

# The Prognostic Value of Cardiopulmonary Exercise Testing in Idiopathic Pulmonary Fibrosis

Charlene D. Fell<sup>1</sup>, Lyrica Xiaohong Liu<sup>2</sup>, Caroline Motika<sup>3</sup>, Ella A. Kazerooni<sup>4</sup>, Barry H. Gross<sup>4</sup>, William D. Travis<sup>5</sup>, Thomas V. Colby<sup>6</sup>, Susan Murray<sup>2</sup>, Galen B. Toews<sup>7</sup>, Fernando J. Martinez<sup>7</sup>, and Kevin R. Flaherty<sup>7</sup>

<sup>1</sup>Division of Respiratory Medicine, University of Calgary, Calgary, Canada; <sup>2</sup>Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan; <sup>3</sup>Section of Pulmonary and Critical Care Medicine, University of Chicago, Chicago, Illinois; <sup>4</sup>Department of Radiology, Division of Cardiothoracic Radiology, and <sup>7</sup>Division of Pulmonary and Critical Care Medicine, University of Michigan Health System, Ann Arbor, Michigan; <sup>5</sup>Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York; and <sup>6</sup>Department of Pathology, Mayo Clinic, Scottsdale, Arizona

**Rationale:** Idiopathic pulmonary fibrosis (IPF) is characterized by progressive dyspnea, impaired gas exchange, and ultimate mortality.

**Objectives:** To test the hypothesis that maximal oxygen uptake during cardiopulmonary exercise testing at baseline and with short-term longitudinal measures would predict mortality in patients with idiopathic pulmonary fibrosis.

**Methods:** Data from 117 patients with IPF and longitudinal cardiopulmonary exercise tests were examined retrospectively. Survival was calculated from the date of the first cardiopulmonary exercise test.

**Measurements and Main Results:** Patients with baseline maximal oxygen uptake less than 8.3 ml/kg/min had an increased risk of death ( $n = 8$ ; hazard ratio, 3.24; 95% confidence interval, 1.10–9.56;  $P = 0.03$ ) after adjusting for age, gender, smoking status, baseline forced vital capacity, and baseline diffusion capacity for carbon monoxide. We were unable to define a unit change in maximal oxygen uptake that predicted survival in our cohort.

**Conclusions:** We conclude that a threshold maximal oxygen uptake of 8.3 ml/kg/min during cardiopulmonary exercise testing at baseline adds prognostic information for patients with IPF.

**Keywords:** idiopathic pulmonary fibrosis; exercise test; mortality

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown etiology characterized by progressive dyspnea and ultimate mortality (1). Mean survival from time of diagnosis to death is 3 years (1). However, the disease course is variable: some patients progress rapidly and others remain stable for many years (2). There is no effective treatment and many patients, if eligible, are referred for lung transplantation. Identification of surrogate short-term measures of mortality is critical to the management and study of patients with IPF.

Several factors have been identified that predict poor survival in patients with IPF, including age, sex, smoking history, diffusion capacity for carbon monoxide ( $DL_{CO}$ ), FVC, degree of fibrosis on high-resolution computerized tomography of the chest, and number of fibroblastic foci on histopathology (3–11). Longitudinal changes in FVC or  $DL_{CO}$  have been found to have important prognostic value. A decrease in FVC of at least 10% or  $DL_{CO}$  of at

## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Prognosis in idiopathic pulmonary fibrosis (IPF) is poor. Predicting prognosis by examining exercise performance with the six-minute-walk test has led to conflicting results.

### What This Study Adds to the Field

This study shows that  $\dot{V}O_{2max}$  predicts mortality in patients with IPF. Patients with  $\dot{V}O_{2max}$  less than 8.3 ml/kg/min at baseline had an increased risk of death.

least 15% over 6 or 12 months is associated with decreased survival (10–15).

Gas exchange worsens with exercise in IPF (1, 16, 17). Several studies have examined this feature using either cardiopulmonary exercise tests (CPET) or the 6-minute-walk test (6MWT). A decrease in  $PaO_2$  during CPET in patients with IPF contributes up to 10.5% of the total clinical, radiographic, and physiologic (CRP) score (5) used to estimate prognosis in IPF. Desaturation during CPET has been shown to predict mortality in some (16) but not all (18, 19) studies. Desaturation below 88% during 6MWT is a more consistent marker of increased risk for mortality (7, 9, 10), whereas shorter walk distance is less predictive (15). Longitudinal change in 6MWT data predicts mortality in patients who do not desaturate less than 88% at baseline (15).

Patients with IPF have impaired ventilatory and cardiovascular responses to exercise (20) due to multiple abnormalities, including low tidal volume; a failure to decrease ventilatory dead space; a rapid, shallow breathing pattern; impaired gas exchange due to interstitial fibrosis; pulmonary hypertension; ventilation/perfusion mismatching; and low mixed venous  $O_2$ .

