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Original Research

DIFFUSE LUNG DISEASE

Physical Activity in Daily Life of Patients With Fibrotic Idiopathic Interstitial Pneumonia

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Background: **The 6-min walk test (6MWT) is commonly used to assess exercise capacity in patients with fibrotic idiopathic interstitial pneumonia (f-IIP). However, it is not known whether patients with f-IIP have reduced levels of physical activity in daily life (DLPA) or whether pulmonary function tests and the 6MWT correlate with their DLPA.**

Methods: **The aim of this study was to measure DLPA in patients with f-IIP and to determine the relationships between DLPA and the 6MWT, pulmonary functional parameters, and anxiety and depression scores. Fifty patients with f-IIP and 25 sex- and age-matched healthy control subjects were enrolled. Markers of DLPA were assessed with a physical activity monitor for 4 consecutive days. Hospital Anxiety and Depression Scale (HADS) scores were evaluated.**

Results: **DLPA parameters were significantly reduced in patients with f-IIP compared with control subjects (all $P < .001$). The mean number of steps per day correlated strongly with diffusing capacity of the lung for carbon monoxide (DLCO), FVC, the 6MWT distance, and the 6MWT lowest oxygen saturation as measured by pulse oximetry (Spo_2). DLPA was unrelated to HADS scores. Multivariate analysis showed that DLCO and 6MWT distance explained only 31% of the variance in the number of steps per day. DLCO, 6MWT distance, 6MWT lowest Spo_2, and DLPA were significant predictors of mortality, but only DLCO and 6MWT distance were independent predictors.**

Conclusions: **Quantitation of DLPA is a novel patient-centered approach to assess function in f-IIP and may be a useful tool for clinical care and assessing response to therapy.**

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Abbreviations: 6MWT = 6-min walk test; DLCO = diffusing capacity of the lung for carbon monoxide; DLPA = physical activity in daily life; f-IIP = fibrotic idiopathic interstitial pneumonia; HADS = Hospital Anxiety and Depression Scale; Hb = hemoglobin; ILD = interstitial lung disease; MET = metabolic equivalent; PFT = pulmonary function test; Spo_2 = oxygen saturation as measured by pulse oximetry

According to the international consensus statement of 2011, idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia can be classified as fibrotic idiopathic interstitial pneumonias (f-IIPs) of unknown cause and poor prognosis.[1] Although the pathologic abnormalities of the diseases are quite different,[2,3] patients display persistent and significant dyspnea, exercise intolerance, and poor health-related quality of life.[4] Physical activity is an important clinical parameter related to morbidity and mortality in many chronic diseases.[5,6] Patients with COPD show reduced physical activity, but this is not completely reflected by the clinical characteristics commonly used to determine disease severity.[7,8]

The 6-min walk test (6MWT) is commonly used to assess exercise capacity in patients with f-IIP. However, it is not known whether patients with f-IIP have reduced levels of physical activity in daily life (DLPA)

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or whether the 6MWT and pulmonary function tests (PFTs) are representative of their DLPA. Indeed, the relationships between DLPA and clinical characteristics reflecting the disease severity, such as the magnitude of lung restriction, the impairment of diffusing capacity of the lung for carbon monoxide (DLCO), and the 6MWT distance, have never been evaluated in patients with f-IIP, to our knowledge. To address this, we measured DLPA in patients with f-IIP and in healthy, age- and sex-matched control subjects and determined the relationships between DLPA and the 6MWT, pulmonary functional parameters, and anxiety and depression scores.

Materials and Methods

Fifty white patients (male to female ratio, 29:21; mean age, 64.3 ± 10 years) with a diagnosis of f-IIP were consecutively referred at the time of diagnosis or before inclusion in a home-based pulmonary rehabilitation program.[9] Inclusion criteria consisted of a diagnosis of idiopathic pulmonary fibrosis according to the international consensus guidelines[1] or a diagnosis of nonspecific interstitial pneumonia (radiographic or histopathologic diagnosis). Exclusion criteria were other pulmonary diseases (including obstructive disease), left-sided heart failure, a history of pulmonary embolism, or the presence of pathologic conditions that could impair DLPA (eg, rheumatism and cerebrovascular diseases). Connective tissue diseases were ruled out. No acute exacerbation was observed in the 3 months preceding inclusion. At the time of inclusion in the study, the majority of patients (66%) were taking no medications, 12 patients were taking corticosteroids, nine patients were taking azathioprine, and three patients were taking mycophenolate mofetil. Only 12 patients used supplemental oxygen during exercise, with a mean duration of 1.2 h per day. Clinical data and the results of PFTs and the 6MWT were collected. Patients were followed up until the end of the study to record mortality. Therefore, the duration of follow-up ranged from 6 to 36 months.

