Determinants of Progression in Idiopathic Pulmonary Fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a progressive form of lung disease with a median survival of less than 5 yr. To address the progressive nature of this disease process, we investigated the determinants of decrements in lung function in patients with IPF. We prospectively evaluated 39 subjects with IPF. Our study subjects were followed for an average of 2 yr (range, 49 to 1,883 days) and lung function was measured on at least two separate occasions (mean = 9.1 separate tests) during the follow-up period. Since IPF is characterized by reduced lung volume and abnormal gas exchange, our analysis focused on the determinants of total lung capacity (TLC) and diffusing capacity of carbon monoxide (D_{LCO}) during the period of observation. Although, on average, there was a 5.3% increase in the TLC and a 9.8% increase in D_{LCO} between the first and last measure of lung function, 25% of the study population experienced a decline in the TLC and 28% of the study population experienced a decline in the D_{LCO}. Decrements in TLC were independently associated with severe dyspnea ($p = 0.01$) and treatment with cyclophosphamide ($p = 0.03$). Decrements in D_{LCO} were significantly and independently associated with more pack-years of cigarette smoking ($p = 0.02$), moderate ($p = 0.03$) or severe ($p = 0.02$) dyspnea, and treatment with cyclophosphamide ($p = 0.0002$). These findings indicate that several clinical characteristics are independently associated with subsequent declines in TLC and D_{LCO} in patients with IPF. These results raise the possibility of using these prognostic factors (clinical symptoms, smoking history, and need for immunosuppressive therapy) to assess the risk for disease progression in patients with IPF. **Schwartz DA, Van Fossen DS, Davis CS, Helmers RA, Dayton CS, Burmeister LF, Hunninghake GW. Determinants of progression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1994; 149;444–9.**

Idiopathic pulmonary fibrosis (IPF) is a progressive form of interstitial lung disease characterized by dyspnea, reduced lung volumes, and abnormal gas exchange (1–3). Importantly, patients with IPF have an expected median survival of less than 5 yr. Moreover, survival appears to be adversely affected by age, male gender, a fibrotic histology showing "usual interstitial pneumonia," and more advanced radiographic and physiologic evidence of interstitial lung disease (4–11). However, few investigations have attempted to identify the clinical features of IPF that are independently predictive of progressive abnormalities in lung function.

Among patients with IPF, excess neutrophils (8, 12–14) and eosinophils (8, 14, 15) in bronchoalveolar lavage (BAL) fluid have been associated with a higher likelihood of disease progression and a failure to respond to immunosuppression. In contrast, the concentration of BAL lymphocytes appears to be directly related to an improved response to immunosuppression (12, 14). However, we have recently found that the concentration of macrophages, neutrophils, and eosinophils in BAL fluid is strongly influenced by cigarette smoking in patients with IPF (16). In addition, cigarette smoking appears to have a profound effect on lung function in patients with IPF (17, 18). These findings suggest that cigarette smoking may significantly enhance the rate of disease progression in IPF. However, previous studies investigating the relationship between BAL cellularity and disease progression in IPF (12–17) have not identified the effect of cigarette smoking on the progressive decline in lung function in this chronic interstitial lung disease.

The purpose of this investigation was to prospectively identify the determinants of progressive loss of lung function in patients with IPF. We were especially interested in investigating whether cigarette smoking enhances the progression of lung function abnormalities and to what extent the concentration of specific cells from the initial BAL sample serves as a prognostic risk factor in this form of inflammatory lung disease.

METHODS

Patient Population

Thirty-nine patients with idiopathic pulmonary fibrosis were included in this study. All of these patients were identified as part of our ongoing NHLBI SCOR Program in Occupational and Immunologic Lung Disease in which

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TABLE 1

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF STUDY POPULATION

	Number	Percentage	Mean ± SD	Range
Age, yr			61.9 ± 12.6	36.2–79.4
Sex				
Male	21	53.8		
Female	18	46.2		
Smoking status				
Never	11	28.2		
Former	24	61.5		
Current	4	10.3		
Pack-years of smoking			26.0 ± 22.6	0–80.0
Initial treatment				
Nothing	18	46.2		
Corticosteroids	14	35.9		
Cyclophosphamide	7	17.9		
Follow-up time, days			621.4 ± 515.5	49–1,883
Follow-up measures of pulmonary function per patient			9.1 ± 7.2	2–36

we are prospectively studying patients with diffuse interstitial lung disease. Although these subjects were largely recruited from the state of Iowa, all bordering states in the Midwest contributed subjects to this study. Recruitment of subjects with IPF was relatively constant throughout the study period (approximately eight per year between 1986 and 1991). Subjects were generally referred to our center either as part of the initial evaluation for their interstitial lung disease or due to progression of IPF despite traditional therapeutic approaches. The demographic features of our study population (table 1) are similar to the demographic characteristics of other reported series of patients with IPF (4, 5), with a larger percentage of older, male cigarette smokers. Forty-six percent of the study population were initially on no therapy for their IPF and the follow-up period was quite variable among subjects, ranging from 49 to 1,883 days with an average of approximately 2 yr (table 1). Each study subject had at least one follow-up measure of pulmonary function, with a mean of approximately nine follow-up measurements of pulmonary function per patient (table 1).