$\dot{V}O_{2max}$  is an integrated measure of cardiovascular, respiratory, and neuromuscular function (21). In prior studies of patients with interstitial lung disease,  $\dot{V}O_{2max}$  correlated poorly with measures of lung volume, suggesting that it more accurately reflects derangements in hemodynamics as well as ventilation during exercise (20). Although change in FVC is a good surrogate for subsequent mortality, it is imperfect as some patients die without a 10% decline in FVC, whereas others can live for prolonged periods even after a 10% decline in FVC (2, 22). Therefore we chose to examine longitudinal change in  $\dot{V}O_{2max}$  *a priori* because it is an integrated measure of cardiovascular, respiratory, and neuromuscular function (21). We tested the hypothesis that a decrease in  $\dot{V}O_{2max}$  during baseline and short-term longitudinal CPETs predicts mortality in patients with IPF.

(Received in original form February 8, 2008; accepted in final form December 11, 2008)

Supported by National Institute of Health NHLBI grant P50HL-56402, NHLBI, 2 K24 HL04212, 1 K23 HL68713, and 1K23 HL077719. C.D.F. was supported by the Alberta Heritage Foundation for Medical Research.

Correspondence and requests for reprints should be addressed to Kevin R. Flaherty, M.D., M.S., Division of Pulmonary and Critical Care Medicine, University of Michigan Health System, 1500 East Medical Center Drive, 3916 Taubman Center, Ann Arbor, MI 48109. E-mail: flaherty@umich.edu

Am J Respir Crit Care Med Vol 179, pp 402–407, 2009

Originally Published in Press as DOI: 10.1164/rccm.200802-241OC on December 12, 2008  
Internet address: www.atsjournals.org

## METHODS

### Patient Selection

This is a retrospective analysis of 117 patients in the University of Michigan Specialized Center of in the Pathobiology of Fibrotic Lung Disease Database. Patients in this database were referred for enrollment in study protocols for suspected IPF based on typical symptoms, physiologic findings, and radiographic findings (1). Patients with a high-resolution computerized tomography scan showing a definite pattern of usual interstitial pneumonitis (23) were not required to undergo surgical lung biopsy ( $n = 42$ ) (24, 25). Patients with underlying connective tissue disease, occupational or environmental exposures, or histopathologic pattern on surgical lung biopsy other than usual interstitial pneumonitis were excluded. Patients were treated with varied regimens, including no therapy, immunosuppression (prednisone  $\pm$  azathioprine or cyclophosphamide), colchicine, and experimental protocols. The lack of a standardized treatment regimen prevented an analysis of the data based on therapy. Approval for the use of these data was provided by our Institutional Review Board. Subgroups of these patients have been previously described (7, 15, 26).

### Pulmonary Function, 6-Minute Walk, and Cardiopulmonary Exercise Tests

Pulmonary function and exercise tests, including FVC,  $DL_{CO}$ , 6MWT, and CPET, were performed as described (7, 18). Desaturation during a 6MWT was defined *a priori* as less than 88% based on published data (7).

### Statistical Analysis

The date of the first CPET was used as the start date for survival analysis. Death date was supplemented by searching the Social Security Death Index (27); patients not listed in this index were censored 3 months prior to the analysis date to account for potential lags in reporting. Multivariate Cox proportional hazard models (28) adjusted for age, sex, baseline forced vital capacity percent predicted, baseline  $DL_{CO}$  percent predicted, and smoking status were constructed for potential  $\dot{V}O_{2max}$  thresholds ranging from 4.4 ml/kg/min to 25.1 ml/kg/min, in increments of 0.3 ml/kg/min. Resulting hazard ratios were plotted against  $\dot{V}O_{2max}$  to determine if a threshold  $\dot{V}O_{2max}$  could be identified that correlated with increased risk of mortality. Similar secondary analyses were performed on resting  $Pa_{O_2}$ . Baseline characteristics between patients with  $\dot{V}O_{2max}$  above and below the thresholds were compared using *t* tests (29) for continuous measures and chi-square (30) tests for categorical measures. Data are expressed as mean  $\pm$  standard deviation (SD) or frequency (%). In secondary analyses, index of concordance (31) was used compare the  $\dot{V}O_{2max}$  threshold, desaturation less than 88% during a 6MWT, and resting  $Pa_{O_2}$  to determine which was the strongest predictor of survival. Survival between patients with baseline  $\dot{V}O_{2max}$  above and below thresholds was examined with unadjusted Kaplan Meier survival curves (32) and log-rank tests (33, 34). Multivariate Cox proportional hazard models studied the predictive value of the  $\dot{V}O_{2max}$  threshold adjusted for age, gender, smoking status, baseline FVC percent predicted (FVC%), and baseline  $DL_{CO}$  percent predicted ( $DL_{CO}\%$ ). Statistical significance was set at  $P = 0.05$ . Statistical analysis was performed with R software (<http://www.r-project.org/index.html>) and SPSS (version 14.0; SPSS Inc., Chicago, IL).

