ORIGINAL ARTICLE

Peripheral muscle strength, dyspnea, and pulmonary function are predictors of incremental shuttle walk test distance in patients with non-tuberculous mycobacterial pulmonary disease

Kazuki Ono[1,2], Mitsuru Tabusadani[1], Satoshi Takao[1], Kosuke Mori[1,2], Yusuke Matsumura[1,2], Kazuma Kawahara[1,2], Shunya Omatsu[1,3], Yuki Toyoda[1,3] and Hideaki Senjyu[4]

1. Department of Clinical Mycobacteriology, Nagasaki University Graduate School of Biomedical Sciences
2. Respiratory Care and Rehabilitation Center, Fukujuji Hospital, Japan Anti-Tuberculosis Association
3. Department of Physical Therapy Science, Nagasaki University Graduate School of Biomedical Sciences
4. Department of Physical Therapy, Faculty of Rehabilitation, Biwako Professional University of Rehabilitation

Abstract

Background: Patients with non-tuberculous mycobacterial pulmonary disease (NTM-PD) have impaired exercise capacity and health-related quality of life (HRQOL). However, the factors that influence the reduction in exercise capacity are unclear. We investigated the associations between exercise capacity and clinical variables and predictors of exercise capacity.

Methods: In total, 150 patients with NTM-PD participated in the study. We assessed incremental shuttle walk test (ISWT), peripheral muscle strength, body mass index (BMI), disease duration, pulmonary function, dyspnea and HRQOL.

Results: The mean ISWT distance (ISWD) was 443 m. A univariate analysis showed a significant correlation between ISWD and BMI, pulmonary function, handgrip force, age, disease duration, dyspnea, and HRQOL. A multiple regression analysis showed that ISWD was significantly associated with age, pulmonary function, handgrip force, and dyspnea.

Conclusions: The present study is the first to identify the relationship between ISWD and clinical variables and predictors of ISWD in patients with NTM-PD.

Keywords: non-tuberculous mycobacteria, Mycobacterium avium complex, incremental shuttle walk test, exercise capacity

Introduction

Pulmonary infections caused by non-tuberculous mycobacteria (NTM) have increased worldwide in recent years [1], and *Mycobacterium avium* complex (MAC) is the most common NTM infection [2]. The main symptoms of NTM pulmonary disease (NTM-PD) are cough, sputum production, fatigue, dyspnea, fever, hemoptysis, weight loss, anxiety, and depression [3, 4]. Patients with NTM-PD are classified as nodular bronchiectatic or fibrocavitary based on imaging findings [3]. Among middle-aged women, nodular bronchiectatic MAC is common [5]. The mainstay of treatment for NTMPD is long-term multidrug therapy, but recurrence after treatment is common and cures are difficult [3]. Therefore, alternative treatment goals such as improvement of symptoms and HRQOL have been suggested [6].

Pulmonary rehabilitation is a component of the treatment for chronic respiratory diseases, such as bronchiectasis, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD). Moreover, evidence to support the use of pulmonary rehabilitation for these diseases has been proposed [7–9]. In a review of nonpharmaco-

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*Corresponding Author: Hideaki Senjyu
E-mail: senjyu@nagasaki-u.ac.jp

logical treatment for patients with NTMPD, pulmonary rehabilitation, including airway clearance and exercise training, has been recommended [10]. However, the only evidence to support chest physical therapy for NTM-PD is that airway clearance improves cough symptoms [11]. The effect of pulmonary rehabilitation for NTM-PD has not been elucidated.

An assessment of functional exercise capacity using the six-minute walk test or the incremental shuttle walk test (ISWT) is commonly undertaken in patients with chronic respiratory diseases, such as bronchiectasis, COPD, and ILD, to evaluate the effects of treatment, such as pulmonary rehabilitation [12]. In this patient population, predictors of exercise capacity include peripheral muscle strength, pulmonary function, dyspnea, and physical activity [13–15]. Exercise capacity is also associated with mortality, health-related quality of life (HRQOL), and exacerbation; thus, exercise capacity is an important clinical assessment [16].

Patients with NTM-PD have a higher prevalence of anxiety and depression [4], as well as a lower HRQOL and exercise capacity [17]. A significant association between exercise capacity and HRQOL has also been reported in patients with pulmonary MAC [18]. However, the factors that influence the decline in exercise capacity are unclear. The aim of this study was to determine the cause of the decrease in exercise capacity in patients with NTM-PD.

