Idiopathic Pulmonary Fibrosis
Prognostic Value of Changes in Physiology and Six-Minute-Walk Test

Kevin R. Flaherty, Adin-Cristian Andrei, Susan Murray, Chris Fraley, Thomas V. Colby, William D. Travis, Vibha Lama, Ella A. Kazerooni, Barry H. Gross, Galen B. Toews, and Fernando J. Martinez

Division of Pulmonary and Critical Care Medicine and the Department of Radiology, University of Michigan Health System, Ann Arbor; Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan; Department of Pathology, Mayo Clinic, Scottsdale, Arizona; and Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York

Rationale and Hypothesis: Idiopathic pulmonary fibrosis is a fatal disease with a variable rate of progression. We hypothesized that changes in distance walked and quantity of desaturation during a six-minute-walk test (6MWT) would add prognostic information to changes in FVC or diffusing capacity for carbon monoxide.
Methods: One hundred ninety-seven patients with idiopathic pulmonary fibrosis were evaluated. Desaturation during the 6MWT was associated with increased mortality even if a threshold of 88% was not reached. Baseline walk distance predicted subsequent walk distance but was not a reliable predictor of subsequent mortality in multivariate survival models. The predictive ability of serial changes in physiology varied when patients were stratified by the presence/absence of desaturation ⩽ 88% during a baseline 6MWT. For patients with a baseline saturation ⩽ 88% during a 6MWT, the strongest observed predictor of mortality was serial change in diffusing capacity for carbon monoxide. For patients with saturation > 88% during their baseline walk test, serial decreases in FVC and increases in desaturation area significantly predicted subsequent mortality, whereas decreases in walk distance and in diffusing capacity for carbon monoxide displayed less consistent statistical evidence of increasing mortality in our patients.
Conclusion: These data highlight the importance of stratifying patients by degree of desaturation during a 6MWT before attributing prognostic value to serial changes in other physiologic variables.

Keywords: idiopathic pulmonary fibrosis; six-minute-walk test; prognosis; pulmonary function; survival

Idiopathic pulmonary fibrosis (IPF) is a uniformly fatal disease with a variable rate of progression. Identification of readily available baseline and short-term serial predictors of survival is critical for physicians and patients considering options such as lung transplantation and for the investigation of novel treatments. Recent studies have suggested several demographic (age, smoking), physiologic (diffusion capacity for carbon monoxide [$D_{L_{CO}}$], FVC, and desaturation), radiologic (high-resolution computed tomography [HRCT] fibrosis score), and histopathologic (fibroblastic foci) features are associated with survival (1–7). Serial change in FVC adds additional prognostic information to data obtained at baseline (8–11).

A central feature in the pathophysiology of IPF is impaired gas exchange, which worsens with exercise (12, 13). This exercise-induced widening of alveolar arterial O_2 gradient and fall in Pa_{O_2} is believed to be secondary to multiple abnormalities, including $\dot{V}/\dot{Q}$ mismatch, decreased Pv_{O_2} and venous admixture (12–16). The six-min-walk test (6MWT) is a safe procedure for patients with IPF. Baseline desaturation during a 6MWT is a powerful predictor of subsequent mortality (4, 6, 7). The relative simplicity, low cost, and reproducibility (7) of the 6MWT makes it an attractive modality for the longitudinal study of patients with IPF.

Given these data, we elected to examine the prognostic value of a baseline and serial changes in 6MWT in relation to changes in FVC and $D_{L_{CO}}$ in patients with IPF. We hypothesized that changes in distance walked and quantity of desaturation would add prognostic value to change in FVC or $D_{L_{CO}}$.

METHODS

Patient Selection

The study used patients in the database of the University of Michigan Specialized Center of Research in the Pathobiology of Fibrotic Lung Disease. Patients in this database were referred for enrollment in study protocols for suspected IPF based on typical symptoms and on physiologic and radiographic findings. Patients with an HRCT scan showing a definite pattern of usual interstitial pneumonia (11, 17) were not required to undergo a surgical lung biopsy (n = 51). Patients were treated with varied treatment regimens, including no therapy, prednisone alone, prednisone with azathioprine or cyclophosphamide, or zileuton. The lack of a prospectively defined treatment regimen and the overlap between treatment regimens in some patients precluded our ability to evaluate the effect of treatment on serial change in pulmonary function, 6MWT, or survival. We excluded patients with underlying connective tissue disease, obvious occupational exposure, or a histopathologic pattern other than usual interstitial pneumonia. Approval for the use of these data was obtained from the Institutional Review Board of the University of Michigan. A subgroup of these patients has been previously described (3, 4, 11, 18–21).

Pulmonary Function and 6MWT

Pulmonary function tests including FVC, $D_{L_{CO}}$, and 6MWT were performed as previously described (4, 22). Desaturation area (DA; Figure 1) was defined as the total area above the curve created using desaturation percentage values observed during each minute of the 6MWT, thereby summing up the differences between a Sa_{O_2} of 100% and the patient's Sa_{O_2} at each minute. For example, a patient with a Sa_{O_2} of 98% at each minute during the 6MWT would have a DA of 12 (100 – 98 = 2 × 6 min = 12). For safety, we stopped the 6MWT when patients reached a Sa_{O_2} of 86%, and a desaturation score of 14% was assigned for that minute and all subsequent minutes of the 6MWT. A higher DA indicates higher overall quantity of desaturation during the 6MWT.

