



Original Article

Factors affecting dyspnea after the 6-minute walk test in idiopathic pulmonary fibrosis patients presenting with exercise-induced hypoxemia

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Abstract. [Purpose] The current study aimed to investigate factors affecting dyspnea after the 6-minute walk test (6MWT) in idiopathic pulmonary fibrosis (IPF) patients presenting with hypoxemia. [Subjects and Methods] The subjects were IPF out-patients with stable symptoms whose percutaneous arterial oxygen saturation fell to 88% during the 6MWT test. Quadriceps force, 6-minute walk distance (6MWD), dyspnea after the 6MWT, and leg fatigue (LF) were evaluated as exercise-related variables. [Results] The subjects were 14 patients (mean age 73.6 ± 6.3 years) classed based on the modified Medical Research Council dyspnea scale as 0 for 2 patients, 1 for 6 patients, and 2 for 6 patients, indicating that the patients were comparatively mild cases. Mean 6MWD was 408.9 ± 102.4 m, and dyspnea after the 6MWT and LF were 3.0 ± 1.4 and 1.5 ± 1.5, respectively. Dyspnea after the 6MWT was correlated with vital capacity (VC), forced vital capacity, and LF. Stepwise multiple regression analysis identified VC and LF as factors significantly affecting dyspnea after the 6MWT. [Conclusion] The results of this study demonstrated that it is necessary to evaluate both pulmonary function and LF in IPF patients presenting with exercise-induced hypoxemia and exertional dyspnea.

Key words: Dyspnea, Exercise-induced hypoxemia, Idiopathic pulmonary fibrosis

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung diseases (ILD) characterized by honeycomb lung secondary to pulmonary fibrosis. The prevalence of the condition is reportedly 11 per 100,000, and the 5 year survival rate is approximately 50%¹⁻⁴⁾. The primary symptoms are dry cough and exertional dyspnea⁵⁾.

IPF patients exhibit exercise-induced hypoxemia (EIH) with progression of the disease. EIH in IPF patients is more serious than in chronic obstructive pulmonary disease (COPD) patients⁶⁾. Moreover, hypoxemia after the 6-minute walk test (6MWT) is reportedly associated with mortality in IPF patients⁷⁾. Additionally, dyspnea in IPF patients is reportedly a prognostic indicator that affects health-related quality of life⁸⁾. The mechanism of exertional dyspnea in IPF patients is complicated, and several factors such as ventilation demand, cardiorespiratory function, and skeletal muscular function are reportedly involved^{9, 10)}. Nishiyama et al.⁶⁾ reported that dyspnea after the 6MWT was correlated with percutaneous arterial

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oxygen saturation (SpO₂). In clinical practice however, despite presenting with EIH, patients suffering from dyspnea are few. In addition, little has been reported on factors affecting dyspnea in IPF patients presenting with EIH. The current study investigated the factors affecting dyspnea after the 6MWT in IPF patients presenting with EIH via laboratory tests, exercise function tests, and mental function tests.

SUBJECTS AND METHODS

The subjects were stable IPF patients who attended the Sapporo Medical University Hospital as out-patients between October 2011 and July 2012, completed the 6MWT, and exhibited a measured SpO₂ of $\leq 88\%$ thereafter. IPF was diagnosed in accordance with the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association consensus statement⁵. Patients with cognition problems (Mini-Mental State Examination score of ≤ 23), mental or orthopedic conditions that could affect their performance in the 6MWT, and those with a high risk of pneumothorax as indicated by a history of pneumonectomy of at least one lobe were excluded. This retrospective study was performed in accordance with the Helsinki Declaration, and the ethical guidelines for clinical studies. This study was approved by the Institutional Review Board of Sapporo Medical University (approval number: 23–66), and all patients provided written informed consent.

Gender, age, body mass index, time elapsed since diagnosis, comorbidities, and drug therapy data were obtained via medical records.

In the arterial blood gas analysis, partial pressure of oxygen in arterial blood (PaO₂) and partial pressure of carbon dioxide in arterial blood (PaCO₂) when resting were measured. The sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6), surfactant protein-A (SP-A), and surfactant protein-D (SP-D) were used as serum markers. Respiratory function tests were performed in all patients, and vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in the first second (FEV₁), and diffusion capacity of carbon monoxide (DLCO) were measured. For all respiratory function test values, the ratio of the measured value to the standard value was used in the analysis. In addition, tricuspid regurgitation pressure gradient was used as the right heart strain index.

Dyspnea in daily living was evaluated via the modified Medical Research Council (MRC) dyspnea scale¹¹ and the Baseline Dyspnea Index (BDI)¹². The BDI evaluates three aspects of dyspnea in daily living, functional impairment, magnitude of a task, and magnitude of effort, at five levels with the scores ranging from 0 to 4. Thus, the total possible score ranges from 0 to 12, where lower scores indicate a greater influence of dyspnea on activities of daily living.

