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Original Article

Daily physical activity affects exercise capacity in patients with idiopathic pulmonary fibrosis

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Abstract. [Purpose] The aim of this study was to determine which factors, including pulmonary, physical, and mental functions; dyspnea; and daily physical activity (PA) affect the 6-minute walk distance (6MWD) in IPF patients. [Subjects and Methods] The pulmonary, physical, and mental functions; dyspnea; PA; and 6MWD were assessed in 38 outpatients with IPF. PA was represented by the mean number of steps per day. [Results] The mean 6MWD was 443.8 m (SD, 98.5), and the mean number of steps per day showing PA was 5148.4 (SD, 3295.7). The 6MWD was correlated with age, base dyspnea index, vital capacity (VC), diffusion capacity of carbon monoxide, quadriceps force (QF), dyspnea during the 6-minute walk test, and PA. Stepwise multiple regression analysis revealed that VC (β=0.382), QF (β=0.272), and PA (β=0.574) were contributing factors of the 6MWD. [Conclusion] In patients with IPF, PA has a greater effect on the 6MWD than VC and QF. The evaluation of daily PA, in addition to physiological and muscle functions, is important in patients with IPF.
Key words: Idiopathic pulmonary fibrosis, Physical activity, 6-minute walk distance

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic and progressive fibrosing interstitial pneumonia associated with the histological feature of usual interstitial pneumonia. The prevalence rate of IPF is 2 to 29 cases per 100,000 in the general population, and the median survival time of IPF is 3 to 5 years after diagnosis[1–4]. The main symptoms are dyspnea and dry cough. Pulmonary and physical functions, exercise capacity, activities of daily living, and health-related quality of life are restricted in patients with IPF.

The 6-minute walk test (6MWT) is a simple assessment and widely used as an index of functional exercise capacity. The 6-minute walk distance (6MWD) is an important parameter that is associated with health-related quality of life and mortality in patients with IPF[5, 6]. Du Bois et al.[7] reported that both the 6MWD and the decrease in the 6MWD were independent predictors of mortality in patients with IPF. In patients with chronic obstructive pulmonary disease (COPD), the 6MWD is well known to be associated with pulmonary and muscle functions, dyspnea, and daily physical activity (PA)[8–11]. However, few studies have focused on the factors that contribute to the 6MWD in patients with IPF.

The relationship between the 6MWD and pulmonary function, quadriceps force (QF), and dyspnea have been reported[12, 13]. Nakayama et al.[14] revealed that PA was associated with the 6MWD. Since the determining factors of exercise capacity are considered to be multifactorial[15], the present study aimed to determine which factors affect the 6MWD, including pulmonary, physical, and mental functions; dyspnea; and PA in patients with IPF.

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SUBJECTS AND METHODS

A prospective observational study design was utilized. This study was approved by the Institutional Review Board of Sapporo Medical University, and all patients provided written informed consent.

Outpatients with IPF who visited the Sapporo Medical University hospital were enrolled from October 2011 to June 2012. The diagnosis of IPF was based on the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association consensus statement[3]. We excluded patients with cognitive impairment (Mini-Mental State Examination ≤23), high risk for pneumothorax, comorbidities affecting exercise performance (e.g., neuromuscular, orthopedic, or cardiovascular disorder), or history of resection of 1 or more lung lobes. Patients who discontinued measurements of daily step count for 2 weeks because of exacerbation of their comorbidities were also excluded. Medical management (e.g., oral corticosteroids, antifibrotic agent, and supplemental oxygen) were optimized before inclusion to this study, and the subjects were required to be clinically stable. Fifty-three patients were screened, and 13 of them were excluded from this study because they had a history of resection of 1 or more lung lobes (n=5), orthopedic or cardiac disorders limiting exercise performance (n=4), cognitive disorder (n=2), and high risk of pneumothorax (n=2). Two patients discontinued measurement of PA because of acute nephritis and acute exacerbation of IPF. Thirty-eight patients were thereby analyzed.

The partial pressure of oxygen and carbon dioxide in arterial blood were measured at rest. The serum levels of sialylated carbohydrate antigen Krebs von den Lungen-6, surfactant protein (SP)-A and SP-D were collected as serum markers of IPF. The tricuspid regurgitation pressure gradient was measured by echocardiography. All patients underwent the pulmonary function test by spirometry. The vital capacity (VC), tidal volume, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and diffusion capacity of carbon monoxide (DLCO) were measured[16, 17]. The values in the pulmonary function test are expressed as percentages of the predicted values. All physiological data were acquired within 3 months before measurements of the physical function and PA.

