Morphologic-Physiologic Correlates of the Severity of Fibrosis and Degree of Cellularity in Idiopathic Pulmonary Fibrosis

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A B S T R A C T Idiopathic pulmonary fibrosis (IPF) is a progressive disease of lung parenchyma characterized by a chronic inflammatory cellular infiltration and varying degrees of interstitial fibrosis. Current data indicate that the severity of fibrosis and the degree of cellularity determine, in part, the prognosis of IPF and the response to therapy. Whereas lung biopsy gives the best assessment of fibrosis and cellularity, physiologic studies are used to stage and monitor the disease process. To determine which physiologic studies correlate best with severity of fibrosis and degree of cellularity, these parameters were graded in lung biopsies of 23 patients with IPF and compared with a variety of physiologic studies.

Although vital capacity, total lung capacity, and diffusing capacity are commonly used as objective monitors of the disease process, none of these parameters correlated with either the severity of fibrosis or the degree of cellularity in biopsy specimens. In contrast, almost all parameters of lung distensibility correlated with the morphologic assessment of degree of fibrosis; compliance had the best correlation. Parameters of distensibility, however, correlated poorly with the degree of cellularity.

In comparison, gas exchange during exercise correlated with both morphologic parameters; the exercise-induced changes in arterial oxygen pressure per liter of oxygen consumed had a high correlation with the degree of fibrosis ($r = 0.89$; $P < 0.001$) and correlated to a lesser extent with the degree of cellularity ($r = 0.56$; $P = 0.009$). In contrast, neither the resting arterial oxygen tension nor the arterial oxygen tension at maximal exercise correlated with the morphologic assessment of degree of fibrosis or the degree of cellularity.

These morphologic-physiologic comparisons suggest that (*a*) lung volumes and diffusing capacity are poor monitors of both the degree of fibrosis and the degree of cellularity; (*b*) the fibrotic process contributes, at least in part, to parameters of lung distensibility, and both fibrosis and cellularity contribute to gas exchange alterations during exercise; and (*c*) parameters of lung distensibility and exercise-induced gas exchange alterations may be useful in staging the severity of disease in IPF.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF)[1] is a progressive, generally fatal disease characterized by an interstitial and intra-alveolar inflammatory process, interstitial fibrosis, and revision of the distal lung architecture (1–12). Early in the disease, most patients with IPF present with exertional breathlessness, an alveolar filling pattern on chest roentgenogram, and reduced diffusing capacity. As the disease progresses, patients develop marked exertional dyspnea, a reticulonodular pattern on x-ray, and resting hypoxemia. Advanced IPF is characterized by breathlessness at rest and roentgenographically by a coarse reticular pattern with cystic lesions.

Current concepts of the pathogenesis of IPF are that

[1] *Abbreviations used in this paper*: A-aDo$_2$, alveolar-arterial oxygen pressure gradient; CR, coefficient of retraction; DL$_{CO}$, diffusing capacity of the lungs; FRC, functional residual capacity; IPF, idiopathic pulmonary fibrosis; P$_{50}$, Pst at 50% of observed TLC; P$_{70}$, Pst at 70% of observed TLC; P$_{max}$, maximum transpulmonary pressure; Pst, static transpulmonary pressure during deflation; TLC, total lung capacity; VC, vital capacity.

the fibrosis is preceded by an inflammatory cellular infiltration. Early disease is characterized by minimal fibrosis and an active cellular response, whereas advanced disease is characterized by severe fibrosis and minimal cellularity (8, 11–13). Furthermore, correlative studies have shown that the prognosis and response to therapy in IPF is determined, in part, by the severity of fibrosis and the degree of cellularity (11, 13). Although the lung biopsy gives the best assessment of the severity of fibrosis and cellularity in IPF, it is generally performed only once in the course of the disease. It would, therefore, be useful to have monitors of the disease process that can be used repeatedly. In general, the currently accepted monitors of the overall severity of the disease in IPF are lung volumes, diffusing capacity, and arterial blood gases (14–17). There are, however, little data on the usefulness of physiologic tests in gauging either the severity of the fibrosis or the degree of cellularity.

To this end, the present study was designed to evaluate the usefulness of lung volumes, diffusing capacity, and arterial blood gases to guage the extent of fibrosis and cellularity in IPF, and to identify other physiologic studies that may be of use. To accomplish this, we have evaluated a group of patients with IPF by (a) grading the severity of fibrosis and cellularity in their lung biopsies; (b) characterizing the physiologic alterations in these patients by a number of tests, including lung volumes, diffusing capacity, tests of distensibility, and gas exchange at rest and exercise; and (c) comparing the results of the morphologic and physiologic data.

METHODS

Patient population

As part of a study of fibrotic lung disease, 250 patients were referred to the Pulmonary Branch of the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md. From this group, 75 were determined to have IPF by the following criteria (8–10).

Clinical. The 75 subjects revealed a history of progressive, exertional breathlessness; no history of exposure to inorganic, organic, gaseous, physical, or pharmacological agents known to cause pulmonary fibrosis; no history suggestive of hypersensitivity lung disease; no history of chronic bronchitis; no history of chronic pulmonary infection; and no history or clinical findings suggestive of left ventricular failure.

Roentgenographic. The presence of a diffuse interstitial pattern with no left ventricular enlargement.

Physiologic. There was presence of reduced lung volumes or diffusing capacity, exercise-induced hypoxemia, normal forced expiratory volume in 1 s/forced vital capacity, and normal airway resistance by body plethysmography.

Morphologic. A biopsy revealed varying degrees of interstitial fibrosis with interstitial and intra-alveolar cells consisting primarily of lymphocytes and macrophages, but including neutrophils and eosinophils; No vasculitis or granulomata was present, or significant inorganic material by polarized light

microscopy, and negative cultures for bacteria, mycobacteria, and fungi.

Patients were included in this study if they met the diagnostic criteria for IPF, had a recent lung biopsy that was taken from a representative area as judged by the chest roentgenogram, and were able to participate in physiologic testing. If the lung biopsy demonstrated "end-stage lung" (see below), they were excluded.

From the initial 75 patients, 23 fit all of the above criteria. Patients who were excluded from the present study were done so because of failure to have a recent biopsy, failure to have a biopsy from an area on the film that was judged to be representative, or inability to participate in physiologic testing because of marked breathlessness or other medical problems. Of the 23 patients, 2 (M.C., V.J.) had rheumatoid arthritis, and 1 (O.N.) had an overlap connective tissue syndrome. These three patients all had lung biopsies that were indistinguishable from the other patients and had no evidence of lung or systemic vasculitis. 12 patients had open lung biopsy at our institution with physiologic testing performed 2–4 wk before biopsy; the other 11 patients had lung biopsies performed at an outside institution with physiologic testing performed at our institution an average of 4 mo after biopsy.