Methods

Participants and study design

This was a cross-sectional study. Patients were recruited from the Respiratory Care and Rehabilitation Center, Fukujuji Hospital, Japan Anti-Tuberculosis Association, Tokyo, Japan, from April 2016 to September 2020. All patients satisfied the American Thoracic Society/Infectious Diseases Society of America diagnostic criteria for NTM-PD [3] and underwent pulmonary rehabilitation in hospital. We excluded 87 patients who did not complete all evaluations and 3 patients over 80 years of age. The present study was approved by the Fukujuji Hospital Institutional Review Board (number: 19011, 19020).

Clinical variables

Demographic data, including age, body mass index (BMI), smoking history, disease duration, comorbidities and laboratory data were collected from medical charts. Imaging findings were classified into four patterns based on chest high-resolution computed tomography findings: non-cavitary nodular bronchiectatic type, cavitary nodular bronchiectatic type, fibrocavitary type, and unclassifiable type [19].

Sputum acid-fast bacillus smears and mycobacterial cultures were performed in accordance with standard methods. In the smear test, we investigated the maximum amount of smear confirmed by the last three sputum tests immediately before the evaluation date. Chronic colonization of other bacteria was defined as two or more positive sputum cultures of the same species in the previous year.

Pulmonary function

Pulmonary function was measured using an electronic spirometer (CHEST AC-8800; Chest, Tokyo, Japan) when the patient was in a stable condition. Pulmonary function was measured using a spirometer in accordance with published guidelines [20]. Pulmonary function test data were examined for forced expiratory volume in 1 second (FEV_1), percentage predicted FEV_1 (%FEV_1), vital capacity (VC), percentage predicted VC (%VC), and FEV_1/forced vital capacity (FVC).

Dyspnea

The modified Medical Research Council Dyspnea Scale (mMRC) was used to evaluate dyspnea perception. This scale ranges from 0 to 4 with higher scores representing greater functional limitations due to dyspnea [21].

Peripheral muscle strength

Quadriceps force (QF) was evaluated as the peak force developed during a maximal isometric knee extension maneuver, using a hand-held dynamometer with a fixing belt (μ-Tas F-1; Anima Corporation, Tokyo, Japan) with a standard protocol [22]. The QF of the dominant side was tested in the sitting position with the hip and knee joint flexed at approximately 90°. The highest value of at least three maneuvers was recorded and expressed in kilogram force (kgf). The handgrip force (HF) of the dominant hand was assessed using a dynamometer (Smedley's hand dynamometer; MIS TOKYO, Tokyo, Japan). The HF was tested in the standing position with the elbow extended. The highest value of two attempts was recorded in kilograms (kg). Percent predicted QF (%QF) and HF (%HF) values were calculated using predictive equations for isometric peripheral muscle strength [23].

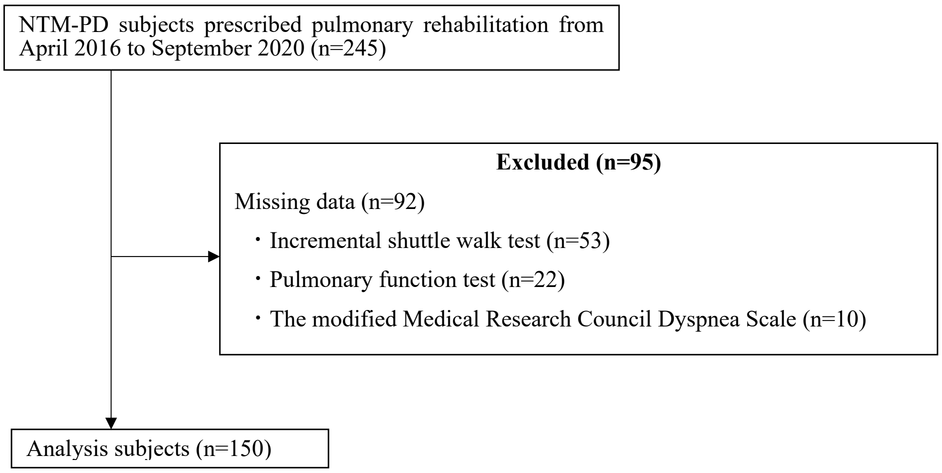

Fig. 1 Flow chart from subject recruitment to study completion

Exercise capacity

Functional exercise capacity was assessed using the ISWT and carried out in accordance with a standardized protocol [24]. This is a threshold symptomatic field test carried out on a 10-m course with the walking speed dictated by an audio signal. The test is continuous and incremental with the speed increasing each minute. The distance walked (ISWD) was recorded in meters and expressed as a percentage of predicted Japanese data [25].