Statistical Analysis

For each patient, 6-mo 6MWT distance walked, DA, FVC, FVC % predicted, $D_{L_{CO}}$ and $D_{L_{CO}}$ % predicted values were obtained as a result
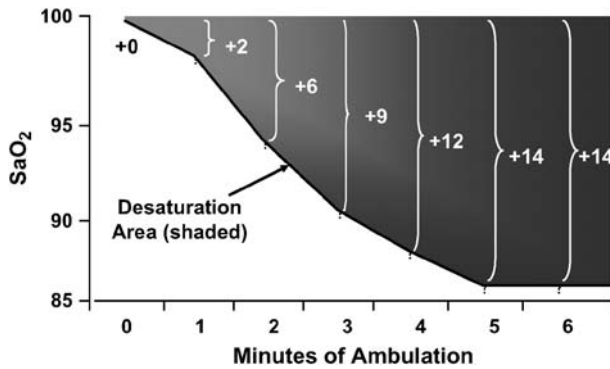
Figure 1. Desaturation area (DA) was defined as the total area above the curve created using desaturation percentage values observed at baseline and at each subsequent minute of the six-min-walk test (6MWT; i.e., summing up the differences between an Sa_{O_2} of 100% and the patient's Sa_{O_2} at each minute). For example, a patient with an Sa_{O_2} of 98% at each minute during the 6MWT would have a DA of 12. For safety, we stopped the 6MWT when patients reached an Sa_{O_2} of 86%, and a desaturation score of 14% was assigned for that minute and all subsequent minutes of the 6MWT. A higher DA indicates higher overall quantity of desaturation during the 6MWT.

of fitting individual regression lines, provided that each patient was able to perform at least two 6MWT within the first 12 mo of follow-up and was alive at the 6-mo time mark. Using the log-rank test, survival experiences were compared overall and in the two groups with baseline $Sa_{O_2} > 88\%$ or $\leqslant 88\%$. Univariate and multivariate Cox regression models adjusting for baseline and serial changes in distance walked, DA, FVC, FVC % predicted, $D_{L_{CO}}$, and $D_{L_{CO}}$ % predicted values were constructed. Adjustments for baseline values, age, sex, and smoking years were made.

RESULTS

Baseline Data

The baseline characteristics for the 197 patients in this study are outlined in Table 1. A total of 51 patients were diagnosed based

on a typical HRCT and appropriate clinical scenario, whereas 146 were diagnosed with the use of surgical lung biopsy (SLB). On average, patients with an HRCT diagnosis were older (66 ± 10 vs. 62 ± 10 yr; p = 0.008) and had a greater exposure to tobacco (38 ± 31 vs. 19 ± 23 pack-years, p = 0.001) compared with patients undergoing surgical lung biopsy. There were no differences in FVC, FVC % predicted, $D_{L_{CO}}$, $D_{L_{CO}}$ % predicted, DA, or proportion of patients with a saturation $\leqslant 88\%$ during the 6MWT in patients with compared with those without an SLB (data not shown). When comparing groups with Sa_{O_2} below or above 88% at any time during the 6MWT, no significant differences were detected in terms of patient age at enrollment, proportion of smokers, or number of pack-years. Patients with $Sa_{O_2} > 88\%$ throughout the 6MWT were more likely to be female; had significantly higher FVC, FVC % predicted, $D_{L_{CO}}$, and $D_{L_{CO}}$ % predicted values; and walked significantly further, with a significantly lower DA, compared with patients with a $Sa_{O_2} \leqslant 88\%$ at any point during the 6MWT. Most patients with a $Sa_{O_2} \leqslant 88\%$ during the 6MWT were stopped before 6 min because they reached a Sa_{O_2} of 86%. Of the 93 patients in the $Sa_{O_2} \leqslant 88\%$ group, 84 stopped before completion of the baseline 6MWT. In contrast, 101 of the 104 patients with a baseline $Sa_{O_2} > 88\%$ throughout the entire 6MWT completed 6 min of ambulation.

Based on the distance walked during the initial 6MWT, the 197 patients were classified into three groups based on thresholds (600 and 1,200 ft). These thresholds were chosen *a priori* based on their approximation to tertiles (actual tertiles between 560 and 580 ft and between 1,246 and 1,260 ft) and for simplicity because they illustrate 100 ft/min structural increments. BD1 was defined as a walk distance of at most 599 ft, BD2 was defined as a walk distance between 600 and 1,199 ft, and BD3 was defined as a walk distance of at least 1,200 ft. Categorical baseline walk distance was a weak predictor of subsequent mortality in the entire cohort (p = 0.038) (Figure 2). Pair-wise comparisons indicate better survival in BD3 patients compared with BD1 patients (p = 0.011). However, the observed difference in survival for BD2 patients was not significant when compared with BD1 patients (p = 0.223) or BD3 patients (p = 0.199). Baseline distance categories did not maintain statistical significance when patients

TABLE 1. BASELINE CHARACTERISTICS FOR 197 PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