The control group included 25 healthy age- and sex-matched subjects (male to female ratio, 14:11; mean age, 59.3 ± 6.9 years; BMI, 24.3 ± 2.3 kg/m^2) who were relatives of employees or students at the hospital. All control subjects had normal spirometry results.

None of the patients or control subjects were engaged in exercise training programs prior to the study. All individuals gave informed consent. Approval for the use of these data were provided by the Institutional Review Board of the French Learned Society for Pulmonology (CEPRO 2011-039).

Pulmonary Function Tests

FVC, FEV_1, and total lung capacity were measured by spirometry and plethysmography with a Jaeger-Masterlab cabin. Single-breath DLCO (mL CO/min/mm Hg) was measured and corrected for hemoglobin (Hb) concentration (g/dL) according to Cotes' equation: corrected (Hb) DLCO = DLCO × (10.2 + Hb)/(1.7 × Hb). Values were expressed as percentages of the predicted normal values calculated according to sex, weight, and age.[10-12] The 6MWT was performed in accordance with international recommendations and was designed to ensure an accurate assessment of oxygen desaturation.[13]

Assessment of DLPA

Subjects were equipped with a physical activity monitor (SenseWear Pro armband and SenseWear software version 6.1; BodyMedia Inc) and instructed to wear the device continuously, except while showering or bathing, for 4 consecutive days. Two of the 4 days were required to be weekends. The device was positioned on the upper right arm at the midpoint between the acromion and the olecranon. The monitor contains a biaxial accelerometer (longitudinal and transverse) and multiple sensors (galvanic skin response, heat flux, skin temperature, and near-body ambient temperature). This device provides objective, accurate, individualized, and detailed descriptions of activity patterns, including time and intensity of physical activities, and has been validated in diverse populations, including patients with chronic diseases.[14-19] DLPA was assessed by measuring four parameters: the number of steps per day, the time (min) spent in activities above an estimated energy expenditure of 2.5 metabolic equivalents (METs), the total energy expenditure above 2.5 METs (kcal), and the daily energy expenditure (kcal).

Evaluation of Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS) was designed to identify and quantify the two most common forms of psychologic disorders in medical patients[20] and in patients with interstitial lung disease (ILD).[21] For both subscales, a score ≥ 8 (scale, 0-21) is indicative of clinically relevant symptoms.

Statistical Analysis

Statistical analysis was performed using the SAS statistical software, version 9.3 (SAS Institute Inc) and GraphPad Prism 5 (GraphPad Software, Inc). Normal distribution was checked with the Shapiro-Wilk test. Quantitative variables are expressed as mean ± SD. Qualitative variables are presented as frequency and percentage. Comparisons of quantitative variables according to the

Table 1—*Characteristics of the 50 Patients With f-IIP*

Characteristic	All Patients	IPF	NSIP
No.	50	29	21
Sex, male (female)	29 (21)	23 (6)	6 (15)
Age, y	63.6 ± 10	64.6 ± 10	62.2 ± 10
BMI, kg/m^2	26.3 ± 4.8	26.6 ± 4.4	26 ± 5.4
Surgical lung biopsy, No.	31	16	15
Treatment, No.			
Clinical trial	18	18	0
Steroids	12	3	9
Immunosuppressive drugs	12	1	11
Supplemental oxygen	12	7	5
FEV_1, %	69 ± 19	71 ± 19	67 ± 18
FVC, %	71 ± 21	71 ± 21	71 ± 21
DLCO, %	37 ± 13	33 ± 13	43 ± 11
6MWT distance	347 ± 109	328 ± 127	371 ± 74
6MWT lowest Spo_2, %	83 ± 7	82 ± 8	84 ± 7
6MWT ΔSpo_2, %	12 ± 7	12 ± 7	11 ± 7
HADS scores	14.6 ± 7.3	15.5 ± 7.9	13.4 ± 6.4
Anxiety	8.2 ± 4.3	8.5 ± 4.6	7.7 ± 3.8
Depression	6.4 ± 4.1	6.9 ± 4.4	5.7 ± 3.5

Values are mean ± SD unless otherwise noted. 6MWT = 6-min walk test; DLCO = diffusing capacity of the lung for carbon monoxide; f-IIP = fibrotic idiopathic interstitial pneumonia; HADS = Hospital Anxiety and Depression Scale; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; Spo_2 = oxygen saturation as measured by pulse oximetry.

