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Abstract

Background: Impaired exercise capacity is one of the most important prognostic factors for patients with chronic obstructive pulmonary disease (COPD). The 6-min walk test (6MWT) is a widely used method for assessing exercise capacity in patients with COPD. However, the 6MWT requires considerable effort from patients. Therefore, a less physically demanding, but also noninvasive, method is warranted. The objective of this study was to determine the predictors of the 6MWT distance (6MWD) in patients with COPD.

Methods: This retrospective observational study enrolled 133 Japanese patients with COPD. All patients underwent the 6MWT, COPD assessment test (CAT), spirometry, respiratory muscle strength evaluation, body composition assessment, and handgrip strength (HGS) measurement. We examined the associations between the 6MWD and evaluated parameters.

Results: From single regression analysis, the 6MWD was significantly correlated with age, CAT score, several spirometric measurements (e.g., percentages of forced vital capacity, forced expiratory volume in 1 s, and carbon monoxide diffusing capacity of the lungs [%DLCO]), respiratory muscle strength parameters (e.g., percentages of maximal expiratory and inspiratory pressures), skeletal muscle mass index, and HGS. In multiple regression analysis, age, CAT score, %DLCO, and HGS were independent predictors of the 6MWD. The %DLCO and HGS were strongly correlated as predictors of the 6MWD ($p < 0.001$).

Conclusions: We found that HGS was significantly correlated with the 6MWD compared with spirometric measurements or respiratory muscle strength parameters in Japanese patients with COPD, suggesting that HGS could be a simple and noninvasive predictor of the 6MWD in patients with COPD.

Keywords: handgrip strength, exercise capacity, 6-min walk test distance, pulmonary function testing, chronic obstructive pulmonary disease

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterized by persistent respiratory symptoms and airflow limitation [1]. It is estimated that COPD accounted for 3 million deaths worldwide in 2016. In 1990, COPD was ranked as the sixth leading cause of death globally, whereas, in 2016, it was ranked as the third leading cause of death [2]. Impaired exercise capacity is frequently observed in patients with COPD, and exercise capacity is an important prognostic factor in these patients [3,4].

The 6-min walk test (6MWT) is a useful method for evaluating functional exercise capacity and suitable outcomes in clinical trials [5, 6]. However, the 6MWT is sometimes limited by the patient's condition or the resources of institutions, such as general clinics. The extent of exercise limitation is generally considered to be proportional to the impairment in pulmonary function. Although pulmonary function parameters strongly correlate with the 6MWT distance (6MWD) [7], a recent report showed that respiratory muscle dysfunction also contributes to dyspnea and exercise limitation in patients with COPD [8]. In addition, peripheral muscle strength was found to be related to impaired exercise capacity in patients with COPD [9,10]. Moreover, leg fatigue symptoms were frequent causes of exercise limitation in patients with COPD and normal subjects [11]. These reports suggest the importance of muscle mass or strength in the exercise capacity of patients with COPD.

However, the correlation between muscle mass or strength and exercise capacity in patients with COPD is not well established. Thus, in this study, we examined the relationship between exercise capacity determined using the 6MWD of patients with COPD and clinical indices including muscle factors, such as respiratory muscle strength, the skeletal muscle mass index (SMI), and handgrip strength (HGS). The objective of this study was to determine the importance of muscle mass or strength in exercise limitation in patients with COPD.

2. Patients and methods

2.1. Study patients

This study retrospectively enrolled 133 Japanese patients with COPD. All patients were stable outpatients who visited the Osaka City University Hospital from September 2015 to August 2018. COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines as a spirometry result of forced expiratory volume in 1 s (FEV1) / forced vital capacity (FVC) < 0.7 after bronchodilator inhalation in adults aged > 40 years. The degree of airflow limitation was classified as follows: GOLD I, %FEV1 ≥ 80%; GOLD II, 80% > %FEV1 ≥ 50%; and GOLD III–IV, 50% > %FEV1 [12]. The patients regularly visited our hospital and adhered to treatment. They had not experienced acute exacerbation or respiratory infection for at least 8 weeks. We excluded patients with disabilities who could not perform the 6MWT, such as those with orthopedic diseases or clinical heart failure.

