



Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant

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ABSTRACT: Pulmonary hypertension (PH) may complicate idiopathic pulmonary fibrosis (IPF) but the prevalence of PH in IPF remains undefined. The present authors sought to describe the prevalence of PH in IPF.

The lung transplant registry for the USA (January 1995 to June 2004) was analysed and IPF patients who had undergone right heart catheterisation (RHC) were identified. PH was defined as a mean pulmonary arterial pressure (\bar{P}_{pa}) ≥ 25 mmHg and severe PH as a $\bar{P}_{pa} > 40$ mmHg. Independent factors associated with PH were determined.

Of the 3,457 persons listed, 2,525 (73.0%) had undergone RHC. PH affected 46.1% of subjects; ~9% had severe PH. Variables independently associated with mild-to-moderate PH were as follows: need for oxygen, pulmonary capillary wedge pressure (P_{pcw}) and forced expiratory volume in one second (FEV₁). Independent factors related to severe PH included the following: carbon dioxide tension, age, FEV₁, P_{pcw} , need for oxygen and ethnicity. A sensitivity analysis in subjects with $P_{pcw} < 15$ mmHg did not appreciably alter the present findings.

Pulmonary hypertension is common in idiopathic pulmonary fibrosis patients awaiting lung transplant, but the elevations in mean pulmonary arterial pressure are moderate. Lung volumes alone do not explain the pulmonary hypertension. Given the prevalence of pulmonary hypertension and its relationship with surrogate markers for quality of life (e.g. activities of daily living), future trials of therapies for this may be warranted.

KEYWORDS: Epidemiology, haemodynamics, idiopathic pulmonary fibrosis, pulmonary hypertension

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown aetiology associated with progressive parenchymal fibrosis [1]. Patients with IPF face substantial morbidity and mortality, and report substantially impaired quality of life [2]. Lung transplant (LT) represents the lone intervention that potentially improves survival in IPF [3].

Pulmonary hypertension (PH) is evolving as an important factor that can adversely affect outcomes in chronic lung disease. In advanced chronic obstructive pulmonary disease (COPD), therapy directed at controlling the pulmonary artery pressure has been recommended [4]. In fibrotic lung diseases more akin to IPF, such as sarcoidosis, secondary PH is common and is a marker for early death [5, 6].

Less is known about PH in IPF. Epidemiologically, several retrospective analyses indicate that PH in IPF may be frequent [7–9]. Illustrating the emerging interest in PH and IPF, GHOFrani *et al.* [10] examined the impact of sildenafil on pulmonary haemodynamics in lung fibrosis and

concluded that it caused pulmonary vasodilation and improved gas exchange. Others have also explored inhaled agents in IPF related to PH [11].

With the advent of newer options for treating PH, coupled with the lack of effective therapies for IPF, targeting PH appears attractive. However, before studying interventions it is important to define the prevalence and extent of this process. With improved information regarding the prevalence of and clinical factors associated with PH in IPF, clinicians can better determine whom to evaluate for PH, and researchers can design more appropriate clinical trials. Thus, to explore the frequency of PH in IPF, the present authors retrospectively analysed the United States LT registry. The specific objectives were to describe the prevalence of PH in IPF, to assess the severity of PH in this population and to identify clinical variables that correlated with PH.

METHODS

Subjects

Patients with PH and IPF were identified by reviewing the LT registry maintained by the

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Received:

August 16 2006

Accepted after revision:

June 25 2007

STATEMENT OF INTEREST

None declared.

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

United Network for Organ Sharing (UNOS) and the Organ Procurement and Transplant Network (OPTN). All adult subjects listed for LT for IPF between January 1995 and June 2004 were included. The diagnoses of IPF were based on the reports of the referring transplant centre. Surgical lung biopsy was not required for the diagnosis of IPF and, given the time period covered, many patients were listed before the development of the recent consensus statement regarding the clinical diagnosis of IPF. The type of proposed LT did not affect eligibility for enrolment in the present study's cohort. Since the focus of the study was PH, patients were required to have undergone right heart catheterisation (RHC) as part of their transplant evaluation. Subjects who did not have an RHC were excluded. There were no additional exclusion criteria.