## RESULTS

Data from 117 patients with at least two cardiopulmonary exercise tests were analyzed. Seventy-five (64%) patients were diagnosed with a surgical lung biopsy. Patients who did not undergo a lung biopsy were significantly older ( $66.73 \pm 8.50$  vs.  $63.07 \pm 8.23$  y,  $P = 0.024$ ) but otherwise not different than those with a lung biopsy (data not shown).

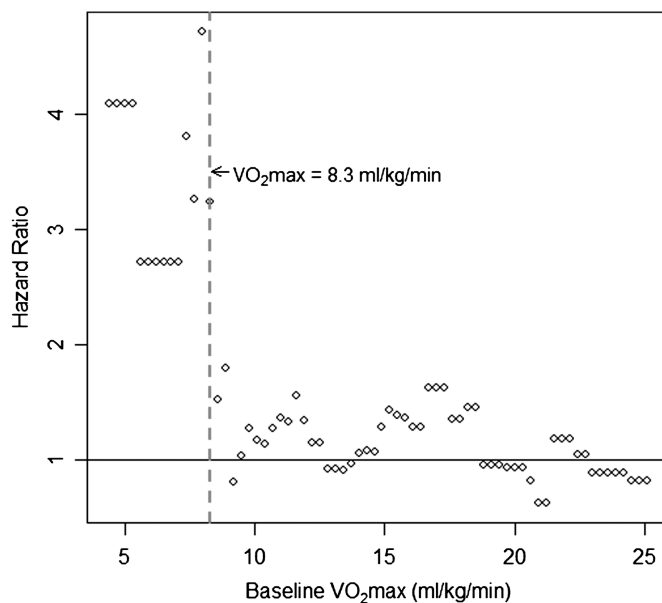
We explored the predictive value of  $\dot{V}O_{2max}$  on survival.  $\dot{V}O_{2max}$  did not predict survival when examined as a continuous variable (hazard ratio [HR], 0.969; 95% confidence interval [CI], 0.88–1.07;  $P = 0.55$ ). Exploratory analyses revealed

a threshold  $\dot{V}O_{2max}$  of 8.3 ml/min/kg that was associated with an increased risk of subsequent mortality (Figure 1). This threshold effectively captures patients with a higher risk of mortality and discriminates these patients from those with a lower risk of mortality.

Demographic data and baseline physiologic data for patients with an initial  $\dot{V}O_{2max}$  above or below 8.3 ml/min/kg are presented in Table 1. Patients whose baseline  $\dot{V}O_{2max}$  was below threshold were more often female ( $P = 0.04$ ), had significantly lower FVC% ( $P = 0.01$ ) and  $DL_{CO}\%$  ( $P = 0.006$ ), shorter 6-minute walk distance ( $P = 0.002$ ), and significantly lower exercise capacity during baseline CPET compared with those with baseline  $\dot{V}O_{2max}$  above threshold (Table 1). Surprisingly, not all patients with  $\dot{V}O_{2max}$  below threshold at baseline desaturated during a baseline 6MWT.

Multivariate relationships between  $\dot{V}O_{2max}$  and baseline demographic and pulmonary function variables were explored (Table 2). In multivariate linear regression models, age, male gender, history of smoking, and baseline FVC were predictors of  $\dot{V}O_{2max}$ . A linear predictor incorporating these variables significantly predicted whether a patient's baseline  $\dot{V}O_{2max}$  would be below threshold (Table 3). With this model, patients who are younger, male, never smokers, with higher FVC% and  $DL_{CO}\%$  are more likely to have a  $\dot{V}O_{2max}$  above 8.3 ml/min/kg, and thus are predicted to have overall improved survival than older, female, ever smokers with lower FVC% and  $DL_{CO}\%$ .

Survival in patients with baseline  $\dot{V}O_{2max}$  below the 8.3 ml/kg/min threshold was lower than that of patients above the threshold over time (log rank  $P < 0.001$ , Figure 2). This difference was maintained in multivariate Cox proportional hazard survival models adjusting for patient age, smoking status, male sex, baseline FVC%, and baseline  $DL_{CO}\%$  (HR for being below



**Figure 1.** Determination of a  $\dot{V}O_{2max}$  threshold of 8.3 ml/kg/min. Multivariate Cox proportional hazard models adjusted for age, sex, baseline FVC percent predicted, baseline diffusion capacity of carbon monoxide percent predicted, and smoking status were constructed for potential  $\dot{V}O_{2max}$  thresholds ranging from 4.4 ml/kg/min to 25.1 ml/kg/min, in increments of 0.3 ml/kg/min. The vertical axis gives hazard ratios comparing risk of patients above and below the corresponding threshold along the horizontal axis. A threshold baseline  $\dot{V}O_{2max}$  of 8.3 ml/min/kg was determined (dashed line).

**TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS WITH BASELINE  $\dot{V}O_2\text{max}$  ABOVE OR BELOW THE 8.3 ml/kg/min THRESHOLD**

	Above Threshold	Below Threshold	P Value
n	109	8	
Age, yr	64.0 ± 8.4	69.1 ± 8.6	0.10
Sex			0.044
Male	78 (78.8%)	3 (37.5%)	
Female	31 (31.3%)	5 (62.5%)	
Diagnosed with lung biopsy	70 (70.7%)	5 (62.5%)	0.92
Smokers			0.30
Never smokers	28 (28.3%)	4 (50%)	
Former smokers	76 (76.7%)	4 (50%)	
Current smokers	5 (5.0%)	0	
Pack-years	39.2 ± 24.9	42.0 ± 44.4	0.84
Spirometry at baseline			
FVC, L	2.8 ± 0.9	1.8 ± 0.6	0.002
FVC%	69.0 ± 17.8	53.0 ± 9.6	0.01
$D_{LCO}$ , ml/min/mm Hg	12.3 ± 4.4	7.1 ± 1.3	0.002
$D_{LCO}\%$	47.8 ± 14.9	31.9 ± 7.7	0.006
Exercise at baseline			
Exercise $Pa_{O_2}$	67.4 ± 15.0	59.4 ± 12.6	0.25
Exercise Aa gradient	41.0 ± 14.7	42.2 ± 13.3	0.85
Exercise saturation	89.5 ± 4.9	88.0 ± 5.7	0.41
Minutes of exercise	7.4 ± 1.9	4.2 ± 1.5	<0.001
Work, W	95.2 ± 35.0	40.0 ± 11.6	<0.001
$\dot{V}O_2\text{max}$ , ml/kg/min	14.0 ± 4.2	6.9 ± 1.4	<0.001
Exercise gas exchange score	12.4 ± 9.8	20.0 ± 14.2	0.04
6MWT at baseline			
Desaturation < 88%	38 (38.4%)	5 (62.5%)	0.12
Distance, ft	1,116.6 ± 456.0	582.2 ± 386.1	0.002

Definition of abbreviations: Aa gradient = alveolar-arterial gradient;  $D_{LCO}\%$  = diffusion capacity for carbon monoxide percent predicted; FVC% = forced vital capacity percent predicted;  $\dot{V}O_2\text{max}$  = maximal oxygen consumption during cardiopulmonary exercise testing; 6MWT = 6-min-walk test.

Data are shown as mean ± standard deviation (SD) or frequency (%).

threshold, 3.24; 95% CI, 1.10–9.56;  $P = 0.03$ ) (Figure 3 and Table 4).

In the majority of patients studied,  $\dot{V}O_2\text{max}$  did not change between baseline and 6 months ( $n = 99$ ). Of the 109 patients with  $\dot{V}O_2\text{max}$  above threshold at baseline, 5 had a further decline in  $\dot{V}O_2\text{max}$  below the threshold with longitudinal measures. However, we were unable to define a unit change in  $\dot{V}O_2\text{max}$  that predicted survival in our cohort (data not shown).

Prior studies have shown that resting  $Pa_{O_2}$  predicts survival in IPF. In secondary analyses, resting  $Pa_{O_2}$  was a significant predictor of mortality (HR, 0.934; 95% CI, 0.88–0.99;  $P = 0.02$ ), when adjusted for age, sex, smoking status, and baseline FVC% and  $D_{LCO}\%$ . A clear threshold for resting  $Pa_{O_2}$  could not be determined (data not shown). An adjusted multivariate Cox

**TABLE 2. MULTIVARIATE LINEAR REGRESSION MODEL DETECTING ASSOCIATIONS WITH  $\dot{V}O_2\text{max}$**

	$\beta$	SE	P Value
Age, yr	-0.23	0.04	<0.001
Male sex	2.53	0.79	0.002
Ever smoker	-1.61	0.72	0.028
Baseline FVC%	0.82	0.28	0.004
Baseline $D_{LCO}\%$	0.30	0.31	0.332

Definition of abbreviations:  $D_{LCO}\%$  = diffusion capacity for carbon monoxide percent predicted; FVC% = forced vital capacity percent predicted; SE = standard error;  $\dot{V}O_2\text{max}$  = maximal oxygen consumption during cardiopulmonary exercise testing.

$n = 103$ .