Morphologic grading of fibrosis and cellularity

All morphologic observations were made without knowledge of the results of physiologic testing. 22 of the biopsies were obtained by open thoracotomy; one was obtained by drill needle biopsy. For control tissue (no fibrosis), lung tissue was obtained at thoracotomy from patients with solitary nodules; in most cases, an entire lobe was removed. Parenchyma at least 1 cm in distance from the nodule was taken as representing normal lung. Before surgery, these patients underwent routine physiologic testing; only those with normal pulmonary function studies were accepted as controls.

All biopsy specimens were fixed in 10% neutral formalin, processed in alcohol and xylene, imbedded in paraffin, and serially sectioned at 6-μm intervals. Sections were stained with hematoxylin–eosin and Masson trichome. Grading of the degree of fibrosis in each biopsy was made with Masson trichome-stained sections and grading of the cellularity was made with hematoxylin–eosin stain. Grading of both the degree of fibrosis and degree of cellularity was made with an estimate of the increase in each compared with noninflated control lung. The grade of minimal (+1) was assigned when there was <10% increase; mild (+2) was assigned when there was a 10–25% increase; moderate (+3) was assigned when there was a 25–40% increase; and severe (+4) was assigned when there was >40% increase.

Each biopsy was graded an average of four times by three observers, and a mean grade of degree of fibrosis and degree of cellularity was determined. For each biopsy, an intra-observer and an inter-observer variability was computed.

Lung volumes, timed expiratory maneuvers, airway resistance and diffusing capacity

Lung volumes, standard-timed expiratory maneuvers, and single breath diffusing capacity for carbon monoxide were measured with a computerized modular lung analyzer (P-1200; Warren E. Collins, Inc., Braintree, Mass.) as previously described (10). Predicted values for vital capacity (VC), forced VC, and forced expiratory volume in 1 s were obtained from the predicted equations of Morris et al. (18); predicted residual volume and functional residual capacity (FRC) were taken from the data of Goldman and Becklacke (19).

Predicted total lung capacity (TLC) was obtained by adding predicted VC and predicted residual volume. The predicted values of diffusing capacity (DL_{CO}) of Gaensler and Wright (20) were used. Airway resistance was determined by the method of DuBois et al. (21) using a constant volume plethysmograph (Warren E. Collins, Inc.), as previously described (10). Normal airway resistance was considered to be 2.5 cm H_2O/liter per s (21).

Static volume-pressure relationship

Measurements of lung volume-pressure relationships were made as previously described (10). Balloon volume was corrected by the methods of Milic-Emili et al. (22) or Lemen et al. (23). A constant volume history was assured by having the patient hyperventilate and then inspire to TLC three times (24). Static transpulmonary pressure at the TLC (P_{max}) was recorded with glottis open while the subject maintained a maximum inspiration for 2–3 s (25–27). Static transpulmonary pressure during deflation (Pst) was measured as the pressure difference between mouth and esophageal balloon with glottis open and flow being interrupted by a solenoid-operated shutter. Static deflation volume-pressure curves were constructed using an average of 4 deflation maneuvers with 12–14 points per maneuver. Volume was corrected to body temperature, pressure saturated and required to be ±5% of VC as recorded by standard spirometry. From these data, the following parameters were quantitated.

Static deflation compliance (compliance). Compliance was measured as the change in volume per unit pressure change between FRC (liters) and FRC + 0.5 liter on the static deflation volume-pressure curve when volume was expressed as observed VC (liters) (Fig. 1A). Compliance was considered to be a monitor of lung distensibility in the tidal volume range. The normal range for compliance was considered to be 0.15–0.30 liters/cm H_2O (27).

Slope of the volume-pressure curve (comparative compliance). To compare compliance data between patients with a wide range of lung volumes, the volume-pressure data was plotted as a percent of predicted TLC vs. Pst (centimeters of H_2O) and the slope of the curve was measured between Pst at 50% observed TLC (P_{50}) and Pst at 70% observed TLC (P_{70}) using the formula: comparative compliance = (volume [as percent of predicted TLC] at P_{70} – volume [as percent of predicted TLC] at P_{50})/(P_{70}[centimeters of H_2O] – P_{50}[centimeters of H_2O]) (Fig. 1B, C). Comparative compliance was considered to be a measure of lung distensibility at mid-lung volumes that could be used to compare patient to patient; the units of comparative compliance are percentages of predicted TLC per centimeters of H_2O. Normal values are age related and range from 2.9 to 3.7%/cm H_2O (24).

Position of the volume-pressure curve (P_{70}). P_{70} was determined by recording the static transpulmonary pressure at 70% observed TLC (Fig. 1B). P_{70} provided an index as to whether the volume-pressure curve (when expressed as a percent of observed TLC) was normal or shifted to the right or left when compared with the normal data of Turner et al. (24). In addition, P_{70} was used as a measure of the pressure necessary to expand the lung at mid-range volume. Normal values are age related and range from 5.5 to 12.0 cm H_2O (24).

Maximum transpulmonary pressure (P_{max}). P_{max} was measured at TLC and expressed in centimeters of H_2O (Fig. 1A). P_{max} was used as an index of recoil pressure at maximum lung volume (TLC). Normal values are age dependent and range from 20 to 45 cm H_2O (24).

Coefficient of retraction (CR). Calculated by the formula of Schlueter et al. (26), CR = P_{max} (centimeters of H_2O)/ TLC (liters) (Fig. 1A). CR was used as an index of maximum recoil
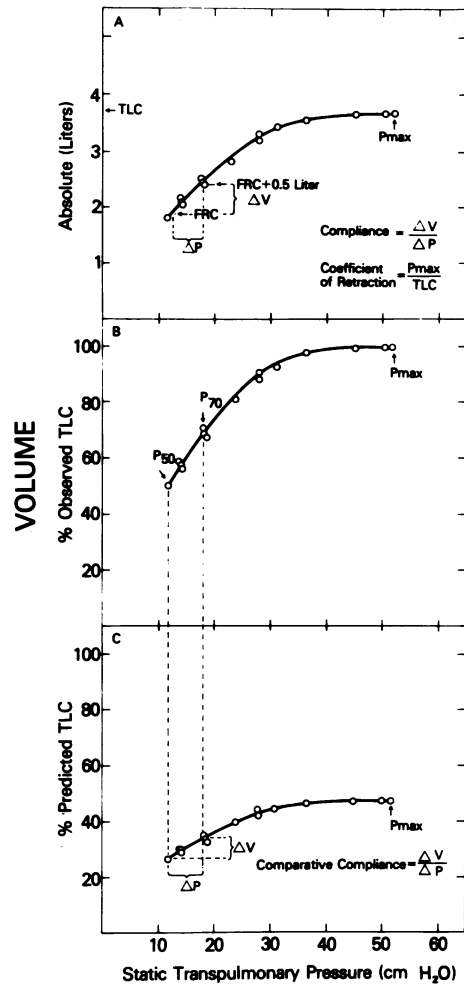

FIGURE 1 Analysis of the static deflation volume-pressure relationship. Illustration of the methods for (A) determining the measurement of compliance and CR, (B) determining the position of P_{70}, and (C) calculating comparative compliance. The data used for this example is from patient W.H.

pressure when adjusted for the lung volume of the individual patient. Normal values range from 4.0 to 8.0 cm H_2O/liter (26, 28).

