Pulmonary Hypertension in Patients With Idiopathic Pulmonary Fibrosis*

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Study objectives: To determine the impact on survival and clinical correlates of pulmonary hypertension (PH) occurring in patients with idiopathic pulmonary fibrosis (IPF).

Design: Retrospective study.

Setting: Tertiary care, referral medical center.

Patients: Among 487 consecutive patients with IPF, we identified 136 patients who underwent transthoracic echocardiography within 3 months of their initial evaluation at our institution. Patients with left ventricular dysfunction, valvular heart disease, incomplete follow-up, and those in whom pulmonary artery pressures could not be assessed were excluded; the remaining 88 patients were included in this study. Correlations were performed between echocardiographic measures of PH and clinical variables including survival.

Measurements and results: The mean (± SD) estimated systolic pulmonary artery pressure (SPAP) for the 88 patients was 48 ± 16 mm Hg (range, 28 to 116 mm Hg). Among pulmonary function parameters, SPAP correlated best with diffusing capacity of the lung for carbon monoxide (DLCO), to which it was inversely related. For survival analysis, patients were stratified into three groups: ≤ 35 mm Hg (14 patients), 36 to 50 mm Hg (47 patients), and > 50 mm Hg (27 patients). Using the Kaplan-Meier method, the median survival rates for these three groups were 4.8 years, 4.1 years, and 0.7 years, respectively. Those patients with SPAP > 50 mm Hg had significantly worse survival compared to other subgroups (p = 0.009).

Conclusion: In patients with IPF, PH correlates inversely with DLCO and has a significant adverse impact on survival, particularly when SPAP is > 50 mm Hg.

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Key words: echocardiography; idiopathic pulmonary fibrosis; prognosis; pulmonary hypertension

Abbreviations: CI = confidence interval; DLCO = diffusing capacity of the lung for carbon monoxide; IPF = idiopathic pulmonary fibrosis; NYHA = New York Heart Association; PH = pulmonary hypertension; RR = relative risk; SPAP = systolic pulmonary artery pressure

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive parenchymal lung disease of unknown cause with an underlying histopathologic pattern of usual interstitial pneumonia.1–4 To our knowledge, no effective medical treatment exists for this disorder.1–4 The overall prognosis is poor, with a median survival of < 3 years.1,2,5,6

Although IPF is associated with a poor prognosis, there is survival heterogeneity that is difficult to predict for individual patients.1,2,5,6 Multiple studies6–12 have attempted to identify clinical and physiologic predictors of survival and have yielded variable and sometimes contradictory results. Although the occurrence of pulmonary hypertension (PH) in patients with IPF is recognized, the clinical implications of this association have not been clear.13,14 Additionally, revisions to the diagnostic criteria for IPF2 warrant a reexamination of this issue. In the present report, we sought to determine the impact on survival and clinical correlates of PH occurring in patients with IPF.

Materials and Methods

Study Population

This study was approved by the Mayo Foundation institutional review board. Using a computer-assisted search, 487 patients...
with IPF evaluated at Mayo Clinic Rochester during the period of January 1, 1994, to December 31, 1996, were identified. The clinical, radiologic, and physiologic features for this population have been published previously. Of these 487 patients, 136 patients (28%) underwent a comprehensive echocardiographic evaluation within 3 months of their initial visit at our medical center (index visit), and the study was available for current review. From this group of 136 patients, 48 patients were excluded for the following reasons: systolic pulmonary artery pressure (SPAP) not obtainable (25 patients), left ventricular ejection fraction < 40% (17 patients), vavular heart disease (3 patients), and incomplete follow-up (3 patients). The median survival of patients in whom SPAP was unobtainable was 2.3 years; the median survival of patients with left ventricular ejection fraction < 40% was 1.4 years. The remaining 88 patients were included in this study. The mean (± SD) interval between echocardiography and the index visit was 3.3 ± 8.2 days.

All 88 patients included in this study manifested characteristic clinical features of IPF plus either typical high-resolution CT findings (n = 71) and/or histopathologic evidence on surgical lung biopsy specimen for usual interstitial pneumonia (n = 17) as described in the American Thoracic Society/European Respiratory Society consensus definition for IPF. The medical records were carefully reviewed to exclude known causes of PH, including prior venous thromboembolism, HIV infection, systemic vasculitis or other connective tissue diseases, chronic liver disease with portal hypertension, left ventricular dysfunction, and history of anorexicogenic drugs.