HRQOL

HRQOL was assessed using the Japanese version of the chronic obstructive pulmonary disease assessment test (CAT). The CAT comprises eight items: cough, sputum, chest tightness, exercise tolerance, ability to perform activities of daily living, confidence in leaving the home, sleep, and energy levels. Each question is scored on a six-point scale (0–5) yielding a total possible score that ranges from 0 (best possible health) to 40 (worst possible health) [26]. The CAT is informative in patients with NTM-PD [27].

Statistical analysis

Statistical analyses were performed using SPSS software version 25 (IBM Corp., Armonk, NY, USA). Data are expressed as mean ± SD for continuous variables and number (percentage) for categorical variables. The distribution of data was assessed using the Shapiro-Wilk test. Associations between ISWD and clinical variables (age, BMI, disease duration, pack year, $\%FEV_1$, %VC, mMRC, CAT, semiquantitative smear score and peripheral muscle strength) were assessed using Pearson's or Spearman's correlation analyses. A stepwise multiple linear regression analysis was performed to determine factors affecting ISWD. Only the variables that showed a significant correlation with ISWD in the univariate analysis (age, BMI, disease duration, $\%FEV_1$, %VC, mMRC, CAT and %HF) were used in the model. A P value of <0.05 was considered statistically significant.

Results

In total, 150 patients with NTM-PD participated in the study (**Fig. 1**). The mean age of patients was 65 years. The clinical characteristics of subjects are shown in **Table 1**.

The mean ISWD was 443 m (**Table 2**). All patients failed to complete the test due to inability to maintain the required speed. On average, patients reached 88% of their percentage predicted ISWD (%ISWD). QF and HF were 109% and 91% of the predicted values, respectively.

The univariate analysis showed a significant positive correlation between %ISWD and BMI, $\%FEV_1$, %VC and %HF, and a significant negative correlation between %ISWD and age, disease duration, mMRC, and CAT (**Table 3**).

The results of the regression analysis are shown in **Table 4**. Age, %HF, %VC, and mMRC were identified as independent predictors of %ISWD.

Discussion

Percent ISWD showed a significant positive correlation with BMI, %VC, $\%FEV_1$, and %HF, and a significant negative correlation with age, disease duration, mMRC, and CAT. Furthermore, age, %HF, %VC and mMRC were

Table 1 Clinical characteristics of the 150 patients with NTM-PD

Variables	
Age, years	65.0 ± 8.4
Male/Female	8 (5.3)/142 (94.7)
Body mass index, kg/m^2	18.6 ± 2.7
Disease duration, years	6.6 ± 5.8
Smoking history	22 (14.7)
Pack years	2.0 ± 8.3
FEV_1, L	1.6 ± 0.5
FEV_1 % predicted, %	77.8 ± 20.8
FEV_1/FVC<70%	21 (14.0)
VC, L	2.0 ± 0.6
VC % predicted, %	75.3 ± 18.9
%VC<80%	84 (56.0)
mMRC, grade 0/1/2/3/4	76 (50.7)/53 (35.3)/19 (12.7)/2 (1.3)/0 (0)
CAT, median (interquartile range)	13 (7–21)
Radiological pattern	
NC-NB/FC/C-NB/unclassified	67 (44.7)/27 (18.0)/55 (36.6) /1 (0.7)
NTM species	
MAC	98 (65.3)
M. abscessus complex	45 (30.0)
MAC + *M. abscessus complex*	4 (2.7)
M. lentiflavum	2 (1.3)
MAC + *M. lentiflavum*	1 (0.7)
Semiquantitative smear score	
-/±/+1/+2/+3	45 (30.0)/34 (22.7)/35 (23.3)/22 (14.7)/14 (9.3)
Underlying pulmonary disease	
Old pulmonary tuberculosis	8 (5.3)
Bronchial Asthma	4 (2.7)
ILD	2 (1.3)
Chronic colonization	
Aspergillus	4 (2.7)
Pneudomonas aeruginosa	8 (5.3)
Staphylococcus aureus	12 (8)
other	11 (7.3)
CRP, mg/dl	1.0 ± 2.0
Albumin, g/dl	3.8 ± 0.5
Lymphocytes,/µl	1327 ± 462

Data expressed as mean ± SD or number (%).
Abbreviations: NTM-PD, non-tuberculous mycobacterial pulmonary disease; FEV1, forced expiratory volume in 1 second; VC, vital capacity; FVC, forced vital capacity; mMRC, modified Medical Research Council dyspnea scale; CAT, chronic obstructive pulmonary disease assessment test; NC-NB, non-cavitary nodular bronchiectatic type; FC, fibrocavitary type; C-NB, cavitary nodular bronchiectatic type; NTM, Nontuberculous mycobacteria; MAC, *Mycobacterium avium* complex; ILD, interstitial lung disease; CRP, C-reactive protein.

