Associations between the Distance Covered in the Incremental Shuttle Walk Test and Lung Function and Health Status in Patients with Chronic Obstructive Pulmonary Disease

Short title

Incremental shuttle walk test in COPD Patients

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Abstract

***Background*:** Field walk tests such as the incremental shuttle walk test (ISWT) are simple tests for assessing the degree of disability in individuals with chronic obstructive pulmonary disease (COPD). In the present study, the correlations between exercise performance in the ISWT, lung function, and health status were examined in patients with COPD of varying severities.

***Methods*:** A retrospective examination of 277 COPD patients was performed using the ISWT and lung function tests along with assessment of health status using St. George's Respiratory Questionnaire (SGRQ). In addition, we assessed the correlations between the walking distance, lung function parameters, and SGRQ scores.

***Results*:** ISWT distances were poorly correlated with lung function parameters and SGRQ scores in mild COPD patients. In contrast, ISWT distances were significantly correlated with pulmonary function parameters, such as vital capacity (%predicted) and forced expiratory volume in one second, and SGRQ scores in moderate and severe COPD patients.

***Conclusions*:** The ISWT is more independent of health status and pulmonary function in patients with mild COPD compared to moderate or severe cases. Therefore, the exercise capacity of patients with mild COPD should be estimated by the ISWT.

Key words

chronic obstructive pulmonary disease; exercise test; incremental shuttle walk test; health status; respiratory function tests

Abbreviations List

ISWT: incremental shuttle walk test

SGRQ: St George's Respiratory Questionnaire

1 Introduction

Exercise testing is useful to assess the degree of disability, survival prognosis, presence of exercise-induced hypoxemia, and response to treatment in patients with chronic obstructive pulmonary disease (COPD) [1]. Field walk tests are simpler to perform than other exercise tests since they require less equipment and are relatively inexpensive [2]. Furthermore, field walk tests show good correlations with other progressive exercise tests such as the electrically braked bicycle ergometer [3]. A variety of field walk tests currently exist, including time-based, fixed-distance, velocity-determined, and controlled-pacing incremental tests [4]. Of note, while time-based tests, such as the 6-min walk test, depend on the motivation of the patient since they are self-paced [5], controlled-pacing incremental tests, such as an incremental shuttle walk test (ISWT), have been reported to correlate well with maximal oxygen consumption [6, 7]. Consequently, an ISWT is considered to be a more standardized test than a 6-min walk test [5].

We have previously reported that ISWT distance significantly correlated with lung function parameters, such as the forced vital capacity and forced expiratory volume in one second (FEV1), and showed a weak correlation with health status in patients with stable COPD [5]. However, other previous studies have reported that ISWT distance did not correlate with forced vital capacity and FEV1 and showed a good correlation with

health status in patients with COPD [8, 9].

We hypothesized that these conflicting results are likely influenced by differences in the severity of airflow limitation between the study patients. However, there are currently few reports in which the investigators assessed the results according to severity. Accordingly, in the present study, we examined and analyzed the correlations between ISWT distance, lung function tests, and health status in consecutive COPD patients according to the severity of air flow limitation.

2 Patients and methods

2.1 Patients

This study was a retrospective study of 277 consecutive patients with stable COPD who visited the outpatient clinic of Shinshu University Hospital from 2007 to 2013. We concurrently examined ISWT, pulmonary function tests, and health status using St George's Respiratory Questionnaire (SGRQ). COPD was diagnosed in accordance with the Global Initiative for Chronic Obstructive Lung Disease guidelines [10]. Patients with a history of long-term oxygen therapy, respiratory tract infection, or exacerbation during the preceding 3 months, and those with ischemic heart disease or locomotor problems were excluded. In contrast, patients under COPD treatment and/or pulmonary rehabilitation were not excluded. The patients were divided into 3 groups according to

severity of airflow limitation: mild (FEV_1 ≥80% predicted), moderate (FEV_1 ≥50% to 80% predicted), and severe groups (FEV_1 < 50% predicted). This study was approved by the institutional research ethics committee of Shinshu University School of Medicine (No. 3083) on January 5, 2015.

2.2 Pulmonary function tests

Spirometry, lung volume, and diffusion capacity for carbon monoxide (DL_{CO}) were measured using Chestac-8800 (Chest Co. Ltd, Tokyo, Japan) in accordance with the American Thoracic Society protocol [11]. The functional residual capacity (FRC) was measured using a gas-dilution method, in which the subject immediately inspired to total lung capacity (TLC) and expired maximally to residual volume (RV), allowing calculation of the lung volume and RV/TLC ratio. DL_{CO} was measured using the single-breath method.