Steady-state gas exchange and physiologic shunt

Steady-state gas exchange studies were performed at rest and, if possible, during graded exercise for a maximum of three levels of power output. Graded exercise was achieved using a motor-driven, variable speed and grade treadmill (model 18–94C, Quinton Instruments, Seattle, Wash.). A low-resistance, high-speed breathing valve (P-316, W. E. Collins) was used, and the gas collected in a 120-liter gasometer (P-1700, Warren E. Collins, Inc.). Breath-by-breath analysis of O_2, CO_2, and N_2 were monitored by a medical gas analyzer (model 1100; Perkin-Elmer, Pomona, Calif.) on line to an eight-channel universal recorder (Gould, Inc., Measurement Systems Div., Oxnard, Calif.). Expired gases in the gasometer

were analyzed with the medical gas analyzer and checked against an infrared CO_2 analyzer (model LB-2, Beckman Instruments, Inc., Electronic Instruments Div., Schiller Park, Ill.) and paramagnetic O_2 analyzer (model OM-11, Beckman Instruments, Inc.). All gas analysis apparatus were calibrated before each study using room air and two gravimetrically determined gas mixtures (4% CO_2, 14% O_2, balance N_2; and 8% CO_2, balance O_2; Landsel Cryogenics, Hyattsville, Md.).

Arterial blood gas pressures were analyzed with a Radiometer blood micro-system (BMS 3-Mk2, The London Co., Cleveland, Ohio) and a direct reading acid base analyzer (PHM71-Mk, The London Co.). Calibration gases for the O_2 and CO_2 electrodes included four gases: 100% O_2, room air; 4% CO_2, balance N_2; and 8% CO_2, 21% O_2, balance N_2 (Liquid Carbonics, Baltimore, Md.). Gas mixtures were gravimetrically determined and checked by gas chromatography. The pH electrode was calibrated with certified Radiometer buffers (pH 6.841 and pH 7.383, The London Co.). The blood gas system was regularly checked against tonometered bloods (type 247; International Laboratories, Rockville, Md.).

After the patient was familiarized with the procedure and instructed in walking on the treadmill, a 20-gauge, thin-walled, Teflon catheter (Becton, Dickinson and Co., Rutherford, N. J.) was placed in the radial artery using local anesthesia. Cardiac monitoring was performed throughout the procedure.

All studies were done at steady state, defined as that point when end expiratory CO_2 and heart rate reached constant values (this usually took 3–6 min). The speed and incline of the treadmill were adjusted such that three levels of exercise could be attached based on the following target heart rates: stage 0, at rest in the sitting position; stage I, exercise with heart rate 110–120 beats/min; stage II, exercise with heart rate 130–140 beats/min; stage III; exercise with heart rate 140–160 beats/min. Patients rested between stages until their heart rates returned to stage 0 (resting level). Studies were terminated if any of the following occurred: (a) the electrocardiogram showed significant segment depression of >1 mV; (b) the electrocardiogram showed >10 premature ventricular contractions/min or >2 premature ventricular contractions in series; (c) the patient did not feel he could continue; or (d) if the arterial oxygen tension (PAO_2) was <45 mm Hg in a patient >40 yr of age.

At each stage, once a steady state was achieved and expired gas had been used to flush the gasometer 3–5 times, expired gas was collected for 2 min. Midway during these 2 min, an arterial blood sample was taken. The collected expired gas was analyzed for the fraction of O_2, CO_2, and N_2; the arterial blood was analyzed for the partial pressure of O_2, and CO_2, and for pH. From these data, minute ventilation, alveolar ventilation, O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), alveolar oxygen tension (PA_{O_2}), and alveolar-arterial oxygen pressure gradient (A-aDO_2), were calculated using standard equations (29). In addition, the following derived parameters were calculated.

Exercise parameter 1: the absolute change in PaO_2 between rest and maximal exercise. Exercise parameter 1 = (PaO_2 [maximal $\dot{V}O_2$ achieved] − PaO_2 [stage 0]).

Exercise parameter 2: the absolute change in the A-aDO_2 between rest and exercise. Exercise parameter 2 = (A-aDO_2 [maximal $\dot{V}O_2$ achieved] − A-aDO_2 [stage 0]).

Exercise parameter 3: change in PaO_2 per liter of oxygen consumed during exercise. PaO_2 was plotted against $\dot{V}O_2$ for stages 0 through the maximal stage achieved; by the method of least squares, the slope ($\Delta PaO_2/\Delta \dot{V}O_2$) was computed (Fig. 2A). The normal range of $\Delta PaO_2/\Delta \dot{V}O_2$ in our laboratory is +5 to −3
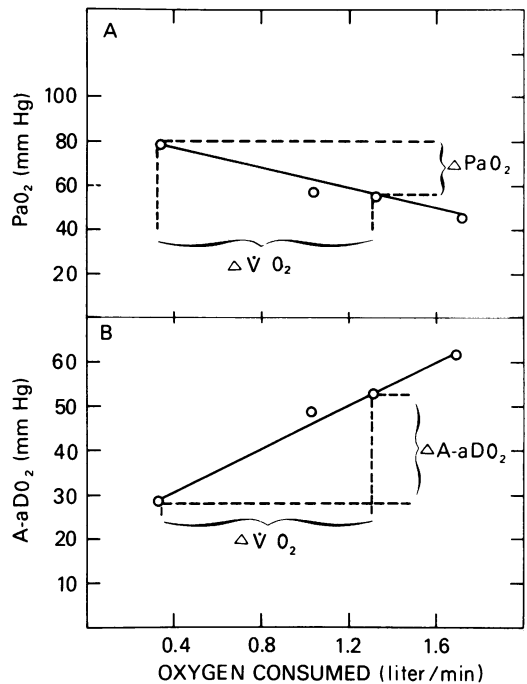

FIGURE 2   Method for calculation of (A) the change in PaO_2 per liter oxygen consumed during exercise ($\Delta PaO_2/\Delta \dot{V}O_2$) and (B) the change in A-aDO_2 per liter oxygen consumed during exercise (ΔA-a$DO_2/\Delta \dot{V}O_2$). The data used for this example is from patient W.H.

mm Hg-min/liter which is in agreement with published data (30, 31).

Exercise parameter 4: the change in A-aDO_2 per liter oxygen consumed during exercise. A-aDO_2 was plotted against $\dot{V}O_2$ for stage 0 through the maximal stage achieved; by the method of least squares, the slope (ΔA-a$DO_2/\Delta \dot{V}O_2$) was computed (Fig. 2B). The normal range of ΔA-a$DO_2/\Delta \dot{V}O_2$ in our laboratory is +4 to +8 mm Hg-min/liter which is in agreement with published data (30, 31).

