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Pulmonary hypertension in idiopathic pulmonary fibrosis does not influence six-minute walk distance: results from a retrospective study

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Abstract. *Background:* The characteristics of the six-minute walk test (6MWT) in patients with idiopathic pulmonary fibrosis (IPF) and pulmonary hypertension (PH) have not yet been described; nevertheless, this test has already been used as a "surrogate end point" in some clinical trials. *Objective:* Goal of this retrospective study was to assess whether the presence of PH in patients with IPF might influence 6MWT performances. *Methods:* We retrospectively reviewed the data of patients with IPF who were referred to our hospital. The study population was divided in two groups according to the presence or absence of PH at right heart catheterization; then, the six-minute walking distance (6MWD) and pulmonary function tests (PFTs) were compared between groups. *Results:* Study population included 30 IPF patients with a mean age of 59.0 years (± 8.3), most of whom (76.7%) were males. A total of 43.3% of patients had PH. PFTs data were similar in IPF patients of the two groups; the only exception was FVC, which was significantly higher in IPF patients with PH (63.8% ± 16.0 vs. 51.6% ± 13.8 in patients without PH, $p < 0.05$). No difference was detected between groups in 6MWD (222.3m ± 118.5 in PH group and 222.1m ± 118.5 in non-PH group, $p > 0.05$). *Conclusions:* Our data suggested that 6MWD does not differ between IPF patients with or without PH. Thus, 6MWD should not be used as a surrogate endpoint in clinical study in patients affected by IPF and PH. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 297-305)*

Key words: Idiopathic pulmonary fibrosis, Pulmonary hypertension, Six-minute walk test, Six-minute walk distance

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing lung disease with a severe prognosis (1). Precapillary pulmonary hypertension (PH), defined by a resting mean pulmonary artery pressure (mPAP) above 25 mmHg together with a pulmonary capillary wedge pressure lower than 15 mmHg, is a frequent complication of interstitial lung diseases (ILD), particularly in IPF (2-8). Among patients with idiopathic interstitial pneumonia, those with IPF are more likely to develop PH. Right heart catheterization (RHC) is the gold standard for the diagnosis of PH. The importance and the frequency of PH in IPF have been a matter of debate for quite a long time, and have been evaluated in several trials (7-11). We now know that PH in IPF pa-

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tients is an important negative prognostic factor (7, 9, 12, 13) and that, until now, no drug has been shown to be effective in managing this condition. In most cases, PH in IPF relates to the pulmonary vascular remodeling in response to chronic hypoxia, which results in medial hypertrophy and intimal fibrosis of pulmonary arterioles. Generally, the degree of PH (as assessed by RHC) in patients with IPF is mild to moderate, even in the advanced disease. This condition belongs to the class III of the Dana Point PH classification, which includes the PH due to lung diseases and/or hypoxia, such as in the cases of chronic obstructive pulmonary disease and related to other parenchymal lung diseases (14).

In few cases, patients develop what is commonly defined an "out-of-proportion" (or "disproportionate") PH. This term refers to an extremely high pulmonary artery pressure that cannot be solely explained by hypoxia and rearrangement of the pulmonary vascular bed; sometimes, an unjustified degree of PH may develop even in the presence of minor pulmonary function abnormalities (15). A mean PAP value of 35 mmHg has been arbitrarily proposed as the cut-off value for diagnosing disproportionate PH and, therefore, to identify and classify patients who suffer from this condition.