Clinical Data Collection

The clinical data, laboratory results, pulmonary function data, high-resolution CT results, and bronchoscopy and lung biopsy results from the initial evaluation at our medical center were extracted from the medical records. Treatments for IPF prior to and after the index visit date, including oxygen therapy, were also recorded. We determined the vital status of patients by reviewing medical records and death certificates as well as by telephone interviews.

Pulmonary function testing was performed using daily calibrated equipment (models 1070 and 1085; Medical Graphics; St. Paul, MN) according to American Thoracic Society specifications as previously described. The pulmonary function tests included lung volumes with total lung capacity, spirometry including FVC and FEV1, diffusion capacity of the lung for carbon monoxide (DLCO), oxygen saturation at rest and with exercise, and arterial blood gas analysis at rest and with exercise. Baseline pulmonary function testing was defined as the test performed at our medical center closest to the index visit, limited to tests within 90 prior or 14 days following the index visit date.

Transthoracic Echocardiography: Doppler and Color Flow Imaging

Two-dimensional transthoracic echocardiography, pulsed and continuous-wave Doppler, and color flow imaging were performed in all patients using previously described techniques. The echocardiographic studies were reviewed by two cardiologists (N.C., P.A.P.) who were unaware of the clinical data. Pulmonary arterial hypertension was defined as a SPAP > 35 mm Hg at rest. SPAP was calculated based on the modified Bernoulli equation, and right atrial pressure was estimated as 5, 10, 15, or 20 mm Hg on the basis of the size and respiratory change of the inferior vena cava using previously described techniques. Right atrial and ventricular size along with right ventricular hypertrophy and systolic function were scored semiquantitatively on a scale of 0 (normal), 1 (mildly impaired or enlarged), 2 (moderately impaired or enlarged), or 3 (severely impaired or enlarged). Left ventricular dimensions, ejection fraction, and cardiac index were obtained by previously recommended techniques.

Statistical Analysis

Baseline characteristics were compared across the three SPAP subgroups (≤ 35 mm Hg, 36 to 50 mm Hg, and > 50 mm Hg) using an exact test for discrete variables and the Kruskal-Wallis test for continuous variables. A Spearman correlation coefficient was used to examine the association of SPAP with pulmonary function parameters and echocardiographic test results. For survival analysis, time zero is defined as the index visit, which was the date the patient was first seen at our medical center during the original study period (January 1, 1994, to December 31, 1996). Cumulative survival probabilities were estimated using the Kaplan-Meier method. Cox proportional hazards regression was used to identify variables associated with survival. Potential predictors considered in the survival analysis included age at index visit, gender, smoking status (current or former vs never), New York Heart Association (NYHA) functional status, history of coronary artery disease, history of congestive heart failure, history of hypertension or a history of diabetes mellitus, digital clubbing, treatment (any vs none), oxygen use prior to index visit, SPAP, estimated cardiac output, estimated cardiac index, estimated right atrial pressure, percentage of predicted FVC, percentage of predicted DLCO, and percentage of predicted FEV1. Oxygen saturation at rest and exercise as well as PaO2, PaCO2, and alveolar-arterial oxygen gradient at rest were not used in the survival analysis because these measures were not consistently obtained. In all cases, p < 0.05 was considered statistically significant.

RESULTS

Clinical Characteristics of IPF Patients With PH

The clinical characteristics of the 88 patients are summarized in Table 1. The mean estimated SPAP for the entire group was 48 ± 16 mm Hg (range, 28 to 116 mm Hg). Evidence of PH (SPAP > 35 mm Hg at rest) was present in 74 patients (84%). Patients were stratified by SPAP into three subgroups: ≤ 35 mm Hg, 36 to 50 mm Hg, and > 50 mm Hg, and included 14 patients (16%), 47 patients (53%), and 27 patients (31%), respectively. The three groups were similar except for gender, NYHA functional status, history of congestive heart failure, and oxygen use prior to index visit. Patients with SPAP > 50 mm Hg were more likely to be men, have a worse NYHA functional status and a history of congestive heart failure, and receive supplemental oxygen.

