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Walking distance on 6-MWT is a prognostic factor in idiopathic pulmonary fibrosis

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Summary
Background and aim of the work: Idiopathic pulmonary fibrosis (IPF) is a progressive disease with high mortality rates and a median survival of 2–3 years from time of diagnosis. The prognosis for any individual patient, however, is variable. To elucidate the clinical significance of 6-min walking test (6-MWT) in patients with IPF, we sought to assess the relationship between distance walked and desaturation during this test and pulmonary function tests (PFTs). We also evaluate the prognostic value of 6-MWT in comparison with PFTs at baseline and during follow-up.
Methods: The clinical data of 44 patients with IPF were retrospectively analysed. Twenty-nine patients had an additional evaluation after 12 month of follow-up.
Results: Distance walked in 6 min was independently related to mortality by multivariate analysis. Patients walking less then 212 m had a significantly lower survival than those walking farther, assessed by Kaplan–Meier survival curves (log-rank test, $p < 0.036$). During a mean follow-up period of 19.8 months (range 3.2–46.4), 11 patients died of causes related to disease. Changes in meters walked at 12 months evaluation were also predictive of survival ($p = 0.05$).
Conclusions: These results confirm that in IPF distance walked in 6 min is independent associated with mortality.

Introduction

Idiopathic pulmonary fibrosis (IPF) is associated with significant morbidity and mortality and with poor response to traditional therapies.[1–5] Median survival is generally reported as 2–3 years from time of diagnosis.[1]

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Although IPF carries a uniquely poor prognosis, there is substantial heterogeneity in survival among patients and it has proven to be difficult to predict survival time in individual patients.[1,6] Additional predictors of survival are important to help patients and physicians to stratify risks and benefits of therapeutic approaches, including experimental protocols, cytotoxic therapies, and lung transplantation.[7,8] Recent efforts to predict prognosis for individuals with IPF have focused on demographic (age, smoking, sex), baseline physiologic parameters (diffusion capacity for carbon monoxide [DL_{CO}], FVC, exercise PaO_2, desaturation on 6-MWT), changes of physiologic tests at 6–12 months (dyspnoea score, FVC, TLC, DL_{CO}), radiographic (amount of fibrosis), and histopathologic features (fibroblastic foci).[9–15]

Most patients with IPF experience exercise dyspnoea as the first symptom and a key feature is impaired to the gas exchange that worsens with exercise.[1,16–18] Clinical exercise testing using cycle ergometer or treadmill protocols has been used in patients with interstitial lung diseases, and most showed a marked drop in oxygen saturation during exercise.[16,19–21] However, these forms of exercise can be unfamiliar to some patients. The 6-MWT is a simple test to evaluate desaturation[22,23]; it is a more familiar form of exercise for patients and more relevant to their everyday live and can be performed even by patients with advanced pulmonary or cardiac diseases.[24] Test is very simple, requires inexpensive equipment, and is reproducible.[17] In addition, it is considered to be safe because patients are self-limited during exercise. The 6-MWT has been shown to have prognostic value in various forms of advanced lung disease.[25–28]

In the present study, we sought: (1) to assess the relation between distance walked and desaturation during 6-MWT and PFTs, (2) to evaluate prognostic value of 6-MWT in comparison with functional parameters at baseline evaluation and (3) to investigate the prognostic value of changes over time of 6-MWT and PFTs variables.

We hypothesized that 6-MWT and its changes during follow-up may provide more reliable and potent prediction of survival than baseline functional evaluation alone.

Some of the results of this study have been previously reported in abstract form.[29]

Methods

Study population

Patients with a clinical–radiological or a histological diagnosis of IPF according to the American Thoracic Society/European Respiratory Society criteria[1] who underwent a 6-MWT on room air from January 2000 to December 2004 constituted the study group.

Clinical data and survival status were obtained from medical records. Patients with an underlying connective tissue disorder, exposure to environmental agents or drugs known to cause pulmonary fibrosis, or other underlying disorders known to cause pulmonary fibrosis were excluded from the study. This study considered patients referred to U.O. di Pneumologia, Ospedale S. Giuseppe, Milan. All subjects had a complete clinical, radiological (high-resolution computed tomography examination were performed in all patients) and lung function evaluation. Moreover, all patients underwent at baseline evaluation on echocardiographic examination.

Surgical lung biopsies of patients with histological diagnosis were all reviewed by our pathologists.

All examinations performed were part of routine screening and follow-up evaluations in our hospital, independently from patients participation in this study.