End-points

The presence of PH represented the primary end-point, while severe PH served as a secondary end-point. PH was defined as a mean pulmonary artery pressure (\bar{P}_{pa}) ≥ 25 mmHg and severe PH as a $\bar{P}_{pa} > 40$ mmHg.

Study co-variables

Information concerning demographics and pulmonary function testing was recorded. The forced expiratory volume in one second (FEV₁) and the forced vital capacity (FVC) comprised the pulmonary function measures of interest. UNOS does not maintain data regarding the diffusion capacity of the lung for carbon monoxide (DLCO) and did not begin collecting the FEV₁/FVC ratio until 1999; therefore, it was impossible to include these variables. The partial pressure of carbon dioxide (PCO₂) and the need for oxygen were also noted. For functional status, the patient's ability to walk >45 m in 6 min and the degree of assistance they required with activities of daily living (ADLs) were gauged. Although an exact distance walked would be preferred for the 6-min walk test, UNOS only records whether the patient had the ability to walk for 45 m. For comorbid diseases, the presence of hypertension, COPD and diabetes were focused on. COPD was defined based on the reports of referring centres and not based on UNOS-calculated FEV₁/FVC ratios. Information regarding the pulmonary capillary wedge pressure (\underline{P}_{pcw}) and the cardiac index were also collected. For each of the variables, the model inputs reflect information available at time of listing.

Sensitivity analysis

Due to the potential for occult left ventricular heart disease and in an effort to control for possible elevations in the \underline{P}_{pcw} directly contributing to elevations in the \bar{P}_{pa} , a sensitivity analysis was conducted in the subgroup of patients with $\underline{P}_{pcw} < 15$ mmHg. In other words, elevations of the \bar{P}_{pa} in this subgroup more properly represent isolated PH.

Statistics

Univariate analyses were performed initially. A Chi-squared test was employed to compare categorical variables. Continuous variables followed a non-normal distribution and, hence, the Wilcoxon test was utilised for comparisons. All tests were two-tailed, and a p-value < 0.05 was assumed to represent statistical significance.

All factors that were significant were entered in the univariate analysis at the ≤ 0.10 level into the model. A backwards

stepwise approach was employed. Candidate variables were removed in a stepwise fashion if $p > 0.10$. Co-linearity was assessed *via* correlation matrices. The model's goodness of fit was assessed with the Hosmer–Lemeshow statistic. The authors also reported 95% confidence intervals (CIs) around odds ratios (ORs).

RESULTS

During the 9.5-yr study period, 3,457 persons were listed for LT for IPF. The final cohort comprised 2,525 (73.0%) subjects who had RHC data available. Those who had undergone RHC were not systematically different from those who did not have an RHC in terms of either demographic characteristics, measures of pulmonary physiology, or assessments of comorbidities. The mean age of the entire study population undergoing RHC was 53.4 ± 8.7 yrs and 61.4% were male. Those not undergoing RHC had a mean age of 54.8 ± 6.3 yrs and 63.3% were male. The mean FVC in both the RHC and non-RHC populations was $\sim 50\%$. Diabetes was reported to occur in nearly 10% of all of these patients, irrespective of whether they had an RHC performed. PH was common, affecting 46.1% of all IPF patients listed for LT. Among those with PH, the \bar{P}_{pa} measured 34.2 ± 9.9 mmHg. Nearly one in 10 subjects had severe PH.

Nonsevere PH

Comparisons between those without PH and those with nonsevere PH are highlighted in table 1. Contrasting those without PH to persons with mild and moderate PH (\bar{P}_{pa} 25–40 mmHg) revealed these groups to be comparable with respect to distribution of sex, while those with mild PH elevations were slightly younger. PH was more frequent among African-Americans. Subjects with PH required more assistance with their ADLs. COPD was 1.31 times (95% CI 1.03–1.67) more prevalent in the PH cohort. Hypertension also occurred more often in persons with PH, while there was a trend towards an increased frequency of diabetes in those with PH. Corticosteroid use was common in all subjects.

