients with IPF-PH especially those with the most severe vasculopathy and relatively preserved lung volumes [21]. Furthermore, trials until now have tested various end-points, and it is conceivable that these may not be appropriate. Interestingly, several trials are currently evaluating the potential use of sildenafil as add-on therapy in IPF in addition to available antifibrotic drugs, in patients with probable PH (assessed noninvasively), using pirfenidone (clinicaltrials.gov NCT02951429) or nintedanib (clinicaltrials.gov NCT02802345).

In conclusion, the study by FURUKAWA *et al.* [18] adds a small stone to building a potential algorithm to detect and possibly manage PH in IPF. Precapillary PH is unlikely in patients with a score of 0, therefore obviating the need to perform a RHC. Precapillary PH has a higher probability to be confirmed at RHC in patients with a score of 3, but this has limited practical consequences in the absence of therapeutic indication and, especially, absence of demonstrated efficacy of drugs approved to treat pulmonary artery hypertension. Indeed at the threshold of mPAP > 21 mmHg, the degree of PH is likely to reflect the underlying lung disease (including the effect of coexistent emphysema) rather than an independent pulmonary vasculopathy. Prospective studies are still needed to determine the best methods to detect PH in IPF, and more importantly, to explore whether a selected group of patients with IPF-PH might benefit from the management of PH with innovative strategies.

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