Table 2—*Daily Physical Activity in 50 Patients With f-IIP and 25 Control Subjects*

Activity	Control Subjects	Patients	AUC
No. of steps/d	12,084 ± 3,717	4,157 ± 3,014[a]	0.967
Duration of physical activity > 2.5 METs, min/d	261 ± 118	149 ± 149[b]	0.8
Total energy expenditure, kcal/d	2,595 ± 519	2,176 ± 510[c]	0.812
Energy expenditure > 2.5 METs, kcal/d	1,033 ± 514	548 ± 551[a]	0.76

Values are mean ± SD. AUC = area under the curve; MET = metabolic equivalent. See Table 1 legend for expansion of other abbreviation.
[a]$P < .0001$.
[b]$P = .006$.
[c]$P = .0008$.

groups (patients and control subjects) were performed with Student *t* test. To adjust the results on confounding factors, multivariate linear regression was performed on each factor. To assess the discriminant power, the area under the curve for each parameter of DLPA was computed.

To explain the number of steps by the clinical and functional variables, bivariate analyses were performed using Pearson correlation coefficient. To illustrate the results with boxplot representations, quantitative variables were dichotomized according to the median value, and the number of steps was compared between these binary variables by the Mann-Whitney *U* test. Variables having *P* values < .2 were introduced into a multivariable stepwise linear regression. A bootstrap validation was carried out to test the stability of the final model,[22] and residual analysis was conducted to assess its validity. The predictive power of the final model was assessed by r^2.

Predictive factors of death were studied with survival analyses to account for differences in the duration of follow-up. Survival curves were computed with the Kaplan-Meier method. Bivariate analyses were performed with the Cox proportional hazards model. Results were expressed as hazard ratios with 95% CIs. The validity of the proportional hazard assumption was checked using Schoenfeld residuals, and parameters were dichotomized when appropriate. Parameters with a *P* value < .2 in bivariate analyses were introduced into a multivariable Cox proportional hazards model. The significance level was set at .05.

Results

Fifty consecutive patients were included between June 2010 and June 2012. The characteristics of the study population are shown in Table 1. Twenty-seven patients (54%) and 14 patients (28%) had clinically relevant symptoms of anxiety and depression, respectively. Patients with f-IIP and control subjects demonstrated equally good compliance and wore the physical activity monitor for 3.90 ± 0.5 and 3.81 ± 0.5 days, respectively. As shown in Table 2, patients walked significantly fewer steps per day than the control subjects and showed significantly reduced participation in physical activities inducing a metabolic demand > 2.5 METs (energy expenditure and duration of activity). The four DLPA parameters were strongly correlated, and the mean number of steps per day was the best discriminant parameter of DLPA between patients and control subjects (data not shown).

The mean number of steps per day was strongly correlated with the distance walked during the 6MWT, the 6MWT lowest oxygen saturation as measured by pulse oximetry (Spo_2), DLCO, FVC, and FEV_1 (Table 3). DLPA was significantly lower in patients with lower DLCO (< 35%) (Fig 1) but was not significantly different according to FVC (> or ≤ 70%), 6MWT distance (> or ≤ 360 m) or 6MWT lowest Spo_2 (> or ≤ 85%). There was no correlation between DLPA and HADS scores ($r < 0.10$ for all correlations). In multivariate regression, DLCO and 6MWT distance were statistically significant predictors of the number of steps per day ($P < .001$ and $P = .008$, respectively). However, the resulting r^2 value indicated that these two variables explained only 31% of the difference in number of steps per day: 20% for DLCO and 11% for 6MWT.

Bivariate survival analyses of variables (Table 4) for mortality prediction showed that DLCO was a predictor of mortality ($P < .001$). Other significant predictors of death were 6MWT distance ($P = .009$), 6MWT lowest Spo_2 ($P = .026$), and the number of steps per day ($P = .033$) (Fig 2). Age, sex, BMI, FEV_1, FVC, and HADS scores were not significantly associated with survival. Multivariate analysis showed that only DLCO and 6MWT distance were significant predictors of mortality (Table 4).