	All Patients (n = 197)	$Sa_{O_2} > 88\%$ (n = 104)	$Sa_{O_2} \leqslant 88\%$ (n = 93)	p Value
Age, yr	63 (10)*	62 (10)	64 (10)	0.37
Male/female	127/70	65/39	62/31	< 0.001
Smokers, yes/no/NA	141/53/3	72/29/3	69/24/0	0.23
Pack-years	23 (26)	21 (25)	25 (26)	0.33
FVC, L	2.54 (0.86)	2.74 (0.91)	2.32 (0.76)	0.001
FVC, %predicted	65 (17)	70 (17)	60 (16)	< 0.001
$D_{L_{CO}}$, mm/min/mm Hg	11.27 (4.29)	13.68 (4.41)	9.08 (2.88)	< 0.001
$D_{L_{CO}}$, %predicted	45 (15)	52 (15)	36 (11)	< 0.001
Walk distance, ft	928 (534)	1314 (355)	497 (333)	< 0.001
Walk < 600 ft	329 (136)	362 (220)	328 (134)	0.81
	n = 72	n = 3	n = 69	
Walk between 600 and 1,200 ft	945 (155)	981 (141)	886.98 (162)	0.04
	n = 50	n = 31	n = 19	
Walk at least 1,200 ft	1,491 (226)	1,502 (230)	1,349 (57)	< 0.001
	n = 75	n = 70	n = 5	
Desaturation area (10 U)	5.52 (1.99)	3.98 (1.46)	7.23 (0.68)	< 0.001

Definition of abbreviations: $D_{L_{CO}}$ = diffusing capacity for carbon monoxide; NA = not available.
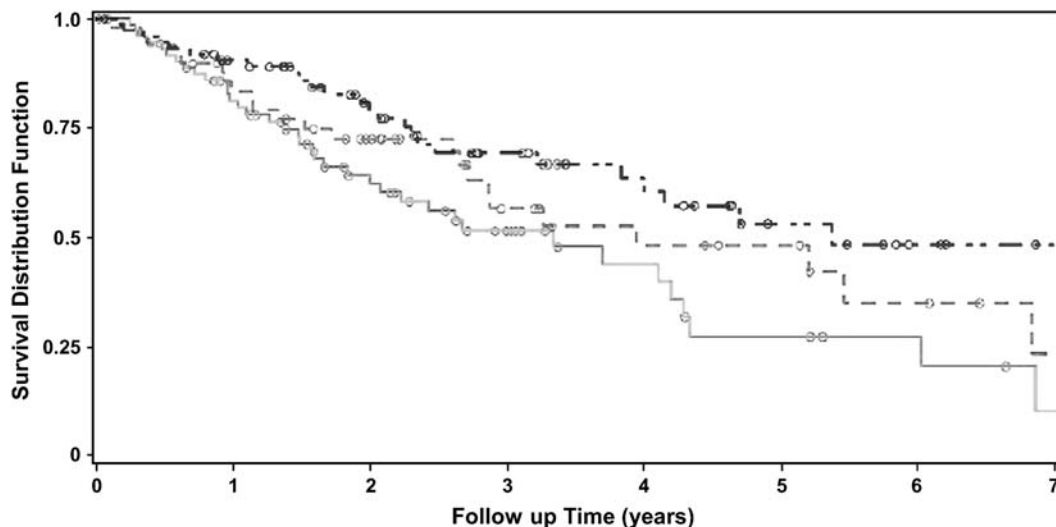* Values are means with SD given in parentheses.

Figure 2. Kaplan-Meier survival curves for 197 patients with idiopathic pulmonary fibrosis stratified by baseline walk distance (*circles* = censored, *solid line* = walked 1–599 ft, *continuous dashed line* = walked 600–1199 ft, *broken dashed line* = walked at least 1,200 ft).

were stratified by the presence/absence of a $Sa_{O_2} \leqslant 88\%$ during the 6MWT (p = 0.94 when $Sa_{O_2} > 88\%$; p = 0.43 when $Sa_{O_2} \leqslant 88\%$). Similar mortality patterns were seen when baseline distance walked was evaluated as a continuous variable, with significant prediction of mortality in a univariate Cox model (hazard ratio [HR], 0.94; p = 0.005, 100-ft increase) that vanished in multivariate Cox models. These data suggest that baseline distance walked has little to no predictive value for predicting subsequent mortality when accounting for the stronger predictor of degree of desaturation at baseline.

Unlike distance walked, even mild baseline desaturation (Sa_{O_2} remained > 88% throughout the 6MWT, but DA increased) was a powerful predictor of subsequent mortality. Patients with a $Sa_{O_2} \leqslant 88\%$ during their initial 6MWT had a median survival time of 3.21 yr, which was lower than the 6.83 yr for those with baseline $Sa_{O_2} > 88\%$ (p = 0.006). A 10-point increase in baseline DA was predictive in the group of patients with initial $Sa_{O_2} > 88\%$ (univariate HR, 1.33; 95% confidence interval [CI], 1.08–1.63; p = 0.007). The magnitude and direction of this DA HR remained similar in a multivariate model adjusting for distance walked in feet, $D_{L_{CO}}$, FVC, age, sex, and smoking years (HR, 1.30; 95% CI, 0.97–1.75; p = 0.08], with marginal statistical significance; possibly due to the strong negative correlation between baseline DA and $D_{L_{CO}}$ ($\rho = -0.34$; p < 0.001). These data confirm the importance of desaturation on subsequent mortality and highlight that even mild desaturation as measured by DA is an important predictor of subsequent mortality in patients not reaching the standard $Sa_{O_2} \leqslant 88\%$ endpoint during their baseline walk.

Serial Change Data

We examined if 6-mo changes in DA, FVC, distance walked, and $D_{L_{CO}}$ were predictive of subsequent mortality. Separate models adjusting for baseline values and 6-mo change were constructed for each of these variables.