All patients underwent the 6MWT, COPD assessment test (CAT), spirometry, respiratory muscle strength evaluation (maximal expiratory [PEmax] and inspiratory [PImax] pressures), body composition assessment, and HGS measurement. All patients provided written informed consent for participation. This study was approved by the by the Institutional Review Board of Osaka City University (approval numbers, 3237 [September 29, 2015], 3330 [February 2, 2016]). All procedures were performed according to the guidelines of the Declaration of Helsinki.

2.2. 6MWT

The 6MWT was performed in accordance with international guidelines [6]. Patients were instructed to walk in a 30-m corridor for 6 min while receiving standard encouragement. Patient heart rate and oxygen saturation, as well as dyspnea and fatigue (measured using the modified Borg scale) [13], were assessed before, during, and after each test. The 6MWD was used for analysis.

2.3. CAT

To investigate patient symptomatology, the CAT questionnaire (validated Japanese version) was applied during an interview [14]. The questionnaire includes questions about the following eight items: cough, catarrh, chest tightness, dyspnea, limitations in home-based activities, confidence in leaving home, sleep, and energy. For each item, the respondent chooses only one option, with a score ranging from 0 to 5, where 0 corresponds to the absence of symptoms and 5 to the maximum perception of symptoms. The final score is the sum of all items, which varies from 0 to 40, with higher values reflecting greater perception of COPD symptoms.

2.4. Pulmonary function testing (spirometry)

All patients underwent pulmonary function testing. The FVC, FEV1, %FEV1 (FEV1/FVC), and carbon monoxide diffusing capacity of the lungs (DLCO) were measured using a spirometer (CHESTAC-8900; Chest M.I., Inc., Tokyo, Japan). All tests were performed in accordance with American Thoracic Society and European Respiratory Society guidelines [15].

2.5. Measurements of respiratory muscle strength

All patients underwent measurements of the percentages of PEmax (%PEmax) and PImax (%PImax). These variables were measured according to the Black and Hyatt method, which was modified using a spirometer (HI-801; Chest Co., Ltd., Tokyo, Japan) [16]. The PEmax was measured at near total lung capacity after a maximal inspiration, whereas the PImax was measured from the residual volume after a maximal expiration. Patients performed at least two attempts, and the highest value was taken.

2.6. Body composition assessment

Analyses of body composition parameters, including body height, weight, the body mass index (BMI), skeletal muscle mass (SMM), and the SMI, were performed using bioelectrical impedance analysis (InBody 3.0 System Analyzer; Biospace Co., Ltd., Seoul, South Korea). The SMI was calculated as SMI (kg/m^2) = SMM (kg) / $height^2$ (m^2).

2.7. HGS measurement

HGS was measured with a Smedley hand dynamometer (Matsumiya Medical Products Co., Ltd., Tokyo, Japan). Peak HGS (kilogram-force, kgf) was bilaterally assessed with the elbow straight and underarm and wrist in a neutral position. The mean of the right and left peak HGS was used for analysis.

2.8. Statistical analysis

Single and multiple regression analyses were used to identify factors affecting the 6MWD. Multiple regression analysis assessed patient age, CAT score, %FVC, %FEV1, %DLCO, %PEmax, %PImax, SMI, and HGS. Statistical analyses were performed using JMP version 10.0.0 software for Windows (SAS Institute, Cary, NC, USA). For all statistical analyses, $p < 0.05$ was considered significant.

3. Results

3.1. Characteristics of the patients

The characteristics of the 133 Japanese patients with COPD who completed the 6MWT, CAT, spirometry, respiratory muscle strength evaluation, body composition test, and HGS measurement are shown in Table 1. This study included 116 men and 17 women with stable COPD. The mean patient age was 71.7 ± 9.3 years. All patients were ex-smokers with a history of smoking 55.2 ± 32.5 pack-years of cigarettes on average. The percentages of patients classified as GOLD I, GOLD II, or GOLD III–IV were 33.8, 44.4, and 21.8%, respectively. The percentages of inhalants with a long-acting muscarinic antagonist (LAMA) alone, long-acting β_2-agonist (LABA) alone, LAMA and LABA, inhaled corticosteroid (ICS) and LABA, or LAMA, LABA, and ICS were 22.6, 4.5, 24.1, 3.8, and 13.5%, respectively.

3.2. HGS measurement and relationship between the 6MWD and other factors

HGS was measured in all patients. Regarding GOLD stage COPD severity, the mean HGS of GOLD III–IV patients (25.7 ± 8.4 kgf) was significantly decreased compared with that of GOLD I patients (31.6 ± 7.9 kgf; $p < 0.05$).