Physiologic shunt was estimated using 100% O_2 after monitoring expired gases until no N_2 could be detected with a Valsava maneuver. Care was taken to periodically have the patient deep breathe to attempt to circumvent airway closure. The standard shunt equation was used with the arterial-venous oxygen content difference assumed to be 5 vol% (32).

Statistical analysis of data

Two-methods were used for data analysis: Spearman rank correlation and the two-tailed Student's t test. To facilitate discussion of the analysis, data were grouped as follows: (a) clinical data included age, sex, duration of symptoms, smoking history; (b) standard physiologic data included VC, TLC, FRC, and DL_{CO}; (c) distensibility data included compliance, comparative compliance, P_{70}, P_{max} and CR; (d) gas exchange data included resting and exercise PaO_2, resting and exercise A-aDO_2, and exercise parameters 1–4 and physiologic shunt; and (e) morphologic data. included the degree of fibrosis and the degree of cellularity assigned to each biopsy.

Spearman rank correlation was used to compare morpho-

logic data to all other data because fibrosis and cellularity were ranked from minimal (+1) to severe (+4), and all other data were either continuous or ranked (33).

The two-tailed t test was used to compare mean values of gas exchange data between patients grouped by the extent of exercise achieved (stages I–III) (34). The Aspen correction was used for degrees of freedom when the variance of one mean value was >3 times the variance of the other mean value (35).

RESULTS

Clinical data

The study patients (16 male, 7 female) ranged in age from 27 to 67 yr (mean±SEM, 48.4±2.9 yr). Duration of symptoms ranged from 0.5 to 10 yr (mean±SEM, 2.0±0.5 yr) (Table I). Although some patients had a history of cough, none had clinical evidence of chronic bronchitis. Nine patients were taking prednisone at the time of evaluation and one patient was taking phenylbutazone (Table I).

Standard physiologic studies, timed spirometry, and airway resistance

Lung volumes were variable with mean values between 55 and 60% of predicted (Fig. 3). Total lung capacity ranged from normal (86% predicted) to severely reduced (33% predicted); DL_{CO} also ranged from normal (96% predicted) to severely reduced (15% predicted). With standard physiologic criteria based on percent predicted values of TLC (65–80% mild, 45–65% moderate, and <45% severe), 7 patients had mild restrictive disease, 12 had moderate disease, and 3 had severe disease. Applying the same criteria to the percent predicted values of DL_{CO}, 3 patients had a mild reduction, 12 had a moderate reduction, and 7 had a severe reduction in DL_{CO}.

Morphologic observations

The grading system used to estimate the degree of fibrosis, and the degree of cellularity in biopsy speci-

TABLE I
Clinical and Morphologic Data on 23 Patients with IPF

		Clinical data					Morphologic data	
Patient	Symbol	Age	Sex	Duration of symptoms	Smoking history*	Drug history‡	Degree of fibrosis	Degree of cellularity
		yr		*yr*				
E.B.	○	48	M	1.5	Heavy	None	+1	+1
M.B.	●	60	F	2.0	Moderate	Prednisone	+3	+2
M.C.	◑	57	F	0.5	Nonsmoker	Phenylbutazone	+4	+3
R.C.	◐	66	M	0.5	Nonsmoker	Prednisone	+3	+3
R.I.C.	◓	32	M	0.5	Moderate	None	+2	+2
N.C.	◔	27	M	2.0	Light	Prednisone	+4	+2
A.D.	□	67	M	0.5	Moderate§	Prednisone	+4	+2
W.D.	■	43	M	0.5	Moderate§	None	+1	+1
G.F.	◧	51	M	2.0	Moderate§	Prednisone	+3	+2
A.H.	◨	27	F	2.0	Light§	None	+2	+2
W.H.	◩	41	M	2.0	Light§	None	+3	+2
V.J.	◪	27	F	0.5	Nonsmoker	None	+1	+1
W.L.	◰	67	M	10.0	Heavy§	None	+4	+2
O.N.	◳	27	F	1.5	Nonsmoker	Prednisone	+4	+2
P.R.	△	31	F	0.5	Moderate§	Prednisone	+2	+3
J.S.	▲	58	M	7.0	Moderate§	None	+4	+2
J.C.S.	◭	61	M	1.5	Heavy§	None	+4	+3
W.E.S.	◮	66	M	1.0	Cigars§	None	+4	+2
R.S.	◬	52	M	2.0	Nonsmoker	Prednisone	+4	+2
J.K.S.	◭	46	M	2.0	Moderate§	Prednisone	+4	+3
W.L.S.	▽	58	M	1.0	Moderate§	None	+2	+2
B.T.	▼	47	F	0.5	Nonsmoker	None	+4	+2
E.T.	▼	55	M	5.0	Nonsmoker	None	+4	+2
Mean		48.4		2.0			+3.0	+2.0
±SEM		±2.9		±0.5			±0.2	±0.1

* Light <10 pack-yr; moderate = 10–25 pack-yr, heavy = >25 pack-yr.
‡ Only anti-inflammatory drugs are listed.
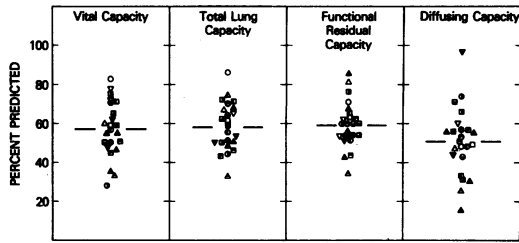§ Stopped smoking >6 mo before study.

FIGURE 3 Distribution of lung volumes and diffusing capacity in 23 patients with IPF. Each symbol represents an individual patient; the key to the symbols is presented in Table I. Horizontal bars present the mean values.

mens was reproducible. Among three blinded observers, the average intra-observer coefficient of variation for grading of fibrosis was $6.2\pm1.2\%$ and for the grading of cellularity was $8.0\pm1.5\%$. The mean inter-observer error was 8.0%.

3 biopsies (13%) demonstrated minimal fibrosis (+1); 4 biopsies had mild fibrosis (+2); 4 (17%) had moderate fibrosis (+3); and 12 had severe fibrosis (+4) (Table I). The average degree of fibrosis for all patients was moderate (+3). 3 (13%) biopsies had minimal cellularity (+1); 15 (65%) had mild cellularity (+2); 5 (22%) had moderate cellularity (+3); and none had severe cellularity (+4). The mean degree of cellularity was mild (+2).

Distensibility data

Compliance ranged from 0.03 to 0.49 liters/cm H_2O (mean 0.13 ± 0.02 liters/cm H_2O). One patient (E.B.) had increased compliance, whereas 7 patients (R.C., R.I.C., W.D., G.F., A.H., P.R., W.L.S.) had normal or nearly normal compliance; the remaining 15 patients had reduced compliance (Fig. 4).