Quadriceps force (QF) was measured using a hand-held dynamometer equipped with quadriceps fixing belts (μ Tas F-1, Anima Corporation, Tokyo, Japan). Isometric knee extension capacity was measured in the seated position with the knee joint at a flexion of 90° and the hip joint at a flexion of 90°, and the sensor pad of the hand-held dynamometer set such that it was at the height of the medial malleolus of the lower thigh. Two measurements were taken on both the left and right sides, and the value obtained when the mean maximum value was divided by the patient's weight was used as the QF. This measurement method has been reported to have good inter-rater and intra-rater reliability¹³.

The 6MWT was performed in accordance with the American Thoracic Society guidelines, using a straight line 50 m in length¹⁴. A standard phrase of encouragement was expressed every minute. For patients on long-term oxygen therapy, the study was performed on the same amount of daily oxygen flow. Moreover, if SpO₂ fell below 84%, patients were allowed to rest until it recovered to 90%. A rest period of 6 min was also included. The evaluation parameters were 6-minute walk distance (6MWD), SpO₂ before, during, and after the test, pulse rate, dyspnea after the 6MWT, and leg fatigue (LF). SpO₂ and pulse rate were measured using a pulse oximeter (PULSOX-300i, Teijin Pharma, Tokyo, Japan). Dyspnea after the 6MWT and LF were rated using the modified Borg scale by selecting a number from 0 to 10¹⁵.

Anxiety and depression were evaluated using the hospital anxiety and depression scale (HADS)¹⁶. The HADS is a self-evaluation test comprised of 14 items, 7 for anxiety and 7 for depression. Each item is scored from 0 to 3 points, therefore, the total score ranges from 0 to 21. A score of ≤ 7 is deemed normal, a score of 8 to 10 is deemed "suspicious", and ≥ 11 points indicates a confirmed diagnosis.

Correlations between dyspnea after the 6MWT and each parameter were investigated using Spearman's rank correlation coefficient. Significantly correlated independent variables were extracted taking multicollinearity into consideration, and multiple regression analysis was performed to investigate the factors affecting dyspnea after the 6MWT. As in previous studies, the modified Borg scale was used as the continuous variable¹⁷. The software used to conduct the statistical analysis was SPSS version 19 (SPSS Japan Inc., Tokyo, Japan), and the level of significance was set at 5%.

RESULTS

Table 1 presents the patients' backgrounds. There were 14 subjects (mean age 73.6 ± 6.3 years). On the modified MRC dyspnea scale, two patients scored 0, six scored 1, and six scored 2, indicating that they were relatively mild cases. In the respiratory function test, mean DLCO was below normal. Table 2 presents the 6MWT results. The mean 6MWD was 408.9 ± 102.4 m, mean dyspnea after the 6MWT and mean LF were 3.0 ± 1.4 and 1.5 ± 1.5 , respectively, and mean minimum SpO₂ was $85.3 \pm 2.1\%$. During the test, no patient required rest due to SpO₂ falling below 84%. Correlations between dyspnea

Table 1. Subject background

Gender (male/female)	9/5
Age (years)	73.6 ± 6.3
Body mass index (kg/m ²)	24.9 ± 2.2
Duration from diagnosis (months)	65.5 ± 57.7
Modified MRC dyspnea scale (0/1/2/3/4), no.	2 / 6 / 6 / 0 / 0
Baseline Dyspnea Index [†]	7.0 (5.0–9.0)
Comorbidities, no. (%)	
COPD	3 (21.4)
Pulmonary hypertension	7 (50.0)
Medication, no. (%)	
Pirfenidone	6 (42.9)
Oral steroid	5 (35.7)
Antipsychotic drug	2 (14.3)
Long-term oxygen therapy, no. (%)	4 (28.6)
Serum markers	
KL-6 (IU/ml)	1071.3 ± 427.1
SP-A (ng/ml)	69.1 ± 20.7
SP-D (ng/ml)	217.0 ± 119.5
Pulmonary function test	
VC (%)	81.1 ± 13.5
FVC (%)	80.1 ± 13.2
FEV1 (%)	86.9 ± 12.2
DLCO (%)	34.5 ± 10.7
TRPG (mmHg)	27.9 ± 9.2
QF (%)	49.2 ± 10.9
HADS [†]	
Anxiety	3.0 (1.8–6.5)
Depression	5.0 (2.0–9.0)

Values are expressed as mean ± SD unless otherwise indicated.

[†]Median (interquartile range)

MRC: Medical Research Council; COPD: chronic obstructive pulmonary disease; KL-6: Krebs von den Lungen-6; SP-A: surfactant protein-A; SP-D: surfactant protein-D; VC: vital capacity; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; DLCO: diffusion capacity of carbon monoxide; TRPG: tricuspid regurgitation pressure gradient; QF: quadriceps force; HADS: hospital anxiety and depression scale

Table 2. Results of the 6-minute walk test

6MWD (m)	408.9 ± 102.4
Lowest SpO ₂ (%)	85.3 ± 2.1
Maximum HR (bpm)	119.1 ± 16.9
Dyspnea	3.0 ± 1.4
LF	1.5 ± 1.5

Values are expressed as mean ± SD.