With single regression analysis, the 6MWD was significantly associated with patient age ($R^2 = 0.19$, $p < 0.001$), CAT score ($R^2 = 0.13$, $p < 0.001$), %FVC ($R^2 = 0.17$, $p < 0.001$), %FEV1 ($R^2 = 0.23$, $p < 0.001$), %DLCO ($R^2 = 0.23$, $p < 0.001$), respiratory muscle strength measurements, such as the %PEmax ($R^2 = 0.11$, $p < 0.001$) and %PImax ($R^2 = 0.05$, $p < 0.05$), SMI ($R^2 = 0.11$, $p < 0.001$), and HGS ($R^2 = 0.33$, $p < 0.001$) (Fig. 1A-I). With multiple regression analysis, patient %DLCO, HGS, age, CAT score, and %FEV1 were significant determinants of the 6MWD, in that order (Table 2). The parameter with the strongest correlation with the 6MWD was the %DLCO, followed by HGS. Significant correlations of the 6MWD with respiratory muscle strength and the SMI with single regression analysis disappeared with multiple regression analysis.

4. Discussion

In this study, we showed through multiple regression analysis that patient %DLCO, HGS, age, CAT score, and %FEV1 were significantly correlated with the 6MWD. Interestingly, we found that the %DLCO and HGS were the first and second most correlated factors with the 6MWD, respectively. The %DLCO is correlated with hypoxemia and exercise intolerance. As expected, the %DLCO had the strongest correlation with the 6MWD. However, the %DLCO can be difficult to measure at some institutions, particularly in clinics, whereas HGS can be measured at any institution without using special equipment.

Our results also confirmed that pulmonary function parameters, such as the %FVC and %FEV1, significantly correlated with the 6MWD in patients with COPD in single regression analysis. The respiration-circulation-muscle axis is essential for physical activity, and ventilation (e.g., %FVC and %FEV1) and diffusion (e.g., %DLCO) parameters are expected to have significant correlations with exercise capacity. However, of the pulmonary function parameters examined, only the %FEV1 and %DLCO were associated with the 6MWD in multiple regression analysis. The ventilation parameters %FVC and %FEV1 closely correlated with and could confound each other. In this study, we showed that the %DLCO was most strongly correlated with the 6MWD. The correlation between the 6MWD and %DLCO has been previously reported [17]. Moreover, our results are consistent with those of a recent report showing that oxygen uptake kinetic parameters were associated with the 6MWD [18]. The functional exercise capacity of patients with COPD deteriorates in a linear fashion with disease severity assessed using GOLD staging criteria based on the %FEV1 [19]. Furthermore, previous researchers have reported that 6MWD decline was greater in patients with COPD who had more severe airflow obstruction [7,20]. Thus, the 6MWD seems to be more closely correlated with the %FEV1, rather than the %FVC. Our findings concerning the relationship between the 6MWD and age or CAT score were also consistent with those of previous reports [21,22].

Correlations between the 6MWD and %PEmax or %PImax were not observed with multiple regression analysis. Some studies have shown a significant correlation between respiratory muscle function and the 6MWD [9,23], whereas other studies have reported that impaired respiratory muscle function in patients with COPD did not affect exercise capacity [24]. Despite significantly higher PImax improvement in an inspiratory muscle training (IMT) group, a significant benefit for dyspnea from IMT was not seen with IMT combined with a pulmonary rehabilitation program (PRP) compared with the PRP alone [25]. Because of these positive and negative studies, the relationship between respiratory muscle strength and the 6MWD remains unclear. Moreover, respiratory muscle strength may be affected by other factors.