The quadriceps muscle force (QF) was measured using a hand-held dynamometer with fixing-belt (μTas F-1, Anima Corporation, Tokyo, Japan). The dimensions of the pressure sensor were 56 mm by 56 mm. The lower edge of the sensor was placed above the elevation of the medial malleolus of the patients. The peak force was measured twice in both legs during a maximal isometric knee extension maneuver with the hip and knee in 90° flexion. This maneuver had good reliability. The interclass correlation coefficient and intraclass correlation coefficient in this maneuver were 0.990 and 0.937, respectively[18]. The highest value of the peak force was multiplied by the length from the axis of the knee joint to the center of the sensor in the sagittal plane in each leg, and the average value was used as the QF.

The 6MWT was performed through a 50-m flat strait corridor following the standard protocol based on published guidelines[19]. In patients who received oxygen therapy during their daily activities, the supplemental oxygen flow was set at the rate of their ordinary prescription. They sat down on a chair for 5 minutes before the test. The patients were informed of the elapsed time and given standard encouragement in each minute during the test. The oxygen saturation (SpO_2) and heart rate (HR) were monitored continuously by pulse oximetry (PULSOX-300i, Teijin Pharma, Tokyo, Japan). If the SpO_2 decreased to less than 84%, patients stopped walking until it exceeded 90%. The 6MWD, nadir SpO2, and peak HR were measured during or after the test. The levels of dyspnea and leg fatigue during the test were assessed by the modified Borg scale with the score ranging from 0 to 10[20].

The mental function was assessed by the hospital anxiety and depression scale (HADS)[21]. The HADS is a self-assessment scale that consists of 7 items for anxiety and 7 items for depression. Each item is rated on a 4-grade scale from 0 to 3. The total anxiety score and the total depression score each range from 0 to 21. For each total score, a score of 8 or more is indicative of clinically relevant symptoms.

Dyspnea in daily living was assessed by the modified Medical Research Council (MRC) dyspnea scale (0 to 4)[22] and the Baseline Dyspnea Index (BDI)[23]. The BDI consists of 3 categories: functional impairment, magnitude of the task, and magnitude of the effort. Each category is rated in a 5-grade scale from 0 to 4, and the total BDI score ranges from 0 to 12. The lower the score, the worse the level of dyspnea.

PA was represented by the steps per day measured with the uniaxial accelerometer (Kenz Lifecorder, Suzuken, Nagoya, Aichi, Japan), which was firmly attached at the waist of the patients. The patients wore the accelerometer for 15 consecutive days from the moment they got up until they went to bed, except while bathing. The data from the first day, when the 6MWD was recorded, was not used for analysis. The mean number of steps per day during 14 days was used as an index of PA. The days when the patients felt sick or wore the device less than 10 hours per day were excluded from the analysis.

The statistical analyses were performed using SPSS software version 19 (SPSS Japan Inc., Tokyo, Japan). To examine the degree of correlation between the 6MWD and each of the clinical characteristics; pulmonary, physical, and mental functions; dyspnea; and PA, bivariate analyses were performed using Spearman's rank correlation coefficients. Furthermore, multivariable stepwise linear regression analysis was performed to investigate the parameters that affected the 6MWD. The variables that were significantly related to the 6MWD in the bivariate analysis were selected as independent variable candidates for the multivariable analysis. The level of statistically significance was set at 5%.

RESULTS

Table 1 shows the clinical characteristics of the 38 patients. Thirteen patients were diagnosed by means of surgical lung biopsies, and the others were diagnosed by high-resolution computed tomography. The severity of dyspnea ranged from mild to moderate. The VC and FVC were slightly decreased. The DLCO could not be measured in 6 patients because of cough, and the mean value was moderately decreased. Two patients had to take a break for resting because of dyspnea during the 6MWT. No patients stopped the test because of oxygen desaturation below 84%.

The patients demonstrated good compliance in wearing the accelerometer, and the average duration of analysis was 13.6 (SD, 0.9) days. The mean number of steps per day, which represented the patients' PA, was 5148.4 (SD, 3295.7), and this value was less than that of healthy people with a similar age (7332; SD, 298)[24].

