Lung Function Tests in Patients With Idiopathic Pulmonary Fibrosis *
Are They Helpful for Predicting Outcome?

Reinhard Erbes, MD; Tom Schaberg, MD; and Robert Loddenkemper, MD, FCCP

Study objective: Idiopathic pulmonary fibrosis (IPF) varies widely in its course. To evaluate predictive parameters at presentation to the hospital, we investigated 99 patients with IPF (47 women), focusing on extensive lung function tests.

Methods: Standard tests of lung volumes, arterial oxygen tension, and gas exchange at rest and during bicycle exercise were performed. Survival rates in relation to functional parameters were calculated using the actuarial method. Differences in survival proportions were summarized as hazard ratios, and significance levels were determined by log-rank test.

Results: At presentation, most patients showed a reduced total lung capacity (TLC) of 79.2±21.1%, an arterial oxygen tension (PaO₂) considered pathologic in 63%, when related to age, a significant decrease of PaO₂ with 11.8±12.1 mm Hg and an increase of the alveolar-arterial oxygen pressure difference with 46.4±16.4 (12.2 to 76.8) mm Hg during bicycle exercise. Diminished survival was associated with an age older than 50 years, a reduced value to more than 2 SDs below the predicted values of both, TLC alone, or in combination with a reduced vital capacity. Factors not influencing survival were gender, parameters of gas exchange at rest, and PaO₂ at rest and during bicycle exercise.

Conclusions: We conclude that standard lung function tests make it possible to assess the prognosis of patients with IPF, while extensive tests like gas exchange measurements at rest and during bicycle exercise do not contribute additional information to make the prognostic estimations more precise.

(CHEST 1997; 111:51-57)

Key words: idiopathic pulmonary fibrosis; lung function; survival

Abbreviations: CI=confidence interval; DCO=diffusion of carbon monoxide; IPF=idiopathic pulmonary fibrosis; P(A-a)O₂=alveolar-arterial oxygen pressure difference; PaO₂=oxygen tension; RV=residual volume; TLC=total lung capacity; VA=alveolar volume; VC=vital capacity

Idiopathic pulmonary fibrosis (IPF) is a disease with an extremely variable course. The interval from first onset to death varies from several months to years; the overall mean survival rates are reported to range between 3 and 6 years. The prognosis of IPF has been investigated in several studies. There is agreement about the clinical defining criteria, but factors affecting prognosis are discussed controversially. Histologic criteria, clinical features, or lung function parameters are not clear prognostic indicators. Increased interstitial abnormalities in the chest radiograph, parameters indicating restrictive lung function, and abnormal gas exchange are possible determinants of survival. Most series reported in the literature were not very large or the patients were not followed up long enough and different histologic classifications were used. Therefore, we retrospectively investigated our patients with IPF histologically confirmed by lung specimens obtained by thoracoscopic or open lung biopsy to analyze survival rates in correlation with lung function parameters, including extensive lung function tests like gas transfer at rest and during bicycle exercise.

*From the Chest Hospital Heckeshorn, Pneumological Department II, Berlin, Germany.

This investigation was supported in part by “Verein zur Förderung der Pneumologie und Thoraxchirurgie in Berlin Heckeshorn.”

Manuscript received January 29, 1996; revision accepted August 14, 1996.

Reprint requests: Dr. Loddenkemper, Pneumological Department II, Lungen Klinik Heckeshorn, Zum Heckeshorn 33, D-14109 Berlin, Germany.
MATERIALS AND METHODS