The six-minute walk test (6MWT) is a marker of functional exercise capacity that is being increasingly used in the initial and longitudinal clinical assessment of patients with IPF. Exercise capacity has been shown to be a better predictor of survival outcomes than pulmonary function tests (PFTs) in a number of independent studies (16-19). The distance walked during the 6MWT is highly reproducible in IPF patients (20). The 6MWT has traditionally been used to evaluate patients with pulmonary artery hypertension (PAH) at baseline and to assess patients' response to therapies over time. Several studies demonstrated its reproducibility and usefulness in these conditions (21, 22); however, in the recent past, some limits to the use of this test have been reported (23). The 6MWT appears to be very helpful in monitoring patients with IPF (24, 25), but, to our knowledge, no study has so far established its role in patients with both IPF and PH, and the effect of PH on 6MWT performance has not yet been fully assessed. Clinical trials evaluating mortality surrogate endpoints usually require smaller sample sizes than trials evaluating patients' survival; however, there may not be a clear correlation between the value or change of surrogate end points and the clinical outcome. Weaknesses of 6MWT include variation in test conduct, a learning effect after repeated testing, variability based on other activities on the day of the testing, and the effect of musculoskeletal conditions on performance. Nevertheless, 6MWT has already been used as surrogate end point for mortality in several clinical trials designed to evaluate the efficacy of some drugs in IPF, including medications used to treat PAH (e.g. bosentan, ambrisentan, sildenafil, etc.). The ambrisentan IPF-PH trial, one of the most recent studies addressed to IPF patients with PH, was interrupted prematurely because of a lack of superior activity of the experimental arm (ClinicalTrials.gov Identifier: NCT00879229). In this randomized clinical trial, conducted on 40 patients (25 of whom were treated with the drug and 15 with placebo), the six-minute walk distance (6MWD) was the primary end point.

The goal of this retrospective study was to evaluate the effect of PH on exercise capacity measured by the 6MWD in patients with IPF.

Materials and Methods

Population

San Giuseppe Hospital is a tertiary care facility and referral center in Milan (Italy) for patients with undiagnosed ILD. We retrospectively reviewed the clinical data of all patients referred at our department from March 2002 to September 2010 who were diagnosed with IPF and underwent RHC. This retrospective study was approved by the San Giuseppe Hospital Institutional Review Board (Comitato Etico degli Ospedali di Milano and Sacra Famiglia di ERBA, approval number 27/12).

IPF was diagnosed according to the 2011 ATS/ERS guidelines (1). Since these guidelines were not published until 2011, all diagnostic procedures for IPF were reviewed to check whether they fulfilled the criteria set by the new ERS/ATS statement. Confirmation of diagnosis with surgical lung biopsy was usually not required, unless otherwise indicated; more complex patient cases underwent a multidisciplinary discussion.

All patients had undergone electrocardiography, echocardiography and PFTs in the week before undergoing RHC. For this study, we selected only those patients with normal left ventricular (LV) ejection frac-

tion at echocardiograph evaluation. Moreover, we excluded subjects with combined pulmonary fibrosis and emphysema syndrome, since these patients usually have an excessive degree of PH (26, 27). None of the study patients was enrolled in a pulmonary rehabilitation program and none of the study patients received PH-specific therapy.

Right Heart Catheterization

RHC was performed as part of lung transplantation candidacy evaluation, or at the discretion of the evaluating physician after round table discussion (for example, clinical suspicion of PH, respiratory failure discordant with functional impairment on PFTs or rapidly otherwise unexplained clinical deterioration).

RHC was performed with patients at rest in the supine position; the procedure was performed by three expert pulmonologists (A.B., R.C., F.L.). Data collected included measurements of right atrial pressure, pulmonary arterial pressure, pulmonary artery wedge pressure (PAWP), cardiac index (CI); Pulmonary Vascular resistence (PVR) values were also calculated.

A LV dysfunction was recognized by the presence of LV ejection fraction lower than 50% at the echocardiograph evaluation or a PAWP greater than 15 mmHg at RHC. Further evaluations to exclude other secondary causes of PH (e.g. sleep apnea or chronic pulmonary embolism) were performed when clinically indicated.

Pulmonary Function Tests

All patients underwent PFTs and gas exchange evaluation in the week before the RHC; these measurements were usually performed on the same day as the 6MWT. Lung volumes, flow rates, and diffusing capacity of the lung for carbon monoxide (DLCO) were measured in the sitting position using a plethysmography (SensorMedics; Yorba Linda, CA) and corrected for temperature and barometric pressure according to the American Thoracic Society recommendations (28). Values were expressed as a percentage of predicted normal values, using published standards (28). The single-breath DLCO was measured according to the American Thoracic Society recommendations and was corrected for hemoglobin concentration (29). Results were expressed as a percentage of the predicted values, using the reference values of Crapo and Morris (30). Arterial blood samples were drawn from the radial artery, after the patients had been breathing room air at rest at least 30 minutes (Rapid Lab 348; Bayer; Leverkusen, Germany).