The relationship between the 6MWD and each of the clinical characteristics; physiologic, physical, and mental functions; and PA are shown in Table 2. The 6MWD was related to each of the pulmonary and physical functions, dyspnea, and PA. However, there was no correlation between the 6MWD and blood gas tension, serum markers, and mental function.

In stepwise multiple regression analysis, VC, QF, and PA were selected as independent parameters of the 6MWD (adjusted R^2=0.640, $p<0.001$) (Table 3).

DISCUSSION

The present study showed that the 6MWD was correlated with pulmonary function, muscle strength, dyspnea, and PA in patients with IPF. Multivariable stepwise linear regression analysis revealed that VC, QF, and PA were the crucial parameters. A previous study reported that exercise tolerance was influenced by QF[12], while the present study showed that PA affected the 6MWD more strongly than QF in patients with IPF. To our knowledge, this is the first report that elucidated the factors affecting 6MWD among pulmonary, physical, and mental functions, as well as dyspnea and PA. To measure PA, we recorded the daily step counts for 14 consecutive days with the uniaxial accelerometer. This duration is longer than that of most previous studies[25] and satisfies the criteria of 90% reliability in the measurement of PA[26].

Zhang et al.[27] revealed that PA and peak oxygen consumption (peak VO_2), which is one of the parameters of exercise tolerance, were lower in healthy subjects without exercise habit than those with exercise habit. Ichihara et al.[28] clarified that the peak VO_2 was correlated with the daily number of steps in asymptomatic middle-aged subjects. In patients with chronic

Table 1. Characteristics of the 38 patients with IPF

Variables	Values	Variables	Values
Gender (male/female, n)	26/12	TRPG (mmHg)	24.5 ± 8.8
Age (years)	71.3 ± 8.4	Pulmonary function	
Body mass index (kg/m^2)	23.9 ± 3.0	VC (%)	89.5 ± 19.7
Time since diagnosis (months)	59.4 ± 59.3	FVC (%)	88.2 ± 19.6
Dyspnea		FEV1 (%)	98.9 ± 20.0
MRC grade (0 to 4)	1.0 ± 0.7	DLCO (%)	47.8 ± 17.0
BDI	8.0 ± 2.7	HADS score	
Treatment		Anxiety	4.2 ± 3.3
LTOT, n (%)	5 (13.2)	Depression	5.5 ± 3.3
Pirfenidone, n (%)	15 (40.0)	Quadriceps force (Nm)	97.8 ± 43.5
Oral corticosteroids, n (%)	6 (15.8)	6MWT	
Blood gas data		6MWD (m)	443.8 ± 98.5
PaO_2 (mmHg)	80.8 ± 15.3	Lowest SpO_2 (%)	89.9 ± 4.3
$PaCO_2$ (mmHg)	39.1 ± 7.4	Highest HR (%)	110.8 ± 17.5
Serum marker		Dyspnea	2.8 ± 1.7
SP-D (ng/ml)	190.3 ± 129.6	Leg fatigue	1.9 ± 1.7
KL-6 (U/ml)	893.2 ± 397.2	PA (steps/day)	5,148.4 ± 3,295.7

Values are mean ± SD unless otherwise stated.
BDI: Baseline Dyspnea Index; DLCO: diffusion capacity of carbon monoxide; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; HADS: hospital anxiety and depression scal; HR: heart rate; KL-6: Krebs von den Lungen-6; LTOT: long-term oxygen therapy; MRC: Medical Research Council; PA: physical activity; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of oxygen in arterial blood; SP: surfactant protein; SpO_2: oxygen saturation; TRPG: tricuspid regurgitation pressure gradient; VC: vital capacity; 6MWT: 6-minute walk test; 6MWD: 6-minute walk distance

lung diseases, physical inactivity may cause cardiovascular and muscular deconditioning[29]. Most patients with COPD have limitation of daily PA[30–32]. A study by van Gestel et al.[33] investigated the effect of the pulmonary function, lower and upper muscle functions, and daily PA on the 6MWD in patients with COPD. The results showed that the number of daily step counts was closely correlated with the 6MWD. Although IPF is distinct from COPD in disease characteristics, the present study revealed that the PA of patients with IPF was lower than that of healthy people and was associated with the 6MWD. Wallaert et al.[34] reported that in patients with familial idiopathic interstitial pneumonia that consisted of IPF and fibrotic nonspecific interstitial pneumonia, the number of daily step counts was related to the 6MWD. The mean number of steps per day in our study was similar to that of their study (4157; SD, 3014) and was less than that of healthy subjects (7332; SD, 298)[24].

