Factors relating to impaired stroke volume during the 6-minute walk test in patients with systemic sclerosis

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ABSTRACT

Objective. *Systemic sclerosis impairs the dilatation of affected pulmonary blood vessels and myocardial diastolic function at rest, but few studies have examined cardiac haemodynamic response during exercise. This study aimed to evaluate the factors affecting cardiac response during submaximal exercise in patients with systemic sclerosis.*

Methods. *Fifty-nine consecutive patients and 27 age- and sex-matched healthy controls underwent the 6-minute walk test with a non-invasive impedance cardiograph device.*

Results. *Stroke volume and cardiac output in patients with systemic sclerosis were significantly lower than those in controls at rest and at the end of the 6-minute walk test, and the distance walked was significantly shorter in patients. Percent predicted of forced vital capacity and diffusion capacity of the lung in patients showed correlations with stroke volume at the end of the 6-minute walk test and the increase in stroke volume during walking. The echocardiographic findings of right ventricular systolic pressure and left ventricular diastolic dysfunction showed no relationship to stroke volume during the 6-minute walk test. The increase in stroke volume during the 6-minute walk test was significantly smaller in patients with pulmonary hypertension diagnosed by right-heart catheterisation than in those without pulmonary hypertension.*

Conclusion. *Impaired stroke volume in patients with systemic sclerosis was observed at rest and during exercise, and the factors relating to the cardiac response seemed to be pulmonary function and the extent of pulmonary hypertension.*

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Introduction

Systemic sclerosis is a connective tissue disease that impairs dilatation of affected pulmonary blood vessels (1) and myocardial diastolic function (2, 3). An endomyocardial biopsy study showed cardiac remodelling due to myocardial fibrosis deposits in patients with systemic sclerosis without heart failure (4). Recently, echocardiography during exercise showed left ventricular impairment before any discernable evidence at rest (5). Moreover, pulmonary hypertension related to systemic sclerosis is frequently induced by exercise due to increases in both left ventricular filling pressure and pulmonary vascular resistance (3, 6), or right ventricular dysfunction (7, 8).

Additionally, previous studies (9, 10) reported that heart rate was the major determinant of exercise-induced increase in cardiac output, while stroke volume did not increase in patients with pulmonary hypertension. However, conflicting studies suggested that cardiac output during exercise is predominantly related to an increase in stroke volume instead of heart rate in patients with pulmonary hypertension (11), or that the heart rate in patients with pulmonary hypertension changed more slowly than that in healthy controls during the 6-minute walk test (6MWT) (12).

The 6MWT is a sub-maximal exercise test for evaluating exercise capacity, and it was reported that stroke volume in healthy subjects reached a plateau within 30 sec of starting of the 6MWT (13). The distance walked was reported to be reduced in patients with systemic sclerosis (14, 15) due to interstitial lung disease, pulmonary hypertension, dyspnea, and lower extremity pain (16). The purpose of this study was to detect the factors related to the cardiac haemodynamic response non-invasively in patients with systemic sclerosis, and the 6MWT was utilised as an exercise task
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Material and methods

Fifty-nine consecutive patients (48 females and 11 males, age 56.6±14.3 years, mean ± SD) with systemic sclerosis were recruited in this study, be-

ing referred for routine evaluation and treatment to our facility from July 2014 to February 2016 (Table I). All patients fulfilled the criteria for classification of definite systemic sclerosis proposed by the American College of Rheumatology. Patients were under treatment for their symptoms and were receiving the necessary medication. Anti-topoisomerase-I antibody was found in 23 patients, anti-centromere antibody in 16 patients, anti-RNA polymerase antibody in 9 patients, others, such as anti-centriole antibody were detected in 4 patients, and 7 patients were negative for antinuclear antibodies (17) (Table II). As controls, 27 healthy volunteers with similar distributions of age and gender (22 females and 5 males, age 56.7±11.7 years) were recruited. Exclusion criteria were a history of heart disease, cancer, renal crisis, lower extremity pain when walking for six minutes, systemic hypertension, or receiving beta-blocker medication. The study was approved by the Ethics Committee of Kanazawa University according to the principles expressed in the Declaration of Helsinki and all subjects gave their written informed content to participate in the study.

