Lung Diffusion Capacity Affects Stroke Volume in Systemic Sclerosis

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Research note

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Abstract

Objective: In our previous cross-sectional study, we reported impaired stroke volume in patients with systemic sclerosis; however, no cardiac parameter using echocardiography was found to be related to stroke volume reduction. As few studies have focused on the hemodynamic clinical course, the patients were re-evaluated in a median interval of 18 months, and correlations between stroke volume and cardiopulmonary parameters were analyzed.

Results: Seventeen patients who were able to complete the 6-minute walk test wearing a non-invasive impedance cardiograph device were assigned for re-evaluation, and individual changes in the stroke volume were noted. The stroke volume was not related to cardiac parameters, but it was significantly related to the diffusion capacity of the lung for carbon monoxide after walking in the first evaluation ($r = 0.63$, $p = 0.006$), and at rest in the re-evaluation ($r = 0.72$, $p = 0.001$). Significant relation was also found between the distance walked and the stroke volume after walking in the first evaluation and re-evaluation, and at rest in the re-evaluation. Thus, a limited lung diffusion capacity may affect stroke volume due to the exercise intolerance in systemic sclerosis without pathological heart involvement.

Introduction

Systemic sclerosis involves multiple organs through the deposition of fibrotic tissue and microvascular obliteration [1]. Pulmonary involvement affects all organ systems [2], and myocardial fibrosis deposits before signs or symptoms of heart failure are observed in those with systemic sclerosis [3], which leads to left ventricular diastolic dysfunction detected by echocardiography. Longitudinal assessment over 3.4 years of follow-up demonstrated the pathological progress in the parameters such as the early filling to early diastolic mitral annular velocity ratio (E/E' ratio) and tricuspid regurgitant maximum velocity [4]. Roque et al. [5] classified the severity of the diastolic dysfunction by other parameters including the early to late mitral peak velocity ratio (E/A ratio). These studies suggested that left ventricular diastolic dysfunction is an independent predictor of mortality.

As another assessment in terms of heart involvement, we previously reported a smaller stroke volume in patients with systemic sclerosis than that in healthy controls using a non-invasive impedance cardiograph device to evaluate real-time hemodynamics under the 6-minute walk test (6MWT) [6]. In that cross-sectional study, the increase in stroke volume during walking was the significant parameter for the distance walked; however, the left ventricular ejection fraction (EF), E/A ratio, and E/E' ratio at rest were not significantly correlated with the exercise-induced change in stroke volume. On the other hand, parameters for stroke volume were correlated with lung function and pulmonary hypertension, and the impaired stroke volume was considered to be due to lung involvement.

Stroke volume is regulated by left ventricular systolic and diastolic functions, which may be predictors for the prognosis, but little is known about the relationship between stroke volume and outcome. The aim of

this study was to find cardiac parameters assessed on echocardiography that affect the stroke volume during the 6MWT in systemic sclerosis by setting the measuring interval for chronological change.

Methods

The patients were recruited at Kanazawa University Hospital for the treatment of systemic sclerosis. The first evaluation of hemodynamics during the 6MWT was carried out using 67 adult patients between 2014 to 2018. Then, re-evaluation of hemodynamics was carried out after a median interval of 18 months (the 25th to 75th percentile range, 6 to 22 months) for 17 patients who were able to walk for at least 6 minutes without oxygen therapy (Table 1). The reason for the small number of patients in this study was that patients are usually transferred from around the country to consult about treatment strategy at the early stage of disease. Subsequently, they receive the treatment at the facilities in their home towns. The median duration from disease onset to the first evaluation was 1.5 years (the 25th to 75th percentile range, 1 to 7 years). Anti-topoisomerase-1 antibody was positive in 11 patients, anti-RNA polymerase antibody in 3, and others in 3. The study was approved by the Ethics Committee of Kanazawa University according to the principles in the Declaration of Helsinki and written informed consent to participate in the study was received from all patients for utilizing their information in research. The participants had no cognitive decline or past history of stroke that would affect task performance and providing ethical consent.