Analysis of longitudinal walk distance by baseline walk distance categories revealed stark differences in how these groups behave over time (as shown in Figures E1a–E2c in the online supplement). Minimal change over time was observed for BD1 and BD3 patients, with BD1 patients showing little improvement and the majority of BD3 patients maintaining their baseline walk distance. However, trajectories for BD2 patients displayed more fluctuations in serial walk distance over time. Of the 72 patients in BD1, nearly all (n = 69) developed an $Sa_{O_2} \leqslant 88\%$ at some

point during the 6MWT. In contrast, nearly all patients in BD3 had an Sa_{O_2} that remained > 88% (n = 70 of 75). Patients in BD2 demonstrated a mix of Sa_{O_2} above (n = 31) or below 88% (n = 19).

We evaluated the association of changes in distance walked, DA, FVC, and $D_{L_{CO}}$ with subsequent mortality using univariate Cox models accounting for the baseline value. These patterns varied according to Sa_{O_2} categorization during their baseline walk (Table 2). In the subgroup of patients with a $Sa_{O_2} > 88\%$ throughout the 6MWT, adjusting for baseline values, increased mortality was observed with a decrease of more than 200 ft in distance walked, worsening of DA treated as a continuous measurement, a 10% relative decrease in FVC, and a 15% relative decrease in $D_{L_{CO}}$. In the group of patients with a $Sa_{O_2} \leqslant 88\%$, during their baseline 6MWT only a decrease in $D_{L_{CO}}$ emerged as predicting subsequent mortality; changes in FVC, DA, or walk distance were not predictive in this group. The prognostic value of $D_{L_{CO}}$ remained statistically significant after making additional multivariate adjustments for age, sex, and smoking history at baseline (HR, 2.95; 95% CI, 1.29–6.76; p = 0.01). Serial predictors uniformly outpredicted their baseline counterparts in terms of statistical and clinical significance.

When each set of serial predictors identified in the subgroup of patients with an $Sa_{O_2} > 88\%$ throughout the 6MWT were added to a multivariate model together in pairs and adjusted for age, sex, and smoking history, the magnitude and direction of most hazards were similar. Exceptions were $D_{L_{CO}}$, which lost statistical significance when paired with serial FVC or serial DA, and WD, which lost statistical significance when paired with DA (Table 3). Baseline DA increased statistical significance when interpreted alongside serial DA in multivariate models. Serial FVC and serial DA measures maintained statistical significance in all pairwise models.

In patients with an $Sa_{O_2} \leqslant 88\%$, during their baseline 6MWT only a relative decrease in $D_{L_{CO}}$ of at least 15% consistently predicted subsequent mortality, although a decrease in WD of at least 200 ft was significant when paired with DA (Table 4). Limitations in the sample size of our study precluded studying triplets of serial predictors in a single multivariate model.

DISCUSSION

IPF is a uniformly fatal disease with a variable rate of progression. In this study, we explored the impact of baseline and serial

TABLE 2. UNIVARIATE SURVIVAL MODELS EXPLORING SERIAL CHANGES IN WALK DISTANCE, DESATURATION AREA, FVC, AND $D_{L_{CO}}$ WHEN ADJUSTING FOR BASELINE VALUES

	n	Hazard Ratio (*95% CI*)	p Value
Patients with baseline $Sa_{O_2} > 88\%$			
Baseline walk distance	68	0.89 (0.78–1.02)	0.094
Decrease in WD > 200 ft	17	4.81 (1.75–13.19)	0.002
Increase in WD or decrease < 200 ft	51	1.00	REF
Baseline DA, 10 U	70	1.73 (1.17–2.54)	0.006
DA relative change	70	3.47 (1.66·7.25)	0.001
Baseline FVC, % predicted	86	0.41 (0.04–3.83)	0.435
Decrease in FVC (% predicted) relative change > 10%	20	3.57 (1.57–8.10)	0.002
Increase in FVC (% predicted) relative change or decrease < 10%	66	1.00	REF
Baseline $D_{L_{CO}}$, % predicted	70	0.19 (0.01–2.90)	0.233
Decrease in $D_{L_{CO}}$ (% predicted) relative change > 15%	10	3.73 (1.44–9.65)	0.007
Increase in $D_{L_{CO}}$ (% predicted) relative change or decrease < 15%	60	1.00	REF
Patients with baseline $Sa_{O_2} \leqslant 88\%$			
Baseline walk distance	48	0.95 (0.84–1.08)	0.443
Decrease in WD > 200 ft	16	2.25 (0.85–5.95)	0.103
Increase in WD or decrease < 200 ft	32	1.00	REF
Baseline DA, 10 U	57	0.83 (0.43–1.60)	0.583
DA relative change	57	0.53 (0.06–4.78)	0.590
Baseline FVC, % predicted	74	0.54 (0.07–4.38)	0.564
Decrease in FVC (% predicted) relative change > 10%	18	1.66 (0.76–3.64)	0.208
Increase in FVC (% predicted) relative change or decrease < 10%	56	1.00	REF
Baseline $D_{L_{CO}}$, % predicted	61	0.32 (0.01–10.05)	0.514
Decrease in $D_{L_{CO}}$ (% predicted) relative change > 15%	14	3.23 (1.41–7.37)	0.006
Increase in $D_{L_{CO}}$ (% predicted) relative change or decrease < 15%	47	1.00	REF

Definition of abbreviations: CI = confidence interval; DA = desaturation area; REF = reference group; WD = walk distance.