PFTs and 6-MWT

All patients underwent PFTs and gas exchange evaluations. Lung volumes, flow rates, and DLCO were measured using a plethysmographic technique (SensorMedics; Yorba Linda, CA), and corrected for temperature and barometric pressure, according to the American Thoracic Society recommendations.[30–33] The single-breath DLCO was measured according to the American Thoracic Society recommendations and was corrected for haemoglobin concentration.[34–36]

The 6-MWT was performed by a trained technician.[37,38] Briefly, patients walked on level ground using standardized instructions, including to walk ''briskly'' and as far as possible, but not to run, for 6 min. Percutaneous arterial saturation was assessed at baseline and during the test by a continuous pulse oximeter (Nellcore; Pleasanton, CA) using a finger sensor. If the resting saturation was less than 90% on room air, patients were not considered eligible for room air 6-MWT. The 6-MWTs were symptom limited, so patients were allowed to stop if necessary, though they were instructed to resume walking as soon as possible. The test was stopped for safety purposes if the arterial oxygen saturation (SaO_2) dropped to $<86\%$. Baseline percentage of SaO_2 (SaO_2-rest), lowest SaO_2 measured during exercise (SaO_2-exercise), and the variation in SaO_2 from rest to exercise (SaO_2-rest $-$ SaO_2-exercise $= \Delta SaO_2$) reported as decrease in units of percentage saturation (1% = 1 U) and the distance walked (in meters) were measured and recorded.

Statistical methods

Continuous variables are presented either as mean $\pm$ standard error (SE) or as median and interquartile range (IQR) when the normality assumptions of the distribution were not satisfied. Counts and percentages are given for categorical variables. Relationships between parameters of the 6-MWT and pulmonary function were assessed with Spearman rank correlation coefficients.

The optimal cut-off value for distance walked during 6-MWT to detect mortality was assessed using the receiver operating characteristics (ROC).

Cox proportional hazards model was used to examine the univariate relationship between 6-MWT parameters measured at the time of the initial diagnosis (walking distance, desaturation on 6-MWT) and mortality. Multivariate Cox model was then performed for each parameter separately, adjusting for covariates clinically and statistically significant such as age and sex. Hazard ratios and 95% confidence intervals are presented. An additional evaluation

of 6-MWT and PFTs was performed at 12 months. Changes between 12 months and baseline were calculated and their prognostic significance on mortality was evaluated in a multivariate Cox model adjusting for their respective baseline value.

Kaplan–Meier curves are presented to analyse the time for death from the time of initial diagnosis according to the distance walked during 6-MWT. The two survival distributions were compared by means of the log-rank test. The statistical significance level was set at $p \leq 0.05$. SAS software (SAS Institute, Cary, NC) and SPSS was used for analyses.

Results

Of the 61 patients who underwent 6-MWT during the study period, 17 were excluded, as their resting saturations was less than 90%, therefore they did not undergo a room air 6-MWT.

Forty-four study patients included 23 men and 21 women with a mean age at presentation of 61.9 ± 1.5 year. Nineteen patients (43%) had histological diagnosis (surgical lung biopsies).

Thirty-five patients received treatment during the study period either with corticosteroids alone ($n = 15$) or corticosteroids and cyclophosphamide or azathioprine ($n = 20$). Eight patients were treated with prednisolone and cyclophosphamide and 5 of this were alive on follow-up. Twelve patients were treated with prednisolone and azathioprine and 8 were alive on follow-up; 9 patients had no therapy.

Their clinical and physiologic data are summarized in Tables 1 and 2.

During a mean follow-up period of 19.8 months (range 3.2–46.4), 11 of the 44 patients (25%) died for causes related to disease; 3 patients fullfill the criteria for acute exacerbation of disease.

Meters walked, SaO_2-exercise and ΔSaO_2 on 6-MWT correlated with principal pulmonary functional parameters (VC, FVC and DLCO) (Table 3).

Table 1 Demographic features of study patients.

Characteristic	Value (%)
Age, year (mean ± SE)	61.9 ± 1.5
Sex	
Male (%)	23 (52)
Female (%)	21 (48)
Smoking status	
Never (%)	29 (66)
Former (%)	12 (27)
Current (%)	3 (7)
Treatment	
None (%)	9 (20.5)
Corticosteroid alone (%)	15 (34.1)
Corticosteroid/cytotoxic agent combined (%)	20 (45.4)
Diagnosis	
Clinical–radiological (%)	25 (57)
Histological (%)	19 (43)

Table 2 Physiologic features and 6-MWT parameters of study patients.