The diagnosis of IPF was based on accepted criteria (4, 19), which included either evidence of diffuse parenchymal infiltrates (peripheral and reticular nodular with a lower lobe predominance) on chest radiograph or restrictive lung function with an open lung biopsy demonstrating varying degrees of interstitial fibrosis and intra-alveolar inflammatory cells. Strict exclusionary criteria were established and consisted of clinically relevant environmental or occupational exposure history; clinical findings of hypersensitivity pneumonitis, left ventricular failure, or systemic disease (i.e., connective tissue diseases); and granulomata or vasculitis on the biopsy specimen. Furthermore, each biopsy specimen was cultured and patients were included only if the cultures were negative for bacteria, mycobacteria, and fungi. Of 39 subjects with IPF, 30 (77%) had open lung biopsies, four (10%) had transbronchial biopsies, and the remaining five fulfilled all of the clinical criteria required for this diagnosis. Study subjects without open lung biopsies were required to have diffuse parenchymal infiltrates on the chest radiograph, restrictive lung function (TLC < 80% predicted), and to meet all of our exclusionary criteria.

Characterization of Smoking History

Participants were classified as "never smokers" (< 20 packs of lifetime cigarettes and no cigarettes in the month before their evaluation), "former smokers" (> 20 lifetime packs of cigarettes but stopped at least 1 month before their evaluation), and "current smokers" (smoked within 1 month of their evaluation). In the classification of pack-years, never smokers were classified as having zero pack-years of cigarette smoking.

Pulmonary Function Tests

The pulmonary function tests consisted of standard spirometry using a Medical Graphics 1070 system (St. Paul, MN) and lung volumes via body plethysmography using a Medical Graphics 1085 system. A single-breath diffusing capacity was measured using the Medical Graphics 1070 system. The measurements of lung function were performed using standard protocols, and the American Thoracic Society guidelines (20) were used to determine acceptability. The predicted normal values used were those of Morris and coworkers (21) for spirometry, Goldman and Becklake (22) for lung volumes, and Van Ganse and coworkers (23) for the diffusing capacity.

Dyspnea Assessment

The dyspnea level was assigned according to the recommendations of the American Medical Association (24) and the American Thoracic Society (25). Dyspnea was assessed by one of the investigators (C. Dayton) who was uninformed of the clinical history and laboratory findings when determining the dyspnea level. This classification system includes the following five levels of dyspnea. Class I dyspnea is dyspnea that is expected given the circumstances of the activity (i.e., dyspnea with extreme exertion). Class II dyspnea is characterized by inability to keep pace with others when walking up stairs or slight hills. Class III dyspnea is characterized by an inability to keep pace on the level with others of the same age and body build. Class IV dyspnea occurs during such activities as climbing one flight of stairs or walking 100 yards on the level. Class V dyspnea occurs at rest and while performing activities of daily living.

Chest Radiographs

Chest radiographs were performed in the posteroanterior projection and independently interpreted by three experienced readers (two A readers and one B reader), who used the International Labor Organization (ILO) 1980 Classification of Radiographs of Pneumonoconioses (26). Each reader was uninformed of the exposure history, clinical data, and the opinions of the other readers when interpreting the radiographs. Agreement between at least two of the three readers was required to identify the major ILO profusion category. In the unusual case that all three readers disagreed on the major ILO profusion category (only two cases), the median reading was chosen.

Bronchoalveolar Lavage and Cell Analysis

Bronchoscopic examination and lavage were performed on all study subjects using our standard method (27). Premedications included 0.8 mg atropine sulfate given intramuscularly, 75 mg meperidine hydrochloride given intramuscularly, and two inhalations of metaproterenol (total 1.3 mg) from a hand-held pressurized canister. The upper airway was anesthetized with Dyclone gargle and aerosolized 4% lidocaine. Lidocaine was also applied topically to the pyriform sinuses and vocal cords. The bronchoscope (4.9-mm diameter at the tip; Model BF4B2; Olympus, Lombard, IL) was advanced into the airways, and the tip was maintained in the wedged position in a subsegmental bronchus throughout the lavage procedure. In all cases, two lavages were performed, and, in most instances (N = 31, 79%), the two lavages were performed in subsegments of the right middle lobe and lingula. Each lavage consisted of 120 ml of saline (6 × 20-ml aliquots; the first 20-ml aliquot was discarded).