Interstitial lung disease was diagnosed by high-resolution computed tomography. Data of percent predicted forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO) from pulmonary function tests (Chestac-9800, Chest Medical Instruments, Tokyo, Japan) were collected. Transthoracic echocardiography at rest (iE33, Philips Health-care, Best, Netherlands) was also included in routine evaluations for patients. Besides ejection fraction of left ventricle (EF), right ventricular systolic pressure (RVsysP) reflecting pulmonary artery systolic pressure (18), the ratio of early to late mitral peak velocity (E/A) and to early diastolic mitral annular velocity (E/E') were collected from the evaluated data by means of tissue Doppler imaging. Patients with high RVsysP (> approximately 35 mmHg) (18) were also examined with standard right-heart catheterisation to confirm pulmonary hypertension (mean pulmonary artery pressure >25 mmHg) (19).

Table I. Characteristics of control subjects and patients with systemic sclerosis.

	Controls (n=27)	Systemic sclerosis (n=59)	*p*
Gender, f/m	22/5	48/11	1.00
Age, yr	56.7 ± 11.7	56.6 ± 14.3	0.97
Height, cm	160 ± 8	158 ± 9	0.33
Weight, kg	55 ± 8	53 ± 11	0.24
Body mass index	21.5 ± 2.2	21.0 ± 3.3	0.40
At rest			
Stroke volume, ml	69.2 ± 11.7	54.2 ± 20.8	< 0.0001*
Heart rate, bpm	78 ± 12	82 ± 15	0.19
Cardiac output, L	5.4 ± 1.1	4.3 ± 1.6	0.0005*
At the end of the 6MWT			
Stroke volume, ml	102.2 ± 15.1	76.8 ± 28.1	< 0.0001*
Heart rate, bpm	122 ± 22	134 ± 22	0.02*
Cardiac output, L	12.4 ± 2.9	10.2 ± 4.1	0.006*
Distance walked, m	535 ± 76	494 ± 107	0.04*
Borg's score	3.1 ± 0.9	3.6 ± 2.1	0.22

Data are presented as number or mean ± SD. 6MWT: 6-minute walk test.

All subjects underwent the 6MWT with a non-invasive impedance cardiograph device, the PhysioFlow Q-Link (Manatec Biomedical, France). Six disposable electrodes, Blue Sensor T (Ambu, Denmark), were placed on the subjects: two pairs of a transmitting electrode and a sensing electrode on the left neck and at the xyphoid area, plus V1 and V6 positions, to monitor the ECG signal (13, 20). Stroke volume, heart rate, and cardiac output were averaged every 10 seconds. The data at rest and at 6 minutes of walking were collected for analyses.

Statistical analyses

Unpaired *t*-tests were used to determine the differences between the patients and control subjects for age, height, weight, distance walked, Borg's score for ratings of perceived exertion, stroke volume, heart rate, and cardiac output. Statistical analysis was performed using ANOVA and Tukey HSD test for multiple comparisons of values and chi-squared test for comparison of frequencies classified by autoimmune antibodies. The relationships between stroke volume and pulmonary parameters, cardiac parameters, and the distance walked during the 6MWT in patients were determined by linear regression using Pearson's correlation coefficient. The comparison of stroke volume between patients with and without interstitial lung disease or pulmonary hypertension was performed by unpaired *t*-test. JMP 11 software (SAS Institute Inc., Cary, NC) was used for statistical analysis. $p<0.05$ was considered significant.

Results

There were no differences in age, height, weight, distance walked, or Borg's score between patients and controls (Table I). Stroke volume and cardiac output at rest and at the end of the 6MWT were significantly lower in patients than in controls, and distance walked was also shorter in patients. Heart rate did not differ between patients and controls at rest, but a significantly higher heart rate was seen in patients at the end of the 6MWT.

In patients, the disease duration was 6.3±6.1 years, and there were no differences in the durations among patients classified according to the presence of each antibody (Table II). Modified Rodnan total skin thickness score was lower in patients with anti-centromere antibody than in patients with anti-topoisomerase-I antibody, which showed the typical clinical characteristic that anti-centromere antibody was the autoimmune antibody frequently found in patients with limited cutaneous systemic sclerosis (17).

The distance walked, Borg's score, and heart rate were not different among the patients with each autoimmune antibody, although the distance walked was correlated to stroke volume at the end of the 6MWT and an increase in stroke

Table II. Clinical characteristics of patients with systemic sclerosis.