Characteristic	Value (median ± IQR)
VC, L	2.26 ± 1.19
VC, % predicted	80.5% ± 40
FVC, L	2.06 ± 1.15
FVC, % predicted	74.5% ± 37
DLCO, (mL/min/mmHg)	11.5 ± 7.8
DLCO, % predicted	52.5% ± 29.5
PaO_2	75.9 ± 14
Meters walked	240 ± 300
Sat.O_2-rest	95 ± 2
Sat.O_2-exercise	89 ± 7
ΔSat.O_2	7 ± 6

At time of presentation, multivariate analysis showed that VC (HR, 0.319; 95% CI, 0.105–0.967; $p = 0.04$), DLCO (HR, 0.723; 95% CI, 0.548–0.954; $p = 0.02$) and meters walked on 6-MWT (HR, 0.995; 95% CI, 0.99–0.999; $p = 0.03$) were independent risk factors for increased mortality in this group of patients. FVC did not reach statistical significance ($p = 0.06$) (Table 4).

Median of 6-MWT distance walked was 375 m (q1 200 m, q3 425 m, minimum 75 m) for 33 patients alive on follow-up and 200 m (q1 75 m, q3 400 m, minimum 50 m) for 11 patients died (Fig. 1). Kaplan–Meier survival curves grouped according to ROC cut-off value of distance walked in 6 min demonstrated that patients walking less than 212 m had a significantly lower survival rate than those walking farther (log-rank test, $p < 0.036$, Fig. 2). The area under the ROC curve was 0.64. The specificity and sensitivity at the rating equal to 212 m was, respectively, 0.74 and 0.6.

Desaturation on 6-MWT was not predictive of mortality in multivariate analysis.

On baseline echocardiography only 3 patients (6.8%) had systolic pulmonary arterial pressure over 40 mmHg.

Twenty-nine patients had an additional evaluation after 12 month of follow-up. Change in meters walked on 6-MWT over 12 months was predictive of mortality and remained so after adjusting for baseline value (HR, 0.994; 95% CI, 0.988–1, $p = 0.05$). Another parameter which changes over 12 months was predictive of mortality was Sat.O_2-rest (HR, 0.25; 95% CI, 0.075–0.837, $p = 0.02$). The changes of FVC and DLCO over 12 months were not statistically significant in predicting patients survival ($p = 0.06$) (Table 5).

Table 3 Correlation between physiologic and 6-MWT parameters.

	Meters walked	Sat.O_2-rest	Sat.O_2-exercise	ΔSat.O_2
VC	$r = 0.39$ $p = 0.02$	$r = 0.38$ $p = 0.03$	$r = 0.39$ $p = 0.02$	$r = -0.38$ $p = 0.02$
FVC	$r = 0.40$ $p = 0.01$	$r = 0.46$ $p = 0.007$	$r = 0.39$ $p = 0.02$	$r = -0.39$ $p = 0.02$
DLCO	$r = 0.42$ $p = 0.01$	$r = 0.17$ $p = 0.36$	$r = 0.37$ $p = 0.04$	$r = -0.47$ $p = 0.007$

Table 4 Multivariate analysis (adjusted for age and sex only) of physiologic and 6-MWT parameters associated with mortality in IPF.

Variable	Hazard ratio (HR)	95% CI	*p* Value
Age	0.985	0.910—1.067	0.7117
Sex	3.174	0.780—12.971	0.1067
Meters walked	0.995	0.990—0.999	**0.0308**
Sat.O_2-rest	0.816	0.537—1.241	0.3416
Sat.O_2-exercise	0.856	0.709—1.033	0.1052
ΔSat.O_2	1.185	0.958—1.466	0.1177
VC (L)	0.319	0.105—0.967	**0.0435**
FVC (L)	0.365	0.124—1.078	0.0681
DLCO (mL/min/mmHg)	0.723	0.548—0.954	**0.0219**
PaO_2 (mmHg)	0.953	0.903—1.007	0.0857

Definition of abbreviation: CI = confidence interval and L = liter.

Correlation between prognosis and extent of fibrosis on CT scan was not evaluated in this study.

Discussion

In this study, we demonstrated that distance walked during 6-MWT was significantly correlated with pulmonary functional parameters (DLCO, VC, FVC). We also demonstrated that distance walked in 6 min was independently related to mortality in IPF and patients walking less than 212 m had a significantly lower survival rate than those walking farther as assessed by Kaplan—Meier survival curves; 212 m in our study group identified a cut-off distance with a bad prognosis and the use of a change in meters walked as a continuous variable confirms the ability of distance walked to predict a less favourable outcome. Thus, our data confirm recent observation that distance walked during 6-MWT may serve as prognostic indicator in IPF, which may complement other prognostic markers. In our study desaturation on 6-MWT was not predictive of mortality in multivariate analysis.