Immediately after the lavage, the lavage fluid was strained through two layers of surgical 4 × 4 gauze into 50-ml conical tubes. The tubes were centrifuged for 5 min at 150 g and the residual pellet of cells was resuspended and washed twice in Hanks' balanced salt solution (without Ca^{2+} or Mg^{2+}). After the second wash, a small aliquot of the sample was removed for a cell count using a Coulter counter (Hialeah, FL). The cells were then washed once more and resuspended in RPMI 1640 medium so that the final concentration was 1×10^6 cells/ml. The cells present in 10–12 µl of the 1×10^6-ml cell suspension were spun onto a glass slide with the use of a filter card and a cytocentrifuge (Cytospin 2; Shanden Southern, Sewickley, PA). After the cells were dried for 2 min, they were stained by using a Diff Quick Stain set (Harleco, Gibbstown, NJ). The cells were counted and classified only after the cytocentrifuge preparation was thought to be satisfactory by the following criteria: negligible staining artifact, uniform dispersal of cells without clumping, essentially no disruption of cells, and < 3% airway epithelial cells.

Statistical Analysis

The primary objective of this investigation was to identify the determinants of lung function changes in patients with IPF. We were specifically interested in evaluating the prognostic importance of initial clinical variables on the progressive decline of lung function. Since IPF is primarily characterized by reduced lung volumes and abnormal gas exchange (1–3), we decided to focus our analysis on the total lung capacity (TLC) and the diffusing capacity of carbon monoxide (D_{LCO}).

The generalized estimating equations (GEE) approach (28–30) was used to develop regression models assessing the relationship between each of the two outcome variables (TLC and D_{LCO}) and a set of confounders and covariates of potential interest. This regression methodology for correlated observations permits unequal numbers (and spacings) of follow-up measurements across subjects, as well as both subject-specific (time-independent) and observation-specific (time-dependent) covariates. Because the outcome variables are continuous and approximately normally distributed, the identity link function and constant variance function were used. Thus, the mean TLC (D_{LCO}) was modeled as a linear function of follow-up time and other covariates. Dichotomous explanatory variables were coded as 0 (absent) or 1 (present) and categorical covariates with $k > 2$ levels, such as smoking history, were coded using k-1 indicator (0, 1) variables. Since both the number and spacing of the repeated measurements varied across subjects, the independence "working" correlation model was used.

The regression procedure was as follows. First, for both TLC and D_{LCO}, we determined whether our potential confounders (age, sex, height, and pack-years of cigarette smoking) interacted with follow-up time. TLC and D_{LCO} did not have time-dependent interactive covariates. Next, we included the confounders or covariates (age, sex, height, pack-years of cigarette smoking, and follow-up time) in a model and evaluated the relationship between changes in either TLC or D_{LCO} during the follow-up period and a variety of clinical characteristics. All of the clinical characteristics that were found to be significantly related to changes in either measures of lung function were then tested to determine whether interaction was observed between that characteristic and the follow-up time. Significant terms were then entered into a backward regression model to determine which clinical characteristics were independently associated with changes in TLC or D_{LCO} while controlling for age, sex, height, pack-years of cigarette smoking, and follow-up time. Two- and three-way interactions were tested following the backwards regression, and interactive terms were included only if the interaction was significantly ($p \leq 0.05$) related to changes in lung function.

RESULTS

Our study subjects tended to have mild reductions in their baseline lung volumes and moderate to severe abnormalities in gas exchange (table 2). Importantly, one-third of the subjects had mild dyspnea (Class I, II, or III), one-third had moderate dyspnea (Class IV), and one-third had severe dyspnea (Class V) (table 2). Interestingly, approximately 10% of the subjects had normal-appearing parenchyma on the chest radiograph and 10% had evidence of very severe fibrosis on the chest radiograph (table 2).

TABLE 2

INITIAL PULMONARY FUNCTION AND EXTENT OF INTERSTITIAL MARKINGS ON THE CHEST RADIOGRAPH FOR ALL STUDY SUBJECTS

	Mean ± SD	Range
Pulmonary function*		
FEV_1	76.6 ± 20.7	33–115
FVC	67.9 ± 21.6	29–124
FEV_1/FVC ratio	72.1 ± 5.2	60–80
RV	82.9 ± 22.7	43–142
TLC	77.1 ± 19.1	38–123
D_{LCO}	45.8 ± 17.6	13–81
Duration of dyspnea, days	677.4 ± 522.0	45–2,160
	N (%)	
Dyspnea Class†		
I	1 (2.6)	
II	7 (17.9)	
III	5 (12.8)	
IV	13 (33.3)	
V	13 (33.3)	
Chest radiograph– ILO Profusion		
0	4 (10.3)	
1	15 (38.5)	
2	12 (30.8)	
3	4 (10.3)	

Definition of abbeviations: RV = residual volume.