**TABLE 3. LOGISTIC REGRESSION MODEL OF PREDICTORS OF  $\dot{V}O_2\text{max} < 8.3$  ml/kg/min**

	OR	95% CI	P Value
Linear predictor	0.57	0.37–0.87	0.01

Linear predictor =  $-0.232(\text{age}) + 2.53(\text{male gender}) - 1.6(\text{ever smoker}) + 0.82(\text{FVC}\%) + 0.30(\text{D}_{LCO}\%)$ .

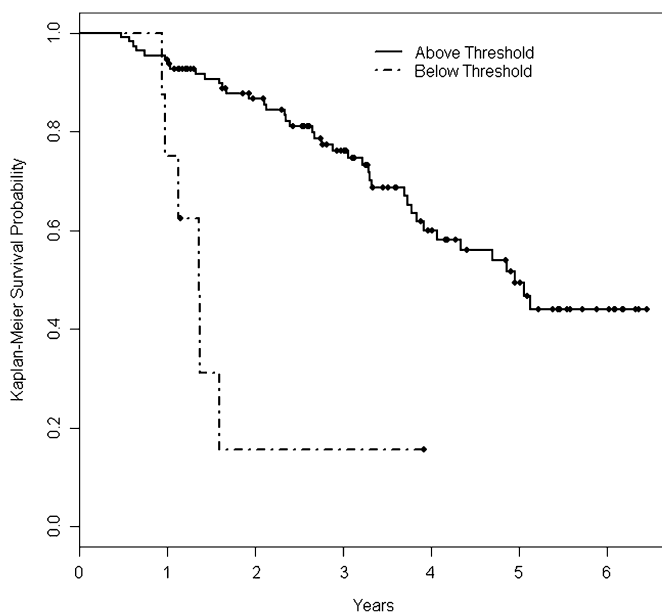
Definition of abbreviations: CI = confidence interval;  $D_{LCO}\%$  = baseline diffusion capacity for carbon monoxide percent predicted; FVC% = baseline forced vital capacity percent predicted; OR = odds ratio;  $\dot{V}O_2\text{max}$  = maximal oxygen consumption during cardiopulmonary exercise testing.

$n = 103$ .

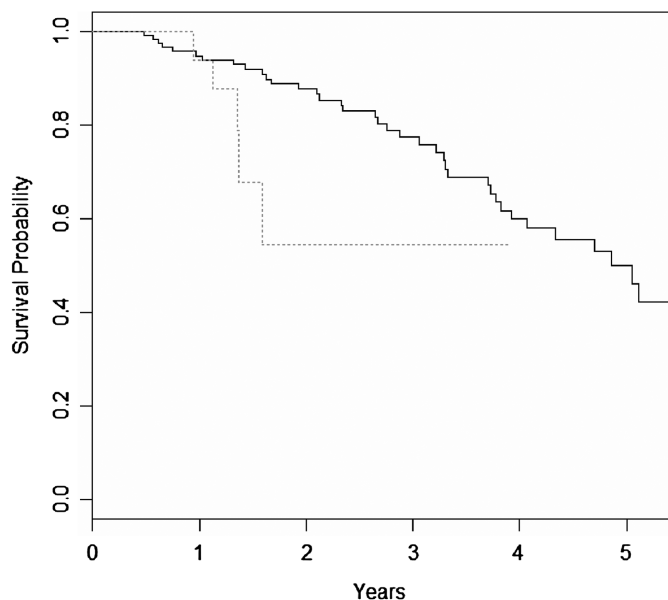
model with the  $\dot{V}O_2\text{max}$  threshold (HR, 2.66; 95% CI, 0.74–9.5;  $P = 0.13$ ) and resting  $Pa_{O_2}$  (HR, 0.95; 95% CI, 0.89–1.00;  $P = 0.09$ ) did not show significance of either predictor. When the  $\dot{V}O_2\text{max}$  threshold, resting  $Pa_{O_2}$ , and desaturation below 88% during a 6MWT were included in an adjusted Cox model, the  $\dot{V}O_2\text{max}$  threshold was a significant predictor of mortality (HR, 3.48; 95% CI, 1.16–10.43;  $P = 0.03$ ), whereas desaturation less than 88% was not (HR, 1.49; 95% CI, 0.617–3.62;  $P = 0.37$ ). Index of concordance analysis demonstrated that the  $\dot{V}O_2\text{max}$  threshold is a more robust predictor of survival than resting  $Pa_{O_2}$  or desaturation less than 88% during a 6MWT (Table 5).

**DISCUSSION**

In this study, we examined the relationship between maximal oxygen uptake during cardiopulmonary exercise testing and mortality. We hypothesized that  $\dot{V}O_2\text{max}$  measured during cardiopulmonary exercise testing predicts mortality in patients with IPF. We found that  $\dot{V}O_2\text{max}$  examined as a continuous variable does not predict mortality in IPF. However, baseline threshold  $\dot{V}O_2\text{max}$  of 8.3 ml/kg/min predicts mortality in these patients. This threshold is a robust predictor of survival when



**Figure 2.** Unadjusted Kaplan-Meier survival curves for patients whose baseline  $\dot{V}O_2\text{max}$  was greater than 8.3 ml/min/kg (Above Threshold,  $n = 99$ ) or less than 8.3 ml/min/kg (Below Threshold,  $n = 8$ ). Survival time was calculated from the date of the first cardiopulmonary exercise test.