Table 1
Characteristics of subjects (n = 17)

	The first evaluation	Re-evaluation	P
Gender, f/m	11/6		
Age, yr	46 ± 16		
Height, cm	162 ± 11		
Weight, kg	59 ± 15		
Body mass index	22 ± 3		
Stroke volume at rest, ml	57 ± 17	59 ± 19	NS
Stroke volume after waking, ml	86 ± 27	92 ± 25	NS
Distance walked, m	554 ± 130	561 ± 122	NS
Ejection fraction, %	69 ± 5	70 ± 4	NS
E/A	1.3 ± 0.5	1.4 ± 0.5	NS
E/E'	8.2 ± 3.5	9.1 ± 4.2	NS
Forced vital capacity, % pred	90 ± 16	89 ± 16	NS
DLCO, % pred	53 ± 17	49 ± 16	NS
Data are presented as number or mean ± SD. 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; DLCO: diffusion capacity of the lung for carbon monoxide; NS: not significant.			

A non-invasive impedance cardiograph device, the Physioflow Q-Link (Manatec Biomedical, France) with 6 disposable electrodes placed on the patients [7], was used to evaluate stroke volume during the 6MWT. The data were averaged every 10 seconds and collected at rest and after 6 minutes of walking for analyses. From patient records, the left ventricular EF, E/A ratio, and E/E' ratio of transthoracic echocardiography at rest, and percent predicted forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO) of pulmonary function tests were collected.

Statistical analyses

Cardiopulmonary parameters were compared between the evaluations using the paired t-test. Simple regression analyses using Spearman's coefficient were applied to identify significant correlation among parameters. JMP 13 software (SAS Institute Inc.) was used for statistical analysis and $p < 0.05$ was considered significant.

Results

There were individual changes in stroke volume over time (Fig. 1). At the early stage from the disease onset, within one or two years, stroke volumes slightly increased, probably due to starting medication. The various changes thereafter reflected the clinical course, and then stroke volumes at rest and after walking were not different after re-evaluation for all patients (Table 1). The values on echocardiography and lung function tests were also not different after re-evaluation, which might be due to the same reason in stroke volumes.

Table 2 showed the result of correlation analyses between stroke volumes and cardiopulmonary parameters according to the various changes. The stroke volume was not related to cardiac parameters, but was significantly related to the DLCO after walking in the first evaluation ($r = 0.63$, 95% CI 0.22–0.85, $p = 0.006$), and at rest in the re-evaluation ($r = 0.72$, 95% CI 0.37–0.89, $p = 0.001$). The distance walked was also significantly related to the stroke volume after walking in the first evaluation and re-evaluation, and at rest in the re-evaluation ($p = 0.05$, 0.03, and 0.02, respectively).

Table 2
Correlation between stroke volume and cardiopulmonary parameters

	Stroke volume at rest		Stroke volume after waking	
	r	P	r	P
Distance walked				
The first evaluation	0.36	0.15	0.48	0.05*
Re-evaluation	0.56	0.02*	0.52	0.03*
Ejection fraction				
The first evaluation	-0.20	0.45	-0.12	0.65
Re-evaluation	-0.43	0.10	-0.12	0.65
E/A				
The first evaluation	-0.11	0.68	0.03	0.91
Re-evaluation	-0.06	0.87	0.11	0.53
E/E'				
The first evaluation	0.03	0.91	0.02	0.93
Re-evaluation	-0.18	0.53	-0.17	0.53
Forced vital capacity				
The first evaluation	0.08	0.77	0.24	0.36
Re-evaluation	0.15	0.56	-0.10	0.70
DLCO				
The first evaluation	0.42	0.10	0.63	0.006**
Re-evaluation	0.72	0.001**	0.46	0.06
*p < 0.05, **p < 0.01. 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; DLCO: diffusion capacity of the lung for carbon monoxide.				