* All pulmonary function tests are expressed as the percent predicted except for the FEV_1/FVC ratio which is presented as an absolute percentage.

† Dyspnea score was independently identified by a blinded observer according to the guidelines established by the American Medical Association (24) and the American Thoracic Society (25).

During the period of observation, there was an average 5.3% increase in the TLC and a 9.8% increase in the D_{LCO} between the first and last measure of lung function. However, 25% of the population experienced a decline in the TLC and 28% of the population experienced a decline in the D_{LCO}. Among the 39 study subjects, there was a very broad range of lung function changes, with TLC ranging from an overall decrease of 32% to an increase of 76% and D_{LCO} ranging from a decrease of 14% to an increase of 41%. However, since lung function varied during the period of observation, limiting the analysis to the first and last measure of lung function oversimplifies the actual longitudinal course of lung function in these subjects with IPF. Thus, our analytic approach includes all follow-up measures of lung function for each study subject.

After controlling for potential confounders, excess longitudinal declines in the TLC were found to be significantly associated with severe dyspnea and treatment with cyclophosphamide (table 3). Interestingly, the degree of interstitial markings on the chest radiograph and the concentration of cells in the BAL fluid were not significantly related to changes in TLC. None of these variables interacted with follow-up time in subsequent analyses. Importantly, our backwards regression model indicated that after controlling for age, sex, height, pack-years of cigarette smoking, and follow-up time, longitudinal declines in TLC were independently related to severe dyspnea and treatment with cyclophosphamide (table 4). These findings demonstrate that the presence of severe dyspnea is associated with a 880-ml longitudinal decrease in the TLC and treatment with cyclophosphamide is associated with a 720-ml longitudinal decrease in the TLC. No interactions were observed between these variables or with these variables and follow-up time.

After controlling for potential confounders, excess longitudinal declines in D_{LCO} were found to be significantly associated with moderate to severe dyspnea, treatment with cyclophospha-

TABLE 3

RELATIONSHIP* BETWEEN LONGITUDINAL DECLINE IN TOTAL LUNG CAPACITY AND CLINICAL PARAMETERS

Clinical Parameter	Coefficient (*L*)	SE	p Value
Cigarette smoking			
Former	0.02	0.35	0.96
Current	1.35	0.54	0.01
Pack-years	0.002	0.01	0.87
Dyspnea			
Moderate	−0.28	0.34	0.41
Severe	−1.14	0.37	0.002
Duration of dyspnea	0.0003	0.0004	0.40
Treatment			
Corticosteroids	0.32	0.34	0.36
Cyclophosphamide	1.06	0.37	0.004
CXR ILO Profusion			
1	0.25	1.78	0.83
⩾ 2	0.91	1.19	0.44
BAL cellularity			
Macrophages/ml	0.001	0.0009	0.26
Lymphocytes/ml	0.006	0.008	0.45
Neutrophils/ml	−0.01	0.008	0.17
Eosinophils/ml	0.002	0.002	0.38

Definition of abbreviations: CXR = chest radiograph; BAL = bronchoalveolar lavage.

* All multivariate models controlled for age, sex, height, pack-years of cigarette smoking, and follow-up time except for the models that explored the relationship between cigarette smoking and longitudinal changes in TLC, which did not control for pack-years of cigarette smoking. The decline in TLC indicated by the coefficients represents the decline during the average duration of follow-up.

TABLE 5

RELATIONSHIP* BETWEEN LONGITUDINAL DECLINE IN DIFFUSING CAPACITY OF CARBON MONOXIDE (D_{LCO}) AND CLINICAL PARAMETERS

Clinical Parameter	Coefficient (*ml/min/mm Hg*)	SE	p Value
Cigarette smoking			
Former	−0.61	1.17	0.60
Current	1.40	2.44	0.57
Pack-years	−0.05	0.03	0.06
Dyspnea			
Moderate	−3.02	0.77	0.0001
Severe	−5.11	0.79	0.0001
Duration of dyspnea	0.0003	0.001	0.80
Treatment			
Corticosteroids	0.63	0.74	0.40
Cyclophosphamide	−4.26	0.79	0.0001
CXR ILO profusion			
1	1.18	2.55	0.64
⩾ 2	−0.23	2.63	0.93
BAL cellularity			
Macrophages/ml	0.005	0.003	0.09
Lymphocytes/ml	0.04	0.05	0.39
Neutrophils/ml	0.002	0.02	0.93
Eosinophils/ml	−0.02	0.006	0.0001

For definition of abbreviations, *see* table 3.