Study Parameters

Lung volumes and its subdivisions, vital capacity (VC), total lung capacity (TLC), residual volume (RV), and FEV₁ were measured by constant-volume body plethysmography (Siemens EH91 S and FD 20 S; Erlangen, Germany), and values were expressed as percentages of the predicted values calculated according to gender, weight, and age using the European Community for Steel and Coal classification.²³ Gas transfer was determined by the single breath-holding method, modified by Brandt et al.¹⁴ and West et al.¹⁵ using argon and C¹⁸O. In this method, gas transfer values are calculated in relation to the balance of caused inspiratory VC in-washed argon test volume and the exhaled argon volume after breath-holding for 10 s and then related to alveolar volume (DCO/VA). The values were expressed as percentages of the predicted values according to the criteria of Cotes.¹⁶ A difference of more than 2 SDs was considered abnormal. Depending on the severity of the clinical presentation, the patients underwent a steady-state spirometry exercise test in the sitting position while breathing room air. Minute ventilation, respiratory rate, heart rate, respiratory CO₂ production, and oxygen consumption per minute at rest, at each steady-state level during the ergometer exercise, and during recovery were recorded with a spirographic system (Siemens FD 88) using a Fleisch-type pneumotachometer. Steady state was defined as the period when heart rate, respiratory CO₂ production, and O₂ consumption reached constant values. The workload was then augmented until the next steady state was achieved or until a further increase in workload was no longer possible. Oxygen tension (PaO₂) was determined in blood of the hyperemic ear lobe caused by nonivamide and nicoboxil with a system (Radiometer Gas Check System AVL 936; AVL 940, or ABL 300) at each step. The maximum decrease in oxygen tension (ΔPaO₂) while exercising and the alveolar-arterial oxygen difference (P[A-a]O₂) at rest and during exercise were calculated and related to body weight and maximum oxygen intake during exercise according to the criteria of Jones.¹⁷ Since 2 SDs of our ΔPaO₂ measurements while exercising were found to be 7 mm Hg, we considered a decrease of at least of 8 mm Hg significant.

The follow-up data were obtained from practicing pneumologists or when the patients presented again at our hospital for examinations. All deaths were checked in the Birth and Death Register of the City of Berlin.

Statistical Analysis

Means of smokers and nonsmokers were compared with the unpaired t test. A p value <0.05 was accepted as significant. If the t test assumed that the values came from populations with different SDs, the alternative Welch t test was used, which does not assume populations with equal SDs. Survival rates were calculated using the actuarial method.¹⁸ The survival estimator given by the actuarial method is the cumulative survival rate at any desired time. It is based on observation of patients, and the period of observation is divided into intervals of half a year (Figure 1). The cumulative survival rates are derived from the combined survival of patients in all preceding intervals. The survival in different groups was compared by log-rank testing according to Peto et al.¹⁹ A p value <0.05 was accepted as significant. The differences in 5-year survival were summarized as the hazard ratio, which is a measure of the relative prognostic value of a parameter. The hazard ratio gives a percentage indicating an estimated change in survival compared with that of the opposite group. Confidence intervals (CIs) were calculated to determine the effects of sampling variation on the precision of the estimated statistics. The survival of all patients was compared with the normal life expectancy at the age of 50 years as given by the Statistical Department of the Federal Republic of Germany (Statistisches Bundesamt, Wiesbaden).

RESULTS

Among all patients who were referred to our department from practicing physicians of pulmonary medicine or from other hospitals in West Berlin with suspicion of a interstitial lung disease between 1973 and 1988, we identified 99 patients (52 women, 47 men) fulfilling the diagnostic criteria for histologically proved IPF. The biopsy specimens were ob-

![Figure 1. Histogram: years of observation; dead or alive at the end of observation.](http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21742/ on 06/26/2017)
tained with the open lung technique\textsuperscript{20} in 58 cases, by thoracotomy\textsuperscript{21} in 38 cases and at autopsy in three cases. Patients with unknown causes of diffuse lung diseases such as sarcoidosis, allergic alveolitis, hypersensitivity reactions, associated chronic left heart failure, and collagen, vascular, or connective tissue diseases were excluded. The mean age at presentation was 53.2±15.4 years. Fifty-six patients were current smokers; the remaining 43 patients had been nonsmokers for at least 5 years. The mean time elapsed from the onset of early symptoms to the time of diagnosis was 21±41 months (range 1 to 234 months). Three patients had no symptoms and only a suspicious radiograph led to the diagnosis. The most frequently encountered symptoms were cough (84/99) and dyspnea (80/99). Chest pain was present in 24/99 patients. Surprisingly, nonsmokers more often complained about cough and dyspnea, and the duration of these symptoms before hospital admission was longer than in smokers. The severity of dyspnea also correlated with its duration before presentation. Based on the clinical presentation and the duration of symptoms, the study population can be considered representative of all stages of the disease. When diagnosed, all patients were treated with corticosteroids, 0.5 to 1 mg/kg weight (maximum dose, 60 mg) over a period of 1 month, then reduced monthly by 10 mg to a dose of 7.5 to 15 mg/d. The remaining dose differed dependently on the clinical response and the improvement of lung function impairment in the course. Nonresponders were treated with additional azathioprine, 100 to 200 mg daily. Almost all patients showed pathologic lung function values on admission to the hospital. Only two patients had normal values in all lung function tests. Patients with a history of smoking had significantly better values of \( P(A-a)O_2 \), TLC, and VC. The mean of these values was normal in smokers while it was pathologic in nonsmokers (Table 1). No differences were found between smokers and nonsmokers in the RV/TLC ratio, although smokers had higher RV values.