The PCO₂ was marginally higher, while the FVC was slightly lower in PH subjects. However, the FEV₁ was lower in persons with PH (50.0 ± 16.5 versus $52.7 \pm 16.5\%$ predicted, $p < 0.0001$). Similarly, individuals with PH required more supplemental oxygen (2.3 ± 1.9 versus 2.9 ± 2.1 L·min⁻¹, $p < 0.0001$). Furthermore, those with PH in IPF were nearly 80% more likely (OR 1.78, 95% CI 1.50–2.11, $p < 0.0001$) to require > 3 L·min⁻¹ of oxygen. Results of invasive haemodynamic monitoring indicated that the cardiac index was equivalent between those with and without PH, although the \underline{P}_{pcw} was higher in the PH cohort.

In multivariate analysis (table 2), several variables were independently associated with the presence of PH. The need for supplemental oxygen, the \underline{P}_{pcw} and the FEV₁ correlated with \bar{P}_{pa} . Those requiring oxygen were significantly more likely to have concomitant PH (OR 1.22, 95% CI 1.14–1.30, $p < 0.001$). Similarly, a higher \underline{P}_{pcw} increased the probability that PH would be present. Neither the FVC nor the cardiac index showed a relationship with PH.

TABLE 1 Correlates of pulmonary hypertension

| Variable | $\bar{P}_{pa} < 25$ mmHg | $\bar{P}_{pa} \geq 25$ mmHg | $\bar{P}_{pa} > 40$ mmHg | p-value [#] | p-value [†] |
|--|--------------------------|-----------------------------|--------------------------|----------------------|----------------------|
| Subjects n | 1362 | 932 | 231 | | |
| Demographics | | | | | |
| Age yrs | 54.0±8.7 | 53.4±8.5 | 49.9±9.2 | 0.040 | <0.0001 |
| Male | 60.9 | 62.8 | 58.7 | 0.360 | 0.560 |
| African-American | 9.0 | 11.8 | 19.1 | 0.030 | <0.0001 |
| BMI kg·m ⁻² | 27.7±4.8 | 28.7±5.1 | 27.7±5.2 | <0.0001 | 0.870 |
| Pulmonary function | | | | | |
| FVC % pred | 49.6±15.7 | 48.4±16.7 | 51.4±20.8 | 0.020 | 0.610 |
| FEV1 % pred | 52.7±16.5 | 50.0±16.5 | 51.5±19.0 | <0.0001 | 0.30 |
| P_{a,CO_2} mmHg | 40.5±5.7 | 41.2±6.9 | 38.7±7.8 | 0.150 | <0.001 |
| 6-min walk distance <45 m | 10.3 | 13.9 | 21.1 | 0.010 | <0.0001 |
| Any need for O ₂ | 75.9 | 86.0 | 92.8 | <0.0001 | <0.0001 |
| Any need for ≥ 3 L·min ⁻¹ O ₂ | 37.3 | 51.4 | 65.4 | <0.0001 | <0.0001 |
| O ₂ used L·min ⁻¹ | 2.3±1.9 | 2.9±2.1 | 3.5±2.4 | <0.0001 | <0.0001 |
| Functional status | | | | | |
| Some or total ADL assistance | 56.7 | 63.3 | 74.4 | 0.001 | <0.0001 |
| Hospitalised | 3.9 | 5.1 | 9.7 | 0.170 | <0.0001 |
| In intensive care unit | 1.4 | 2.3 | 4.0 | 0.140 | 0.010 |
| Comorbid illnesses | | | | | |
| COPD | 12.4 | 15.7 | 16.2 | 0.030 | 0.0130 |
| Hypertension | 18.1 | 21.6 | 22.8 | 0.040 | 0.011 |
| Diabetes | 10.4 | 13.0 | 7.5 | 0.060 | 0.150 |
| Corticosteroids | 60.5 | 63.4 | 58.4 | 0.170 | 0.560 |
| Haemodynamic monitoring | | | | | |
| Cardiac index L·min ⁻¹ ·m ⁻² | 2.8±0.7 | 2.8±0.8 | 2.5±0.9 | 0.82 | <0.0001 |
| \bar{P}_{pcw} mmHg | 8.3±4.2 | 12.1±5.5 | 14.0±8.2 | <0.0001 | <0.0001 |

Data are presented as mean±SD or %, unless otherwise stated. \bar{P}_{pa} : mean pulmonary artery pressure; BMI: body mass index; FVC: forced vital capacity; % pred: % predicted; FEV1: forced expiratory volume in one second; P_{a,CO_2} : carbon dioxide arterial tension; ADL: activities of daily living; COPD: chronic obstructive pulmonary disease; \bar{P}_{pcw} : pulmonary capillary wedge pressure. #: $\bar{P}_{pa} > 25$ versus ≤ 25 mmHg; †: $\bar{P}_{pa} > 40$ versus ≤ 25 mmHg. n=2,525. 1 kPa=0.133 mmHg.