* All multivariate models controlled for age, sex, height, pack-years of cigarette smoking, and follow-up time except for the models that explored the relationship between cigarette smoking and longitudinal changes in D_{LCO}, which did not control for pack-years of cigarette smoking. The decline in D_{LCO} indicated by the coefficients represents the decline during the average duration of follow-up.

mide, and higher concentrations of eosinophils in BAL fluid (table 5). More pack-years of cigarette smoking was marginally associated (p = 0.06) with greater declines in D_{LCO} longitudinally. Again, interstitial changes on the chest radiograph were not significantly related to longitudinal changes in gas exchange. In subsequent analyses, none of these variables interacted significantly with follow-up time. Backwards regression of these significant variables indicated that after controlling for age, sex, height, and the follow-up time, longitudinal declines in the D_{LCO} were significantly associated with more pack-years of cigarette smoking, moderate or severe dyspnea, and treatment with cyclophosphamide (table 6). These findings demonstrate that the presence of moderate dyspnea is associated with a 2.7 ml/min/mm Hg longitudinal decrease in the D_{LCO}, the presence of severe dyspnea is associated with a 3.7 ml/min/mm Hg decrease in the D_{LCO}, treatment with cyclophosphamide is associated with a 3.6 ml/min/mm Hg decrease in the D_{LCO}, and for every pack-year of cigarette smoking the D_{LCO} will decline longitudinally by 0.04 ml/min/mm Hg. No interactions were observed between these variables or with these variables and follow-up time.

DISCUSSION

Our findings indicate that several clinical factors are predictive of subsequent measures of lung function in patients with IPF. The most influential variable associated with subsequent measures of either lung volume or gas exchange is the symptom of dyspnea. However, after accounting for the effect of this very important factor, other clinical features of pulmonary fibrosis, such as smoking status and treatment with cyclophosphamide, are also independently associated with prognosis. These findings indicate that patients with IPF can be placed in lower and higher risk categories based on clinical symptoms, smoking history, and need for immunosuppressive therapy.

Interpretation of these results requires that the reader under-

TABLE 4

MULTIVARIATE MODEL* THAT MOST CLOSELY APPROXIMATES LONGITUDINAL CHANGES IN TOTAL LUNG CAPACITY IN PATIENTS WITH IPF

Variable	Coefficient (*L*)	SE	p Value
Dyspnea			
Moderate	−0.24	0.33	0.48
Severe	−0.88	0.34	0.01
Treatment			
Prednisone	0.03	0.28	0.90
Cyclophosphamide	−0.72	0.34	0.03

* Multivariate model controlled for age, sex, height, pack-years of cigarette smoking, and follow-up time. The decline in TLC indicated by the coefficients represents the decline during the average duration of follow-up.

TABLE 6

MULTIVARIATE MODEL* THAT MOST CLOSELY APPROXIMATES LONGITUDINAL CHANGES IN DIFFUSING CAPACITY OF CARBON MONOXIDE IN PATIENTS WITH IPF

Variable	Coefficient (*ml/min/mm Hg*)	SE	p Value
Pack-years of smoking	−0.04	0.02	0.02
Dyspnea			
Moderate	−2.72	0.77	0.0004
Severe	−3.71	0.93	0.00007
Treatment			
Corticosteroids	−0.89	0.67	0.18
Cyclophosphamide	−3.65	0.99	0.0002

* Multivariate model controlled for age, sex, height, and follow-up time. The decline in D_{LCO} indicated by the coefficients represents the decline during the average duration of follow-up.

stand some basic principles guiding our analytic approach. A multivariate analysis allows one to identify the primary manifestations of a disease that are independently related to a complex outcome, such as prognosis. Because many clinical features of IPF are intimately related to each other, a multivariate analysis is essential to identify the primary factors that significantly contribute to a particular outcome. This does not imply that other features of the disease, not included in the multivariate model, are not related to prognosis. Rather, the multivariate models presented in this study simply identify the principal risk factors that independently contribute to prognosis in IPF. Perhaps this point is best illustrated by the relationship between BAL eosinophils and prognosis. We (15) and others (8, 14) have previously shown that excess eosinophils in BAL fluid are associated with a higher likelihood of disease progression and failure to respond to immunosuppression. In fact, in this current study, we have found that higher concentrations of eosinophils in the BAL fluid are significantly associated with greater longitudinal declines in the D_{LCO} ($p = 0.0001$). However, in our multivariate model, after accounting for the effects of cigarette smoking, dyspnea, and treatment with cyclophosphamide, the concentration of eosinophils in the BAL fluid was no longer related to prognosis. This should not be interpreted to indicate that the concentration of cells in the BAL fluid is not related to prognosis. Rather, our results indicate that the concentration of cells in BAL fluid is not the most important independent factor that contributes to prognosis. Other features of the disease appear to contribute far greater prognostic information than is obtained by the concentration of eosinophils in the BAL fluid.

