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Cardiopulmonary factors affecting 6-minute walk distance in patients with idiopathic inflammatory myopathies

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Short running title: exercise capacity in inflammatory myopathies

Abstract

Idiopathic inflammatory myopathies involve skeletal muscles and can be associated with interstitial lung disease and/or heart dysfunction, which may reduce exercise capacity. We aimed to clarify cardiopulmonary factors affecting the 6-minute walk distance in patients who were able to walk without leg pain or fatigue. Twenty-three patients with inactive adult idiopathic inflammatory myopathies, and 18 age- and gender-matched healthy controls were evaluated for hemodynamic responses using noninvasive impedance cardiography during the 6-minute walk test. The patients were also examined by the pulmonary function test for forced vital capacity and diffusing capacity for carbon monoxide (DLCO), and by echocardiography for left ventricular ejection fraction. Interstitial lung disease was diagnosed in 19 patients using high-resolution computed tomography. There was no difference in 6-minute walk distance or cardiac output after walking between the patients and healthy controls. However, stroke volume during the 6-minute walk test was significantly lower in the patients than in healthy controls, suggesting malfunction in the heart. Moreover, the increased heart rate matched the cardiac output. Single regression analysis demonstrated a correlation between 6-minute walk distance and stroke volume, cardiac output and DLCO, but not left ventricular ejection fraction. Furthermore, based on the stepwise regression analysis, DLCO and cardiac output after walking affect the 6-minute walk distance. In conclusion, impaired DLCO due to interstitial lung disease was suggested to be a fundamental parameter affecting exercise capacity, in addition to heart involvement, in patients with idiopathic inflammatory myopathies.

Key words: polymyositis, dermatomyositis, exercise capacity, pulmonary function test, hemodynamic response, interstitial lung disease

Introduction

Interstitial lung disease is a common extra-muscular complication of idiopathic inflammatory myopathies, and low diffusing capacity for carbon monoxide (DLCO) is known to increase the risk of mortality [1, 2]. A recent study demonstrated that recovery of skeletal muscle strength and reduced creatine kinase levels by medication for idiopathic inflammatory myopathies may improve forced vital capacity (FVC) due to muscular strength reinforcement; however, DLCO and interstitial infiltrates on CT were not ameliorated in most cases [3]. In general, distance during the 6-minute walk test (6MWT) correlates with FVC and DLCO in patients with idiopathic pulmonary fibrosis [4]. Therefore, we hypothesized that accompanying interstitial lung disease may be a factor affecting exercise capacity in patients with idiopathic inflammatory myopathies, and examined which pulmonary function parameters affect exercise capacity.

Heart involvement in idiopathic inflammatory myopathies was also detected by cardiac magnetic resonance tomography [5] or echocardiography [6], and these findings may lead to therapeutic treatment for the cause of morbidity [7]. An increased risk of myocardial infarction or conduction abnormalities was reported in patients with idiopathic inflammatory myopathies [8]. Moreover, left ventricular diastolic dysfunction [6] and reduced left ventricular ejection fractions (EF) [5] were observed in patients regardless of the presence of myalgia, paresis, and exhaustion. Few studies have demonstrated the relationship between cardiac functions and exercise capacity in patients with idiopathic inflammatory myopathies. It may be difficult to clarify cardiac parameters likely associated with exercise capacity using conventional echocardiography,

however, when cardiac impairment was assessed by global longitudinal strain measurement, subclinical heart disease was found in up to 50% of patients [9].

Referring to other estimates for cardiac parameters, recent studies have demonstrated that impedance cardiography with real-time monitoring can noninvasively evaluate hemodynamic responses during the 6MWT (10, 11). Pulmonary hypertension patients with a normal ejection fraction had a lower stroke volume (SV) and cardiac index (CI) compared with healthy controls during walking [10], and patients with chronic obstructive disease exhibited slower responses to increasing cardiac output (CO) [11]. Moreover, the maximal CO in patients with pulmonary hypertension was observed during the 6MWT by the inert gas rebreathing method [12]. Thus, these noninvasive methods may be available for evaluation of hemodynamic responses during walking to examine the relation between exercise capacity and heart involvement in patients with idiopathic inflammatory myopathies.