We found that VC and QF were also contributing factors of the 6MWD. Previous studies clarified that pulmonary function affected the 6MWD in patients with IPF. Each of the pulmonary function parameters and the 6MWD were considered clinical parameters affected by the disease severity. Nishiyama et al.[12] showed that in IPF, the peak VO_2 was affected by the VC, QF, and ventilatory equivalent ratio for carbon dioxide in the cardiopulmonary exercise test. Kozu et al.[35] reported that the MRC dyspnea scale score, which was correlated with the impairment of pulmonary function, was associated with the 6MWD in patients with IPF. The oxygen availability in the quadriceps muscle, the biggest muscle in the lower extremity, was reported to determine the exercise tolerance of patients with COPD[36]. Previous studies reported that muscle weakness, atrophy, shift in fiber-type, mitochondrial dysfunction, and poor oxidative capacity were major structural changes of the lower extremity muscles in patients with COPD[37]. As muscle training of the lower extremities in pulmonary rehabilitation improved the exercise tolerance in patients with IPF as well as COPD[38], patients with IPF may have muscle dysfunctions that are similar

Table 2. Correlation between the clinical variables and the 6-minute walk distance

Variables	r
Age	−0.368 *
BDI	0.619 ***
TRPG	−0.096
KL-6	−0.008
PaO_2	0.316
VC % predicted	0.408 *
FEV1 % predicted	0.144
DLCO % predicted	0.547 **
Depression	−0.273
Quadriceps force	0.564 ***
Lowest SpO_2 during 6MWT	0.334 *
Dyspnea during 6MWT	−0.448 **
Leg fatigue during 6MWT	−0.241
PA	0.646 ***

*p<0.05, **p<0.01, ***p<0.001
BDI: Baseline Dyspnea Index; TRPG: tricuspid regurgitation pressure gradient; KL-6: Krebs von den Lungen-6; PaO_2: partial pressure of oxygen in arterial blood; VC: vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusion capacity of carbon monoxide; SpO_2: oxygen saturation; 6MWT: 6-minute walk test; PA: physical activity

Table 3. Result of stepwise multiple regression analysis

Variables	Unstandardized		Standardized β	p-value	95% CI
	B	SE			Lower bound−Upper bound
(Constant)	117.135	55.850		0.045	2.732−231.537
PA	0.017	0.003	0.574	<0.001	0.010−0.024
VC % predicted	1.975	0.581	0.382	0.002	0.785−3.166
QF	0.593	0.272	0.260	0.037	0.037−1.150

Adjusted R^2: 0.640, p<0.001
CI: confidence interval; PA: physical activity; QF: quadriceps force; VC: vital capacity

to those of patients with COPD. Further investigations are needed to elucidate how muscular changes affect the exercise tolerance of patients with IPF.

Depression is one of the factors that may deteriorate the PA of patients with COPD. Di Marco et al.[39] reported that the exercise tolerance of depressed patients with COPD was lower than that of nondepressed patients with COPD. Ryerson et al.[40] found that depression assessed by the Center for Epidemiologic Studies Depression Scale was associated with the 4-meter walk time in patients with interstitial lung diseases including IPF (40% of the total patients), connective tissue disease-associated interstitial lung disease (35%), chronic hypersensitivity pneumonitis (15%), and others (10%). However, the 4-meter walk time does not seem to represent the exercise tolerance of subjects with pulmonary dysfunction, as it measures the time while walking a short distance of 4 meters. The present study revealed no significant relationship between the HADS depression score and the 6MWD in the patients with IPF. The absence of a relationship between the 6MWD and depression may be a characteristic of patients with IPF. Dyspnea at the end of the 6MWT was less severe in patients with IPF than in patients with COPD[41].

Our study has some limitations that need to be addressed. First, the sample size in our study was small as the prevalence rate of IPF is much lower than that of COPD. Second, the severity of dyspnea was restricted to mild-to-moderate in this study, because all patients were outpatients who were able to perform the 6MWT.

In conclusion, PA has a stronger effect on the 6MWD than pulmonary and muscle functions. This finding may be important in the identification of crucial parameters of exercise intolerance in patients with IPF. The present study findings suggest that the evaluation of daily PA, in addition to physiological and muscle functions, is important in patients with IPF.

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