Our results raise the possibility of using markers of disease severity (dyspnea classification and need for immunosuppressive therapy) and demographic features (cigarette smoking) to predict the risk of disease progression in patients with IPF. Although other investigators (32) have developed a clinical, radiographic, and physiologic scoring system for patients with IPF which appears to correlate with histologic evidence of interstitial fibrosis, the predictive utility of this scoring system has not been evaluated. Identifying those individuals who are at particularly high risk of disease progression is important because this will enhance our ability to develop suitable intervention studies within this heterogeneous population. Moreover, the prognostic information derived from these risk estimates may provide valuable information for clinicians and patients.

Interestingly, the degree of interstitial abnormalities on the chest radiograph was not associated with progressive physiologic declines in our study population. This suggests that the chest radiograph is relatively insensitive to the activity of the interstitial process. Once patients with IPF develop extensive interstitial lung disease that is radiographically evident, "end-stage" interstitial fibrosis may not progress physiologically. Importantly, the subtle, heterogeneous manifestations of interstitial lung disease are probably not apparent on the composite images provided by the chest radiograph. High-resolution CT scanning may contribute important prognostic information and may assist in understanding which types of radiographic lesions are potentially reversible. Future studies should include information from the high-resolution CT scan in assessing the prognostic importance of specific interstitial abnormalities in patients with IPF.

The assessment of dyspnea appears to be a particularly important prognostic factor among patients with IPF. Patients with moderate to severe dyspnea were found to have accelerated declines in both lung volumes and gas exchange. Moreover, others (32) have shown that improvement in dyspnea after 6 months of therapy appears to be more strongly associated with a more cellular histology than standard measures of lung function, the physiologic response to exercise, and interstitial abnormalities on the chest radiograph. These findings suggest that a simple assessment of dyspnea may be particularly helpful in managing patients with IPF. However, since we only observed progressive lung function decrements among those with moderate to severe dyspnea, more precise methods of characterizing dyspnea (33, 34) may improve the specificity of this prognostic factor. Additionally, these findings suggest that the assessment of the functional health status may be particularly useful in patients with pulmonary fibrosis. Multidimensional instruments, such as the Sickness Impact Profile (35–37), objectively measure basic activities of daily living (sleep and rest, eating, working, home management, recreation, ambulation, mobility, body care, social interactions, emotional behavior, and communications) which are clearly important to the patient and may provide prognostic information regarding the interstitial process. Additional studies are needed to identify the prognostic utility of dyspnea and to critically assess other complementary measures of functional ability in patients with pulmonary fibrosis.

Our results indicate that cigarette smoking may enhance the decrement in diffusing capacity among patients with IPF. This is particularly interesting since cigarette smoking profoundly alters the concentration of BAL cells among those with either IPF (16) or asbestosis (38) and appears to increase the risk of developing pulmonary fibrosis among workers exposed to asbestos (39) and among persons with rheumatoid arthritis (40). Importantly, cigarette smoking has been shown to profoundly alter the constituents and function of alveolar lining cells (41–45) and enhance the permeability of the airway epithelia (46). Given the results from this investigation, one could hypothesize that cigarette smoking augments the inflammatory process in IPF and contributes to the progression of interstitial fibrosis. Alternatively, two independent processes (IPF and emphysema) may both be contributing to the progressive decline in gas exchange. The absence of a relationship between cigarette smoking and changes in lung volume may reflect the opposing effects that interstitial fibrosis and emphysema have on this measure of lung function in patients with IPF (17). Future investigations should incorporate sophisticated radiographic methods to precisely define the parenchymal abnormalities in patients with IPF who have smoked cigarettes. The results of this study, which demonstrate an enhanced decrement in gas exchange attributable to cigarette smoking, and earlier studies, which show a biologic effect of smoking (16), raise the provocative hypothesis that cigarette smoking is a risk factor for the development and progression of fibrosis, as well as emphysema, of the lung.

Although we found that treatment with cyclophosphamide was significantly associated with decrements in TLC and D_{LCO}, we do not interpret these results to imply that treatment with this agent caused progressive abnormalities in lung function. Our study was not designed as a treatment intervention trial. Treatment with immunosuppressive agents was a consequence of progressive lung disease and should not be thought of as a risk factor for disease progression. However, treatment intervention trials are clearly needed to determine if these therapies actually benefit patients and/or alter the natural history of the lung disease.

Our results indicate that patients with more severe manifestations of IPF are at higher risk of progressive deterioration in lung function. Alternatively, those with less lung involvement, as assessed by dyspnea classification and standard measures of lung function, appear to have a more benign course. These findings are further supported by the observation that more advanced radiographic and physiologic evidence of interstitial lung disease adversely affects survival in patients with IPF (4–11). These findings also appear to suggest that treatment for IPF may be more effective before the manifestation of severe interstitial fibrosis. This interpretation, however, assumes that those with mild IPF are at high risk of disease progression. The results of this study suggest that those with mild disease will continue to have mild disease. However, this finding should be validated in a more extensive study where later deterioration in lung function might be observed.