2.3 Health status

Health status was assessed using the Japanese version of SGRQ, which consists of 76 items and calculates 3 component scores (symptoms, activity, and impact) and a total score. The symptom component contains items related to symptomatology, including frequency of cough, sputum production, wheezing, and breathlessness. The activity

component is concerned with physical activities that either cause or are limited by breathlessness. The impact component covers factors such as employment, being in control of one's health, panic episodes, medication needs and side effects, and disturbance of daily life activities. Each score ranges from 0 to 100, with a score of 100 indicating maximum disability [12]. The Japanese version of the SGRQ is a valid and reliable measure of impaired health in COPD [13].

2.4 Incremental shuttle walk test

The ISWT was performed according to a previously reported method [6]. In summary, the patient walked up and down a 10-m course. The walking speed was defined by an audio signal and was increased every minute by a small increment, which meant that the patient was required to walk at a progressively faster pace. The test ended if the patient was too breathless to maintain the required speed, or if the investigator assessed that the patient failed to complete a shuttle in the time allowed. Oxygen saturation (SpO_2) and pulse rate were continuously monitored. Before and after the test, SpO_2, pulse rate, respiration rate, and blood pressure were measured, and dyspnea was rated using the modified Borg breathlessness scale.

2.5 Statistical analysis

The data distributions of variables for all groups were first assessed using a goodness-of-fit test. When data for variables showed a normal distribution, the 3 groups were compared using a one-way analysis of variance. When data for variables did not show a normal distribution, variables among the 3 groups were compared using Dunnett's test. Sex distribution differences among the 3 groups were compared using a Chi-square test. Simple correlations between ISWT distance and various parameters were examined using Pearson's correlation coefficient. An absolute value of the correlation coefficient equal to 0.40 or above was considered a strong correlation, while values between 0.20 and 0.40 were considered to indicate a weak correlation. Multiple regression analysis was used to identify the factors that were most strongly and independently related to ISWT distance. All variables with a p-value of < 0.15 in the univariate analyses were entered in the regression model. For all analyses, a p value of < 0.05 was considered statistically significant.

3 Results

3.1 Patient details

Patient characteristics are shown in Table 1. Among the 277 patients, 85 (2 women), 136 (3 women), and 56 patients (3 women) were classified into the mild, moderate, and severe groups, respectively. Some of the patients were recruited from our previous study

[7]. The age was significantly higher and the body weight and body mass index (BMI) were significantly lower in the severe group compared to the mild and moderate groups.

The pulmonary function values and mean SGRQ scores of the study patients are shown in Table 2. Although VC (%predicted) was significantly lower in the severe group than in the mild and moderate groups, VC (%predicted) was within the normal range in all groups. Pulmonary hyperinflation occurred in all groups, as determined by increases in RV (%predicted) and RV/TLC. RV and RV/TLC were significantly higher, whereas DL_{CO} was significantly lower, in the severe group compared to the mild and moderate groups. The mean SGRQ symptom, activity, impact, and total scores in the severe group were significantly higher than those in the mild and moderate groups.

ISWT results are also shown in Table 2. Walking distance, pre SpO_2, and post SpO_2 were significantly lower in the severe group compared to the mild and moderate groups.

3.2 Relationship between ISWT distance and pulmonary function or health status (Table 3)

The relationships between ISWT distance and pulmonary function parameters or SGRQ scores are shown in Table 3. In all patients, ISWT distance showed significantly strong negative correlations with SGRQ activity, impact, and total scores; significantly weak positive correlations with VC (%predicted), FEV_1 (%predicted), TLC

(%predicted), and DL_{CO} (%predicted); and significantly weak negative correlations with RV/TLC ratio and SGRQ symptom score. In the mild group, ISWT distance showed a significantly strong positive correlation with DL_{CO} (%predicted) and a significantly weak negative correlation with SGRQ activity score. In the moderate group, ISWT distance showed a significantly strong negative correlation with SGRQ activity score; significantly weak positive correlations with VC (%predicted), RV (%predicted), TLC (%predicted), and DL_{CO} (%predicted); and significantly weak negative correlations with RV/TLC, SGRQ symptom score, SGRQ impact score, and SGRQ total score. In the severe group, ISWT distance showed significantly strong positive correlations with VC (%predicted) and FEV_1 (%predicted), significantly strong negative correlations with all SGRQ components, a significantly weak positive correlation with DL_{CO} (%predicted), and a significantly weak negative correlation with RV/TLC ratio.