In the present study, we investigated lung and cardiac function parameters related to limited exercise capacity in patients with idiopathic inflammatory myopathies. For cardiac function, we compared measurements obtained from patients and age- and gender-matched healthy controls during the 6MWT using noninvasive impedance cardiography.

Methods

Patients receiving medication for idiopathic inflammatory myopathies were recruited among patients

referred to the Rehabilitation Division of Kanazawa University Hospital between November 2014 and September 2017 for consultation on further treatments. They received muscular training, pulmonary rehabilitation, and education about activities of daily living. Exclusion criteria for this study were juvenile dermatomyositis, overlap with other connective tissue diseases, muscle weakness in the extremities of less than 4 on manual muscle testing, leg discomfort or pain during the 6MWT, and active myositis, i.e., period of increased serum creatine kinase. In total, 23 patients were assigned to this study (Table 1). On autoantibody analysis, 7 had anti-ARS (anti-Jo-1, PL-7, EJ, and OJ), 10 had anti-MDA5, 2 had anti-SRP, 3 had anti-TIF1- γ , and 1 was unknown. Interstitial lung disease was diagnosed in 19 patients by specialists of respiratory medicine using high-resolution computed tomography. The study was approved by the human ethics committee of Kanazawa University, conforming to the provisions of the Declaration of Helsinki. Written informed consent for the study was obtained from all patients and 18 healthy controls before the performance of the 6MWT.

Hemodynamic responses during the 6MWT were measured using the PhysioFlow Q-Link (Manatec Biomedical, France), which weighed 200 g and was wearable. Six disposable electrodes (BlueSensor SP, Ambu, Denmark) connecting to the equipment were placed around the chest for impedance cardiography, as previously described [10]. The 6MWT was performed following the Guidelines of the American Thoracic Society in a 30-m corridor [13]. SV, heart rate, CO, and CI were recorded at rest for autocalibration for 30 sec before the 6MWT. Subsequently, the data were automatically averaged every 10 sec during the

6MWT, and values at 6 minutes of walking were collected for analyses (Figure 1).

The clinical data of percentages of predicted FVC and DLCO (FVC% and DLCO%) from pulmonary function tests, and left ventricular EF from echocardiography was collected by reviewing the medical records of the patients. These evaluations were not performed for healthy controls, as we expected the values to be normal.

Statistics

Clinical characteristics were compared between the patients and healthy controls using the t test for numerical data, and chi-square test for gender distribution. The relation between SV at rest and that at 6 minutes was examined using Pearson correlation coefficients for all subjects. Single and stepwise regression analyses were performed for 6MWT distance and FVC%, DLCO%, EF, SV, and CO at rest and at 6 min. JMP 11.0 (SAS Institute Inc., Cary, NC) was used for statistical analysis. A p-value of < 0.05 was considered significant.

Results

There was no difference in gender distribution, age, or anthropometric measurements between patients and healthy controls. The mean DLCO% was low at 61.8% in patients, and seemed to be poorer than the mean FVC%, which was 95.4% (Table 1). The EF in patients was not impaired at $68.4 \pm 8.2\%$, mean \pm SD. The

SV, CO, and CI at rest, and SV at 6 minutes were significantly lower in patients than in healthy controls.

Patient heart rates were high, but there was no significant difference between patients and healthy controls.

The CO at 6 minutes was lower and 6MWT distance was shorter for patients, but neither difference was significant. A strong correlation between SV at rest and that at 6 minutes was observed in all subjects ($r = 0.87$, $p < 0.0001$) (Figure 2).