changes in FVC, $D_{L_{CO}}$, DA, and walk distance on subsequent survival in a large cohort of patients with IPF, including those diagnosed with typical HRCT and those requiring SLB for diagnosis. We demonstrate that (*1*) subtle desaturation defined by increased DA during a baseline 6MWT (without reaching a threshold of ≤ 88%) increases the risk of subsequent mortality even if saturation remains greater than 88%; (*2*) baseline walk distance is a reasonable predictor of subsequent walk distance but does not consistently predict risk of subsequent mortality in multivariate analyses; and (*3*) the predictive ability of serial change in FVC, $D_{L_{CO}}$, walk distance, and DA varies when patients are stratified by the presence/absence of desaturation greater than 88% during a baseline 6MWT. A graphical representation of the how serial change in $D_{L_{CO}}$, FVC, walk distance, and DA varies when stratified by the presence/absence of desaturation greater than 88% during a baseline 6MWT is provided in Figure 3. These data provide clear guidance for the care and study of patients with IPF.

Our data highlight that even mild desaturation is a risk factor for subsequent mortality. Previous studies demonstrate that desaturation during a 6MWT is associated with increased risk of subsequent mortality when evaluated as a continuous variable (6, 23) or using a threshold of ≤ 88% (4, 7). Furthermore, the latter threshold was noted to be a reproducible parameter during short-term testing (7). In the current study, we extend these findings by illustrating that even subtle degrees of desaturation, as assessed by DA, increases a patient's risk for subsequent mortality even if a threshold of ≤ 88% is not surpassed. A recent study has used a similar approach as an endpoint of a therapeutic trial, although mortality was not rigorously assessed during this short-term study (24).

Baseline distance walked failed to be a strong predictor of subsequent mortality once information on Sa_{O_2} was accounted for. This finding differs from previous studies (6, 23) and likely reflects differences in walk protocols. In the current study, patients were tested without supplemental oxygen, and the walk was halted if Sa_{O_2} decreased to 86%. Previous studies allowed the use of supplemental oxygen and also tolerated greater degrees of desaturation (6, 23). In the current study, 87 (44%) of the patients failed to complete the 6MWT; 84 (97%) of these patients were stopped due to an Sa_{O_2} of less than 86%. The early termination of the 6MWT due to desaturation may have diluted the possible effects of walk distance as an outcome measure.

Baseline walk distance tended to predict subsequent walk distance in that patients with a high level of performance (long walk distance) tended to preserve their walk distance throughout the study, whereas patients with poor performance (short walk distance) rarely improved. The most variation in change in walk distance was in the group of patients with an intermediate baseline walk distance. This illustrates the importance of baseline function when considering walk distance as an outcome measure in clinical trials for patients with IPF. These data suggest that "ceiling" (patients too mild to get detectably better with treatment) and "basement" (patients too sick to get detectably better with currently available treatment) exist when change in 6MWT distance is used as an outcome variable. This effect has been reported in studies of patients with primary pulmonary hypertension where patients with a higher baseline 6MWT distance showed less improvement in distance walked when treated with an endothelin receptor antagonist (25). It is possible that pulmonary hypertension was present in some of the more severe patients in our population. These concepts are important because

TABLE 3. MULTIVARIATE COX SURVIVAL MODELS EXPLORING THE PAIRWISE PREDICTIVE VALUE OF SERIAL CHANGES IN WALK DISTANCE, DESATURATION AREA, FVC, AND $D_{L_{CO}}$ IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS AND AN $Sa_{O_2} > 88\%$ THROUGHOUT A BASELINE 6-MIN-WALK TEST

	n	Hazard Ratio (*95% CI*)	p Value
Baseline FVC, % predicted	68	0.21 (0.01–8.61)	0.408
Baseline WD, 100 feet units	68	0.96 (0.82–1.13)	0.644
Decrease FVC (% predicted) relative change > 10%	13	3.01 (1.03–8.79)	0.043
Increase in FVC (% predicted) relative change or decrease < 10%	55	1.00	REF
Decrease in WD > 200 ft	17	5.12 (1.70–15.36)	0.004
Increase in WD or decrease < 200 ft	51	1.00	REF
Baseline FVC, % predicted	69	0.34 (0.02–7.19)	0.490
Baseline DA, 10 U	69	2.03 (1.24–3.31)	0.005
Decrease FVC (% predicted) relative change > 10%	14	3.98 (1.27–12.46)	0.018
Increase in FVC (% predicted) relative change or decrease < 10%	55	1.00	REF
DA relative change, 10% U	69	1.10 (1.02–1.19)	0.019
Baseline FVC, % predicted	70	0.23 (0.01–9.09)	0.436
Baseline $D_{L_{CO}}$, % predicted	70	0.04 (0.01–1.24)	0.066
Decrease FVC (% predicted) relative change > 10%	15	4.82 (1.30–17.81)	0.018
Increase in FVC (% predicted) relative change or decrease < 10%	55	1.00	REF
Decrease in $D_{L_{CO}}$ (% predicted) relative change > 15%	10	1.39 (0.46–4.18)	0.559
Increase in $D_{L_{CO}}$ (% predicted) relative change or decrease < 15%	60	1.00	REF
Baseline DA, 10 U	62	2.59 (1.35–4.95)	0.004
Baseline $D_{L_{CO}}$, % predicted	62	2.42 (0.05–117.02)	0.656
DA relative change, 10% U	62	1.17 (1.05–1.30)	0.004
Decrease in $D_{L_{CO}}$ (% predicted) relative change > 15%	9	1.06 (1.00–1.12)	0.101
Increase in $D_{L_{CO}}$ (% predicted) relative change or decrease < 15%	53	1.00	REF
Baseline $D_{L_{CO}}$, % predicted	60	0.07 (0.01–3.41)	0.177
Baseline WD, 100 feet units	60	0.87 (0.75–0.99)	0.044
Decrease in $D_{L_{CO}}$ (% predicted) relative change > 15%	8	6.47 (1.68–24.87)	0.007
Increase in $D_{L_{CO}}$ (% predicted) relative change or decrease < 15%	52	1.00	REF
Decrease in WD > 200 ft	15	7.94 (2.28–27.65)	0.001
Increase in WD or decrease < 200 ft	45	1.00	REF
Baseline DA, 10 U	68	1.40 (0.79–2.48)	0.253
Baseline WD, 100 feet units	68	0.90 (0.77–1.06)	0.199
DA relative change, 10% U	68	1.13 (0.99–1.28)	0.067
Decrease in WD > 200 ft	17	2.38 (0.63–8.96)	0.201
Increase in WD or decrease < 200 ft	51	1.00	REF