6MWD: 6-minute walk distance; SpO₂: percutaneous oxygen saturation; HR: heart rate; bpm: beats per minute; LF: leg fatigue

Table 3. Correlation between dyspnea after the 6-minute walk test and the parameters investigated

Parameter	Correlation coefficient	p value
Age	-0.171	0.559
Baseline dyspnea index	-0.550	0.034
SP-D	0.540	0.046
VC	-0.792	<0.001
FVC	-0.765	0.001
FEV1	-0.454	0.103
DLCO	-0.362	0.247
QF	0.024	0.936
HADS depression	0.038	0.896
6MWD	-0.423	0.132
LF	0.634	0.015

SP-D: surfactant protein-D; VC: vital capacity; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; DLCO: diffusion capacity of carbon monoxide; QF: quadriceps force; HADS: hospital anxiety and depression scale; 6MWD: 6-minute walk distance; LF: leg fatigue

after the 6MWT and the various parameters investigated are presented in Table 3. Dyspnea after the 6MWT was significantly correlated with VC, FVC, and LF. In the stepwise multiple regression analysis, VC and LF were identified as factors affecting dyspnea after the 6MWT (Table 4).

DISCUSSION

This study investigated factors affecting dyspnea after the 6MWT in IPF patients presenting with EIH. VC and LF significantly affected dyspnea. Dyspnea is one of the primary symptoms of IPF, and is significantly associated with mortality. IPF is a progressive disease, and there is no effective treatment that improves pulmonary function. However, improvement of exercise function in patients with mild to moderate IPF is reportedly possible¹⁸. It is now evident that improvable lower-limb muscle function affects dyspnea, and this is of clinical significance.

In the current study, LF was significantly associated with dyspnea. Peripheral skeletal muscle disorder occurs not only in COPD, but also in chronic respiratory diseases including ILD. Moreover, as well as muscle atrophy and reduced muscle strength, reduced muscle metabolizing capacity and changes in muscle fiber such as type 1 fibrosis are also triggered in this functional disorder. These changes are due to increased production of lactic acid and muscle fatigue that accompany exercise^{19, 20}. In addition, although the mechanism of dyspnea has not been fully clarified, increased ventilation drive is

Table 4. Factors affecting dyspnea after the 6-minute walk test

	Non-standardized coefficient		Standardized coefficient	p value	95% confidence interval of B	
	B	SE	β		Lower limit	Upper limit
(Constant)	7.704	1.365		<0.001	4.729	10.678
VC	-0.065	0.016	-0.628	0.001	-0.099	-0.031
LF	0.381	0.140	0.410	0.018	0.076	0.685

Adjusted R²=0.733, p<0.001

VC: vital capacity; LF: leg fatigue

thought to be involved¹⁰). The increased plasma lactic acid level accompanying increased intramuscular lactic acid likely enhances that ventilation drive, resulting in dyspnea. Miki et al.²¹) reported that at maximum stress in an exercise stress test in IPF patients under compressed air inhalation, PaO₂ decreased by up to 49.9 torr. At that time, changes in dyspnea and plasma lactic acid level tended to be similar. In that study, VC also affected dyspnea. Nishiyama et al.²²) reported that VC and QF affected the exercise tolerance of IPF patients who ended an exercise stress test due to LF, and that result supports those of the current study.

IPF entails restrictive ventilatory impairment and reduced VC due to lung fibrosis. When VC is low, the breathing rate needs to be increased during exercise, to ensure adequate ventilation. Miki et al.²¹) reported a significantly higher breathing rate at the end of an exercise stress test of 44 ± 2 per min in IPF patients compared to 34 ± 2 per min in healthy adult volunteers. An increased breathing rate is a factor of dyspnea that causes fatigue of respiratory muscles. Because of that, VC is considered to affect dyspnoea.

One of the limitations of the current study was that only patients with mild to moderate symptoms were included. In IPF patients, the more the symptoms worsen the more EIH and exertional dyspnea worsen. In the future, an investigation that includes severely affected patients is warranted. Another drawback of the study is that patients on long-term oxygen therapy were included. Miki et al.²¹) reported that in IPF patients, there is no difference in the dyspnea mechanism under oxygen inhalation and under compressed air inhalation. Furthermore, Nishiyama et al.¹⁷) reported that though oxygen therapy is effective for preventing hypoxemia in IPF patients presenting with exertional dyspnea, it is not effective for reducing dyspnea. Although it is not clear whether the presence or absence of long-term oxygen therapy affects the outcome, it is necessary to elucidate the factors that affect dyspnea in patients on long-term oxygen therapy and those that are not in a study with a large patient cohort.

In the current study, dyspnea after the 6MWT in patients presenting with EIH was affected by both respiratory function and lower-limb muscle function. These results demonstrate the need to evaluate lower-limb fatigue in IPF patients presenting with EIH and exertional dyspnea.

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