Six-Minute Walk Test

6MWT was performed at least 2 hours after PFT, and was conducted under supervision of a trained technician (31). Patients walked on level ground over a distance of 25 meters using standardized instructions, including to walk as fast as possible, but not to run, for 6 minutes, and were gently encouraged using set phrases every 30 seconds (31). Baseline blood pressure, heart rate and oxygen saturation were measured. 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 86% on room air, patients were not considered eligible for room air 6MWT and underwent 6MWT with oxygen supply, using a portable liquid oxygen tank. The 6MWTs were symptom-limited, and so patients were allowed to stop and rest 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 (SaO2) dropped to less than 86%. Baseline percentage of SaO2 (SaO2-rest), lowest SaO2 measured during exercise (SaO2-exercise), and the final percentage of SaO2 were measured and recorded. During the entire study period, the protocol used to conduct the 6MWT did not change. In order to minimize variability, all assessments (PFTs, RHCs, and 6MWTs) were always performed and supervised by the same physicians and technicians.

Statistical analysis

Study population was classified in two groups according to the absence or presence of PH, as defined by a resting mean PAP above 25 mmHg at RHC. In IPF patients, resting levels of mPAP not exceeding 25 mmHg were considered normal; patients with resting mPAP levels greater than 35 mmHg were classified as having out-of-proportion PH. Patients who didn't undergo 6MWT were excluded. Analyses were carried out on the whole population and on the population stratified by PH.

Results were reported as frequency for discrete variables, and as median and mean values (± standard

deviation) for continuous variables. Differences between proportions (discrete variables) were tested with Fisher's exact test. Comparisons between mean values were performed through Student's t-test - if the normal assumption of distribution was respected (Shapiro-Wilk and Kolmogorov-Smirnov tests); contrariwise, the Wilcoxon rank-sum test was used. Finally, median values were compared with Mood's median test. Linear correlations between continuous variables were evaluated with Pearson correlation coefficient and its statistical significance was tested with Student's t-test.

We used the Kaplan-Meier method to estimate survival time after diagnosis of IPF, and compared the results between groups through log-rank test.

For all statistical tests, a pre-specified two-sided α of 0.05 was regarded as statistically significant.

All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

From March 2002 to September 2010, a total of 38 consecutive patients who referred to our Department with a diagnosis of IPF underwent RHC. Of these patients, a total of 15 (39.5%) subjects had a histological diagnosis of IPF, as confirmed by the presence of the usual interstitial pneumonia (UIP) pattern. The remaining 23 (60.5%) patients had a clinical-radiological diagnosis; in particular, in 14 patients a radiological UIP pattern was seen, and in 9 patients the high resolution computed tomography (HRCT) features were indicative of a possible UIP. The clinical conditions of these patients were too compromised and thus were not considered for lung biopsy. Out of these 38 IPF patients consecutively admitted to our hospital, 8 subjects were excluded from the retrospective analysis since they had not performed the 6MWT.

Therefore, the study population included 30 patients with IPF, without LV dysfunctions, who carried out the 6MWT before undergoing RHC. Demographic and clinical characteristics of the study patients are summarized in Table 1. Most of the patients were males (76.7%), and the mean age was 59.0 years (±8.3). Analyses stratified by presence (PH group, n=13) or absence (non-PH group, n=17) of PH did not highlight significant differences in demographic characteristics between groups. Time from diagnosis to RHC did not differ between groups (25.6 ± 25.8 months for non-PH group, and 37.2 ± 26.2 months for PH group). The mean survival of non-PH patients from RHC was 12.5 months (± 11.9) and 21.5 months (± 17.0) in PH patients and these values were not statistically different. The mean survival times from the diagnosis of IPF differed significantly between the two groups (36.8 ± 26.8 months in non-PH group, 58.9 ± 31.5 months in PH group; $p < 0.05$).

Descriptive statistics of the clinical parameters measured during RHC are reported in Table 2: most of IPF patients with PH had only a slight increase of their

Table 1. Demographic and clinical characteristics of the study population (n = 30 patients with IPF), stratified by presence (PH) or absence (non-PH) of pulmonary hypertension.