The volume-pressure curve, when expressed as a percent a predicted TLC, was shifted down and to the right in the majority of the patients (curves not shown). To quantitate the position of the curve when volume was expressed as a percent of observed TLC, P_{70} was computed (Fig. 1A). Whereas the average patient had a P_{70} of 7.6 cm H_2O (a value nearly normal for the mean age of these patients), seven patients (E.B., R.I.C., N.C., V.J., O.N., B.T., E.T.) had a reduced P_{70} (curves were shifted leftward). The remaining 10 patients had an increased P_{70}, indicating a rightward shift in their volume-pressure curves.

The comparative compliance of all patients ranged from 0.39 to 5.73% predicted TLC/cm H_2O. 74 percent (17 of 23) of the patients had values of comparative compliance that were reduced compared with those of age-matched controls; 4 patients (R.I.C., W.L.S., G.F., P.R.) had normal comparative compliance and 2 patients (E.B., R.C.) had increased comparative compliance (Fig. 4).
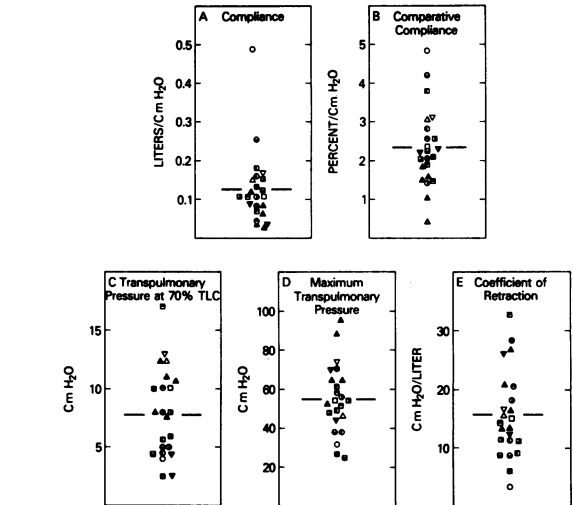

FIGURE 4 Distribution of (A) compliance, (B) comparative compliance, (C) P_{70}, (D) P_{max}, and (E) CR in 23 patients with IPF. Each symbol represents an individual patient; the key to the symbols is presented in Table I. Normal values are age dependent for compliance and comparative compliance and P_{70} (24, 27). The upper limits of normal for P_{max} and CR are 36 cm H_2O and 8 cm H_2O/liter, respectively (24, 26, 28).

The maximum transpulmonary pressure at TLC (P_{max}) was increased in 78% of the patients (18 of 23) (Fig. 4); the average P_{max} of all patients was 54.4 ± 3.8 cm H_2O. Of the 5 patients with normal P_{max}, 3 (V.J., R.C:, P.R.) were between the ages of 25 and 35 yr.

CR was increased in 91% (21 of 23) patients; it was normal in 1 patient (W.D.) and was reduced in 1 patient (E.B.). In the entire group of patients, the average CR was 16.0 ± 1.6 cm H_2O/liter compared with the normal range of 4.0–8.0 cm H_2O/liter.

Gas exchange data (Figs. 5 and 6)

Resting. In the entire group of 23 patients, the resting PaO_2 ranged from 55.0 to 100.9 mm Hg (mean 73 ± 3.0 mm Hg) and was normal (>80 mm Hg) in 8 patients (35%). The resting A-aDO_2 ranged from 12 to 74 mm Hg (mean 38.8 ± 3.7) but was normal (<15 mm Hg) in only 1 patient (M.C.) (4%). The average patient had mild alveolar hyperventilation ($PaCO_2$, 34.6 ± 0.8 mm Hg) that was compensated to yield a normal pHa (7.42 ± 0.09); no patient had CO_2 retention (data not shown). Assuming a normal arterial-venous oxygen content difference of 5 vol%, the average patient had a physiologic shunt of $10.9\pm1.4\%$ (data not shown).

Exercise. Two patients were unable to exercise; M.B. had advanced osteoarthritis of the hips and W.L. required supplemental O_2 even with minimal exertion. Eight patients completed only stage I of the exercise protocol; four patients completed stages I and II: and nine patients completed all three stages. In general
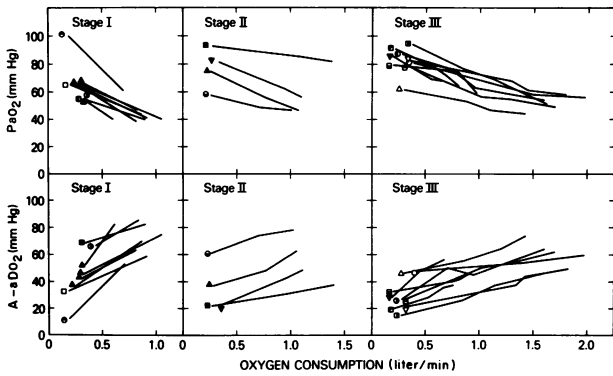
FIGURE 5 Resting and exercise gas exchange data in 23 patients with IPF. Each curve represents data from an individual patient; the key to the symbols presented to the left of each curve is shown in Table I. Values of PaO_2 and $A\text{-}aDO_2$ are plotted against power output ($\dot{V}O_2$). Stage I presents all patients who could only exercise one stage, stage II presents all patients who exercise two stages, and stage III presents all patients who exercised all three stages.

the three stages of exercise reflected increasing $\dot{V}O_2$. The average $\dot{V}O_2$ at stage I for those who completed only stage I was 0.834 ± 0.047 liters/min; this value did not differ significantly from the $\dot{V}O_2$ at stage I (0.928 ± 0.108 liters/min) for subjects who completed all three stages ($P > 0.1$). In addition, the average $\dot{V}O_2$ at stage II for those who completed only stage II (1.140 liters/min) did not differ significantly from the average $\dot{V}O_2$ at stage II for those who completed all three stages (1.104 liters/min, $P > 0.1$).

All 21 patients who completed stage I or greater demonstrated a fall in PaO_2 and a rise in $A\text{-}aDO_2$ with exercise. In general, exercise did not cause a significant alteration in $PaCO_2$ or pHa except in the few patients who developed a mild metabolic acidosis at stage II or III.

For all patients, the PaO_2 at the maximum stage of exercise achieved ranged from 38.3 to 81.8 mm Hg. The mean exercise PaO_2 of patients who completed only stage I was 43.8 ± 2.7 mm Hg, whereas the mean exercise PaO_2 (at the highest $\dot{V}O_2$) of patients who completed stage III was 59.0 ± 3.0 mm Hg; these values were significantly different ($P = 0.002$). For all patients, the exercise $A\text{-}aDO_2$ at the maximum stage of exercise ranged from 26.7 to 85.5 mm Hg. As a group, the maximum exercise $A\text{-}aDO_2$ of those who completed only stage I (70.9 ± 4.1 mm Hg) was significantly higher than the maximum exercise $A\text{-}aDO_2$ of those who completed stage III (55.3 ± 0.4 mm Hg) ($P = 0.016$).