Given the 5-yr, 50% mortality that is associated with this disease, it is critical that clinical endpoints be identified that are potentially reversible, such as dyspnea and lung function abnormalities. This investigation has identified some potentially important clinical features that were predictive of progressive lung disease in our population of patients with IPF. It will be important to prospectively test these prognostic factors in other populations of patients with IPF to assess the validity and generalizability of our findings. Our results do suggest, however, that risk stratification among patients with IPF is feasible and should be incorporated into intervention trials that evaluate patients with IPF.

References

1. Fulmer JD, Roberts WC, Von Gal EW, Crystal RG. Morphologic-physiologic correlates of the severity of fibrosis and degree of cellularity in idiopathic pulmonary fibrosis. J Clin Invest 1979; 63:665–76.
2. Pande JN. Interrelationship between lung volume, expiratory flow, and the lung transfer factor in fibrosing alveolitis. Thorax 1981; 36:858–62.
3. Cherniack RM, Crystal RG, Kalica AR. Current concepts in idiopathic pulmonary fibrosis: a road map for the future. Am Rev Respir Dis 1991; 143:680–3.
4. Carrington CB, Gaensler EA, Coutu RE, Fitzgerald MX, Gupta RG. Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med 1978; 298:801–9.
5. Turner-Warwick M, Burrow B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival. Thorax 1980; 35:171–80.
6. Tukiainen P, Taskinen E, Holsti P, Korhola O, Valle M. Prognosis of cryptogenic fibrosing alveolitis. Thorax 1983; 38:349–55.
7. Stack BHR, Choo-Kang YFJ, Heard BE. The prognosis of cryptogenic fibrosing alveolitis. Thorax 1972; 27:535–42.
8. Rudd RM, Haslam PL, Turner-Warwick M. Cryptogenic fibrosing alveolitis. Am Rev Respir Dis 1981; 124:1–8.
9. Livingstone JL, Lewis JG, Reid L, Jefferson KE. Diffuse interstitial pulmonary fibrosis. Quart J Med 1964; 33:71–103.
10. Hiwatari N, Shimura S, Sasaki T, Aikawa T, Ando Y, Ishihara H, Sekizawa K, Sasaki H, Takishima T. Prognosis of idiopathic pulmonary fibrosis in patients with mucous hypersecretion. Am Rev Respir Dis 1991; 143:182–5.
11. Schwartz DA, Helmers RA, Galvin JR, Van Fossen DS, Frees KL, Dayton CS, Burmeister LF, Hunninghake GW. Determinants of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1994; 149: 450–4.
12. Turner-Warwick M, Haslam PL. The value of serial bronchoalveolar lavages in assessing the clinical progress of patients with cryptogenic fibrosing alveolitis. Am Rev Respir Dis 1987; 135:26–34.
13. Watters LC, Schwarz MI, Cherniack RM, Waldron JA, Dunn TL, Stanford RE, King TE. Idiopathic pulmonary fibrosis: pretreatment bronchoalveolar lavage cellular constituents and their relationships with lung histopathology and clinical response to therapy. Am Rev Respir Dis 1987; 135:696–704.
14. Haslam PL, Turton GWG, Heard B, Lukoszek A, Collins JV, Salsbury AJ, Turner-Warwick M. Bronchoalveolar lavage in pulmonary fibrosis: comparison of cells obtained with lung biopsy and clinical features. Thorax 1980; 35:9–18.
15. Peterson MW, Monick M, Hunninghake GW. Prognostic role of eosinophils in pulmonary fibrosis. Chest 1987; 92:51–6.
16. Schwartz DA, Helmers RA, Dayton CS, Merchant RK, Hunninghake GW. Determinants of bronchoalveolar lavage cellularity in idiopathic pulmonary fibrosis. J Appl Physiol 1991; 71:1688–93.
17. Schwartz DA, Merchant RK, Helmers RA, Gilbert SR, Dayton CS, Hunninghake GW. The influence of cigarette smoking on lung function in patients with idiopathic pulmonary fibrosis. Am Rev Respir Dis 1991; 144:504–6.
18. Hanley ME, King TE, Schwarz MI, Watters LC, Shen AS, Cherniack RM. The impact of smoking on mechanical properties of the lungs in idiopathic pulmonary fibrosis and sarcoidosis. Am Rev Respir Dis 1991; 144:1102–6.
19. Leibow AA, Carrington CB. The interstitial pneumonias. In: Simon M, ed. Frontiers in pulmonary radiology. New York: Grune and Stratton, 1968; 102–41.
20. American Thoracic Society Statement. Snowbird workshop on standardization of spirometry. Am Rev Respir Dis 1979; 119:831–8.