The patients were followed up as long as possible (mean, 5.5 years; range, 6.6 months to 18 years), at least until April 1993 (Figure 1).

The mean survival from the moment of presentation for all patients who died was 41.4±41 months. The survival rate of all patients considered independently of the therapeutic regimen and calculated with the actuarial method 5 years after presentation at our department was 63.2 months with a 95% CI of 50.3 to 77.2% (Figure 2). No difference in survival was found between genders. The survival analysis and log-rank test demonstrated that an age older than 50 years was associated with diminished survival (Figure 2) with an estimated reduction in survival 5 years after diagnosis to 25% of that of the opposite group (hazard ratio, 0.251; 95% CI=0.125 to 0.507). Survival was significantly shorter in patients with a TLC of more than 2 SDs below the predicted values with an estimated reduction in survival 5 years after diagnosis to 51% of that of the opposite group (hazard ratio, 0.506; 95% CI=0.249 to 1.028) and in patients with a combined reduction of TLC and VC to more than 2 SDs below the predicted values, which is a reliable parameter of restrictive pulmonary function impairment, with an estimated reduction in survival 5 years after diagnosis to 46% of that of the opposite group (hazard ratio, 0.458; 95% CI=0.185 to 1.136) (Figure 3).

Factors not influencing survival rates were age during spiroe-

---

**Table 1—Lung Function Parameters and Number of Patients With IPF at Presentation to our Hospital**

<table>
<thead>
<tr>
<th>Parameters (Mean)</th>
<th>All</th>
<th>95% CI</th>
<th>n=</th>
<th>Smokers</th>
<th>n=</th>
<th>Nonsmokers</th>
<th>n=</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC, % predicted</td>
<td>79.18</td>
<td>75.0–83.4</td>
<td>95</td>
<td>88.6</td>
<td>46</td>
<td>71.0</td>
<td>49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>89.19</td>
<td>83.5–95.1</td>
<td>96</td>
<td>74.4</td>
<td>46</td>
<td>63.4</td>
<td>50</td>
<td>&lt;0.0182</td>
</tr>
<tr>
<td>FEV(_1), % predicted</td>
<td>69.16</td>
<td>64.9–73.5</td>
<td>96</td>
<td>63.8</td>
<td>46</td>
<td>73.4</td>
<td>50</td>
<td>&lt;0.0058</td>
</tr>
<tr>
<td>FEV(_1/VC), %</td>
<td>70.30</td>
<td>67.6–73.0</td>
<td>96</td>
<td>98.1</td>
<td>46</td>
<td>78.6</td>
<td>49</td>
<td>NS</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>88.1</td>
<td>78.3–97.8</td>
<td>106</td>
<td>105.3</td>
<td>38</td>
<td>109.6</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>RV/TLC, %</td>
<td>98.6–114.3</td>
<td>70</td>
<td>51.0</td>
<td>38</td>
<td>40.9</td>
<td>32</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>Dco, % predicted</td>
<td>46.30</td>
<td>41.6–51.0</td>
<td>70</td>
<td>53.4</td>
<td>38</td>
<td>54.0</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>Dco/VA, % predicted</td>
<td>53.36</td>
<td>49.0–57.7</td>
<td>70</td>
<td>76.9</td>
<td>42</td>
<td>69.9</td>
<td>46</td>
<td>&lt;0.0077</td>
</tr>
<tr>
<td>PaO(_2) at rest, mm Hg</td>
<td>73.28</td>
<td>70.7–75.9</td>
<td>88</td>
<td>44.6</td>
<td>31</td>
<td>49.9</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>Exercised with (Watt)</td>
<td>50</td>
<td>39</td>
<td>56</td>
<td>44.6</td>
<td>31</td>
<td>49.9</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>P(A-a)O(_2), mm Hg</td>
<td>46.6</td>
<td>42.0–51.1</td>
<td>52</td>
<td>73.5</td>
<td>31</td>
<td>91.7</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>VO(_2) related*</td>
<td>80.9</td>
<td>69.9–91.9</td>
<td>52</td>
<td>10.5</td>
<td>32</td>
<td>13.5</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>PaO(_2) decrease, mm Hg</td>
<td>–11.8</td>
<td>–8.3–15.1</td>
<td>52</td>
<td>–5.5</td>
<td>31</td>
<td>25.0</td>
<td>22</td>
<td>NS</td>
</tr>
</tbody>
</table>