Table 2 Incremental shuttle walk test and peripheral muscle strength

Variables		
ISWD, m		443 ± 134
%ISWD, %		87.5 ± 22.8
Borg scale*		
Dyspnea	Initial point	0 (0–0.5)
	Final point	4 (3–5)
Leg fatigue	Initial point	0 (0–0)
	Final point	3 (1–4)
QF, kgf		23.4 ± 6.9
%QF, %		109.1 ± 29.8
HF, kg		21.6 ± 6.3
%HF, %		90.5 ± 20.2

Data expressed as mean ± SD or median(interquartile range)
Abbreviations: ISWD, incremental shuttle walk test distance; %ISWD, percentage predicted ISWD; QF, quadriceps force; %QF, percentage predicted QF; HF, handgrip force; %HF, percentage predicted HF.

Table 3 Univariate analysis of the variables and the %ISWD

variable	r	p
Age*	-0.59	<0.001
BMI†	0.19	0.019
Disease duration*	-0.22	0.010
$\%FEV_1$†	0.34	<0.001
%VC†	0.38	<0.001
mMRC*	-0.45	<0.001
CAT*	-0.21	0.009
%HF*	0.36	<0.001

*Spearman r; †Pearson r.
Abbreviations: %ISWD, percentage predicted incremental shuttle walk test distance; BMI, body mass index; $\%FEV_1$, percentage predicted forced expiratory volume in 1 second; %VC, percentage predicted vital capacity; mMRC, modified Medical Research Council dyspnea scale; CAT, chronic obstructive pulmonary disease assessment test; %HF, percentage predicted handgrip force.

independent predictors of %ISWD. To our knowledge, the present study is the first to identify a relationship between %ISWD and clinical variables, including pulmonary function and peripheral muscle strength in patients with NTM-PD. It is also the first study to describe %ISWD predictors.

In previous studies, decreased exercise capacity in bronchiectasis was reported [28, 29]. In the present study, similar results for exercise capacity in patients with NTM-PD were reported. In bronchiectasis, age, pulmonary function, and dyspnea are predictors of exercise capacity [15, 30–32]. Age is part of the prediction equation for ISWD [25] and was thus expected to influence exercise capacity. In bronchiectasis, chronic inflammation and destruction of the bronchial wall cause limited airflow. Effects on pulmonary function can be seen as obstructive, restrictive, or mixed disturbance [31]. Previous studies have indicated a significant association between percentage predicted force vital capacity and dyspnea in patients with bronchiectasis [15]. In the present study, patients with NTM-PD had a reduced %VC, which may have caused dyspnea.

In addition to age, pulmonary function, and dyspnea, muscle strength was also a predictor of exercise capacity in the present study. Peripheral muscle strength is a predictor of exercise capacity in patients with COPD and ILD [13, 14]. It was previously reported that peripheral muscle strength decrease in patients with bronchiectasis [31, 33]. In the present study, the mean %HF was 91% and 104 patients (69.3%) had muscle weakness. The mechanism of muscle weakness is still unclear in bronchiectasis, including NTM infection. Disabled oxidative capacity, alternations in muscle structure, disuse atrophy, aging, and hypoxia may be probable factors in the same way as has been demonstrated in COPD [15]. Additionally, dyspnea during daily activities could cause a sedentary lifestyle and lead to poorer physical function [15]. Although physical activity was not measured in the present study, decreased physical activity could have caused muscle weakness.

To our knowledge, the present study is the first to evaluate exercise capacity using the ISWT in patients with NTM-PD and compare standard values. Exercise capacity in patients with COPD and ILD is associated with mortality, frequency of exacerbation, and HRQOL. In patients with NTM-PD, it is unclear whether exercise capacity affects mortality and the frequency of exacerbation, but the results of the present study provide meaningful information for further studies.