Table 3—*Correlation of Clinical and Functional Variables With the Number of Steps per Day in 50 Patients With f-IIP*

	Bivariate Analyses		Multivariate Analysis	
Variable	*r*	*P* Value	Partial r^2	*P* Value
Age	−0.017	.902	…	…
BMI	−0.047	.741	…	…
FVC[a,b]	0.434	.001	…	…
FEV_1[a,b]	0.290	.041	…	…
DLCO[a,b]	0.473	< .001	0.20	.001
6MWT lowest Spo_2,%[b]	0.33	.020	…	…
6MWT ΔSpo_2,%[b]	−0.3	.032	…	…
6MWT distance[b]	0.45	.001	0.11	.008
HADS scores	−0.046	.749	…	…

See Table 1 legend for expansion of abbreviations.
[a]Results are expressed as percentage of predicted values.
[b]Parameters included in multivariate analysis with stepwise selection.

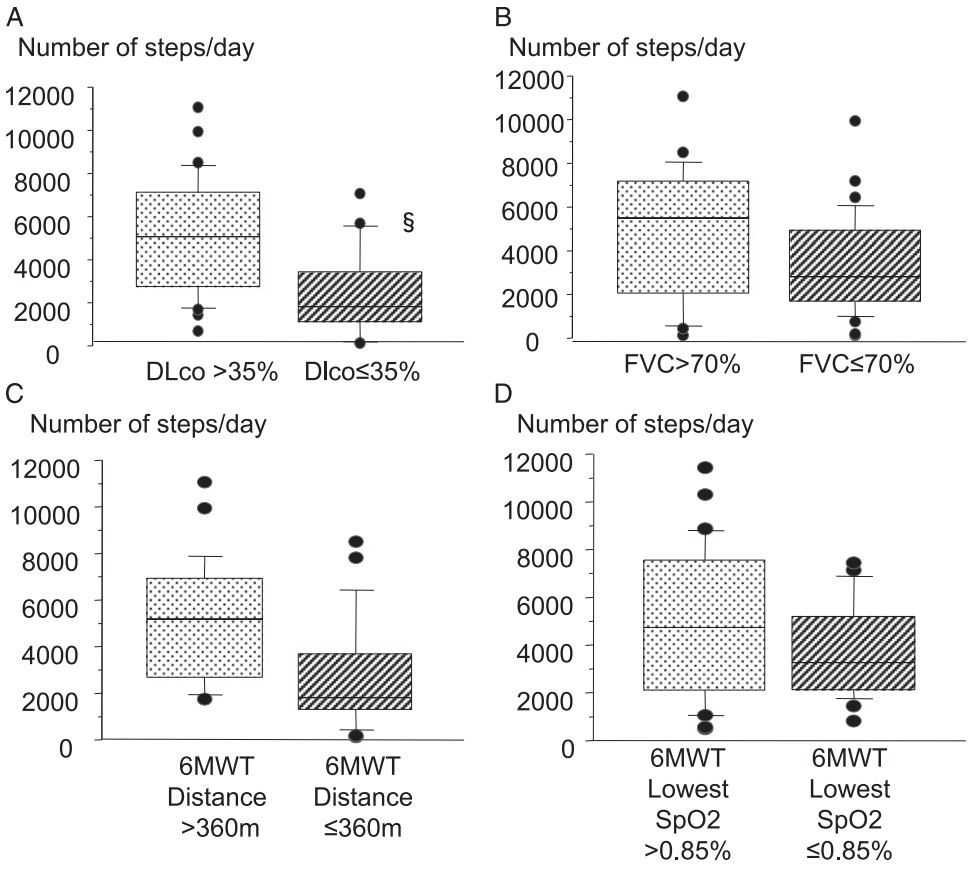

FIGURE 1. Comparison of the number of steps per day according to lung function and 6MWT values in patients with fibrotic idiopathic interstitial pneumonia (f-IIP). A, The medians and interquartile range are shown for the number of steps per day according to DLco. B, The medians and interquartile range are shown for the number of steps per day according to FVC. C, The medians and interquartile range are shown for the number of steps per day according to 6MWT distance. D, The medians and interquartile range are shown for the number of steps per day according to 6MWT lowest SpO2. FVC and DLco are expressed as percentages of predicted values. §$P < .05$. 6MWT = 6-min walk test; DLco = diffusing capacity of the lung for carbon monoxide; SpO2 = oxygen saturation as measured by pulse oximetry.

Discussion

The results of the present study show that assessment of DLPA in patients with f-IIP using accelerometry is well tolerated and that these patients have profound limitations in DLPA compared with healthy control subjects. Patients exhibited a 65% decrease in the number of steps per day and a 45% decrease of energy expenditure > 2.5 METs per day compared with the sedentary healthy control population. No correlation was observed between DLPA and the HADS scores.