\*parameter

\( VO_2 \) max/VO\(_2\) predicted. \( VO_2 \) = oxygen consumption.
grometric exercise (Figure 5), age-related PaO₂, and a history of cigarette smoking (Table 2).

**Discussion**

With the possibility of lung transplantation, it has become an important issue to assess the individual prognosis of patients with IPF. To take into consideration such a treatment at the right moment, it is desirable to have as many reliable parameters as possible. Our study shows that only some of the recorded parameters may be helpful in estimating the individual prognosis in patients with IPF. In aggregate, our findings suggest that factors influencing prognosis include degree of restrictive lung function and age at presentation, while parameters of extensive lung function tests, especially gas transfer (Dco) and gas transfer values during exercise (δPaO₂, P[A-a]O₂), were not helpful in estimating a patient’s prognosis.

![Figure 2. Survival of all patients in relation to age at presentation (p<0.01). Heavy line = all patients (n=99); large dashed line = younger than 50 years (n=33); short dashed line = 50 years or older (n=66); thin line = life expectancy at 50 years.](image)

![Figure 3. Survival in relation to the lung volumes of the patients at presentation (p<0.05). Heavy line = TLC ≥ 78% predicted (n=45); short dashed line = TLC <78% predicted (n=50); thin line = TLC ≥78% and VC ≥83% predicted (n=29); heavy dashed line = TLC <78% and VC <83% predicted (n=39).](image)
The overall prognosis of IPF is poor. Only 64% of our patients survived 5 years. There is close agreement about survival in the various series reported (Stack et al, Carrington et al, Turner-Warwick et al, Tukiainen et al, Johnson et al) with a 5-year survival rate of 50% and a range of 23 to 93%, although criteria for inclusion of patients vary widely. No agreement exists about the factors influencing survival. Our study supports the findings of other authors that survival is better in patients with a higher lung capacity. Stack et al reported that 38 of 40 patients with a VC ≤60% of the predicted value died in contrast to eight of 19 patients with a VC >60% during an average observation period of 47.4 months. After 5 years, 27 of 32 of the patients of Jezek et al with a VC >60% of the predicted value were still alive as opposed to only 29 of 67 with a VC ≤60%. In a trial comparing treatment with prednisolone alone and combined with cyclophosphamide, Johnson et al found that patients with a TLC...
below 60% of the predicted value did poorly, while those with a TLC of 80% or more did well with either regimen. We found, like others, that patients with a lower value of PaO₂ at rest had poorer survival rates. However, this point must be evaluated with the knowledge that PaO₂ is dependent on the age of the patient, as reported by Sorbini et al.\textsuperscript{25} Calculation of survival rates on the basis of an age-related PaO₂ did not reveal any appreciable difference. Besides that, we conclude from our findings that investigation of gas transfer is of no prognostic value. The extent of a decrease in DCO and DCO/VA, a significant decrease of PaO₂ during exercise, or an increase of P(A-a)O₂ is not associated with any differences in survival. The prognostic value of these parameters is discussed controversially. Tukiainen et al.\textsuperscript{9} and Jezek et al.\textsuperscript{5} found a reduced survival in patients with a DCO below 45%, but they did not relate this parameter to VA. A study of Augusti et al.\textsuperscript{26} suggests that the assessment of pulmonary gas exchange at diagnosis may predict the progression of the disease. However, Carrington et al.\textsuperscript{23} reports results obtained with the spiroergometric lung function tests in accordance with our findings.