For definition of abbreviations, *see* Table 2.
Values are adjusted for age, sex, and smoking history at baseline.

6-min walk testing has become increasingly used as an outcome measure in IPF therapeutic trials (24, 26).

Our data illustrate that the predictive ability of serial change in FVC or $D_{L_{CO}}$ varies with baseline desaturation during exercise. In univariate Cox models among patients with a baseline Sa_{O_2} greater than 88% during the 6MWT, we observed an increased risk of subsequent mortality associated with a relative decrease in FVC of 10%, a relative decrease in $D_{L_{CO}}$ of 15%, a decrease in walk distance of at least 200 ft, or an increase in DA. In the group of patients with a baseline $Sa_{O_2} \leq 88\%$, during the 6MWT only a serial decline in $D_{L_{CO}}$ predicted subsequent mortality. This variability was also reflected in multivariable models where the predictive ability of these variables changed depending on patient stratification by the level of baseline desaturation. This suggests that in a group of patients already at risk for subsequent mortality (i.e., $Sa_{O_2} \leq 88\%$) (4), serial change in $D_{L_{CO}}$ can further refine the prognosis, whereas change in DA, walk distance, and FVC do not. In contrast, in patients with a baseline Sa_{O_2} during a 6MWT greater than 88%, a decrease in walk distance of at least 200 ft, a relative decrease in FVC of at least 10%, and relative decrease in DA predicted subsequent mortality to varying degrees, whereas change in $D_{L_{CO}}$ was less useful. These data extend the concept that serial change in FVC is most predictive of subsequent mortality in IPF longitudinal studies (8–11, 27)

and provide a rationale for previously discordant observations regarding the predictive ability of $D_{L_{CO}}$ (8, 9, 11). These data highlight the importance of stratification by baseline level of desaturation when selecting dynamic outcome measures for clinical trials and/or patient treatment decisions. These concepts should prove valuable in decision making during clinical care, in optimizing timing of lung transplantation, and in the design and conduct of therapeutic trials in patients with IPF.

The explanation for the variable predictive ability of FVC or $D_{L_{CO}}$ based on stratification by degree of desaturation remains conjectural. Although FVC and $D_{L_{CO}}$ are related, they reflect different aspects of pulmonary physiology. The degree of restriction is reflected by FVC, whereas abnormal gas exchange, which can involve pulmonary vasculopathy or mismatches in ventilation and perfusion, is reflected by $D_{L_{CO}}$. Patients with a baseline $Sa_{O_2} \leq 88\%$ during a 6MWT had a lower FVC compared with patients with saturation above 88%. Therefore, we initially considered that their FVC was already decreased to a level where further change was unlikely. This is not a likely explanation because a similar number of patients experienced a decline in FVC of at least 10% even when patients were stratified by baseline desaturation. Previous studies have also illustrated that patients may remain stable for prolonged periods of time and then present with an acute exacerbation and death (27–29).

TABLE 4. MULTIVARIATE COX SURVIVAL MODELS EXPLORING THE PAIRWISE PREDICTIVE VALUE OF SERIAL CHANGES IN WALK DISTANCE, DESATURATION AREA, FVC, AND $D_{L_{CO}}$ IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS WHO EXPERIENCED A SATURATION $\leqslant$ 88% DURING A BASELINE 6-MIN-WALK TEST