For all patients, the absolute change in PaO_2 between rest and exercise (exercise parameter 1) ranged from -9.6 to -39.9 mm Hg. Interestingly, even though the $\dot{V}O_2$ of patients completing stage III (1.38 ± 0.162 liters/min) was significantly greater than

the $\dot{V}O_2$ of patients completing only stage I of the exercise protocol (0.83 ± 0.047 liters/min; $P = 0.004$), the mean values of exercise parameter 1 for groups I and III were not significantly different (stage I = -22.4 ±2.8 mm Hg; stage III = -20.8 ± 2.3 mm Hg; $P = 0.64$). Similarly, for all patients, the absolute change in $A\text{-}aDO_2$ between rest and exercise (exercise parameter 2) ranged from 13.0 to 48.2 mm Hg and there was no difference between the mean value of exercise parameter 2 for those completing only stage I compared with that of those completing stage III ($P = 0.39$).

In comparison to the absolute changes in PaO_2 or $A\text{-}aDO_2$ with exercise (exercise parameters 1 and 2), the change in PaO_2 and $A\text{-}aDO_2$ with increasing power output ($\dot{V}O_2$) (exercise parameters 3 and 4) showed marked differences between the patients grouped according to the stage of exercise they were able to complete. Although $\Delta PaO_2/\Delta\dot{V}O_2$ (exercise parameter 3) of the entire patient group varied from -9.2 to -78.1 mm Hg-min/liter, the mean value for those competing stage I (-43.8 ± 6.1 mm Hg-min/liter) was significantly different from the mean value of those completing stage III (-21.5 ± 3.3 mm Hg-min/liter, $P = 0.038$). In addition, although the $\Delta A\text{-}aDO_2/\Delta\dot{V}O_2$ (exercise parameter 4) of the entire patient group ranged from 8.0 to 106.6 mm Hg-min/liter, the mean value for patients completing stage I (53.6 ± 10.6 mm Hg-min/liter) was
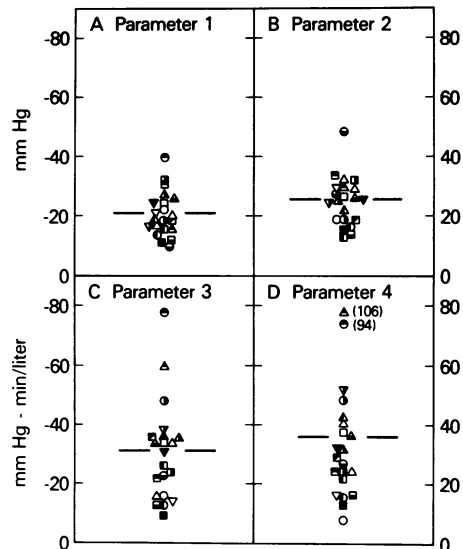

FIGURE 6 Derived exercise parameters in 23 patients with IPF. Each symbol represents an individual patient; the key is presented in Table I. All parameters are derived from the data presented in Fig. 4. A: exercise parameter 1 = PaO_2 at maximal levels of exercise − resting PaO_2; B: exercise parameter 2 = $A\text{-}aDO_2$ at maximal level of exercise − resting $A\text{-}aDO_2$; C: exercise parameter 3 = change in PaO_2 per liter oxygen consumed during exercise; D: exercise parameter 4 = change in $A\text{-}aDO_2$ per liter oxygen consumed during exercise.

significantly different from the mean value of those completing stage II (24.4±4.5 mm Hg-min/liter, $P = 0.005$).

Comparison of morphologic data with clinical and standard physiologic data

The morphologic assessment of the degree of fibrosis and cellularity in lung biopsy specimens of the 23 patients did not correlate with age, sex, drug history, smoking history, or duration of symptoms (comparisons not shown). Of all clinical comparisons, only patient age had a trend toward correlation with the degree of fibrosis ($P = 0.054$); older patients tended to have more advanced fibrosis (+3 to +4).

Of the standard physiologic studies (V.C., T.L.C., F.R.C., and DL_{CO}), none correlated significantly with either the morphologic assessment of degree of fibrosis or degree of cellularity. Vital capacity did, however, show a trend toward correlation with the degree of fibrosis ($P = 0.05$), but could account for only $\cong 17\%$ of the total variability ($r = 0.422$, $r^2 = 0.168$).

Similarly, when standard physiologic studies were ranked as mildly (+1), moderately (+2), or severely (+3) reduced compared with the predicted values (using Spearman rank correlation), there were no significant correlations with the morphologic data.

Comparison of the morphologic data with distensibility data (Table II)

Although almost all parameters derived from the static deflation volume-pressure curve correlated with the morphologic assessment of degree of fibrosis, compliance had the highest correlation coefficient ($r = 0.746$, $P = 0.001$). Comparative compliance, P_{max}, and CR also correlated significantly with the degree of fibrosis, but none could account for more than 42% of the observed variability (r^2 ranged from 0.31 to 0.42). In contrast, the morphologic assessment of degree of cellularity did not correlate with either compliance, comparative compliance, P_{max} or CR. There was a correlation between P_{70} and degree of cellularity ($r = 0.509$, $P = 0.013$); but this acounted for only 25% of the observed variability ($r^2 = 0.25$).

Comparison of morphologic data with gas exchange data (Table II)

There was no significant correlations between the morphologic assessment of either the degree of fibrosis or the degree of cellularity and either resting or exercise PaO_2 and A-aDO_2 or the absolute change in PaO_2 between rest and maximum exercise (exercise parameter 1). In contrast, there was a strong correlation between the morphologic assessment of degree of

TABLE II
Comparisons of Morphologic Data with Distensibility and Gas Exchange Data in 23 Patients with IPF

| Physiologic parameter | Morphologic comparisons* | | | |
| | Degree of fibrosis | | Degree of cellularity | |
	r	p	r	p
Distensibility data				
Compliance	−0.746	<0.001	−0.155	0.481
Comparative compliance	−0.583	0.004	−0.639	0.772
P_{70}	0.124	0.400	0.509	0.013
P_{max}	0.578	0.002	0.334	0.119
CR	0.655	<0.001	0.213	0.329
Gas exchange data				
Resting PaO_2	−0.231	0.288	−0.238	0.275
Resting A-aDO_2	0.377	0.735	0.095	0.667
Exercise PaO_2	−0.408	0.066	−0.362	0.107
Exercise A-aDO_2	0.208	0.367	0.383	0.087
$\dot{V}O_2$ (highest)	−0.692	<0.001	−0.200	0.385
Exercise parameter 1	0.356	0.113	−0.195	0.396
Exercise parameter 2	0.319	0.159	0.474	0.030
Exercise parameter 3	−0.890	<0.001	0.556	0.009
Exercise parameter 4	0.845	<0.001	0.449	0.041

* All comparisons were made with Spearman rank correlation.

fibrosis with both the change in PaO_2 per liter oxygen consumed during exercise (exercise parameter 3, $r = 0.890$, $P < 0.001$) and the change in A-aDO_2 per liter oxygen consumed (exercise parameter 4, $r = 0.845$, $P < 0.001$). However, these latter two significant correlations were not selective for the degree of fibrosis; both exercise parameters 3 and 4 correlated with the degree of cellularity ($r = 0.556$ and $r = 0.449$; $P < 0.01$ for both). In addition, there was a significant negative correlation between $\dot{V}O_2$ at maximum exercise and the morphologic assessment of degree of fibrosis ($r = 0.692$; i.e., those patients with the most fibrosis were able to exercise the least). There was, however, no correlation between the degree of cellularity and $\dot{V}O_2$.