In the healthy controls, the 6MWT distance was correlated with CO at 6 minutes, but not with SV (Table 2). On the other hand, single regression analysis revealed a significant correlation between 6MWT distance, and DLCO% and SV at rest and at 6 minutes, and CO at 6 minutes in the patients. There was no correlation between 6MWT distance and EF. A best fit model for 6MWT distance in patients with DLCO% and CO at 6 minutes was created by stepwise regression analysis ($r^2 = 0.61$, $p = 0.02$).

Discussion

This is the first study to evaluate exercise capacity in patients with idiopathic inflammatory myopathies in relation to lung and heart function parameters. EF is a widely used parameter representing cardiac function [14], and if patients with idiopathic inflammatory myopathies have reduced EF ($< 60\%$), late gadolinium enhancement by cardiac magnetic resonance tomography is observed [5]. In this study, EF was normal in patients and there was no correlation with 6MWT distance, whereas the SV was significantly lower than that in healthy controls. Therefore, EF was unable to be used to estimate the exercise capacity in our cohort.

SV at 6 minutes in healthy controls was not correlated with 6MWT distance. It was previously reported that in healthy subjects, heart rate response contributed to CO or oxygen uptake rather than the SV response during exercise [15]. Additionally, varying response patterns in SV to exercise were previously observed in healthy subjects, but the mechanism was not clarified [16]. On the other hand, in this study, SV at rest was highly correlated with SV at 6 minutes in all subjects, and little variation in SV was noted in response to the 6MWT. Therefore, the significant deterioration in SV at rest in patients implied proportionally low SV during walking, which affected 6MWT distance. Impaired SV at rest or at 6 minutes suggests malfunction in the heart not detected by EF.

CO is known to be correlated with oxygen uptake during exercise in healthy subjects [17], and CO at 6 minutes was also correlated with 6MWT distance in healthy controls and patients on single regression analysis. As CO and CI at 6 minutes were compensated for by the increased heart rate despite lower SV in patients, the difference in 6MWT distance between patients and healthy controls was unclear. However, stepwise regression analysis supported the relationship between 6MWT distance and CO at 6 minutes, but not SV, in patients, which suggests that CO compensation during exercise influences exercise capacity.

The other variable affecting 6MWT distance was DLCO% according to the fit model for 6MWT distance in patients, and this result was considered to confirm our hypothesis that accompanying interstitial lung disease affects the exercise capacity in patients. As interstitial lung disease was diagnosed in 82% (19 of 23 patients) of the patients in this study, it may be the principal manifestation affecting exercise capacity in

our cohort. A significant relationship between DLCO and exercise capacity was previously confirmed in patients with idiopathic pulmonary fibrosis [4, 18]. In addition, DLCO better represented impairment of pulmonary gas exchange than other parameters such as PaO₂, alveolar-arterial oxygen pressure difference, and pulmonary capillary blood volume [19, 20].

FVC is another parameter on the pulmonary function test, but it was not related with 6MWT distance in the patients. For this reason, the value of FVC%, which had a mean value of 95.4%, was normal compared with DLCO%, which was 61.8%. As the patients had inactive myositis, FVC may have been recovered [3] when we evaluated them. If the patients were more impaired, the exercise capacity may have been affected, as reported for patients with idiopathic pulmonary fibrosis [4].

Regarding other factors for exercise capacity, a previous study failed to find a correlation between serum creatine kinase and peak oxygen uptake or peak isometric torque in patients with inactive idiopathic inflammatory myopathies [21]. In addition, glucocorticoids and other medications may cause muscle weakness that lasts for several weeks or years [22]. Thus, many factors should be taken into consideration when evaluating the exercise capacity in patients with idiopathic inflammatory myopathies. However, we set the exclusion criteria for this study as muscle weakness in the extremities of less than 4 on manual muscle testing and leg discomfort or pain during the 6MWT to clarify the effects of cardiopulmonary functions on exercise capacity by excluding muscle factors. If all factors, such as muscle fatigue during active myositis, were included in the analysis, a different result may have been obtained.