Severe PH

Comparisons between those with normal \bar{P}_{pa} values and patients with severe PH are also shown in table 1. Many of the differences seen in the analysis with the nonsevere PH subjects were noted in the comparison between those lacking PH and those with severe PH. For example, the need for both assistance with ADLs or admission to the hospital at time of listing was more common in severe PH. Hypertension was more often noted in patients with severe PH. It was concerning that ethnicity again correlated with PH. Nearly 20% of the severe PH group were African-American versus only 9% of the

non-PH population (OR 2.37, 95% CI 1.63–3.46, p<0.001). In terms of physiology, FVC failed to segregate patients with severe PH from those with normal \bar{P}_{pa} values and was, in fact, numerically higher in those with worse \bar{P}_{pa} values. The FEV1 did not differ as a function of the \bar{P}_{pa} . Interestingly, although the P_{CO_2} was higher in those with mild and moderate elevations of \bar{P}_{pa} compared with those with normal \bar{P}_{pa} values, the P_{CO_2} was lowest in the severe PH patients.

Multivariate analysis (table 3) identified several variables independently linked with severe PH. Unlike the present

TABLE 2 Independent correlates of mild-to-moderate pulmonary hypertension[#]

| Variable | Adjusted odds ratio | 95% CI | p-value |
|---|---------------------|-----------|---------|
| Need for any O₂ | 1.22 | 1.14–1.30 | <0.001 |
| \bar{P}_{pcw} per 1 mmHg increase above mean value for cohort | 1.19 | 1.16–1.21 | <0.001 |
| FEV1 per 1% increase from mean value for cohort | 0.99 | 0.99–1.00 | 0.050 |

CI: confidence interval; \bar{P}_{pcw} : pulmonary capillary wedge pressure; FEV1: forced expiratory volume in one second. The Hosmer–Lemeshow Goodness-of-Fit test yields a Chi-squared value of 14.8 (p=0.06). #: defined as mean pulmonary artery pressure between 25–40 mmHg. n=2,296. 1 kPa=0.133 mmHg.

observations in the nonsevere PH cohort, it was noted that ethnicity significantly correlated with the presence of severe PH. Specifically, African-Americans were twice as likely to have severe PH compared with Caucasians (OR 1.93, 95% CI 1.02–3.66, $p=0.043$). The need for supplemental oxygen also identified subjects who were more likely to have severe elevations in \bar{P}_{pa} . With respect to invasive haemodynamics, P_{pcw} remained a significant factor associated with a diagnosis of severe PH. While cardiac performance did not appear to be related to severe PH, age, PCO_2 and FEV₁ were independently associated with the presence of severe PH.

Sensitivity analysis

Out of the entire population, ~18% had a $P_{pcw} >15$. After excluding patients with $P_{pcw} >15$, the results of the logistic regressions to identify factors independently related to PH varied somewhat from those observed in the entire PH population. Table 4 indicates variables associated with mild-to-moderate PH not associated with an increased P_{pcw} . As seen in the overall analysis of PH, oxygen use, FEV₁ and P_{pcw} remained significantly correlated with isolated PH. Additionally, the need for assistance with ADLs and the presence of hypertension now appeared linked to mild-to-moderate PH. Table 5 reveals the findings from the multivariate analysis in persons with severe, isolated \bar{P}_{pa} elevations. Younger age along with the PCO_2 were “protective”. In general, factors independently associated with severe PH also correlated with severe, isolated PH. For example, African-Americans again faced a nearly two-fold increased probability of having severe PH. In addition to variables noted in the overall analysis of severe PH, a low 6-min walk distance and need for assistance with ADLs additionally were associated with the presence of severe, isolated PH.