In patients with bronchiectasis, COPD, and ILD, it has become clear in many clinical studies that dyspnea, muscle strength, and exercise capacity are improved by pulmonary rehabilitation [7, 8]. Yagi reported a significant correlation between exercise capacity and HRQOL

Table 4 Multiple liner regression analysis with the %ISWD as the independent variable

Independent variables	B	β	95%CI	p	Adjusted R^2
Age	-7.24	-0.45	-9.18 to -5.31	<0.001	0.530
%HF	1.79	0.27	0.99 to 2.60	<0.001	
%VC	1.46	0.20	0.53 to 2.38	0.002	
mMRC	-36.32	-0.20	-60.45 to -12.18	0.003	

Abbreviations: %ISWD, percentage predicted incremental shuttle walk test distance; B, unstandardized regression coefficient; β, standardized coefficient; CI, confidence interval; %HF, percentage predicted handgrip force; %VC, percentage predicted vital capacity; mMRC, modified Medical Research Council dyspnea scale.

in patients with pulmonary MAC disease [18]. In patients with NTM-PD, as with COPD and ILD, an improvement in exercise capacity may improve HRQOL. The results of this study indicate that it is necessary to design a protocol for rehabilitation of patients with NTM-PD and to examine its effect.

Our study has some limitations. First, the present study was a single-center study. This study enrolled patients with a comparable age to subjects in previous studies [18, 27]. However, pulmonary function, body mass index, and HRQOL were worse in the present study compared with previous studies. Therefore, the present study may have included patients with more severe disease than those in general hospitals. Second, all patients in the present study underwent pulmonary rehabilitation, which suggests that we may have targeted patients with stronger subjective symptoms or impaired physical function. It is necessary to carefully interpret whether the results of the present study can be regarded as representative for NTM-PD.

Conclusions

In conclusion, %ISWD showed a significant positive correlation with BMI, %FEV_1, %VC, and %HF, and a significant negative correlation with age, disease duration, mMRC, and CAT in patients with NTM-PD. Furthermore, age, %HF, %VC, and mMRC are independent predictors of %ISWD. The results of the present study are important to investigate the effectiveness of pulmonary rehabilitation for patients with NTM-PD.

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The authors confirm that there is no conflict of interest

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肺非結核性抗酸菌症における筋力，呼吸困難，呼吸機能は Incremental shuttle walk test の予測因子である

大野一樹[1,2]，髻谷満[1]，髙尾聡[1]，森広輔[1,2]，松村佑介[1,2]，川原一馬[1,2]，大松峻也[1,3]，豊田裕規[1,3]，千住秀明[4]

1. 長崎大学大学院　医歯薬学総合研究科　新興感染症病態制御学系専攻
2. 結核予防会複十字病院　呼吸ケアリハビリセンター
3. 長崎大学大学院　医歯薬学総合研究科　医療科学専攻
4. びわこリハビリテーション専門職大学　リハビリテーション学部　理学療法学科

要旨

背景：肺非結核性抗酸菌症（non-tuberculous mycobacterial pulmonary disease; NTM-PD）患者では，運動耐容能の低下が報告されているが，その要因は不明である．本研究では，同患者における運動耐容能の関連因子および予測因子について検討した．

方法：NTM-PD 患者 150 名を対象に，Incremental shuttle walk test により運動耐容能を評価し，予測歩行距離の割合（% predicted incremental shuttle walk test distance; %ISWD）を算出した．その他の臨床指標として，Body mass index（BMI），大腿四頭筋力，握力，罹病期間，呼吸機能（%1 秒量，%肺活量），modified Medical Research Council Dyspnea Scale（mMRC），Chronic obstructive pulmonary disease assessment test（CAT）の評価を実施した．また，%ISWD と各評価項目の関連を単変量解析で検討し，%ISWD を従属変数，単変量解析で有意な相関を認めた項目を独立変数とした重回帰分析を行い，%ISWD の予測因子を検討した．

結果：平均 ISWD は 443 m，平均%ISWD は 88%であった．単変量解析では，ISWD と BMI，%肺活量，%1 秒量，%握力との間に有意な正の相関があり，年齢，罹病期間，mMRC，CAT との間には有意な負の相関が認められた．重回帰分析では，年齢，%肺活量，%握力，mMRC が%ISWD の予測因子として抽出された．

結論：NTM-PD 患者における運動耐容能の予測因子は，年齢，握力，呼吸困難，%VC が運動耐容能の予測因子であった．