The limitation of this study was the extraction condition of patients mentioned above. These results cannot be extended to patients who are unable to walk sufficiently. Our aim was to clarify the effects of lung and heart involvement on exercise capacity in patients with a certain condition. We demonstrated the influence of pulmonary factors in addition to cardiac factors on exercise capacity in these patients, and pulmonary rehabilitation is recommended to improve their functional status and quality of life [23]. However, idiopathic inflammatory myopathies generally involve skeletal muscle, and the relationship between muscle symptoms and exercise capacity should be examined in the future.

Conclusion

Among the manifestations of idiopathic inflammatory myopathies, we evaluated deterioration in the lung and the heart in relation to exercise capacity using the 6MWT. The SV during the 6MWT was impaired in patients compared with in healthy controls, and the parameters influencing 6MWT distance were CO at 6 minutes and DLCO%. Interstitial lung disease may be a factor limiting exercise capacity in patients with idiopathic inflammatory myopathies who can walk.

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No conflicts of interest exist.

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Table 1. Characteristics of subjects

	Healthy controls (n = 18)	Myopathy patients (n = 23)	P
Gender (f/m)	12/6	13/10	0.51
Age (year)	59 ± 12	57 ± 13	0.63
Height (cm)	161 ± 10	161 ± 7	0.87
Weight (kg)	57 ± 9	56 ± 9	0.68
Body-Mass Index	22 ± 2	22 ± 4	0.63
6MWT distance (meters)	539 ± 80	498 ± 97	0.15
FVC (% prediction)	-	95.4 ± 22.3	
DLCO (% prediction)	-	61.8 ± 17.2	
EF (%)	-	68.4 ± 8.2	
At rest			
Stroke volume (mL)	71.6 ± 12.4	55.2 ± 16.9	0.0009
Heart rate (beats/min)	78 ± 13	86 ± 13	0.051
Cardiac output (L)	5.6 ± 1.2	4.6 ± 1.4	0.03
Cardiac index	3.5 ± 0.7	2.9 ± 0.8	0.02
At 6 min of 6MWT			
Stroke volume (mL)	106.6 ± 13.7	79.4 ± 27.9	0.0003
Heart rate (beats/min)	122 ± 23	134 ± 28	0.14
Cardiac output (L)	13.0 ± 2.9	10.7 ± 4.6	0.06
Cardiac index	8.2 ± 1.6	6.7 ± 2.9	0.054

Values are mean ± SD. 6MWT; 6-min walk test, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, EF; ejection fraction. FVC, DLCO, and EF were not measured in healthy controls.

Table 2. Correlation between 6-minute walk distance and cardiopulmonary parameters using single regression analysis

Parameters	Healthy controls		Myopathy patients	
	R ²	P	R ²	P
FVC (% prediction)	-	-	0.14	0.11
DLCO (% prediction)	-	-	0.33	0.03
EF (%)	-	-	0.0002	0.96
Stroke volume (mL), at rest	0.02	0.57	0.23	0.02
Cardiac output (L), at rest	< 0.01	1.00	0.15	0.07
Stroke volume (mL), at 6 min on 6MWT	< 0.01	0.80	0.40	0.001
Cardiac output (L), at 6 min on 6MWT	0.39	0.006	0.40	0.001

6MWT; 6-min walk test, FVC; forced vital capacity, DLCO; diffusing capacity for carbon monoxide, EF; ejection fraction. FVC, DLCO, and EF were not measured in healthy controls.