Echocardiographic Findings

The echocardiographic findings of the 88 patients with IPF are summarized in Table 2.
right ventricular enlargement were found in 20 patients (23%) and 18 patients (20%), respectively. Right ventricular systolic function was impaired in 10 patients (11%). On the basis of color flow imaging, tricuspid regurgitation was present in 56 patients (64%). Continuous-wave Doppler study was satisfactory for evaluation of SPAP in all 88 patients. The median peak velocity of tricuspid regurgitation was 2.9 ± 0.6 m/s (range, 2.0 to 4.9 m/s). Twenty-seven patients (31%) had an estimated SPAP > 50 mm Hg. Among 14 patients who had an estimated SPAP ≤ 35 mm Hg, none had right atrial or right ventricular enlargement or an impaired right ventricular function. Of 10 patients with an impaired right ventricular systolic function, 8 patients had an estimated SPAP > 60 mm Hg. The mean left ventricular ejection fraction was 60 ± 8% (range, 40 to 79%). Of 88 patients, 5 patients had minimal pericardial effusion without evidence of cardiac tamponade. Two patients had patent foramen ovale with trivial shunt.

**Correlation of Pulmonary Function With Echocardiographic Measures of PH**

All 88 patients had pulmonary function testing (Table 3). The patients with SPAP > 50 mm Hg had more impaired DLCO and PaO₂, but no other significant differences were found among the three subgroups. There was an inverse correlation between DLCO and SPAP \( (r = -0.47, p < 0.001) \). There was also an inverse correlation between SPAP and PaO₂ at rest \( (r = -0.36, p = 0.007) \) and oxygen saturation at rest \( (r = -0.33, p = 0.013) \), as well as a direct correlation with the alveolar-arterial oxygen tension gradient at rest \( (r = 0.29, p = 0.035) \). None of the remaining indexes of pulmonary function including FVC, FEV₁, and FEV₁/FVC correlated with echocardiographic-derived SPAP.

**Survival**

The median and estimated 1-year and 3-year survival rates for the three subgroups are as follows: ≤ 35 mm Hg (median, 4.8 years; 1 year = 100%; 95% confidence interval [CI], 100 to 100%; 3 year = 64%; 95% CI, 44 to 95%); 36 to 50 mm Hg (median, 4.1 years; 1 year = 79%; 95% CI, 68 to 91%; 3 year = 61%; 95% CI, 49 to 77%); and > 50 mm Hg (median, 0.7 years; 1 year = 44%; 95% CI, 29 to 68%; 3 year = 32%; 95% CI, 19 to 57%) [Fig 1]. Increased SPAP was associated with shortened survival (relative risk [RR], 1.34 per 10 mm Hg increase; 95% CI, 1.17 to 1.53; \( p < 0.001 \)).

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<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SPAP ≤ 35 mm Hg (n = 14)</th>
<th>SPAP &gt; 35 to ≤ 50 mm Hg (n = 47)</th>
<th>SPAP &gt; 50 mm Hg (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at index visit, yr</td>
<td>14 (100) 72.7 ± 8.2</td>
<td>47 (100) 72.9 ± 8.3</td>
<td>27 (100) 73.8 ± 9.6</td>
</tr>
<tr>
<td>Male gender</td>
<td>5 (35.7)</td>
<td>31 (66.0)</td>
<td>22 (81.5)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>5 (35.7)</td>
<td>17 (36.2)</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>Former</td>
<td>8 (57.1)</td>
<td>28 (59.6)</td>
<td>18 (69.2)</td>
</tr>
<tr>
<td>Current</td>
<td>1 (7.1)</td>
<td>2 (4.3)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (14.3)</td>
<td>1 (2.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>II</td>
<td>11 (78.6)</td>
<td>31 (66.0)</td>
<td>14 (51.8)</td>
</tr>
<tr>
<td>III</td>
<td>1 (7.1)</td>
<td>15 (31.9)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>IV</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Digital clubbing</td>
<td>2 (14.3)</td>
<td>10 (21.3)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 (35.7)</td>
<td>14 (29.8)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0 (0)</td>
<td>2 (4.3)</td>
<td>8 (29.6)</td>
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<tr>
<td>Hypertension</td>
<td>5 (35.7)</td>
<td>21 (44.7)</td>
<td>13 (48.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (14.3)</td>
<td>7 (14.9)</td>
<td>5 (18.5)</td>
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<tr>
<td>Recommended treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>1 (7.1)</td>
<td>8 (17.0)</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>4 (28.6)</td>
<td>11 (23.4)</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>Prednisone/colchicine</td>
<td>3 (21.4)</td>
<td>6 (12.8)</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>4 (8.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>None</td>
<td>6 (42.9)</td>
<td>18 (38.3)</td>
<td>11 (40.7)</td>
</tr>
<tr>
<td>Oxygen use prior to index visit</td>
<td>0 (0)</td>
<td>7 (14.9)</td>
<td>9 (36.0)</td>
</tr>
</tbody>
</table>