**Figure 3.** Cox proportional hazard survival curves for patients with baseline  $\dot{V}O_2\text{max}$  greater than 8.3 ml/kg/min (solid line) and less than 8.3 ml/kg/min (dashed line) adjusted for age, sex, smoking status, baseline FVC percent predicted, and baseline  $DL_{CO}$  percent predicted. Survival time was calculated from the date of the first cardiopulmonary exercise test.

compared with desaturation less than 88% during a 6MWT and resting  $Pa_{O_2}$ . Demographic and pulmonary function data can be used to estimate whether  $\dot{V}O_2\text{max}$  is above or below the 8.3 ml/kg/min threshold.

We found a threshold baseline  $\dot{V}O_2\text{max}$  less than 8.3 ml/kg/min predicts mortality in patients with IPF. A similar threshold value has not been reported in fibrotic lung disease. In a study of 86 patients with primary pulmonary hypertension, Wensel and colleagues (35) found a  $\dot{V}O_2\text{max}$  threshold of 10.4 ml/kg/min predicts mortality. Various measures of exercise capacity have been examined for their ability to predict survival in IPF. A CRP score was developed by Watters and colleagues (36) as a tool to assess and follow patients' clinical impairment from IPF. The score used an exercise gas exchange score, which assigned points based on change in saturation during exercise, change in  $\dot{V}O_2$ , and predicted  $\dot{V}O_2\text{max}$ . The maximum points attributable to exercise gas exchange in the CRP score was 30, greater than the radiological, symptoms, and pulmonary func-

**TABLE 4. MULTIVARIATE COX PROPORTIONAL HAZARD SURVIVAL MODEL ASSESSING THE PREDICTIVE VALUE OF  $\dot{V}O_2\text{max} < 8.3$  ml/min/kg**

	HR	95%CI	P Value
$\dot{V}O_2\text{max}$ below threshold	3.24	1.10–9.56	0.03
Age, yr	1.04	1.00–1.08	0.08
Male sex	1.29	0.62–2.69	0.50
Ever smoker	1.33	0.71–2.48	0.37
Baseline FVC%	0.93	0.72–1.21	0.58
Baseline $DL_{CO}$ %	0.66	0.49–0.90	0.01

*Definition of abbreviations:* CI = confidence interval;  $DL_{CO}$ % = diffusion capacity for carbon monoxide percent predicted; FVC% = forced vital capacity percent predicted; HR = hazard ratio;  $\dot{V}O_2\text{max}$  = maximal oxygen consumption during cardiopulmonary exercise testing.

n = 103.

**TABLE 5. INDEX OF CONCORDANCE ANALYSIS COMPARING THE STRENGTH OF  $\dot{V}O_2\text{max} < 8.3$  ml/kg/min, DESATURATION < 88% DURING A 6-MINUTE WALK TEST, AND RESTING  $Pa_{O_2}$  AS PREDICTORS OF SURVIVAL IN IDIOPATHIC PULMONARY FIBROSIS**

Model	Ratio	Concordance
$\dot{V}O_2\text{max} < 8.3$ ml/kg/min	0.716	2342.5
Desaturation < 88%	0.708	2316.5
Resting $Pa_{O_2}$	0.702	2322.7

*Definition of abbreviations:*  $DL_{CO}$ % = diffusion capacity for carbon monoxide percent predicted; FVC% = forced vital capacity percent predicted;  $Pa_{O_2}$  = arterial partial pressure of oxygen;  $\dot{V}O_2\text{max}$  = maximal oxygen consumption during cardiopulmonary exercise testing; 6MWT = 6-min-walk test.

Covariates in each model were: age, male sex, smoking status, FVC%, and  $DL_{CO}$ %. Number of paired observations: 3,271.

tion components of the score, reflecting the importance of exercise gas exchange in clinical impairment in IPF. More recently, Miki and colleagues (37) calculated the change in  $Pa_{O_2}$  per change in  $\dot{V}O_2$  during CPET ( $\Delta Pa_{O_2}/\Delta \dot{V}O_2$  or  $Pa_{O_2}$  slope) and found this relationship to predict mortality in patients with IPF. However, not all studies show that CPET measurements of gas exchange predict survival (18, 19). Studies that have used multistep scores (CRP score) or slope calculations ( $Pa_{O_2}$  slope) to define the risk of mortality attributable to exercise gas exchange in IPF may be too cumbersome for routine use outside of clinical trials. Our data suggest that a simple threshold for  $\dot{V}O_2\text{max}$  of 8.3 ml/kg/min predicts mortality in patients with IPF, without the need for lengthy calculations.