	Non-PH (mPAP≤25mmHg)	PH (mPAP>25mmHg)	Population
N (%)	17 (56.67)	13 (43.33)	30 (100.00)
Males, n (%)	13 (76.47)	10 (76.92)	23 (76.67)
Age (years), mean ± SD	60.41 ± 8.82	57.08 ± 7.55	58.97 ± 8.33
Smokers†, n (%)	9 (52.94)	9 (69.23)	18 (60.00)
BMI (kg/m2), mean ± SD	26.52 ± 3.43	28.46 ± 2.35	27.36 ± 3.12
BSA (m2), mean ± SD	1.79 ± 0.17	1.88 ± 0.19	1.83 ± 0.18
Follow-up			
Dropouts, n (%)	4 (23.53)	2 (15.38)	6 (20.00)
Deaths, n (%)	10 (83.33)	9 (100.00)	19 (90.48)
Survival time (months) after:			
• RHC, mean ± SD	12.47 ± 11.91	21.54 ± 17.05	16.40 ± 14.81
• Diagnosis of IPF, mean ± SD	36.82 ± 26.79	58.92 ± 31.55*	46.40 ± 30.53
Time (months) from diagnosis SD	25.65 ± 25.80	37.15 ± 26.21	30.63 ± 26.17to RHC, mean ±

*†Data are missing for 1 patient; BMI=Body Mass Index; BSA=Body Surface Area; RHC=Right Heart Catheterization; SD=Standard Deviation; mPAP=Mean Pulmonary Artery Pressure; *p-value < 0.05.*

mean PAP value. A total of 10 out of 30 patients (33.3%) underwent RHC as part of lung transplantation candidacy evaluation, and the remaining 20 patients (66.7%) underwent the procedure at the discretion of the evaluating physician (Table 2).

Results of 6MWT are summarized in Table 3: no significant difference in 6MWD was observed between groups (222.3m ± 118.5m in the IPF-PH group, and 222.1m ± 118.5 in the non-PH group; $p > 0.05$). Moreover, most of the patients (28/30) who performed 6MWT walked with oxygen supply, respectively 88.2% and 100.0% in non-PH and PH group (for one patient without PH the information about oxygen supply was missing) and these values didn't differ statistically.

Generally, the PFTs were very similar in the two groups of patients, with the only exception of the FVC, which was significantly more preserved in the group of IPF patients with PH (63.8 ± 16.0 vs. 51.6 ± 13.8 in IPF patients without PH, $p < 0.05$).

Furthermore, no association was found between

Table 2. Right heart catheterization (RHC) evaluation of IPF patients with (PH) or without (Non-PH) pulmonary hypertension.

	Non-PH (mPAP≤25mmHg)	PH (mPAP>25mmHg)	Population
Reasons for RHC			
Lung transplantation, n (%)	7 (70.00)	3 (23.08)	10 (33.33)
Medical indication, n (%)	10 (30.00)	10 (76.92)	20 (66.67)
RHC measurements, mean ± SD			
PAP (mmHg)			
• Systolic	32.18 ± 6.07	49.00 ± 8.33*	39.47 ± 11.00
• Diastolic	13.06 ± 3.11	24.15 ± 6.31*	17.87 ± 7.29
• Mean	19.43 ± 3.65	32.44 ± 6.00*	25.07 ± 8,07
CO (l/min)	6.03 ± 0.77	5.45 ± 1.62	5.78 ± 1.23
CI (l/min•m2)	3.40 ± 0.55	2.88 ± 0.70*	3.17 ± 0.66
RAP (mmHg)	3.18 ± 2.83	8.15 ± 4.18*	5.33 ± 4.24
PCWP (mmHg)	7.59 ± 3.22	10.31 ± 3.17*	8.77 ± 3.43
PVR (mmHg•min/l)	3.56 ± 1.13	7.99 ± 2.24*	5.48 ± 2.79
PVR index (mmHg•min/l•m2)	1.99 ± 0.60	4.26 ± 1.17*	2.97 ± 1.44

*RHC=Right Heart Catheterization; PAP=Pulmonary Arterial Pressure; CO=Cardiac output; CI=Cardiac Index; RAP=Right Atrial Pressure; PCWP=Pulmonary Capillary Wedge Pressure; PVR=Pulmonary Vascular Resistance (MPa·s/m3); SD=Standard Deviation; mPAP=mean Pulmonary Artery Pressure; *p-value < 0.05.*

Table 3. Pulmonary function test (PFT) results in IPF patients with (PH) or without (Non-PH) pulmonary hypertension.