	n	Hazard Ratio (95% CI)	p Value
Baseline FVC, % predicted	49	0.13 (0.01–4.41)	0.259
Baseline WD, 100 feet units	49	1.00 (0.87–1.15)	0.996
Decrease FVC (% predicted) relative change > 10%	10	1.34 (0.41–4.39)	0.633
Increase in FVC (% predicted) relative change or decrease < 10%	39	1.00	REF
Decrease in WD > 200 ft	15	1.72 (0.59–4.98)	0.320
Increase in WD or decrease < 200 ft	34	1.00	REF
Baseline FVC, % predicted	54	0.06 (0.01–2.14)	0.124
Baseline DA, 10 U	54	0.64 (0.28–1.49)	0.304
Decrease FVC (% predicted) relative change > 10%	13	1.95 (0.62–6.13)	0.255
Increase in FVC (% predicted) relative change or decrease < 10%	41	1.00	REF
DA relative change, 10% U	54	0.87 (0.66–1.15)	0.322
Baseline FVC, % predicted	61	0.60 (0.02–14.73)	0.752
Baseline $D_{L_{CO}}$, % predicted	61	0.40 (0.01–27.36)	0.669
Decrease FVC (% predicted) relative change > 10%	13	0.87 (0.29–2.61)	0.803
Increase in FVC (% predicted) relative change or decrease < 10%	48	1.00	REF
Decrease in $D_{L_{CO}}$ (%f predicted) relative change > 15%	14	3.08 (1.25–7.55)	0.014
Increase in $D_{L_{CO}}$ (% predicted) relative change or decrease < 15%	47	1.00	REF
Baseline DA, 10 U	47	0.67 (0.25–1.77)	0.414
Baseline $D_{L_{CO},}$ (% predicted)	47	0.25 (0.01–54.06)	0.609
DA relative change (10% units)	47	0.80 (0.59–1.15)	0.165
Decrease in $D_{L_{CO}}$ (% predicted) relative change > 15%	9	5.77 (1.66–20.05)	0.006
Increase in $D_{L_{CO}}$ (% predicted) relative change or decrease < 15%	38	1.00	REF
Baseline $D_{L_{CO}}$, % predicted	44	0.20 (0.01–85.07)	0.602
Baseline WD, 100 feet units	44	1.12 (0.94–1.34)	0.197
Decrease in $D_{L_{CO}}$ (% predicted) relative change > 15%	9	7.72 (1.42–41.95)	0.018
Increase in $D_{L_{CO}}$ (% predicted) relative change or decrease < 15%	35	1.00	REF
Decrease in WD > 200 ft	14	0.41 (0.07–2.31)	0.313
Increase in WD or decrease < 200 ft	30	1.00	REF
Baseline DA, 10 U	51	0.41 (0.12–1.43)	0.162
Baseline WD, 100 feet units	51	0.83 (0.66–1.05)	0.119
DA relative change, 10% U	51	0.87 (0.66–1.15)	0.339
Decrease in WD > 200 ft	16	3.67 (1.12–12.07)	0.032
Increase in WD or decrease < 200 ft	35	1.00	REF

For definition of abbreviations, *see* Table 2.
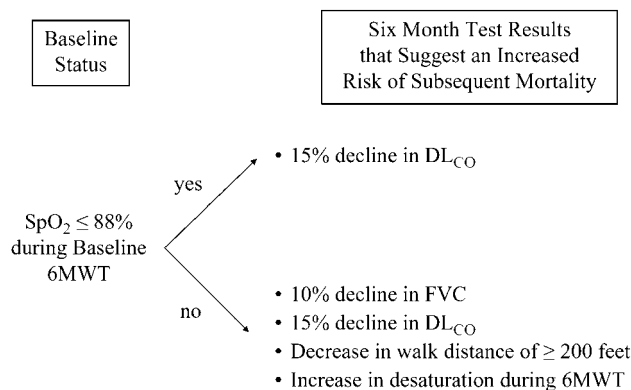Values are adjusted for age, sex, and smoking history at baseline.

Figure 3. Graphic representation of how the predictive ability of serial changes in FVC, diffusion capacity of carbon monoxide ($D_{L_{CO}}$), change in walk distance, and change in desaturation varies by the presence/absence of desaturation to $\leqslant$ 88% during a baseline 6MWT. These data suggest that decline in $D_{L_{CO}}$ over 6 mo is the sole predictor of increased risk of subsequent mortality and that declines in $D_{L_{CO}}$, FVC, walk distance, and worsening desaturation can be used to follow patients who do not desaturate $\leqslant$ 88% during a baseline 6MWT.

Further research is required to understand the mechanisms associated with decline in pulmonary physiology and subsequent mortality.

Strengths of this study include a large sample size and the inclusion of patients with an SLB and also patients with a typical HRCT not requiring a SLB for diagnosis. This latter point reflects the usual care of patients with IPF and helps generalize the results of this study. Weaknesses of this study include its retrospective study design, the lack of predefined data collection points, the format for terminating 6-min walk testing based on saturation, and the lack of prospectively defined treatment regimens. The effect of varied treatments on study outcome is likely minimal given the lack of rigorous, positive efficacy data for the treatments used during the course of this study. Additional prospective data collection is required to confirm our findings.

In conclusion, this study highlights that desaturation at baseline increases the risk of subsequent mortality; baseline walk distance is a good predictor of subsequent walk distance but does not reliably predict risk of subsequent mortality; and the predictive ability of serial change in FVC, $D_{L_{CO}}$, walk distance, and DA varies when patients are stratified by the presence/absence of a saturation greater than 88% during a baseline 6MWT. This study highlights the importance of stratifying patients by degree of desaturation at baseline before examining changes in

physiology as outcomes in clinical trials or when making treatment decisions for individual patients (e.g., when the risk of subsequent mortality justifies the risk of interventions such as lung transplantation).

References

1. King T Jr, Tooze J, Schwarz M, Brown K, Cherniack R. Predicting survival in idiopathic pulmonary fibrosis: Scoring system and survival model. *Am J Respir Crit Care Med* 2001;164:1171–1181.

2. King T Jr, Schwarz M, Brown K, Tooze J, Colby T, Waldron J Jr, Flint A, Thurlbeck W, Cherniack R. Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. *Am J Respir Crit Care Med* 2001;164:1025–1032.

3. Flaherty K, Toews G, Travis W, Colby T, Kazerooni E, Gross B, Jain A, Strawderman R III, Paine R III, Flint A, *et al.* Clinical significance of histological classification of idiopathic interstitial pneumonia. *Eur Respir J* 2002;19:275–283.