21. Morris JF, Koski A, Johnson LC. Spirometric standards for healthy nonsmoking adults. Am Rev Respir Dis 1971; 103:57–67.
22. Goldman HI, Becklake MR. Respiratory function tests: normal values at median altitudes and the prediction of normal results. Am Rev Tuberc 1959; 79:457–67.
23. Van Ganse WF, Ferris BG, Cotes JE. Cigarette smoking and pulmonary diffusing capacity (transfer factor). Am Rev Respir Dis 1972; 105:30–41.
24. American Medical Association. Guides to the evaluation of permanent impairment. Chicago: AMA, 1989.
25. Renzetti AD, Bleeker ER, Epler GR, Jones RN, Kanner RE, Repsher LH. Evaluation of impairment/disability secondary to respiratory disorders. Am Rev Respir Dis 1986; 133:1205–9.
26. International Labor Organization. International classification of radiographs of pneumoconioses: guidelines for the use of International Labor Organization (ILO). Geneva: International Labor Office, 1980.
27. Zavala DC, Hunninghake GW. Lung lavage. In: Fleney DC, Petty TL, eds. Recent advances in respiratory medicine. Vol. 3. Edinburgh: Churchill Livingston, 1983; 21–33.
28. Zerger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986; 42:121–30.
29. Davis CS. A computer program for regression analysis of repeated measures using generalized estimating equations. Comput Methods Programs Biomed 1993; 40:15–31.
30. Kleinbaum DG, Kupper LL. Applied regression analysis and other multivariate methods. Boston, MA: Duxbury, 1978.
31. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules: applications and methodological standards. N Engl J Med 1985; 313:793–9.
32. Watters LC, King TE, Schwarz MI, Waldron JA, Stanford RE, Cherniack RM. A clinical, radiographic, and physiologic scoring system for the longitudinal assessment of patients with idiopathic pulmonary fibrosis. Am Rev Respir Dis 1986; 133:97–103.
33. Killian KJ, Campbell EJ. Dyspnea and exercise. Ann Rev Physiol 1983; 45:465–79.
34. Simon PM, Schwartzstein RM, Weiss JW, Fencl V, Teghtsoonian M, Weinberger SE. Distinguishable types of dyspnea in patients with shortness of breath. Am Rev Respir Dis 1990; 142:1009–14.
35. Bergner M, Bobbitt RA, Kressel S, Pollard WE, Gilson BS, Morris JR. The Sickness Impact Profile: conceptual formulation and methodology for the development of a health status measure. Int J Health Serv 1976; 6:393–415.
36. Bergner M, Bobbitt A, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981; 19:787–805.
37. Bergner M. Quality of life, health status, and clinical research. Med Care 1989; 27:S148–56.
38. Schwartz DA, Galvin JR, Merchant RK, Dayton CS, Burmeister LF, Merchant JA, Hunninghake GW. The influence of cigarette smoking on bronchoalveolar lavage cellularity in asbestos-induced lung disease. Am Rev Respir Dis 1992; 145:400–5.
39. Blanc PD, Golden JA, Gamsu G, Aberle DR, Gold WM. Asbestos exposure–cigarette smoking interactions among shipyard workers. JAMA 1988; 259:370–3.
40. Hunninghake GW, Fauci AS. Pulmonary involvement in the collagen vascular diseases. Am Rev Respir Dis 1979; 119:471–503.
41. Barbers RG, Gong H, Takhkin DP, Oishi J, Wallace JM. Differential examination of bronchoalveolar lavage cells in tobacco cigarette and marijuana smokers. Am Rev Respir Dis 1987; 135:1271–5.
42. Harris JO, Swenson EW, Johnson JE. Human alveolar macrophages: comparison of phagocytic ability, glucose utilization, and ultrastructure in smokers and nonsmokers. J Clin Invest 1970; 49:2086–96.
43. Gadek JE, Fells GA, Crystal RG. Cigarette smoking induces functional antiprotease deficiency in the lower respiratory of humans. Science 1979; 206:1315–6.
44. Merrill WW, Goodenberger D, Strober W, Matthay RA, Nagel GP, Reynolds HY. Free secretary component and other proteins in human lung lavage. Am Rev Respir Dis 1980; 122:156–61.
45. Villiger B, Broekelmann T, Kelley D, Heymach GJ, McDonald JA. Bronchoalveolar fibronectin in nonsmokers and smokers. Am Rev Respir Dis 1981; 124:652–4.
46. McFadden D, Wright JC, Wiggs B, Churg A. Cigarette smoke increases the penetration of asbestos fibers in airway walls. Am J Pathol 1986; 123:95–9.