Antibody	Topo-I	ACA	RNAP	Others	Negative	*p*-value
number	23	16	9	4	7	
Duration, yr	5.5 ± 5.4	6.8 ± 7.0	3.8 ± 3.6	8.1 ± 5.7	9.6 ± 8.2	NS
TSS	15 ± 12	5 ± 5	14 ± 10	8 ± 7	13 ± 8	P = 0.02 (Topo-I vs. ACA)
ILD, n (%)	21 (91)	3 (19)	6 (67)	2 (50)	4 (57)	0.0003
PH, n (%)	1 (4)	0 (0)	1 (11)	0 (0)	3 (43)	NA
Distance walked, m	482 ± 123	508 ± 94	515 ± 83	477 ± 163	481 ± 107	NS
Borg's score	3.6 ± 2.3	4.1 ± 2.0	2.3 ± 1.5	4.0 ± 0	3.9 ± 2.5	NS
EF	69 ± 7	69 ± 8	72 ± 4	68 ± 6	67 ± 10	NS
E/A	1.1 ± 0.3	1.3 ± 0.6	1.3 ± 0.3	1.1 ± 0.5	1.0 ± 0.6	NS
E/E'	9.6 ± 3.6	9.4 ± 2.4	9.0 ± 1.6	9.7 ± 1.7	9.0 ± 1.6	NS
RVsysP, mmHg	30 ± 8	23 ± 6	26 ± 9	23 ± 3	36 ± 18	P = 0.04 (ACA vs. Negative)
FVC, % pred	85 ± 21	114 ± 30	106 ± 19	91 ± 37	94 ± 23	P = 0.007 (ACA vs. Topo-I)
DLCO, % pred	52 ± 18	71 ± 26	60 ± 16	66 ± 16	45 ± 20	NS
At rest						
Stroke volume, ml	58 ± 19	58 ± 22	55 ± 18	55 ± 22	33 ± 18	P = 0.049 (Topo-I vs. Negative)
Heart rate, bpm	83 ± 15	80 ± 13	76 ± 18	84 ± 10	89 ± 12	NS
Cardiac output, L	4.6 ± 1.5	4.6 ± 1.7	3.9 ± 0.9	4.7 ± 1.9	3.0 ± 1.8	NS
At the end of the 6MWT						
Stroke volume, ml	79 ± 25	85 ± 34	76 ± 20	76 ± 33	54 ± 25	NS
Heart rate, bpm	136 ± 25	128 ± 22	130 ± 19	138 ± 28	139 ± 16	NS
Cardiac output, L	10.7 ± 3.9	10.9 ± 4.9	9.8 ± 2.7	10.8 ± 5.2	7.7 ± 3.8	NS

Data are presented as number or mean ± SD; Topo-I: anti-topoisomerase-I antibody; ACA: anti-centromere antibody; RNAP: anti-RNA polymerase antibody; TSS: modified Rodnan total skin thickness score; ILD: interstitial lung disease; PH: pulmonary hypertension; EF: ejection fraction; E/A: the ratio of early to late mitral peak velocity; E/E': the ratio of early mitral peak velocity to early diastolic mitral annular velocity; RVsysP: right ventricular systolic pressure; FVC: forced vital capacity; DLCO: diffusion capacity of the lung for carbon monoxide; 6MWT: 6-minute walk test; NS: not significant; NA: not available.

Table III. Correlation between stroke volume and cardiopulmonary parameters in patients with systemic sclerosis.

	SV at rest		SV at the end of the 6MWT		Increase in SV during the 6MWT	
	R^2	*p*	R^2	*p*	R^2	*p*
EF, %	0.02	0.32	0.005	0.59	0.002	0.72
E/A	<0.001	0.95	0.002	0.72	0.006	0.57
E/E'	0.04	0.12	0.02	0.34	0.002	0.76
RVsysP, mmHg	0.01	0.50	0.02	0.29	0.02	0.34
FVC, % pred	0.13	0.005*	0.23	0.0001*	0.16	0.002*
DLCO, % pred	0.07	0.054	0.16	0.003*	0.14	0.006*
Distance walked, m	0.03	0.15	0.09	0.005*	0.12	0.001*
Borg's score	0.01	0.43	0.01	0.43	0.005	0.59

*p<0.05. 6MWT: 6-minute walk test; SV: stroke volume; EF: ejection fraction; E/A: the ratio of early to late mitral peak velocity; E/E': the ratio of early mitral peak velocity to early diastolic mitral annular velocity; RVsysP: right ventricular systolic pressure; FVC: forced vital capacity; DLCO: diffusion capacity of the lung for carbon monoxide.