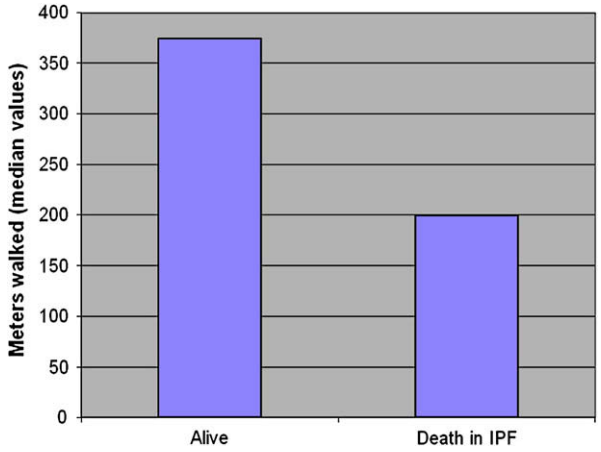

Figure 1 Distance walked expressed in meters according to patient's outcome.

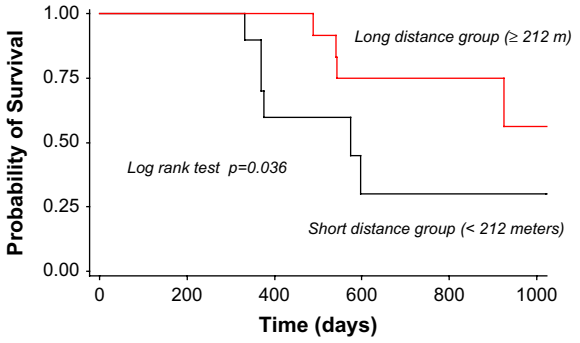

Figure 2 Kaplan—Meier survival curves according to the distance walked during 6-MWT in patients with IPF. Patients walking <212 m had a significantly lower survival rate than those walking farther (log-rank test, $p = 0.036$).

IPF is a progressive disease with high mortality rates and median survival of 2—3 years from time of diagnosis.[1,3,9] However, the disease course for individual patients with UIP can vary greatly. Although the typically poor prognosis of IPF and the relative inefficacy of current therapies are broadly understood, highly variable rates of progression among individual patients remain both common and enigmatic. Therefore, developing an improved understanding of the predictors of progression and survival is critical.[39]

Despite the numerous variables used in monitoring this disease, none have consistently proven to be a reliable marker of disease progression or risk of death. Pulmonary function evaluation at presentation is disappointingly imprecise, prognostically.[15,40,41] Change in FVC and DLCO are today considered markers of disease progression but patients with stable spirometric indices are not without risk of dying; therefore, stability of PFTs does not necessarily translate to stability of the disease. The 6-MWT has been shown to correlate with function and outcomes in patients with numerous advanced diseases.[25—28] In our study DLCO together with VC and FVC correlated with various parameters of 6-MWT (distance walked, SaO_2-exercise and

Table 5 Multivariate analysis (adjusted for age and sex only) of physiologic and 6-MWT parameters variation at 12 months follow-up evaluation associated with mortality in IPF.

Variable (change 12 months — basal value)	Hazard ratio (HR)	95% CI	*p* Value
Meters walked	0.994	0.988—1	**0.05**
Sat.O_2-rest	0.25	0.075—0.837	**0.02**
Sat.O_2-exercise	0.831	0.614—1.124	0.2294
ΔSat.O_2	1.04	0.774—1.399	0.7926
VC (L)	0.165	0.011—2.503	0.19
FVC (L)	0.142	0.018—1.1	0.06
DLCO (mL/min/mmHg)	0.49	0.232—1.036	0.06
PaO_2 (mmHg)	0.954	0.889—1.023	1.1832

Definition of abbreviation: CI = confidence interval and L = liter.

ΔSaO_2). The 6-MWT has an advantage over static measures of lung function: it provides a functional measurement of the patient's overall cardiopulmonary reserve. As such, it may also account for other important prognostic parameters not measured by standard PFTs, such as the effect of pulmonary hypertension.[7,42] However, only few data are available regarding clinical significance of 6-MWT in patients with IPF. Lama et al.[14] demonstrate a strong correlation of measures of fall in saturation on 6-MWT and survival independent of the format used to define desaturation. In our study, in contrast with Lama et al.[14], desaturation on 6-MWT was not predictive of mortality in multivariate analysis. This difference may be in part explained by the format used to define desaturation in these two studies. The relatively small number of cases in our study may also have been a factor. This study included only patients who had 6-MWT in room air and thus had a selection bias. However, the causes for the discrepancy between our study and Lama et al. are not clear.