*Percentages may not total 100 due to rounding.
†Data were missing in one patient for smoking status, one patient for digital clubbing, and two patients for oxygen use, all in > 50 mm Hg subgroup.
‡Exact test for categorical variables and Kruskal-Wallis test for continuous variables.
Univariate analysis for the entire cohort also demonstrated shorter survival to be associated with male gender (RR, 2.6; 95% CI, 1.37 to 4.95; \( p = 0.004 \)), oxygen use prior to index visit (RR, 1.90; 95% CI, 1.02 to 3.51; \( p = 0.042 \)), lower DLCO (RR, 1.61 per 10 percentage point decrease; 95% CI, 1.26 to 2.04; \( p < 0.001 \)), history of coronary artery disease (RR, 1.96; 95% CI, 1.13 to 3.40; \( p = 0.017 \)), and worse NYHA class (RR, 1.62; 95% CI, 1.17 to 2.15; \( p = 0.044 \)).

Table 3—Baseline Pulmonary Function Data by SPAP Subgroups*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SPAP ≤ 35 mm Hg (n = 14)</th>
<th>Mean ± SD (Median, Range)</th>
<th>SPAP &gt; 35 to ≤ 50 mm Hg (n = 47)</th>
<th>Mean ± SD (Median, Range)</th>
<th>SPAP &gt; 50 mm Hg (n = 27)</th>
<th>Mean ± SD (Median, Range)</th>
<th>( p ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, % predicted</td>
<td>14</td>
<td>72.3 ± 15.2 (72.0, 52.2–109.6)</td>
<td>36</td>
<td>63.5 ± 15.1 (60.7, 35.1–95.4)</td>
<td>22</td>
<td>68.0 ± 20.2 (68.2, 34.2–113.3)</td>
<td>0.229</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>11</td>
<td>53.9 ± 16.5 (53.5, 27.2–79.1)</td>
<td>36</td>
<td>54.3 ± 15.8 (52.6, 32.7–100.5)</td>
<td>20</td>
<td>38.8 ± 12.3 (38.0, 17.8–60.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>FEV(_1), % predicted</td>
<td>14</td>
<td>77.1 ± 14.9 (77.8, 59.4–115.0)</td>
<td>36</td>
<td>67.0 ± 16.5 (61.4, 35.4–103.6)</td>
<td>22</td>
<td>68.8 ± 17.9 (69.5, 29.1–91.4)</td>
<td>0.151</td>
</tr>
<tr>
<td>Oxygen saturation at rest, %</td>
<td>7</td>
<td>93.9 ± 1.8 (94.0, 91.0–96.0)</td>
<td>24</td>
<td>93.3 ± 1.9 (93.0, 90.0–97.0)</td>
<td>17</td>
<td>91.6 ± 3.4 (93.0, 84.0–95.0)</td>
<td>0.211</td>
</tr>
<tr>
<td>Oxygen saturation with exercise, %</td>
<td>7</td>
<td>87.4 ± 6.2 (90.0, 74.2–92.0)</td>
<td>24</td>
<td>85.3 ± 5.6 (86.0, 75.0–97.0)</td>
<td>13</td>
<td>84.8 ± 6.8 (86.0, 67.0–92.0)</td>
<td>0.360</td>
</tr>
<tr>
<td>Pa(_O2) at rest, mm Hg</td>
<td>8</td>
<td>74.9 ± 9.1 (75.5, 57.0–85.0)</td>
<td>34</td>
<td>74.2 ± 11.5 (74.0, 47.0–96.0)</td>
<td>15</td>
<td>62.1 ± 14.3 (60.0, 42.0–93.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Pa(_CO2) at rest, mm Hg</td>
<td>8</td>
<td>36.1 ± 3.2 (36.2, 31.0–40.0)</td>
<td>34</td>
<td>36.5 ± 3.3 (36.0, 30.0–46.0)</td>
<td>15</td>
<td>34.3 ± 5.6 (36.0, 20.0–40.0)</td>
<td>0.655</td>
</tr>
<tr>
<td>Alveolar-arterial oxygen gradient at rest</td>
<td>8</td>
<td>23.9 ± 12.3 (25.0, 11.0–48.0)</td>
<td>34</td>
<td>24.0 ± 11.6 (23.5, 5.0–56.0)</td>
<td>13</td>
<td>34.4 ± 14.0 (38.0, 7.0–55.0)</td>
<td>0.076</td>
</tr>
</tbody>
</table>