In the multiple stepwise regression analysis, DL_{CO} (%predicted) and SGRQ activity score were found to be independently associated with ISWT distance in the mild group; RV (%predicted), RV/TLC, DLCO (%predicted) and SGRQ activity score were independently associated with ISWT distance in the moderate group; and FEV1 (%predicted), FRC (%predicted), and SGRQ total score were independently associated with ISWT distance in the severe group (Table 4).

4 Discussion

In this study, patients in the severe group had lower body weight, BMI, and DL_{CO} than patients in the mild and moderate groups. A previous report showed that severe COPD is more frequently associated with nutritional abnormalities [14], which have been reported to be caused by increased calorie consumption of respiratory muscles, elevated inflammatory cytokine levels [15], reduced leptin secretion [16], and elevated ghrelin secretion [17]. Moreover, another report showed that low BMI was an independent risk factor for mortality in COPD patients [18]. Thus, nutritional therapy is important, especially in patients with severe COPD.

The purposes of a health status assessment are to perform interpatient comparisons, to assess treatment effects, and to estimate the prognosis of the patients [19]. Hence, assessment of health status in COPD patients is very important. In this study, all SGRQ component (symptom, activity, and impact) scores were lower in the severe group than in the mild and moderate groups, similar to previous reports [20, 21].

In this study, the mean ISWT distances in the mild, moderate, and severe groups were 420.7, 415.9, and 313.8 m, respectively. The ISWT distance in the severe group was significantly lower than in the mild and moderate groups. These results suggest that exercise capacity measured by ISWT was not reduced in the mild and moderate groups, but only in the severe group. Although some studies have examined the ISWT distance

of COPD patients, there are currently few reports on the ISWT distance of patients with mild COPD [22]. In the present study, the ISWT distance of mild COPD patients was found to be almost similar to that of moderate COPD patients.

Importantly, our results suggested that the ISWT may better reflect pulmonary function in patients with severe or moderate COPD compared to mild COPD patients. In particular, FEV_1 (%predicted) correlated with ISWT distance only in the severe group. Differences in FEV_1 between each individual patient were not considered to influence ISWT distance since pulmonary function impairment was small in the mild and moderate groups. On the other hand, a study by Chin et al. reported that exercise capacity assessed by an electronically braked cycle ergometer reached its physiologic limit in mild COPD at a lower peak work rate and ventilation than in healthy participants [23]. In our study, healthy individuals were not recruited, so we need to compare the results between healthy individuals and COPD patients in the future.

Furthermore, the RV/TLC ratio showed a correlation with ISWT distance in the moderate and severe groups. The RV/TLC ratio is an indicator of hyperinflation and the exercise capacity is reduced by dynamic hyperinflation in COPD patients [24]. Moreover, DL_{CO} (%predicted) also correlated with ISWT distance in all groups. A previous study showed similar results, and indicated that DL_{CO} (%predicted) was a good indicator of exercise capacity measured by the ISWT [25].

Moreover, the correlation between the SGRQ and ISWT distance gradually increased along with COPD severity in this study. Of note, the SGRQ activity score showed correlations with ISWT distance in all groups since it involves the physical activities of the patients. In the severe group, exercise capacity and health status were greatly impaired as a result of the remarkable pulmonary function impairment. Consequently, ISWT distance and SGRQ scores showed a good correlation. Conversely, in the mild group, differences in ISWT distance did not greatly influence SGRQ scores, since the exercise capacity impairment was small.

Exercise capacity and health status have been shown to significantly correlate with mortality in COPD patients, independent of FEV_1 [19]. In the present study, exercise capacity estimated by the ISWT was found to be more independent of health status and pulmonary function in patients with mild COPD compared to moderate or severe COPD. Therefore, the ISWT is suitable for estimation of exercise capacity in patients with mild COPD.

There were several limitations in the present study. First, this was a single-center trial including a relatively small number of patients, especially in the severe group. Second, as mentioned above, we did not compare healthy individuals and COPD patients. Third, we did not use the COPD assessment test (CAT) for assessment of health status. The CAT is a short simple questionnaire that is widely used in clinical

practice, even more so than the SGRQ. In 2009, a study by Jones et al. first reported the validity of the CAT for assessment of health status in COPD patients [26]. However, since this was a retrospective study and patients were recruited from 2007 to 2013, we did not use the CAT in the present study.