There are many factors that disturb gas transfer. The degree of impaired lung function due to inflammation, fibrosis, or changes in the ventilation-perfusion ratio is reflected by changes in gas transfer. In normal subjects, normal measurements of gas exchange during exercise indicate that there is an efficient matching of ventilation and blood flow. In patients with severe lung disease, gas transfer both at rest and during exercise is usually abnormal because of the pathologic defect in the arterio-alveolar unit. But most importantly, mismatching of ventilation and perfusion may cause considerable abnormalities in gas transfer parameters in patients with less severe lung disease as well. Examinations using multiple inert gas elimination techniques revealed that gas exchange alterations in patients with IPF were due to ventilation-perfusion inequality in 80% and due to alveologapillary diffusion limitation in only 20%. Ventilation-perfusion inequality, alveologapillary diffusion limitation, and alterations in pulmonary hemodynamics may correlate with the DCO and also with the DCO/VA ratio, depending on the severity of the underlying pulmonary disease.\textsuperscript{27} Both DCO/VA and δPaO₂ during exercise reflect the extent of pulmonary lesions but cannot discriminate between fibrosis and infiltration of the lung by inflammatory cells.\textsuperscript{28} It is therefore not possible to predict the extent of pulmonary destruction from disturbances in gas transfer.\textsuperscript{3} We assume, according to other authors,\textsuperscript{23,29} that the inflammatory component of lung impairment in IPF may be reversed by an anti-inflammatory regimen. Thus, gas transfer parameters can be helpful in estimating the efficiency of such a regimen.

Furthermore, there was no difference in survival between male and female subjects. The same results were found in most of the other series except in those of Turner-Warwick et al.\textsuperscript{24} and Schwartz et al.\textsuperscript{7} where women showed a better survival, but men were overrepresented in these series compared with the others. Our results confirm the observation of a better survival of younger patients, which was likewise noted in most other reports.

IPF is an uncommon disease with a wide variation in its course, and it is thus difficult to study a sufficiently large number of patients. In some series, rheumatoid arthritis or other connective tissue diseases were not excluded.\textsuperscript{8,23,24,30} A histologic examination was missing in some patients of other series.\textsuperscript{5,7,8,23,24,31} To obtain a large series to ensure adequate follow-up, most studies were done retrospectively with all the limitations such an approach implies. Although a comparison between series is difficult, we can at least state that we do not agree with Keogh and Crystal\textsuperscript{32} and Fulmer et al.\textsuperscript{33} who

### Table 2—Summary of Differences in Survival 5 Years After Diagnosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Predicted Value</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ at rest</td>
<td>&lt;N*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>δPaO₂ during exercise</td>
<td>&gt;8 mm Hg</td>
<td>1.679</td>
<td>0.457-6.171</td>
<td>NS</td>
</tr>
<tr>
<td>P(A-a)O₂</td>
<td>&gt;35 mm Hg</td>
<td>1.239</td>
<td>0.255-6.011</td>
<td>NS</td>
</tr>
<tr>
<td>Age at presentation</td>
<td>&gt;50 yr</td>
<td>0.251</td>
<td>0.125-0.507</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>0.822</td>
<td>0.416-1.626</td>
<td>NS</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td>0.574</td>
<td>0.290-1.134</td>
<td>NS</td>
</tr>
</tbody>
</table>

*\textsuperscript{a}N=109-(0.43Xage) mm Hg

*\textsuperscript{b}VO₂-related, VO₂=oxygend consumption.
concluded that lung function parameters do not allow any prediction about the prognosis of patients with IPF.

In summary, we found that lung function parameters, which may reflect the extent of fibrosis, can be helpful in estimating the prognosis of IPF. Gas transfer parameters are affected by both inflammatory activity and the extent of fibrosis. They reflect the degree of functional impairment and are suited for the monitoring of patients and in particular for the evaluation of a therapeutic regimen. We conclude that standard lung function tests offer the possibility to assess the prognosis of patients with IPF, while extensive lung function tests do not yield any additional information to make more precise prognostic estimations. However, due to the great variability in the natural history of the disease, close monitoring of the patients may be necessary to evaluate the individual course of each patient.

REFERENCES

12 Watters LC, King TE, Schwarz MI, et al. Clinical, radiographic and physiologic scoring system for the longitudinal assessment of patients with IPF. Am Rev Respir Dis 1986; 133:97-103
17 Jones NL. Clinical exercise testing. Philadelphia: WB Saunders, 1975
22 Stack BHR, Choo-Kang YPJ, Heard BE. The prognosis of cryptogenic fibrosing alveolitis. Thorax 1972; 27:535-54
32 Keogh BA, Crystal RG. Clinical significance of pulmonary function tests: pulmonary function testing in interstitial pulmonary disease: what does it tell us? Chest 1980; 78:856-65