	Non-PH (mPAP≤25mmHg)	PH (mPAP>25mmHg)	Population
6-Minute Walk Test Distance			
Distance (m), mean ± SD	222.06 ± 118.55	222.31 ± 118.54	222.17 ± 116.48
Use of oxygen, n(%)†	15 (88.23)	13 (100.00)	28 (93.33)
Pulmonary Function Tests, mean ± SD			
FEV1 (% pred)	58.33 ± 16.30	65.85 ± 18.77	61.82 ± 17.58
FVC (% pred)	51.60 ± 13.83	63.85 ± 16.03*	57.29 ± 15.87
FEV1/FVC (%)	84.80 ± 8.17	82.77 ± 6.51	83.86 ± 7.38
TLC (% pred)	46.93 ± 8.13	52.15 ± 9.68	49.36 ± 9.11
RV (% pred)	36.87 ± 14.61	34.92 ± 13.12	35.96 ± 13.72
DLCO (% pred)	31.42 ± 9.58	25.83 ± 11.32	28.63 ± 10.64
DLCO/VA (% pred)	70.08 ± 19.35	54.50 ± 21.50	62.29 ± 21.53
FIO2 (%)	25.06 ± 5.56	24.00 ± 5.89	24.59 ± 5.63
PO2 (mmHg)	70.47 ± 13.51	61.72 ± 13.22	66.55 ± 13.87
PCO2 (mmHg)	39.76 ± 4.10	39.99 ± 5.53	39.87 ± 4.70

*†Data are missing for 1 patient; SD=Standard Deviation; mPAP=mean Pulmonary Artery Pressure; *p-value < 0.05*

presence of PH and PFT data, including DLCO; however, a significant ($p < 0.05$) linear correlation was found between DLCO and 6MWD (Pearson's correlation coefficient = 0.455) (data not shown). Finally, in the PH group, 4 patients (30.8%) had out-of-proportion PH (mPAP > 35 mmHg): their mean 6MWD was 203.7 meters (± 128.3), which did not statistically differ from the distances walked by the other 26 patients. Moreover, their mean survival time from RHC was significantly lower (8.7 ± 2.9 months; $p < 0.05$) than that of the other patients (22.3 ± 3.0 months) (data not shown).

Discussion

Goal of this retrospective study was to assess the impact of PH on 6MWT performances in patients with IPF.

We retrospectively review the data of 30 subsequent patients referred to our Department for IPF from March 2002 to September 2010 who underwent at least one RHC.

The two groups of IPF patients - with and without PH - were very similar for demographics characteristics and almost all PFT values, including DLCO; however, FVC was found to be significantly higher ($p < 0.05$) in the group of patients with PH than in IPF patients without PH. The two groups of patients significantly differed for RHC data.

In both groups, the vast majority of patients performed 6MWT with continuous oxygen supply. Oxygen supply is thought to increase 6MWD in patients with parenchymal lung diseases; however, in our study this was not an issue, as the proportion of patients who needed oxygen supply was very similar for the two groups. Moreover, the offer of oxygen supply is recommended for patients with baseline or exercise hypoxia, and reflects the daily clinical practice.

In our study, IPF patients with or without PH walked during the 6MWT nearly identical distances (222.1 meters for non-PH vs. 222.3 meters for PH group; overall 6MWD = 222.2m). None of the patients in this study was enrolled in pulmonary rehabilitation program or received PH-specific therapy that may have influenced the 6MWT performance.

We also did not observe any significant difference in the distance walked (203.7 ±128.3 meters) during 6MWT by the 4 patients who had out-of-proportion PH (mPAP > 35 mmHg), when compared with the distances walked by the other 26 patients of the study population.