DISCUSSION

This large retrospective analysis reveals that PH is common in persons with IPF awaiting LT. Although PH affects ~45% of these subjects, severe PH is relatively infrequent. Multivariate analysis indicates that several variables are independently associated with PH and severe PH, but that only three factors, FEV₁, the need for supplemental oxygen and an elevated P_{pcw} , consistently correlate with the presence of PH across varying degrees of severity. In the sensitivity analysis of persons who

meet the definition for isolated PH (e.g. elevated \bar{P}_{pa} and $P_{pcw} <15$ mmHg), FEV₁, need for assistance with ADLs, P_{pcw} and oxygen use appear linked to all degrees of this.

Several earlier analyses have gauged the prevalence of PH in IPF. KING *et al.* [7] found that 20% of those with IPF had evidence of PH. However, the presence of PH was only assessed by chest radiography [7]. In a study of 25 persons, AGARWAL *et al.* [12] determined that 36% had PH; however, these authors [12] relied only on echocardiography, which may overestimate or underestimate pulmonary arterial pressure in persons with interstitial lung disease [13]. In a larger analysis also relying on echocardiography, NADROUS *et al.* [8] concluded that PH was common in advanced IPF and that it correlated with both a lower DL_{CO} and a lower resting arterial oxygen tension [8]. The study by NADROUS *et al.* [8] was limited in that there was the potential for substantial selection bias as only 136 (28%) out of 487 of patients with IPF had undergone echocardiography [8]. Finally, relying on RHC, LETTIERI *et al.* [9] noted that PH was documented in approximately one-third of persons with IPF [9]. Additionally, these authors demonstrated that even moderate elevations of \bar{P}_{pa} (>25 mmHg) correlated with increased mortality [9].

The present analysis confirms the findings of these earlier reports and clearly demonstrates that PH is a common complication of IPF. More importantly, the present study builds on these efforts, in that it represents the largest experience with RHC in IPF. As a result, the larger sample size used herein allows more certainty as to the estimation of the prevalence of PH in IPF. Additionally, since only RHC was relied on, the estimates of \bar{P}_{pa} are likely to be more accurate than those based solely on echocardiography. Moreover, all prior studies represented the experience of single centres. Since UNOS and OPTN serve as the registry for all USA LTs, it was possible to draw on patients seen at multiple centres.

Pathophysiologically, the factors independently related to the presence of PH suggest some mechanisms as to the evolution of PH in IPF. The correlation between lower FEV₁ and PH implies that superimposed airflow limitation may accelerate potential elevations in the \bar{P}_{pa} . Furthermore, an abnormal PCO_2 may mean that underlying gas exchange abnormalities increase the risk for PH. However, for both of these factors the statistical relationships observed may not be clinically

TABLE 3 Independent correlates of severe pulmonary hypertension[#]

| Variable | Adjusted odds ratio | 95% CI | p-value |
|---|---------------------|-----------|---------|
| PCO_2 per 1-point increase | 0.92 | 0.89–0.96 | 0.0001 |
| Age at listing | 0.95 | 0.92–0.97 | <0.0001 |
| FEV ₁ per 1% increase from mean value for cohort | 0.96 | 0.93–0.99 | 0.003 |
| P_{pcw} per 1 mmHg increase above mean value for cohort | 1.22 | 1.17–1.28 | <0.001 |
| Any O ₂ needed | 1.29 | 1.12–1.49 | 0.004 |
| O ₂ need >3 L·min ⁻¹ | 1.89 | 1.03–3.47 | 0.041 |
| African-American | 1.93 | 1.02–3.66 | 0.043 |

[#]: defined as mean pulmonary artery pressure >40 mmHg. CI: confidence interval; PCO_2 : carbon dioxide tension; FEV₁: forced expiratory volume in one second; P_{pcw} : pulmonary capillary wedge pressure. The Hosmer–Lemeshow Goodness-of-Fit test yields a Chi-squared value of 7.2 ($p=0.51$). $n=1,594$. 1 kPa=0.133 mmHg.