5 Conclusions

The findings of the present study revealed that the ISWT is more independent of health status and pulmonary function in patients with mild COPD compared to moderate or severe COPD. Therefore, the exercise capacity of patients with mild, but not moderate or severe, COPD should be estimated by the ISWT.

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7. Conflicts of interest

Keisaku Fujimoto received honoraria from Novartis Pharma K.K., GlaxoSmithKline K.K., Nippon Boehringer Ingelheim Co., Ltd., and TEIJIN Ltd.; research funding from

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Table 1. Patient characteristics

	All (n = 277)	Mild group (n = 85)	Moderate group (n = 136)	Severe group (n = 56)
Age (years)	71.3 ± 7.0	71.3 ± 6.9	70.9 ± 7.4	72.5 ± 6.1*†
Sex, n (male/female)	269/8	83/2	133/3	53/3
Height (cm)	163.7 ± 6.2	164.7 ± 6.2	163.6 ± 6.2	162.6 ± 6.3
Weight (kg)	59.1 ± 9.3	61.2 ± 8.5	60.3 ± 9.2	53.1 ± 8.4*†
BMI (kg/m^2)	22.0 ± 2.9	22.5 ± 2.8	22.4 ± 2.6	20.1 ± 2.9*†
Medication				
LAMA, n (%)	71 (25.6)	18 (21.2)	31 (22.8)	22 (39.3)
LABA, n (%)	43 (15.5)	7 (8.2)	15 (11.0)	21 (37.5)
ICS, n (%)	26 (9.4)	4 (4.7)	8 (5.9)	14 (25.0)
Others, n (%)	30 (10.8)	6 (7.1)	11 (8.1)	13 (23.2)

Values are presented as the mean ± standard deviation, unless otherwise specified.

BMI: body mass index, LAMA: long-acting muscarinic antagonist, LABA: long-acting β2 agonist, ICS: inhaled corticosteroid

*$p<0.05$ vs. mild group, †$p<0.05$ vs. moderate group.

Table 2. Pulmonary function values, St George's Respiratory Questionnaire scores, and ISWT summary

	All (n = 277)	Mild group (n = 85)	Moderate group (n = 136)	Severe group (n = 56)
Pulmonary function				
VC (%predicted)	101.0 ± 17.6	114.6 ± 13.2	99.3 ± 13.5	84.2 ± 15.8*†
FEV_1 (%predicted)	68.0 ± 19.5	96.3 ± 6.6	67.4 ± 7.6#	38.1 ± 8.2*†
FEV_1/FVC	55.8 ± 10.9	63.0 ± 4.4	57.5 ± 8.2	40.8 ± 9.5*†
FRC (%predicted)	101.1 ± 20.5	102.5 ± 16.8	99.0 ± 19.3	103.8 ± 26.8
RV (%predicted)	144.2 ± 37.3	132.9 ± 27.2	140.4 ± 35.5	168.9 ± 42.5*†
TLC (%predicted)	114.0 ± 15.9	119.6 ± 12.4	111.7 ± 15.9	110.5 ± 18.4
RV/TLC (%)	41.9 ± 8.2	36.7 ± 5.2	41.7 ± 5.7	50.1 ± 9.8*†
DL_{CO} (%predicted)	63.4 ± 24.9	67.4 ± 22.5	67.1 ± 25.3	48.1 ± 21.6*†
SGRQ				
Symptoms score	35.4 ± 19.9	27.6 ± 15.4	34.1 ± 18.3	50.2 ± 21.6*†
Activity score	30.6 ± 23.7	21.2 ± 19.2	26.6 ± 19.0	54.1 ± 24.7*†
Impact score	13.8 ± 14.4	9.7 ± 11.0	11.8 ± 12.8	24.6 ± 16.9*†
Total score	24.5 ± 16.9	17.7 ± 12.1	22.5 ± 15.0	39.3 ± 18.2*†
ISWT				
Distance (m)	396.8 ± 127.0	420.7 ± 125.6	415.9 ± 118.2	313.8 ± 16.2*†
Pre SpO2 (%)	95.6 ± 1.6	96.2 ± 1.4	95.7 ± 1.4	94.7 ± 1.9*†
Post SpO2 (%)	90.7 ± 5.2	92.3 ± 3.7	91.4 ± 4.4	86.6 ± 6.6*†
Pre PR (/min)	72.9 ± 13.6	71.1 ± 12.0	73.1 ± 14.0	75.1 ± 14.8
Post PR (/min)	109.6 ± 22.9	110.6 ± 22.4	109.3 ± 22.9	108.6 ± 23.5
Pre modified BS	0 (0-3)	0 (0-3)	0 (0-3)	0.5 (0-3)
Post modified BS	4 (0-10)	3 (0-7)	4 (0-7)	5 (1-10)