No association was found between mPAP and PFT data, including DLCO; however, a significant ($p < 0.05$) linear correlation was found between DLCO and 6MWD (r-squared = 0.455). That makes sense, as variations in DLCO may be related both to parenchymal lung involvement and vascular changes, and could have an important impact on exercise tolerance.

Increasing attention has been paid to the presence of PH in patients with IPF, since it has been shown to be associated with a poor prognosis (32, 33). Based on scientific literature, the prevalence of PH in IPF patients varies greatly due to differences in diagnostic procedures and/or severity of IPF in patient populations (2, 7, 8, 10, 11). A mild PH is commonly observed in advanced IPF, whereas moderate to severe PH rarely occurs (2, 8). The impact of PH on IPF is known, but much less is known on its influence on 6MWT performance. It is unclear whether PH per se may reduce exercise capacity in IPF patients or may reflect the presence of a more advanced lung disease.

The 6MWT is a simple test, and the distance walked during the 6MWT is highly reproducible. The test is used to evaluate sub-maximal functional capacity in patients with different kinds of parenchymal and vascular pulmonary diseases and to assess response to therapies. The 6MWT in IPF patients appears highly reproducible (test-retest reliability 0.98) over short time intervals (e.g. 1-2 weeks) (34). For IPF patients, 6MWT appears to be a valid reflection of global functional capacity (34). The test is frequently used as a clinically meaningful measure of changes in IPF disease status over time, though few data support this practice. More importantly, the 6MWT (desaturation and distance walked) has been used as an outcome measure in trials enrolling subjects with IPF (35-37). However, there are large knowledge gaps regarding certain important aspects of this test in IPF patients. In recent studies, for selected groups of well-defined subjects with IPF, no significant change from baseline in 6MWD was found at 6 and 12 months (25, 38, 39).

The role of 6MWT in patients with IPF and PH has not been fully investigated, even if it has already been used as surrogate end point for mortality and drug response in clinical trials. This test has not yet been validated as a reliable screen test for PH in IPF, and its prognostic significance is still unknown.

Lettieri et al. (7) evaluated 79 IPF patients undergoing pre-transplant evaluation procedures including PFT, 6MWT and RHC. Only 17,6% of the 54 IPF patients without PH were provided with oxygen supply, while the percentage of patients breathing supplemental oxygen raised to 66,7% in the group of IPF patients with PH (n=25). The 6MWT was only performed in 34 patients (10 without PH and 24 with PH), and the distance walked was significantly higher in the group of IPF patients without PH (365.9 ± 81.8 meters vs. 143.5 ± 65.5 meters for PH patients; $p < 0,001$). However, it is not known how many patients of these two subgroups were breathing supplemental oxygen, nor were known their PFT values and whether the two groups of patients were homogenous and balanced (as in our study). In Lettieri' s study, PH was an important predictor of mortality, while in our study the presence of PH did not influence survival. The only explanation for the discrepancy between the results in Lettieri's and our study might be related to the limited number of patients enrolled into our study. Another explanation for the surprising results about survival in our patients cohort is that the two groups statistically differed for FVC values: patients without PH showed lower FVC value when compared with patients with PH, and this indicated a more severe parenchymal involvement and a more severe IPF disease. This may explain the shorter survival in IPF patients without PH observed in our study. Moreover, even if the two patient's groups were similar in age, patients with PH were a bit younger compared with patients without PH (57.1 ± 7.5 years vs. 60.4 ± 8.8 years, respectively): even this small difference of about 3 years may be important in a disease with a severe prognosis as IPF. In a recently proposed model that uses commonly measured clinical and physiological data, FVC and age have been indicated as important variables to predict mortality (40). In another study, FVC and age also were indicated as accurate determinants of prognosis and 1-year mortality (together with respiratory hospitalization and 24-week change in FVC) (41). Nevertheless, our study was designed to compare 6MWT, PFT and RHC in IPF patients with or without PH rather than primarily assessing survival.

In a recent study, Minai et al. (42) evaluated the impact of altered pulmonary hemodynamics on functional capacity in a cohort of patients with advanced IPF. A total of 124 patients with IPF underwent RHC and 6MWT as part of the lung transplant evaluation process. PH was diagnosed in 44% of the patients in this study population. IPF patients with PH had significantly lower 6MWD compared with that measured in IPF patients without PH. Like in the Lettieri's study, there was no mention on the proportion of patients who needed oxygen supply during 6MWT. Most of the patients included in the study had advanced IPF and were being evaluated for lung transplantation; therefore, it is strongly questionable whether these results might be applicable to the IPF population as a whole.