*Percentages may not total 100 due to rounding.
†Kruskal-Wallis test.
**Discussion**

This study describes echocardiographic characteristics and survival of patients with PH associated with IPF. Our data suggest that significant PH is not limited to patients with advanced IPF. SPAP correlated inversely with DLCO. The estimated survival from the time of IPF diagnosis of patients with SPAP > 50 mm Hg was substantially worse than that of patients with SPAP ≤ 50 mm Hg. PH is likely more common than currently suspected in patients with IPF and has prognostic and management implications. This subgroup of patients may warrant more aggressive management or early referral for lung transplantation.

Secondary PH is more common than primary PH, and there is a consensus that PH in patients with interstitial lung disease is associated with worse survival. However, little has been known about the association between PH and IPF. Effective treatment of PH may prolong survival in patients who have IPF and PH. The major obstacle in treating PH has been the limited availability of oral or IV drugs that affect the pulmonary vasculature without causing excessive systemic vasodilation or increasing ventilation-perfusion mismatching. With the increasing availability of drugs for the treatment of PH such as bosentan, sitaxsentan, treprostinil, iloprost, beraprost, sildenafil in addition to epoprostenol, it may be reasonable to explore their role further in treating PH associated with IPF.

It has been difficult to accurately predict the clinical course in individual patients with IPF. Published studies have identified several demographic (age, sex, smoking), physiologic (DLCO, FVC), radiologic, and histopathologic features (eg, fibroblastic foci), and combinations of these parameters that correlate with survival. However, conclusions from these studies have not been entirely consistent. Other studies have examined the association between survival of patients with IPF and the trends in pulmonary function over time. Flaherty et al found a decrease of > 10% in FVC over a 6-month follow-up period to be an independent risk factor for mortality. Collard et al showed that changes in clinical as well as physiologic variables over 6-month and 12-month periods are predictive of survival and provide more accurate prognostic information than baseline values alone. Latsi et al showed that serial pulmonary function trends have considerable prognostic value, not only for patients with IPF but also in patients with fibrotic nonspecific interstitial pneumonia.

The prevalence and prognostic significance of PH in patients with IPF as well as the impact of therapy for PH on these patients needs to be explored further. Harari et al examined the prognostic value...
of PH in patients with chronic interstitial lung disease referred for lung transplantation including 43 patients with “IPF” and found that neither hemodynamic nor respiratory parameters obtained during the preoperative clinical screening predicted survival. In addition, there was no correlation between pulmonary function parameters and PH in these patients. However, the mean survival of these patients with advanced lung disease in their study was short (5.67 ± 0.42 months), making the detection of any impact of PH on survival difficult. In contrast, Jezek14 noted PH to have a significant impact on survival of patients with “idiopathic diffuse interstitial lung fibrosis.”

An important limitation of this study is its retrospective design and the lack of right-heart catheterization to confirm the presence and degree of PH. These patients underwent echocardiography for a variety of reasons, and potential biases exist based on this selection process. In addition, there are recognized limitations to the use of echocardiography in evaluating PH in patients with advanced lung disease.15,30 Care must be taken to align the Doppler beam with the direction of flow or underestimation of the pulmonary artery pressure may result. Even if there is insufficient tricuspid regurgitation to allow measurement of pulmonary artery pressure, it cannot be assumed that the pulmonary artery pressure is normal. With these caveats, Doppler echocardiography is a convenient, noninvasive, and relatively accurate tool for evaluating PH.16,17,37,38 A recent study39 suggests that plasma level of brain natriuretic peptide may be a predictor of moderate to severe PH in patients with pulmonary fibrosis. Interestingly, lung function parameters did not correlate with brain natriuretic peptide level or the presence of PH. Plasma brain natriuretic peptide level and echocardiography may have complementary roles in the evaluation of patients with IPF.

CONCLUSIONS

Our data demonstrate that SPAP correlates inversely with DLCO and PH has a significant adverse impact on survival, particularly when SPAP is > 50 mm Hg. Further studies are needed to define the prevalence of PH as well as management implications for patients with IPF.

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