TABLE 4 Independent correlates of mild-to-moderate isolated pulmonary hypertension

| Variable | Adjusted odds ratio | 95% CI | p-value |
|---|---------------------|-------------|---------|
| FEV ₁ per 1% increase from mean value for cohort | 0.99 | 0.990–0.997 | 0.006 |
| \bar{P}_{pcw} per 1 mmHg increase above mean value for cohort | 1.22 | 1.18–1.26 | <0.001 |
| Need for assistance with ADLs | 1.24 | 1.00–1.54 | 0.047 |
| Hypertension | 1.33 | 1.03–1.72 | 0.030 |
| O ₂ need >3 L·min ⁻¹ | 2.84 | 2.30–3.50 | <0.001 |

CI: confidence interval; FEV₁: forced expiratory volume in one second; \bar{P}_{pcw} : pulmonary capillary wedge pressure; ADLs: activities of daily living. The Hosmer–Lemeshow Goodness-of-Fit test yields a Chi-squared value of 18.1 ($p=0.02$). $n=1,883$. 1 kPa=0.133 mmHg.

meaningful; differences in the mean values for these variables across the strata of \bar{P}_{pa} values are small (e.g. 2% difference in FEV₁) and thus any correlation is likely to be speculative rather than causative. It therefore appears likely that, in IPF, additional causes for elevated \bar{P}_{pa} values exist. Other investigators have reached similar conclusions when exploring the mechanisms for PH in COPD. CHAOUAT *et al.* [14] performed extensive evaluations in persons with severe COPD and PH. Their data demonstrated that factors other than the extent of the COPD itself contributed to \bar{P}_{pa} increases [14]. With respect to COPD, patients with concurrent IPF and emphysema may be at particularly increased risk for PH. For example, COTTIN *et al.* [15] noted that nearly half of such subjects had PH. Although no such independent association between COPD and PH was found in the present study, the link between FEV₁ and PH indicates that patients with both conditions may be at high risk for PH.

The following three factors correlated with PH across the range of pressure elevations: FEV₁, the need for supplemental oxygen and \bar{P}_{pcw} . In the cohort without elevated \bar{P}_{pcw} , assistance with ADLs also appeared important. The interaction between ADLs and PH is likely to underscore the morbidity burden associated with PH. In other words, inability to perform ADLs does not cause PH but reflects the burden of this on a patient's performance status [2].

Multiple potential factors could account for the association between the need for supplemental oxygen and PH. This may indicate the impact of chronic pulmonary vasoconstriction due to alveolar hypoxia, although the connection between chronic alveolar hypoxia and pulmonary vasoconstriction has not been conclusively demonstrated. It could also represent that, due to regulations regarding the use of supplemental oxygen, these patients might simply be more likely to have oxygen prescribed as a result of underlying cor pulmonale. Conversely, PH may cause hypoxaemia due to both a low cardiac output and low central venous oxygen saturations, along with increased perfusion of pulmonary shunt vessels or low ventilation/perfusion ratio areas.

The interaction between \bar{P}_{pcw} and PH appears to be more complicated. The correlation between the two suggests that some component of left ventricular (LV) dysfunction is contributing to PH in IPF. However, several aspects of the present data reveal that more nuanced issues may be involved.

First, there was no independent relationship between CI and PH. If LV dysfunction was contributing to PH, one would predict that the CI would be lower in those with PH. Secondly, despite the association between PH and \bar{P}_{pcw} , the average \bar{P}_{pcw} s in the population were, nonetheless, in the normal range. Thirdly, the gradient between the \bar{P}_{pa} and the average \bar{P}_{pcw} in this population was higher than one would expect if this process represented passive congestion. This discordance underscores that some process other than purely LV dysfunction must be contributing to the PH. Similarly, since the population analysed is relatively selected as these subjects are felt to be candidates for LT, overt congestive heart failure is unlikely to be present. The sensitivity analysis of patients meeting criteria for isolated PH used in the present study shows a persistent relationship between \bar{P}_{pa} and \bar{P}_{pcw} . Given that, by design, these persons have no elevations of the \bar{P}_{pcw} , the elevation in \bar{P}_{pa} cannot be ascribed to passive congestion or occult LV dysfunction.