Although some studies have reported an association between HGS and the 6MWD in healthy adults, few reports have examined the relationship between HGS and the 6MWD in Asian, particularly Japanese, patients with COPD. Japanese patients with COPD differ from those in western countries. For example, Japanese patients with COPD tend to be older, have a lower BMI, and suffer from emphysema-dominant lung disease [26,27]. Therefore, evaluating the relationship between HGS and the 6MWD in Japanese patients is warranted. Moreover, when the 6MWD cannot be measured because of patient- or institution-specific factors, a simpler, but also noninvasive, predictor of exercise capacity other than the 6MWT is needed. Interestingly, our multiple regression analysis found that, except for the %DLCO, HGS was more closely correlated with the 6MWD than the other factors examined. Moreover, the SMI was not correlated with the 6MWD. A previous study reported that lower limb muscle strength was significantly and positively correlated with maximum walking speed, whereas lower limb muscle mass was not significantly correlated with maximum walking speed [28]. Furthermore, lower limb muscle strength is an important factor that contributes to the 6MWD in patients with COPD [9,10], suggesting that muscle strength may be more important than muscle mass for exercise capacity. Although these studies did not describe a detailed mechanism, based on the present clinical literature, HGS, which is also significantly correlated with general muscle strength, might serve as a predictor of the 6MWD [29-33]. Moreover, three recent studies on the relationship between HGS and various clinical indices have provided relevant findings. In one study, HGS was more strongly related to clinical state and prognosis in patients with COPD than the 6MWD [34]. Moreover, HGS has been shown to have a stronger correlation with quality of life, including activities of daily living, in patients with COPD compared with those without COPD, but it was not associated with the degree of air flow limitation in the COPD group [35]. Another study found that HGS may be a good predictor of mechanical ventilation duration, extubation outcomes, intensive care unit mortality, and prognosis [36]. In several clinical populations (e.g., obese or healthy elderly populations) and in Japanese cohort studies, HGS was shown to be significantly correlated with the 6MWD and physical activity [37-39]. These reports indicated that a simple and noninvasive muscle strength parameter, such as HGS, may be more important than muscle mass, respiratory muscle strength, or the degree of airflow limitation for predicting exercise capacity in patients with

COPD.

Because the measurement of HGS does not require special equipment or extra space, HGS is a more convenient, noninvasive parameter than the 6MWD or pulmonary function parameters.

This study has some limitations. The number of included patients was small. Although we excluded patients with disabilities who could not perform the 6MWT, we could not exclude patients with asymptomatic complications that could have affected the 6MWT. Because our study did not include measurements of lower limb muscle force, which is a promising predictor of the 6MWD, we could not compare HGS with upper and lower limb force. Because this was a retrospective, cross-sectional study, we did not assess the association between changes in HGS and the 6MWD or clarify underlying consequences. However, our results provide greater clinical understanding of exercise tolerance in COPD. This study was a single-institution, retrospective study; however, we plan on conducting a multicenter, prospective study in the future.

5. Conclusions

After the %DLCO, HGS was significantly and more closely correlated with the 6MWD than the other factors examined with multiple regression analysis. HGS might be an extremely useful parameter for predicting the exercise capacity of patients with COPD.

Conflict of interest

All authors have no conflicts of interest.

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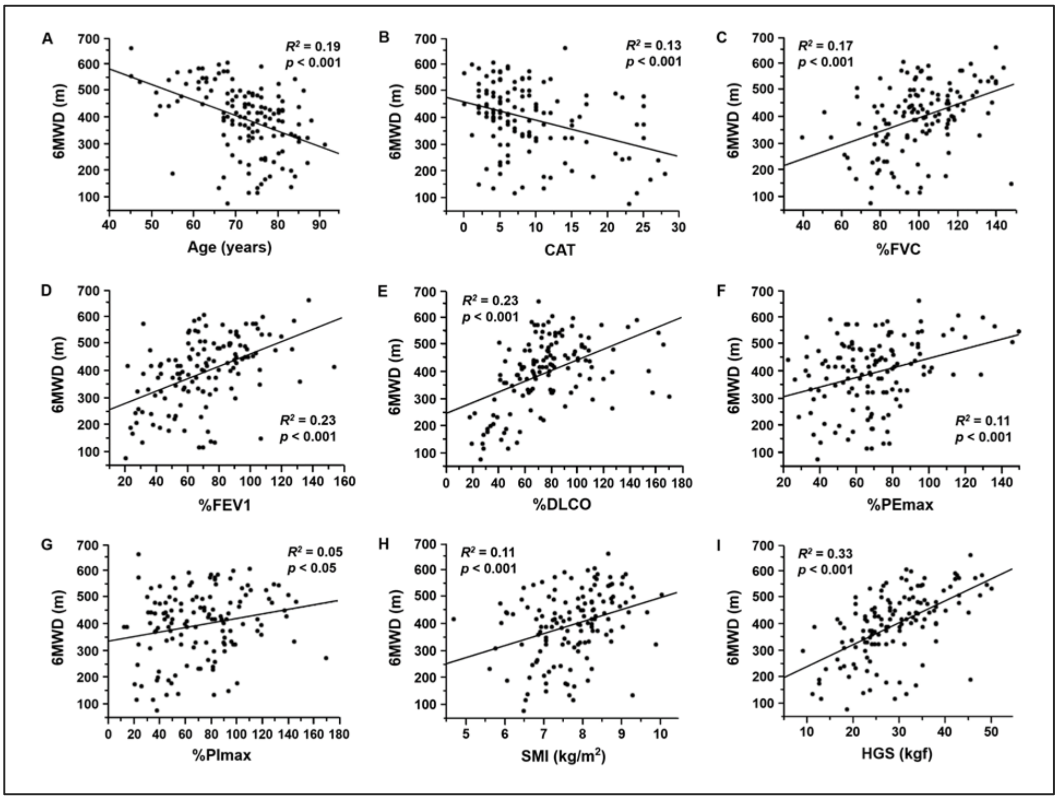
Figure captions