4. Lama V, Flaherty K, Toews G, Colby T, Travis W, Long Q, Murray S, Kazerooni E, Gross B, Lynch J III, *et al.* Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003;168:1084–1090.

5. Mogulkoc N, Brutsche MH, Bishop PW, Greaves SM, Horrocks AW, Egan JJ. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. *Am J Respir Crit Care Med* 2001;164:103–108.

6. Hallstrand TS, Boitano LJ, Johnson WC, Spada CA, Hayes JG, Raghu G. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. *Eur Respir J* 2005;25:96–103.

7. Eaton T, Young P, Milne D, Wells AU. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. *Am J Respir Crit Care Med* 2005;171:1150–1157.

8. Jegal Y, Kim DS, Shim TS, Lim CM, Do Lee S, Koh Y, Kim WS, Kim WD, Lee JS, Travis WD, *et al.* Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. *Am J Respir Crit Care Med* 2005;171:639–644.

9. Latsi PI, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, Veeraraghavan S, Hansell DM, Wells AU. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med* 2003;168:531–537.

10. Collard H, King T, Bartelson B, Vourlekis J, Schwarz M, Brown K. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;168:538–542.

11. Flaherty K, Mumford J, Murray S, Kazerooni E, Gross B, Colby T, Travis W, Flint A, Toews G, Lynch J, *et al.* Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003;168:543–548.

12. Agusti AG, Roca J, Rodriguez-Roisin R, Xaubet A, Agusti-Vidal A. Different patterns of gas exchange response to exercise in asbestosis and idiopathic pulmonary fibrosis. *Eur Respir J* 1988;1:510–516.

13. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000;161:646–664.

14. Jernudd-Wilhelmsson Y, Hornblad Y, Hedenstierna G. Ventilation-perfusion relationships in interstitial lung disease. *Eur J Respir Dis* 1986;68:39–49.

15. Wagner PD. Ventilation-perfusion matching during exercise. *Chest* 1992;101:192S–198S.

16. Hansen J, Wasserman K. Pathophysiology of activity limitation in patients with interstitial lung disease. *Chest* 1996;109:1566–1576.

17. Hunninghake G, Lynch D, Galvin J, Muller N, Schwartz D, King T Jr, Lynch JIII, Hegele R, Waldron J Jr, Colby T, Hogg J. Radiologic findings are strongly associated with a pathologic diagnosis of usual interstitial pneumonia. *Chest* 2003;124:1215–1223.

18. Flaherty K, Thwaite E, Kazerooni E, Gross B, Toews G, Colby T, Travis W, Mumford J, Murray S, Flint A, *et al.* Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax* 2003;58:143–148.

19. Flaherty K, Travis W, Colby T, Toews G, Kazerooni E, Gross B, Jain A, Strawderman R III, Flint A, Lynch J III, *et al.* Histologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med* 2001;164:1722–1727.

20. Flaherty KR, King TE Jr, Raghu G, Lynch JP III, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q, *et al.* Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med* 2004;170:904–910.

21. Fraley C, Martinez F, Lama V, Colby T, Travis W, Toews G, Flint A, Chang A, Flaherty K. Distance walking during a six minute walk test (6MWT) relative to the quantity of desaturation predicts mortality in patients with idiopathic pulmonary fibrosis (IPF). *Proc Am Thorac Soc* 2005;2:A316.

22. Gay S, Kazerooni E, Toews G, Lynch J III, Gross B, Cascade P, Spizarny D, Flint A, Schork M, Whyte R, *et al.* Idiopathic pulmonary fibrosis: predicting response to therapy and survival. *Am J Respir Crit Care Med* 1998;157:1063–1072.

23. Kawut SM, O'Shea MK, Bartels MN, Wilt JS, Sonett JR, Arcasoy SM. Exercise testing determines survival in patients with diffuse parenchymal lung disease evaluated for lung transplantation. *Respir Med* 2005;99:1431–1439.

24. Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, Taguchi Y, Nagai S, Itoh H, Ohi M, *et al.* Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005;171:1040–1047.

25. Frost AE, Langleben D, Oudiz R, Hill N, Horn E, McLaughlin V, Robbins IM, Shapiro S, Tapson VF, Zwicke D, *et al.* The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect. *Vascul Pharmacol* 2005;43:36–39.

26. Bosentan studies in pulmonary fibrosis show no effect on primary exercise improvement endpoint: secondary endpoints related to death or disease worsening provide strong rationale for Phase III mortality/morbidity study in Idiopathic Pulmonary Fibrosis (IPF).Available from: www.actelion.com/uninet/www/www_main_p.nsf/Content/me+28+Nov+2005 (accessed April 4, 2006).

27. King TE Jr, Safrin S, Starko KM, Brown KK, Noble PW, Raghu G, Schwartz DA. Analyses of efficacy end points in a controlled trial of interferon-gamma1b for idiopathic pulmonary fibrosis. *Chest* 2005;127:171–177.

28. Martinez FJ, Safrin S, Weycker D, Starko KM, Bradford WZ, King TE Jr, Flaherty KR, Schwartz DA, Noble PW, Raghu G, *et al.* The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med* 2005;142:963–967.

29. Egan JJ, Martinez FJ, Wells AU, Williams T. Lung function estimates in idiopathic pulmonary fibrosis: the potential for a simple classification. *Thorax* 2005;60:270–273.