The study of Modrykamien et al. (43) considered 58 patients who were transplanted due to IPF. Right ventricular systolic pressure, 6MWD, distance-saturation product (DSP), and lowest pulse oximetry (SpO2) during 6MWT were compared between PH and non-PH groups. The mean distance walked during the 6MWT by patients with PH (mPAP = 33 mmHg) or without PH (mPAP = 19 mmHg) did not differ significantly (321 meters for patients with PH vs. 346 meters in patients without PH, $p = 0.38$). Our results are consistent with this study; however, patients' populations are quite different. In fact, in the Modrykamien' study the patients cohort was highly selected, as it included subjects who had survived long enough on a transplant list to undergo transplantation. It is conceivable that patients with more severe PH were more apt to die while on the waiting list.

Andersen et al. (44) found a large difference in 6MWD between patients with and without PH suffering from different ILDs. The multivariate analysis performed in this study showed that PH significantly reduced walking distance independently of lung function, and also that this effect could be attributed to the patients with severe PH. In this study only few patients were evaluated for PH by RHC (only 18 out of 212 of patients); this could have led to the potential for substantial selection bias and might partly explain the differences between that study and our results. We know that false-positive and -negative results may occur during echocardiography for PH evaluation in interstitial lung diseases, and it cannot be excluded that some of the patients who did not underwent RHC were wrongly diagnosed with PH.

Our study presents several limitations. One is that the number of patients is rather small. This is due to the rarity of PH in IPF and to the fact that we selected only IPF patients who underwent at least one RHC, which is an invasive procedure that is indicated only in a few well-selected cases. However, we had calculated

the sample size (45) necessary to detect a 20% difference in the mean 6-minutes walking distance between the two groups (IPF patients with or without PH), based on the assumptions that the number of IPF patients without PH is the double of that of IPF-PH patients, and that the average distance walked during the 6MWT is 250 meters, with a SD value varying between 100 and 175 meters. These values were chosen according to literature data (13). According to these assumptions, we calculated that the appropriate sample size was varying between 37 and 114 patients, depending on the SD value. Therefore, considering a SD value of 100 meters, the sample size of our population study seemed to be adequate to detect the hypothesized difference.

A number of studies have investigated lung transplant candidates in whom RHC was routinely performed (7, 8, 32, 33). However, lung transplant candidates only constitute a small group of patients at referral centers (i.e. younger patients, patients without significant medical comorbidities and with greater level of social support), and have very advanced lung disease; thus, the extrapolation of findings from studies performed on this study population to all patients with IPF may be questionable. In our study, we did not only consider lung transplant candidates - as usually done in most of the studies published so far, but also evaluated patients with milder degree of parenchymal impairment as well as patients who were older than lung transplant candidates and had clinical suspicion of PH, based on clinical ground.

Our study represents a single-centre experience. In one hand, the number of patients enrolled is limited; in the other hand, the operator-dependent variability of the 6MWT, PFT and RCH measurements is minimized, thus allowing good reproducibility of results.

Selection bias may be a concern in our study. The non-PH group had significantly lower FVC. This may mean that the group without PH had a more severe parenchymal disease and that this, rather than the vascular compromise, has led the medical history of these patients.

Despite these limitations, we believe that our study adds some significant knowledge. Despite the small size, the study has provided strong results indicating that six-minute distance walked by patients with IPF and PH is nearly identical to that walked by IPF patients without PH; moreover, we observed that even IPF patients with out-of-proportion PH could walk on a 6MWT for a distance that was very close to that of all other IPF patients.

In conclusion, patients with IPF have functional limitations and a decreased exercise capacity, as measured with 6MWT. However, 6MWD does reflect neither the presence nor the severity of PH in IPF patients and, thus, should not be used as surrogate end point of mortality in clinical studies. Larger studies are needed to identify functional markers of disease severity in patients with IPF and PH.

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