Fig 1. (A-I) Relationships between the 6MWD and other factors in patients with COPD from single regression analysis.



Abbreviations: 6MWD, 6-min walk test distance; CAT, chronic obstructive pulmonary disease assessment test; COPD, chronic obstructive pulmonary disease; %FVC, percentage of forced vital capacity; %FEV1, percentage of forced expiratory volume in 1 s; %DLCO, percentage of carbon monoxide diffusing capacity of the lungs; %PEmax, percentage of maximal expiratory pressure; %PImax, percentage of maximal inspiratory pressure; SMI, skeletal muscle mass index; HGS, handgrip strength.

Table 1 – Characteristics of study patients.

	COPD (n = 133)
Sex (male / female)	116 / 17
Age (years)	71.7 ± 9.3
Height (cm)	163.8 ± 8.1
BMI (kg/m^2)	22.6 ± 3.5
Smoking history (pack-years)	55.2 ± 32.5
CAT	8.91 ± 6.63
FVC (L)	3.29 ± 0.94
%FVC	99.6 ± 20.5
FEV1 (L)	1.84 ± 0.80
%FEV1	70.5 ± 26.5
GOLD stage I	45
GOLD stage II	59
GOLD stage III	21
GOLD stage IV	8
%DLCO	75.4 ± 30.8
%PEmax	69.3 ± 24.2
%PImax	71.5 ± 32.3
SMI (kg/m^2)	7.72 ± 0.94
HGS (kgf)	28.8 ± 8.8
Percentages of inhalation at evaluation	
None (%)	31.6
LAMA alone (%)	22.6
LABA alone (%)	4.5
LAMA + LABA (%)	24.1
ICS + LABA (%)	3.8
LAMA + LABA + ICS (%)	13.5

Data shown as mean ± standard deviation**.** COPD, chronic obstructive pulmonary disease; BMI, body mass index; CAT, COPD assessment test; FVC, forced vital capacity; %FVC, percentage of forced vital capacity; FEV1, forced expiratory volume in 1 s; %FEV1, percentage of forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; %DLCO, percentage of carbon monoxide diffusing capacity of the lungs; %PEmax, percentage of maximal expiratory pressure; %PImax, percentage of maximal inspiratory pressure; SMI, skeletal muscle mass index; HGS, handgrip strength; LAMA, long-acting muscarinic antagonist; LABA, long-acting β_2-agonist; ICS, inhaled corticosteroid.

Table 2 – Multiple regression analysis

	Beta*	*t*	*p*
Age (years)	-0.26	-3.60	< 0.001
CAT	-0.14	-2.24	< 0.05
%FVC	-0.05	-0.59	N.S.
%FEV1	0.21	2.42	< 0.05
%DLCO	0.35	5.66	< 0.001
%PEmax	0.04	0.64	N.S.
%PImax	0.10	1.67	N.S.
SMI (kg/m^2)	-0.04	-0.60	N.S.
HGS (kgf)	0.32	4.01	< 0.001

*Beta-standardized coefficients. CAT, chronic obstructive pulmonary disease assessment test; %FVC, percentage of forced vital capacity; %FEV1, percentage of forced expiratory volume in 1 s; %DLCO, percentage of carbon monoxide diffusing capacity of the lungs; %PEmax, percentage of maximal expiratory pressure; %PImax, percentage of maximal inspiratory pressure; SMI, skeletal muscle mass index; HGS, handgrip strength; N.S., not significant.