Although the role of 6-MWT in risk-stratifying potential lung transplant recipients is uncertain, the 6-MWT may yet play an important role in the assessment of selected groups of patients with IPF. Recently published guidelines on selection and evaluation for lung transplantation in IPF patients consider decrease of saturation below 88% during 6-MWT an important prognostic parameter.[43] Recently, Lederer et al.[44] reported that lower 6-MWT distance in 454 patients in waiting list for lung transplantation was strongly and independently associated with an increased mortality rate. In this study patients walking less than 207 m had a more than fourfold greater mortality rate than those walking 207 m or more. Our observation provides support for this data. Nevertheless, populations in these two studies are very different: our patients are older but with less severe disease, 6-MWT was always performed at the same institution by trained nurses and with a strict protocol, only patients that had a 6-MWT in room air were considered and finally an analysis of the possible correlation with PFT was also performed whereas only correlation with FVC was performed in Lederers' study. Patients with IPF referred and listed for lung transplantation are a distinct cohort; extrapolation of survival analyses from these patients in another context may not be appropriate. The very similar conclusions of our and Lederer's studies confirm the prognostic significance of distance walked on 6-MWT in IPF patients. Our data suggests that such a reasonable 6-MWT distance ambulated ''screening'' threshold may be 212 m or less: 2.7-year survival rate of IPF patients who walked $<$212 m was 27% compared with 54% in patients who walked $\geq$212 m. Within-subject reproducibility of data is a crucial consideration. Serial trends in indices with low ''measurement noise'' can be interpreted with greater confidence.[17] A recent study has showed that 6-MWT distance is highly reproducible in fibrotic idiopathic interstitial pneumonia, more then desaturation.[17] This observation supports the importance of our data.

DLCO and VC correlate with mortality in multivariate models; FVC did not reach statistical significance ($p = 0.06$), however, this is possible due to the limited number of patients considered in our study population that may have limited our ability to detect statistically significant value in predicting mortality.

A further novel aspect of our study is that change in distance walked on 6-MWT over 12 months is predictive of survival. Importantly, changes in this variable predict survival even after adjustment for the baseline value, suggesting that the rate of progression, independent of the initial degree of disability, is important for determining prognosis. In our study for each unitary decrease in meters walked at 12 months observation, mortality increased by 1%. The only physiologic parameter that was predictive of survival over time was basal Sat.O2. It suggests that stability of PFTs might not reflect periods of disease quiescence as previously thought, but rather the inability of spirometry to detect ongoing disease activity and progression. However, patients' number in our study is small and change in FVC and DLCO over 12 months that have not reached statistical significance ($p = 0.06$) could be statistically significant in a larger group of patients.

There are several potential sources of bias in our study. First, the most severe form of IPF were excluded from the study because if resting saturation was less than 90% on room air, patients were not considered eligible for room air 6-MWT and were excluded from this study. These patients performed 6-MWT with supplemental oxygen administered using a threshold similar to that of other investigators in this field[45,46] and following published recommendations.[47] Second, this is a retrospective analysis, with possible limitations, and third it is a monocenter study with small number of patients. The modest study sample size confers low statistical power to detect significant survival indices. While the size of our study population is limited, the fact that each patient was cared with a standardized protocol by a multi-disciplinary team in an experienced national centre lends strength to our observations.

Only 3 patients had moderate pulmonary hypertension; it seems unlikely therefore that this could affect our results.

In conclusion, we demonstrated that distance walked in 6 min was independently related to mortality in IPF and those patients walking $<$212 m had a significantly lower survival rate than those walking farther as assessed by Kaplan–Meier survival curves. Our observations confer validation (in a non-technical sense) to recently published studies on prognostic significance of 6-MWT distance. An important new information is that a downward trend in distance walked at 12 months (when adjusted for baseline value) is an independent determinant of survival and that for each unitary decrease in meters walked at 12 months observation, mortality increased by 1%.

Our data provide compelling argument for the clinical use of 6-MWT in the evaluation of patients with IPF. The simplicity of 6-MWT and its probable ability to assess complex physiologic interaction and predict prognosis make the 6-MWT an important tool for the management and follow-up of patients with IPF. Furthermore, distance walked during a 6-MWT give additional prognostic information to previously described factors.

Survival is the most important outcome measure in IPF, but requires large numbers of patients followed for long periods of time. In IPF, 6-MWT distance is a measurement of disease severity that can serve as a surrogate outcome measurement and reflects the risk of progression to death.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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