It might be hypothesised that progressive parenchymal destruction would lead to PH in IPF. However, in the present study, a strong correlation between FVC and PH was not observed. Similarly, the two other studies expressly exploring the nexus between FVC and PH, those by NADROUS *et al.* [8] and by LETTIERI *et al.* [9], also did not report a positive relationship between FVC and PH. Likewise, in an analysis of the physiology of PH in lung fibrosis, LEUCHTE *et al.* [16] did not note a correlation between PH and FVC. These results, together with data from the present study, imply that issues other than decrements in FVC contribute to PH. Alternatively, the failure of the present study to detect an interaction between FVC and PH may reflect that many subjects already had advanced IPF with low FVC. However, this is doubtful, since both the mean FVC and SD around the FVCs across all three populations studied (normal, mild-to-moderate PH and severe PH) were similar.

African-Americans faced a greater probability of suffering from severe PH. This observation is troubling, given that earlier analyses noted previously show that PH portends worse outcomes in IPF. This connection between severe \bar{P}_{pa} elevations and ethnicity might reflect later referral during the disease's natural history. However, that ethnicity independently remained strongly associated with severe PH (irrespective of the \bar{P}_{pcw}) after controlling for other conventional markers of severity of illness and performance status in IPF

TABLE 5 Independent correlates of severe isolated pulmonary hypertension

| Variable | Adjusted odds ratio | 95% CI | p-value |
|---|---------------------|-----------|---------|
| PCO_2 | 0.88 | 0.85–0.92 | <0.001 |
| Age at listing | 0.94 | 0.92–0.96 | <0.001 |
| P_{pcw} per 1 mmHg increase above mean value for cohort | 1.26 | 1.18–1.34 | <0.001 |
| 6-min walk distance <45 m | 1.71 | 1.00–2.94 | 0.050 |
| Need for assistance with ADLs | 1.78 | 1.15–2.74 | 0.010 |
| African-American | 1.78 | 1.02–3.09 | 0.042 |
| O_2 need >3 L·min ⁻¹ | 4.49 | 2.99–6.74 | <0.001 |

CI: confidence interval; PCO_2 : carbon dioxide tension; P_{pcw} : pulmonary capillary wedge pressure; ADLs: activities of daily living. The Hosmer–Lemeshow Goodness-of-Fit test yields a Chi-squared value of 5.9 ($p=0.66$). $n=1,308$. 1 kPa=0.133 mmHg.

argues against this conclusion. Differences in access to care may in some way also contribute to this finding, and this suggests that clinicians must work to ensure that there is not some form of subtle discrimination in their management of African-Americans suffering from IPF. Alternatively, differences in vascular biology could help to explain this finding. African-Americans, for instance, have been reported to respond differentially, when compared with Caucasians, to certain vasodilators administered in the treatment of heart failure [17]. Future investigations are necessary to explore the meaning and cause of this observation.

The present study has several limitations. The retrospective design exposes the analysis to bias. However, unlike the data generated in other reports dealing with PH in IPF, the UNOS/OPTN registry represents data collected contemporaneously at listing. Thus, recall bias and coding bias are unlikely. Additionally, some of the patients listed for LT for IPF may not have had IPF, but some other form of interstitial lung disease. However, the demographic distribution indicates that this is not likely, as the cohort resembles the general composition of patients with IPF. Information was also lacking on certain variables that could have been of interest, such as DL_{CO} . Consequently, the noting of a relationship between the need for supplemental oxygen and PH may simply indicate that the need for supplemental oxygen is a surrogate for a lower DL_{CO} . Finally, only patients who were actually listed for LT were studied. Information on potential subjects not evaluated for LT was not available; this limits the generalisability of the present conclusions. If the cohort included persons with less advanced IPF, it might have been possible to detect a correlation between lung function and PH. Despite these considerations, the present study is the largest experience with RHC in IPF.

In conclusion, pulmonary hypertension is common in idiopathic pulmonary fibrosis. Generally, the degree of pulmonary hypertension in idiopathic pulmonary fibrosis is mild to moderate, with few subjects developing severe pulmonary hypertension by the time of listing for lung transplant. Several clinical variables correlate with the presence of pulmonary hypertension. In light of the prevalence of pulmonary hypertension in idiopathic pulmonary fibrosis, coupled with the absence of highly effective therapies for this disease, clinical trials of agents directed at controlling the mean

pulmonary arterial pressure in idiopathic pulmonary fibrosis seem warranted.

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