Several authors have examined the prognostic value of the 6MWT or other walk tests in IPF. Desaturation during 6MWT (7, 9), distance walked (9), and progressive impairment in longitudinal 6MWTs (15) have been found to predict mortality in IPF. One criticism of the 6MWT is that it is a patient-driven, symptom- and effort-limited test. This may explain the controversy in the literature about whether distance walked or desaturation is a better predictor of mortality. It may also explain why not all patients in this study with a baseline  $\dot{V}O_2\text{max}$  below threshold had desaturation during 6MWT: these patients might not have walked sufficiently fast or far enough to produce desaturation.

Using index of concordance techniques, we compared the ability of desaturation less than 88% during a 6MWT and the  $\dot{V}O_2\text{max}$  threshold to predict mortality in IPF. Despite the small number of patients with  $\dot{V}O_2\text{max}$  below threshold at baseline, this variable was a stronger predictor than desaturation less than 88% in our cohort in multivariate Cox models. The  $\dot{V}O_2\text{max}$  threshold is also more robust than resting  $Pa_{O_2}$  and desaturation less than 88% during a 6MWT in concordance analyses.

We were unable to identify a unit change in  $\dot{V}O_2\text{max}$  per time that predicts survival in short-term follow-up. This may be due to the small number of patients who had a decline in  $\dot{V}O_2\text{max}$  during the follow-up period. This could suggest that  $\dot{V}O_2\text{max}$  is more stable over time compared with other measures, such as FVC or  $DL_{CO}$ . It could also reflect a selection bias in that as patients became sicker they may have declined exercise testing but still been able to perform pulmonary function testing. Further prospectively collected data are needed to explore the changes in  $\dot{V}O_2\text{max}$  over time and their impact on survival.

There are several limitations to this study. Patients in this study were not evaluated for the presence of pulmonary hypertension. Pulmonary hypertension has been shown to be an important predictor of mortality in IPF (38–40), although its presence does not universally portend a poor outcome (40).

Patients included in this study were enrolled in a number of treatment protocols; the varied nature of the protocols prevents an analysis of the data based on therapy. However, none of the therapies in use in these protocols has been found to slow, halt, or reverse pulmonary fibrosis in this population, and prior analyses of the effects of therapy on this population have shown no benefit (7, 18, 41). In our cohort of 117 patients, 8 had a baseline  $\dot{V}_{O_2\max}$  below threshold and 5 had a decrease in  $\dot{V}_{O_2\max}$  to below threshold over the course of follow-up, yet 46% of the patients died during follow-up. Other measures that demonstrate significant change over time, such as serial measures of FVC%, may be more sensitive predictors of mortality in this population. Alternately, deaths could have been due to acute exacerbations of IPF or other acute events, which we did not measure.

In this study, we examined the prognostic value of CPET in IPF. A baseline  $\dot{V}_{O_2\max}$  less than 8.3 ml/kg/min threshold was identified, below which the risk of death was greatly increased. This study provides an easy-to-use threshold for  $\dot{V}_{O_2\max}$  for patients with IPF that predicts an increased risk of death. An unexpected finding was that not all patients with  $\dot{V}_{O_2\max}$  below threshold desaturated during a 6MWT. Direct comparison of baseline  $\dot{V}_{O_2\max}$  less than 8.3 ml/kg/min during CPET and desaturation less than 88% during a 6MWT shows that the  $\dot{V}_{O_2\max}$  threshold is a better predictor of survival in IPF. CPET and the 8.3 ml/kg/min threshold provide additional information to clinicians and their patients to help guide therapeutic decisions in IPF.

**Conflict of Interest Statement:** C.D.F. has been compensated for serving on an advisory board in 2007 for Actelion. L.X.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. E.A.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. B.H.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. W.D.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.V.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. G.B.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. F.J.M. is a consultant for Altana Pharma and has received compensation greater than \$10K. F.J.M. has been a member of several Advisory Boards, CME committees, and the Speaker's Bureau for Boehringer Ingelheim, Pfizer, and GlaxoSmithKline. His total compensation per company is greater than \$10K. In addition, F.J.M. is on the advisory board for Novartis and the Speaker's Bureau for Sepracor, Schering Plough, and Astra, receiving less than \$10K per company. F.J.M. has been an investigator for industry-sponsored studies for GlaxoSmithKline, Boehringer Ingelheim, and Actelion. K.R.F. has served as a consultant for companies evaluating novel treatments for idiopathic pulmonary fibrosis, including Genzyme, Intermune, and Boehringer Ingelheim.