Comparisons between the various physiologic studies

There was a significant correlation between compliance and the following: TLC ($r = 0.622$; $P = 0.002$), VC ($r = 0.582$; $P = 0.004$), P_{max} ($r = −0.538$; $P − 0.008$), and CR ($r = −0.661$; $P < 0.001$). In addition, compliance correlated with the change in PaO_2 per liter O_2 consumed during exercise (exercise parameter 3:

$r = -0.574, P = 0.007$) and the change in A-aDO$_2$ per liter O$_2$ consumed during exercise (exercise parameter 4: $r = -0.469, P = 0.032$). Similarly, there was a weak, but significant correlation between P$_{max}$ and CR with exercise parameters 3 and 4 ($r < 0.4; P < 0.04$). There were no other remarkable correlations among the various physiologic studies.

DISCUSSION

To identify those physiologic studies that are most useful in staging and following the severity of the disease in IPF, we characterized the physiologic alterations in a relatively homogenous group of patients with this disease in mid-course and compared these data with the morphologic assessment of the degree of fibrosis and the degree of cellularity in their biopsies. These correlations demonstrate that (a) physiologic parameters assessing lung distensibility correlate very well with the morphologic assessment of the degree of fibrosis, but poorly with the degree of cellularity; (b) exercise-induced changes in gas exchange correlate with the degree of fibrosis and to a lesser extent with the degree of cellularity; and (c) lung volumes and diffusing capacity do not correlate with either morphologic parameter.

Physiologic alterations in IPF. The average patient in the current study had reduced lung volumes and diffusing capacity, reduced compliance, and hypoxemia that worsened with exercise. These physiologic alterations are classic for IPF and useful diagnostically (2, 4, 8–10).

All patients had either reduced lung volumes (V.C., T.L.C.) or reduced DL$_{CO}$, and the majority had a reduction in both. Lung compliance at FRC was, however, less sensitive to the presence of disease; only two-thirds of all patients had reduced compliance, whereas nearly one-third had normal or nearly normal compliance. Furthermore, the sensitivity of this measurement was only minimally improved by adjusting this value for the reduction in lung volume (comparative compliance).

P$_{max}$ was increased in 80% of the study patients. Although the maximum value of P$_{max}$ in the current study was higher than those previously recorded by Yernault et al. (28), the mean values were similar in both studies. It has been suggested that the discriminatory power of P$_{max}$ in interstitial lung disease is greater when it is related to the measured lung volume as the CR (26). Our data support this; CR was increased in the majority of patients, being normal or reduced in only two patients (W.D., E.B.), both of whom had minimal fibrosis.

Although the average patient in the current study had mild resting hypoxemia, over one-third had normal values. In contrast only one patient (M.C.) had a normal

A-aDO$_2$ at rest, suggesting that the A-aDO$_2$ is a sensitive test for the detection of interstitial lung disease.

Exercise gas exchange in IPF. Arterial hypoxemia that worsens during exercise is a well-documented and diagnostically useful feature of IPF (8, 38–40). Although the hypoxemia of IPF was initially thought to be the result of an oxygen diffusion defect, it has been shown that both resting and exercise-induced hypoxemia in this disease mainly results from ventilation-perfusion imbalance (36, 37). Uncommonly, patients with IPF exhibit an improvement in PaO$_2$ during exercise. This has been reported mainly in patients with co-existing obstructive lung disease (11). Other associated conditions that could result in improvement of PaO$_2$ during exercise include chronic bronchitis, and localized lower lobe on lobar diseae. All of these conditions would be expected to improve ventilation-perfusion imbalance during exercise by either mobilizing secretions or by improving ventilation to areas that are relatively hypoventilated at rest (40, 41). For this reason, to attempt to make the study population as homogeneous as possible, we only included IPF patients in the current study who had roentgenographic evidence of diffuse disease, no history of bronchitis, and a normal forced expiratory volume in 1 s/forced VC.

To help quantitate the changes in exercise-induced gas exchange alterations in IPF, four parameters were derived from the exercise data. Exercise parameters 1 and 2 quantitate the absolute changes in PaO$_2$ and A-aDO$_2$ from rest to maximum exercise. Although the study population varied in the clinical assessment of the severity of their disease and with the stage attained during exercise, there was no difference between the mean values of either exercise parameter 1 or exercise parameter 2 among those completing stage I compared with those completing stage III. It is evident, however, that exercise parameters 1 and 2 disregard the relative changes in power output ($\dot{V}O_2$) required to bring about these alterations. To circumvent this problem, we adjusted the absolute changes in PaO$_2$ and A-aDO$_2$ for the change in power output; exercise parameter 3 quantitates the change in PaO$_2$ during exercise per liter oxygen consumption, and exercise parameter 4 quantitates the change in A-aDO$_2$ during exercise per liter oxygen consumption. It is possible to do this because the changes in PaO$_2$ and A-aDO$_2$ during exercise in IPF are essentially linear (Fig. 2). In general, there was a good correlation between the value of exercise parameters 3 and 4 and the stage of exercise they were able to complete. Furthermore, those patients with clinically more severe disease and who completed only stage I, had a significantly higher value of exercise parameters 3 and 4 compared with those with less severe disease who completed all three stages of the exercise protocol.

Morphologic evaluation of IPF. Using current tech-

nology, the definitive assessment of fibrosis and cellularity in IPF must be based on morphologic standards. To use morphology to assess the usefulness of various physiologic parameters in IPF, we used specific morphologic criteria to semi-quantitate the degree of fibrosis and cellularity in biopsy specimens. With these criteria, the assessment of the degree of fibrosis and the degree of cellularity was reproducible with a small intra- and inter-observer variability.

Based on clinical presentation and duration of symptoms, the study population was judged to be mid-course in their disease (8–10, 42). This judgment was complemented by the morphology of the biopsy specimens. No patient had hyaline membranes (e.g., no early disease), none had honeycomb lung (13), and the average patient had moderate (+3) fibrosis and mild (+2) cellularity.