Values are presented as the mean ± standard deviation, unless otherwise specified. Pre and post -modified BS are presented as the median (range).

VC: vital capacity, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, FRC: functional residual capacity, RV: residual volume, TLC: total lung

capacity, DL_{CO}: diffusion capacity for carbon monoxide, SGRQ: St George's Respiratory Questionnaire scores, ISWT: incremental shuttle walk test, SpO_2: oxygen saturation, PR: pulse rate, BS: Borg breathlessness scale.

*$p<0.05$ vs. mild group, $^{\dagger}p<0.05$ vs. moderate group.

Table 3. Correlations between ISWT distance and pulmonary function parameters or SGRQ scores

	All (n = 277)		Mild group (n = 85)		Moderate group (n = 136)		Severe group (n = 56)	
	Coefficient	p value	Coefficient	p value	Coefficient	p value	Coefficient	p value
VC (%predicted)	0.37	<0.001	0.04	0.70	0.30	<0.001	0.42	0.001
FEV_1 (%predicted)	0.30	<0.001	-0.09	0.44	0.003	0.97	0.44	<0.001
FRC (%predicted)	0.14	0.02	0.14	0.21	0.19	0.02	0.24	0.07
RV (%predicted)	-0.04	0.50	0.15	0.16	0.20	0.02	-0.12	0.38
TLC (%predicted)	0.24	<0.001	0.21	0.06	0.30	<0.001	0.18	0.18
RV/TLC	-0.32	<0.001	-0.15	0.18	-0.24	0.004	-0.29	0.03
DL_{CO} (%predicted)	0.37	<0.001	0.40	<0.001	0.27	0.002	0.32	0.02
SGRQ symptom	-0.38	<0.001	-0.04	0.71	-0.22	0.01	-0.43	<0.001
SGRQ activity	-0.50	<0.001	-0.33	0.002	-0.41	<0.001	-0.42	0.001
SGRQ impact	-0.46	<0.001	-0.17	0.10	-0.35	<0.001	-0.43	<0.001
SGRQ total	-0.47	<0.001	-0.20	0.057	-0.34	<0.001	-0.47	<0.001

ISWT: incremental shuttle walk test, SGRQ: St George's Respiratory Questionnaire, VC: vital capacity, FEV_1: forced expiratory volume in one second, FRC: functional residual volume, RV: residual volume; TLC: total lung capacity, DL_{CO}: diffusion capacity for carbon monoxide.

Table 4. Results of the multiple regression analysis of associations between ISWT distance and pulmonary function parameters or SGRQ scores

	Mild group (n = 85)		Moderate group (n = 136)		Severe group (n = 56)	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
FEV_1 (%predicted)			0.88 (-0.20 to 1.96)	0.11	4.87 (1.30 to 8.35)	0.008
FRC (%predicted)					1.03 (0.03 to 2.03)	0.04
RV (%predicted)			1.01 (0.44 to 1.71)	0.001		
TLC (%predicted)						
RV/TLC			-8.90 (-12.4 to -5.39)	<0.001		
DL_{CO} (%predicted)	1.69 (0.47 to 2.92)	0.007	0.98 (0.27 to 1.69)	0.007	0.83 (-0.42 to 2.09)	0.18
SGRQ activity	-2.61 (-5.20 to -0.02)	0.05	-1.80 (-2.72 to -0.88)	<0.001		
SGRQ total	2.59 (-1.34 to 6.51)	0.19			-1.68 (-3.33 to -0.07)	0.04
adjusted R^2	0.17		0.36		0.33	

ISWT: incremental shuttle walk test, SGRQ: St George's Respiratory Questionnaire, CI: confidence interval, FEV_1: forced expiratory volume in one second, FRC: functional residual volume, RV: residual volume; TLC: total lung capacity, DL_{CO}: diffusion capacity for carbon monoxide.