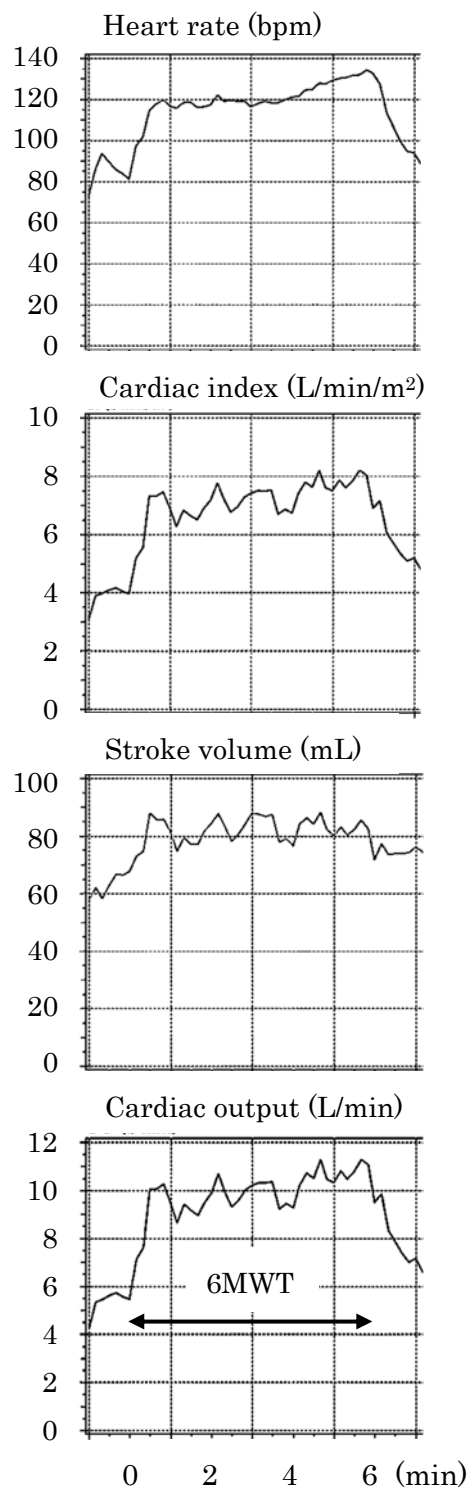


Figure 1

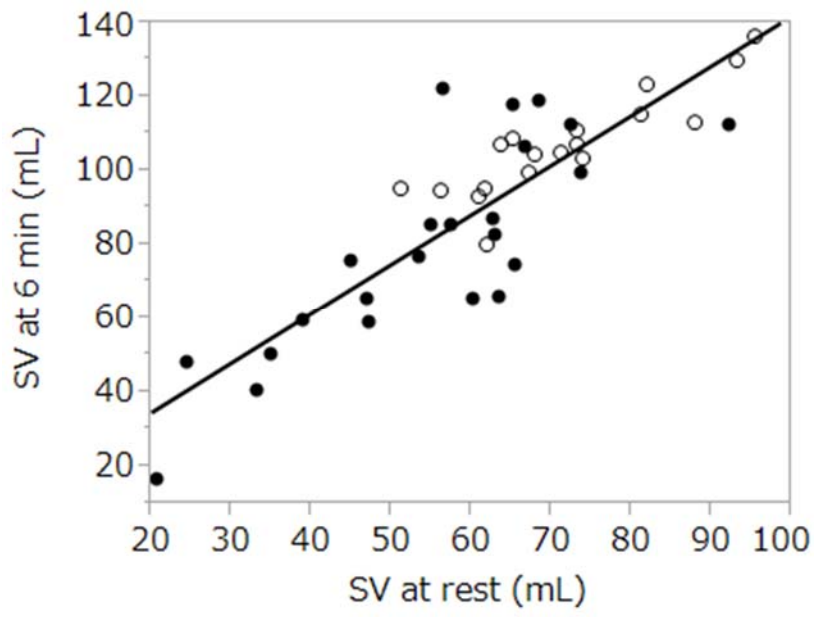


Figure 2

Figure legends

Figure 1. Hemodynamic responses recorded by noninvasive impedance cardiography during the 6-minute walk test (6MWT) in a patient.

Figure 2. Relationship between stroke volume (SV) at rest and at 6 minutes during the 6-minute walk test.

Open circles represent healthy controls and closed circles represent patients with idiopathic inflammatory myopathies. $R = 0.87$, $p < 0.0001$.