It could be argued that a lung biopsy is not representative of the overall morphologic alterations in IPF and that multiple samples from an inflated post-mortem lung are necessary to accurately assess the degree of fibrosis and cellularity. It is critical, however, that the evaluation of fibrosis and cellularity be done on biopsy specimens because (a) the assessment of fibrosis and cellularity in IPF is of most interest early and mid-course in the disease, at which time response to therapy is most likely to be best; (b) the most common cause of death in patients with IPF is overwhelming pulmonary infection (42). Such an insult is accompanied by large numbers of inflammatory cells that will alter the status of the overall cellularity grading, and inflammatory cells may release enzymes such as collagenase that may alter the status of interstitial fibrous tissue (43); and (c) for correlates to be made between morphologic and physiologic findings in IPF, the morphology must be obtained in proximity to the time of physiologic evaluation; this is impossible when relying on postmortem material.

Thus, to semi-quantitate the degree of fibrosis and cellularity in IPF in mid-course, it is mandatory that biopsy, and not autopsy material be used. To minimize error, the degree of fibrosis and the degree of cellularity were graded independently, using special stains for fibrous tissue (Masson) and hematoxylin–eosin for cells. In addition, only patients with diffuse disease were included in this study. Furthermore, to attempt to obtain tissue that is representative of the overall disease process, biopsies were performed in areas that appeared average on chest roentgenogram. This was complimented by direct vision at thoracotomy. Those biopsies from outside institutions were used in this study only when it was clear that they had been obtained from a representative area.

Morphologic-physiologic correlates in IPF. Although lung volumes and diffusing capacity are com-

monly used to stage and monitor patients with IPF, comparison of the morphologic data with VC, TLC, and DL_{CO} demonstrated no significant correlates. Whereas the comparison of VC and the morphologic grading of fibrosis approached significance, this correlation is at best a weak one. These findings are consistent with those of Gaensler et al. (44), who demonstrated a "fair correlation" between VC and the "overall severity of the anatomic lesion" among a group of patients with IPF, and no correlation with DL_{CO}. Thus VC, TLC, and DL_{CO} do not appear to be useful objective monitors of either the degree of fibrosis or the degree of cellularity in this disease. The reasons for the failure of these parameters to correlate with morphology are only speculative, but because TLC is largely determined by maximum inspiratory strength and by chest wall and lung recoil (45), it follows that fibrosis and(or) cellularity would contribute only to lung recoil and thus modulate only one of the factors that determines TLC. It also follows that the reduction in lung volumes allow for a greater mechanical advantage of inspiratory muscles such that the net inspiratory force can be increased beyond that normally attained, allowing for a greater distension of parenchyma at TLC (46). The fact that VC appeared to correlate more closely with the degree of fibrosis suggests that fibrosis contributes more toward determining residual volume than TLC. Possibly this is related to the increase in lung tissue volume and reduction in recoil pressure at functional residual capacity (46).

It is somewhat surprising that DL_{CO} fails to correlate with the morphologic assessment of either fibrosis or cellularity. This is possibly related to the number of factors that modulate the DL_{CO}, including ventilation-perfusion abnormalities, resistance to transport across the alveolar capillary bed, and capillary blood volume (47, 48).

Although standard physiologic studies did not correlate with the morphologic data, four of the five parameters used to assess lung distensibility correlated with the degree of fibrosis. Compliance was the best correlate, although comparative compliance, CR, and P_{max} also correlated with the degree of fibrosis. The fact that parameters of lung distensibility correlate with the degree of fibrosis is not surprising, because fibrous tissue is composed mainly of collagen, and collagen with its limited extensibility should affect lung distensibility (45). In contrast, the position of the volume pressure curve (P_{70}) did not correlate with the morphologic assessment of the degree of fibrosis, suggesting that many factors (e.g., cystic lung disease, lung tissue volume) also modulate the position of the volume pressure curve in this disease. In comparison to the significant correlates with the degree of fibrosis, only one parameter of lung distensibility (P_{70}) cor-

related with the morphologic assessment of degree of cellularity, and even this correlate was barely significant ($r^2 = 0.25$).

PaO_2 and $A\text{-}aDO_2$ at rest and at maximal levels of exercise are commonly used to evaluate patients with IPF. There were, however, no significant correlates between either the severity of fibrosis or degree of cellularity and these parameters. In contrast, Gaensler et al. (44), in a morphologic-physiologic correlative study of a variety of fibrotic lung diseases, found a significant correlation between $A\text{-}aDO_2$ at maximum exercise and an "overall histologic index." However, this latter study combined several different types of fibrotic lung disease with varying pathophysiology (4, 30, 49, 50) (IPF, asbestosis, silicosis, honeycomb lung) in the correlative morphologic-physiologic comparisons, whereas the current study used a homogeneous population of patients with IPF.

Whereas the PaO_2 and $A\text{-}aDO_2$ failed to correlate with morphologic data in our study patients, derived parameters from the exercise study did correlate with the morphologic data. Exercise parameters 3 and 4, which quantitate the changes in PaO_2 and $A\text{-}aDO_2$ in relation to power output, strongly correlated with the degree of fibrosis. These parameters were not, however, selective for fibrosis; both exercise parameters 3 and 4 also correlated to a lesser extent with the degree of cellularity. The failure of morphologic data to correlate with the resting and exercise PaO_2, $A\text{-}aDO_2$, and the absolute changes in PaO_2 and $A\text{-}aDO_2$ suggest that although fibrosis and cellularity may contribute to ventilation-perfusion imbalance, other factors apparently contribute more. This concept is supported by the recent studies in IPF demonstrating small airways disease, an alteration that may contribute to ventilation-perfusion imbalance (10). In addition, it has been suggested that pulmonary circulatory alterations can also contribute to ventilation-perfusion imbalance (51). Neither airways disease nor pulmonary vascular alterations appear to relate to the morphologic changes of fibrosis or cellularity (10, 52). However, when gas-exchange alterations are related to power output (exercise parameters 3 and 4), there are significant correlations with morphology, suggesting that both fibrosis and cellularity affect ventilation-perfusion imbalance and that the contribution of these morphologic features to gas exchange is constant during exercise.

Significance of anatomic-physiologic correlates in IPF. The demonstration of significant correlates between the morphologic grading of the degree of fibrosis and cellularity have important functional and clinical implications. First, these results suggest that the fibrotic process contributes, at least in part, to the physiologic alterations in IPF, especially those involv-

ing lung distensibility. Second, fibrosis and cellularity clearly contribute to gas exchange alterations during exercise in this disease. Third, because the prognosis and response to therapy is dependent upon the severity of fibrosis and degree of cellularity, these correlates may be useful in determining prognosis and response to chemotherapy. Preliminary data in our laboratory suggest that those parameters that correlate with fibrosis, particularly the parameters of distensibility, are good predictors of prognosis.

ACKNOWLEDGMENTS

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