volume during the 6MWT in patients. EF was almost normal in patients in this study, and 5 patients showed low EF (<60%). Whereas low E/A (<1) was seen in 25 patients (49% of patients), there was no difference in E/A among autoimmune antibodies, and no relationship was found between E/A and stroke volume (Table III). There were 5 patients (8%) who showed pulmonary hypertension by right-heart catheterisation, and 3 of them were negative for antinuclear antibodies. RVsysP was also high and stroke volume at rest was low in the subgroup of patients (Table II). RVsysP did not correlate with stroke volume (Table III), while the increase in stroke volume was low in patients with pulmonary hypertension (Fig. 1).

Interstitial lung disease was highly prevalent in patients with anti-topoisomerase-I antibody (91% of systemic sclerosis patients), and in those patients the percent predicted FVC was lower than that in patients with anti-centromere antibody. Stroke volume was correlated to percent predicted FVC at rest, and to percent predicted FVC and DLCO at the end of the 6MWT. Additionally, the increase in stroke volume during the 6MWT was also correlated with percent predicted FVC and DLCO (Table III). However, stroke volume in patients with anti-topoisomerase-I antibody was not low compared to those in patients with other autoimmune antibodies. Moreover, the presence of interstitial lung disease (39 of 59 patients) did not affect stroke volume at rest and during exercise (Fig. 2).

Discussion

In this study, the distance walked, Borg's score, and heart rate were similar among the patients with each autoimmune antibody, which suggested that the 6MWT provided almost the same exercise load to the patients including perceived exertion. However, stroke volume was lower and heart rate during walking was higher in patients than in controls. The cardiac output in patients was thought to be partially compensated for by the higher heart rate during walking, but the compensation was insufficient compared to the control value due to their low stroke

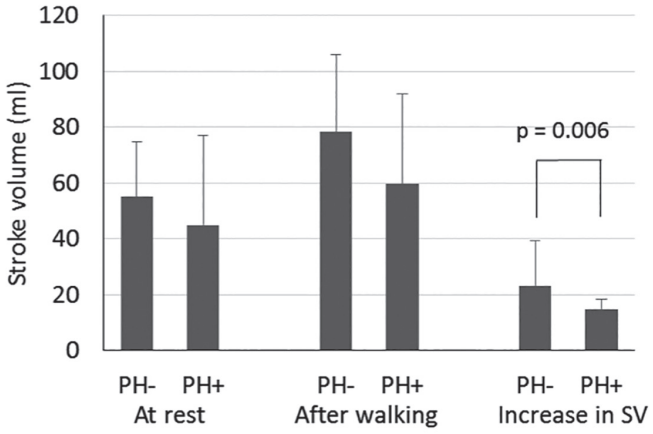

Fig. 1. Stroke volume in patients with and without pulmonary hypertension (PH+ and PH-, n=5 and 54, respectively). The increase of stroke volume during the 6MWT was significantly higher in patients without pulmonary hypertension than in those with pulmonary hypertension.

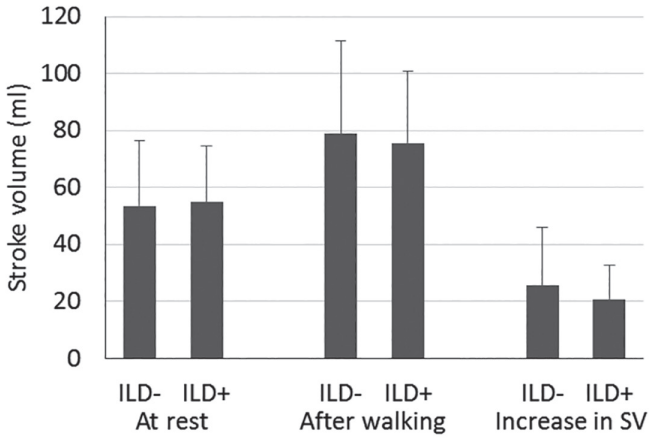

Fig. 2. Stroke volume in patients with and without interstitial lung disease (ILD+ and ILD-, n=36 and 23, respectively). There was no significant difference between the sub-divided groups.

volume, resulting in a shorter distance walked. Previously, the heart rate in patients with impaired cardiopulmonary function showed no difference (8, 10) or increased less (12) compared with that of healthy controls during exercise. A possible explanation for the higher heart rate in this study is the difference of subjects' experience of the 6MWT. No control subjects had performed the 6MWT before this study, while some of the patients had repeated experience of it because the 6MWT had been conducted as one of their routine evaluations, and experience of the 6MWT was reported to increase the distance walked (21). Borg's score for ratings of perceived exertion was similar between them, which suggests that the difference in heart rate was not important.