## References

- King TE Jr, Costabel U, Cordier J-F, DoPico GA, du Bois RM, Lynch D, Lynch JP, Myers J, Panos R, Raghu G, *et al*. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000;161:646-664.
- 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.
- Hubbard R, Johnston I, Britton J. Survival in patients with cryptogenic fibrosing alveolitis: a population-based cohort study. *Chest* 1998;113:396-400.
- 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.
- 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.
- 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.
- Lama VN, Flaherty KR, Toews GB, Colby TV, Travis WD, Long Q, Murray S, Kazerooni EA, Gross BH, Lynch JP 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.
- Mogulkoc N, Brutsche MH, Bishop PW, Greaves SM, Horrocks AW, Egan JJ, Consortium GMPF. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. *Am J Respir Crit Care Med* 2001;164:103-108.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- Flaherty KR, Andrei A-C, Murray S, Fraley C, Colby TV, Travis WD, Lama V, Kazerooni EA, Gross BH, Toews GB, *et al*. Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six minute hallwalk. *Am J Respir Crit Care Med* 2006;174:803-809.
- Lama VN, Martinez FJ. Resting and exercise physiology in interstitial lung diseases. *Clin Chest Med* 2004;25:435-453.
- Agusti AG, Roca J, Rodríguez-Roisin R, Xaubert 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.
- Gay SE, Kazerooni EA, Toews GB, Lynch JP III, Gross BH, Cascade PN, Spitzarmy DL, Flint A, Schork MA, Whyte RI, *et al*. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. *Am J Respir Crit Care Med* 1998;157:1063-1072.
- Erbes R, Schaberg T, Loddenkemper R. Lung function tests in patients with idiopathic pulmonary fibrosis: are they helpful for predicting outcome? *Chest* 1997;111:51-57.
- Hansen JE, Wasserman K. Pathophysiology of activity limitation in patients with interstitial lung disease. *Chest* 1996;109:1566-1576.
- American Thoracic Society/American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211-277.
- 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.
- Lynch DA, David Godwin J, Safrin S, Starko KM, Hormel P, Brown KK, Raghu G, King TE Jr, Bradford WZ, Schwartz DA, *et al*. High-resolution computed tomography in idiopathic pulmonary fibrosis: diagnosis and prognosis. *Am J Respir Crit Care Med* 2005;172:488-493.
- Hunninghake G, Zimmerman M, Schwartz D, King T Jr, Lynch J, Hegele R, Waldron J, Colby T, Muller N, Lynch D, *et al*. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001;164:193-196.
- 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.
- 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.

27. Social Security Death Index (SSDI) Interactive Search [Internet]. Provo, UT: The Generations Network, Inc. c1998– [updated 2008 Dec 23; accessed 2008 Dec 22]. Available from: <http://ssdi.rootsweb.ancestry.com>. (SSDI is generated from the U.S. Social Security Administration's Death Master File.)
28. Cox D. Regression models and life tables (with discussion). *J R Stat Soc [Ser A]* 1972;B34:187–220.
29. Gosset WSS. The probable error of a mean. *Biometrika* 1908;6:1–25.
30. K. Pearson. On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. *Philosophical Magazine, Series 5* 1900;50:157–175.
31. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–387.
32. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
33. Savage IR. Contributions to the theory of rank-order statistics—the two sample case. *Ann Math Stat* 1956;27:590–615.
34. Mantel N. Evaluation of survival data and two new rank-order statistics arising in its consideration. *Cancer Chemother Rep* 1966;50:163–170.
35. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken G, Kleber FX, Sharma R, Hummel M, Hetzer R, Ewert R. Assessment of survival in patients with primary pulmonary hypertension: importance of cardio-pulmonary exercise testing. *Circulation* 2002;106:319–324.
36. Watters L, King T, Schwarz M, Waldron J, Stanford R, Cherniack R. A clinical, radiographic, and physiologic scoring system for the longitudinal assessment of patients with idiopathic pulmonary fibrosis. *Am Rev Respir Dis* 1986;133:97–103.
37. Miki K, Maekura R, Hiraga T, Okuda Y, Okamoto T, Hirotsu A, Ogura T. Impairments and prognostic factors for survival in patients with idiopathic pulmonary fibrosis. *Respir Med* 2003;97:482–490.
38. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest* 2006;129:746–752.
39. Nadrous HF, Pellikka PA, Krowka MJ, Swanson KL, Chaowalit N, Decker PA, Ryu JH. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Chest* 2005;128:2393–2399.
40. Hamada K, Nagai S, Tanaka S, Handa T, Shigematsu M, Nagao T, Mishima M, Kitaichi M, Izumi T. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. *Chest* 2007;131:650–656.
41. Flaherty KR, Brewer GJ, Andrei A, Murray S, Toews GB, Martinez FJ. A phase I/II trial of tetrathiomolybdate for patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007;175:A497.