A review of studies measuring physical activity in healthy subjects determined that 3 to 5 days of monitoring with an accelerometer was required to obtain reliable measurements.[23] The data presented here for patients with f-IIP were collected over 4 consecutive days and are, thus, in line with this recommendation. It is important to note that the number of steps per day in this control population was highly variable (12,087 ± 3,823), and similar variation was observed in the study of Troosters et al[8] (9,372 ± 3,574). To date, there are no standard values for DLPA, and many factors could contribute to the high variability among individuals of the same age—for example, differences in lifestyle, leisure activities, and profession.

It is not surprising that patients with chronic respiratory diseases are relatively inactive. Troosters et al[8] found that patients with COPD walked fewer steps per day than healthy individuals, and the DLPA of this f-IIP population was comparable to that of patients with COPD classified as GOLD (Global Initiative for Chronic Obstructive Lung Disease) III. The number of steps per day was also severely reduced in patients with ILD who were awaiting lung transplants, because of the advanced stage of the disease.[24,25]

Among the DLPA parameters measured in our study, the number of steps per day not only best captured the overall DLPA but also clearly differentiated between

Table 4—*Survival Analysis for Mortality Prediction*

Variable	Bivariate Analyses		Multivariate Analysis	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Age	1.01 (0.97-1.05)	.503	…	…
Male sex	1.70 (0.65-4.44)	.276	…	…
BMI	1.01 (0.93-1.10)	.688	…	…
FVC%	0.98 (0.96-1.01)	.712	…	…
FEV_1%	0.99 (0.97-1.02)	.941	…	…
DLco (< 35%)[a]	6.08 (2.19-16.91)	< .001	4.98 (1.76-14.07)	.002
6MWT distance (< 360)[a]	4.40 (1.44-13.37)	.009	3.58 (1.17-10.97)	.025
6MWT lowest SpO_2 (< 85)[a]	3.00 (1.13-7.91)	.026	…	…
No. of steps/d (< 3,287)[a]	2.72 (1.08-6.86)	.033	…	…
HADS score (< 16)	1.37 (0.56-3.32)	.483	…	…

See Table 1 legend for expansion of abbreviations.
[a]Parameters included in multivariate analysis with stepwise selection.

the patients and the control subjects. This contrasts with the findings in patients with COPD, for whom the daily energy expenditure was more affected than the number of steps per day.[8] The actual number of steps taken in that study may have been higher than the recorded number, because the SenseWear armband underestimates the daily steps in people with slow walking speeds.[26] The recommendations of learned societies for levels of daily physical activity include both time and intensity goals. In our study, there was a correlation between the intensity parameters and the number of steps taken, although patients able to walk long distances did not necessarily have intense DLPA. The time spent in physical activity and the total energy expenditure might, thus, represent different facets of the DLPA.

In this study, we found a weak correlation between the parameters of physical activity and the resting PFTs.