Cardiac parameters did not show any correlation with stroke volume in this study. Left ventricular diastolic dysfunction was the most common cardiac abnormality in systemic sclerosis (22), and a low E/A ratio and a high E/E' implied impaired diastolic function of the left ventricle (5, 23, 24). Even in healthy untrained subjects, an increasing diastolic filling time was thought to lead to a plateau in stroke volume compared with endurance-trained subjects with increasing exercise intensity (25). In this study, there was no relationship between left ventricular diastolic dysfunction and impaired stroke volume in patients with systemic sclerosis. Pulmonary hypertension can be detected using RVsysP evaluated by Doppler echocardiography (18), although RVsysP was not correlated with stroke volume. Thus, cardiac parameters by tissue Doppler imaging were thought to be insufficient to detect the response in stroke volume with the measurement method used in this study.

In contrast, an impaired stroke volume was found in patients who were negative for antinuclear antibodies; they showed relatively frequent presence of pulmonary hypertension (17), and low increase in stroke volume during the 6MWT was seen in 5 patients with pulmonary hypertension detected by right-heart catheterisation. Since the incidence of pulmonary hypertension in unselected systemic sclerosis was reported to be 4–5% at 5 years from onset (26), the number of patients with pulmonary hypertension in this study was not low (8%). It was reported that pulmonary artery systolic pressure showed an abnormal rise during exercise in 46% of patients with systemic sclerosis, even when it was normal at rest (27), and exercise-induced pulmonary hypertension was reported to be higher in the presence of interstitial lung disease (8). As interstitial lung disease was observed in 61% of the patients in this study, we expected that there would be some patients with exercise-induced pulmonary hypertension among the subset of patients without pulmonary hypertension at rest. A previous study showed that cardiac output increased in response to medication therapy for pulmonary arterial hypertension (28). Thus, pulmonary hypertension should affect haemodynamics.

Stroke volume at rest was correlated to only percent predicted of FVC, while percent predicted DLCO was also correlated to stroke volume after the load of the 6MWT. Generally, systemic sclerosis patients with pulmonary hypertension have low percent predicted lung volumes and DLCO (29). Moreover, a low DLCO (<55% of predicted) develops into pulmonary hypertension (30), and DLCO was one of the factors that predict pulmonary hypertension (26). It is suggested that FVC and DLCO could be indirect but useful indicators of stroke volume during exercise, although the presence of interstitial lung disease itself was not a factor affecting stroke volume. This might be because we did not examine the degree of severity of interstitial lung disease as diagnosed by high-resolution computed tomography. Additionally, in this study, patients with anti-topoisomerase-I antibody had more severe interstitial lung disease and showed lower percent predicted FVC than patients with anticentromere antibody. However, there were no differences in stroke volumes between two subsets of patients. The results also suggested that FVC was not a

direct factor in reducing stroke volume. Our study had some limitations. We did not examine pulmonary hypertension during exercise. Further study is required regarding cardiac impairment in cases of exercise-induced pulmonary hypertension to clarify the relationship to stroke volume response during exercise. This was a study at a single facility, and treatment was individually provided. Therefore, the effects of various treatments on patients could not be isolated from the results. Moreover, all patients could complete the 6MWT, which suggested that none of them were burdened by the test. Cardiac functional abnormality would be more detectable in patients who were not able to perform the 6MWT. There is a need for a larger study including patients with various degrees of involvement.

Conclusion

Stroke volume in patients with systemic sclerosis was significantly less than that in healthy controls. The factors relating to stroke volume in patients were percent predicted FVC and DLCO, especially during the 6MWT. However, cardiac parameters including RVsysP measured at rest, were not correlated with stroke volume. Systemic sclerosis patients with pulmonary hypertension showed a low increase of stroke volume during the 6MWT, which implied that exercise-induced pulmonary hypertension might warrant further examination in relation to stroke volume in future study.

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