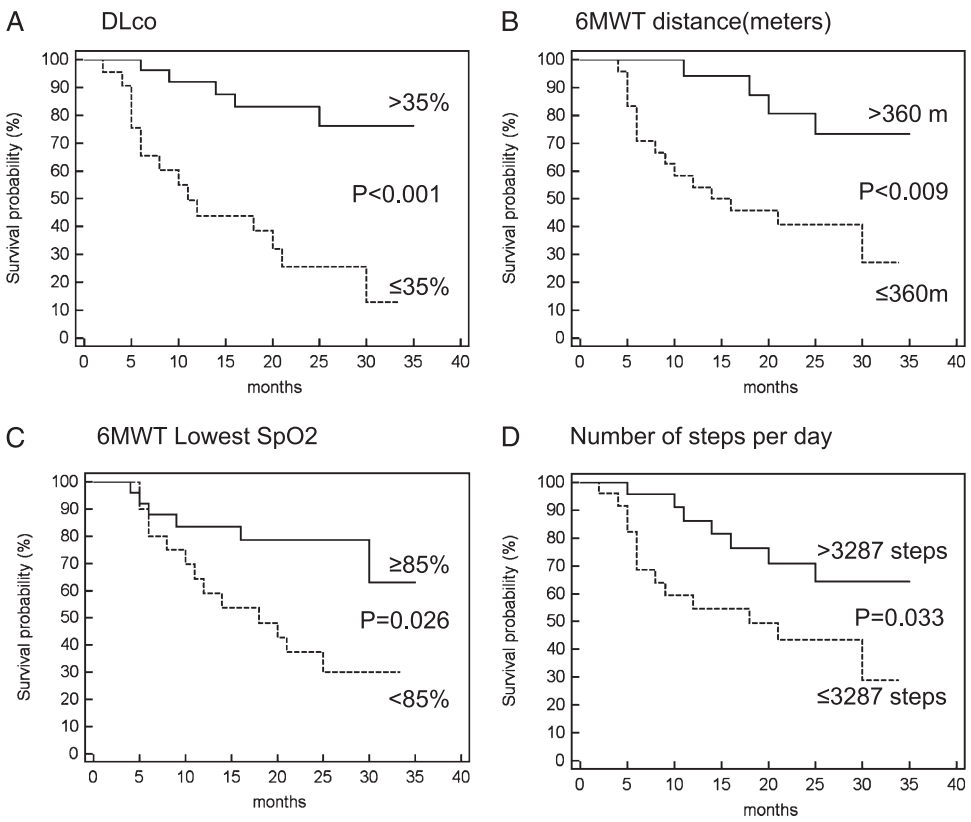

FIGURE 2. A, Survival of patients with f-IIP according to DLco. B, Survival of patients with f-IIP according to 6MWT distance. C, Survival of patients with f-IIP according to 6MWT lowest SpO2. D, Survival of patients with f-IIP according to number of steps per day. See Figure 1 legend for expansion of abbreviations.

IIP disease severity is usually determined by physiologic parameters, such as FVC and DLCO.[27] Although impairment of these parameters is representative of the state of the lung parenchyma in IIP, they do not seem to be the major factors limiting the DLPA. Similarly, only weak to moderate correlations between lung function parameters and DLPA were observed in patients with COPD.[8,28,29]

Our study demonstrates that the 6MWT distance correlates with DLPA in patients with f-IIP. The 6MWT also reflects the DLPA in COPD[15,28,29] and in pulmonary arterial hypertension.[30,31] In the COPD study of Garcia-Rio et al,[28] multivariate analysis showed that the 6MWT and dynamic hyperinflation were the only independent parameters predictive of the DLPA, accounting for 84% of the variance. Our results show that the 6MWT distance and DLCO are not good surrogates for daily activity, because as independent predictive parameters they accounted for only 31% of the variance. In their study of 27 patients with ILD, Langer et al[24] also found good correlation between the 6MWT and DLPA but not between functional parameters and DLPA. To date, no trial has evaluated DLPA in f-IIP, and it will be interesting to determine whether changes in the 6MWT observed in response to treatment or to pulmonary rehabilitation translate into comparable changes in DLPA in patients with ILD.

A number of PFT variables have been used to predict survival in idiopathic pulmonary fibrosis, of which FVC, total lung capacity, and DLCO are most consistently associated with prognosis.[32-34] The 6MWT is widely used to assess exercise tolerance in f-IIP, given its ease of administration and reproducibility.[35,36] Both distance walked[37] and desaturation[38] during the 6MWT have been found to predict mortality of patients with f-IIP. In our study, the number of steps per day was also found to predict mortality but was not an independent predictor of mortality.

DLPA has a strong behavioral component and is influenced by a complex set of factors, many of which are nonphysiologic factors, including depression and anxiety.[39-42] Strikingly, we found no significant correlation between the HADS scores and DLPA in the patient population, although the scores varied greatly (15 ± 8, range 8.5-18.5). Ryerson et al[43] established that symptoms of anxiety and depression are prevalent in patients with ILD and that depression is related to pain levels and sleep quality. Studies in other chronic diseases have failed to demonstrate that an improvement of DLPA can reduce symptoms of anxiety and depression.[44-46]

In conclusion, this study is the first to our knowledge to demonstrate a significant reduction in DLPA in patients with f-IIP. We found a weak correlation between DLCO, 6MWT, and the level of DLPA; however, these two variables explained only 31% of DLPA variance. Quantitation of DLPA is a novel patient-centered approach to assess function in chronic respiratory diseases and may be a useful tool for clinical care and assessing response to therapy. Future work will determine whether pulmonary rehabilitation programs can affect DLPA in patients with f-IIP.

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Dr Wallaert: contributed to study conception and design, analysis and interpretation, and drafting the manuscript for important intellectual content.
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Dr Salleron: contributed to statistical analysis and interpretation of data, writing the manuscript, and revision of the manuscript for important intellectual content.
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