Discussion

There was a significant relationship between the stroke volume and the DLCO in this study. It is well known that lung diffusing capacity reduction [8, 9] and pulmonary hypertension [10] in systemic sclerosis are predictors of high mortality, regardless of the preservation of left ventricular systolic function [11]. The EF in patients of this study was preserved at 60% or more, suggesting that systolic function remains normal on conventional echocardiography. If slight systolic dysfunction was not evaluated by EF, other

methods, such as speckle tracking echocardiography, might be useful to detect early cardiac involvement which could not be found by conventional echocardiography [12, 13]. In general, systolic dysfunction does not affect mortality compared with diastolic dysfunction in systemic sclerosis [14]; however, the causes of systolic dysfunction are defined as coronary artery disease, arterial hypertension, and acute myocarditis [15]. When the left ventricular EF is lower than 50%, myocardial fibrotic scarring can be detected by late gadolinium enhancement using cardiac magnetic resonance in systemic sclerosis [16].

In this study, the 6MWT was applied to an exercise task to show left ventricular diastolic function. In healthy subjects, the left ventricular end-diastolic volume was reported to be directly related to the change in stroke volume during exercise [17]. Cadeddu et al. [18] demonstrated that bicycle exercise affected left ventricular diastolic function through global longitudinal strain using speckle tracking echocardiography, although the dysfunction was not observed at rest in systemic sclerosis. Thus, the assessment of hemodynamic function during exercise may increase heart involvement compared with at rest. Whereas, our study did not demonstrate the relationship between the left ventricular diastolic function and the stroke volume. For this reason, the left ventricular diastolic function, i.e. the E/A ratio and the E/E' ratio, was assessed at rest and not severely impaired as shown in Table 1, while the DLCO was as low as about 50% and the significant relation to the stroke volume was observed even at rest.

The patients also have a risk of exercise-induced pulmonary artery hypertension, who are known to have left ventricular diastolic dysfunction with an increased E/E' ratio [19]. As an E/E' ratio > 15 is considered abnormal for diastolic function even in systemic sclerosis [20], only one patient receiving medication for pulmonary artery hypertension in this study had diastolic dysfunction based on the E/E' ratio. Therefore, it was difficult to show the relationship between the E/E' ratio and the stroke volume. Moreover, the E/A ratio was not a significant parameter for stroke volume in this study, either. A possible reason for this was, as Lee et al. [20] demonstrated, the E/E' ratio was more sensitive than the E/A ratio for identifying left ventricular diastolic dysfunction.

It was not shown in the result section, but the strong correlations between the DLCO and the distance walked were found (the first evaluation: $r = 0.66$, $p = 0.004$; the re-evaluation: $r = 0.61$, $p = 0.01$). The similar relationship between DLCO and distance walked was demonstrated by Garin et al [21]. As right ventricular systolic dysfunction was reported not to correlate with FVC in early systemic sclerosis [22], it seems that the heart and lung involvements are mutually independent. However, Cuomo et al. [23] noted that impaired exercise performance associated with heart and lung involvement. That suggested that the relationship between the stroke volume and the DLCO might be indirect through exercise tolerance. That is, impaired lung perfusion capacity reduced exercise tolerance, which affected the stroke volume without pathological heart involvement. In addition, it must be noted that diastolic dysfunction according to the E/E' ratio was reported to reduce cardiopulmonary exercise tolerance in patients with normal EF [11, 18, 24, 25]. Therefore, the exercise tolerance is regulated by multiple factors.

Conclusion

To clarify the parameters related to stroke volume in systemic sclerosis, we analyzed hemodynamic function utilizing the clinical course of individual patients. The DLCO, which represents the lung perfusion capacity, affected the stroke volume due to the limitation of exercise tolerance. This suggests a future direction of studies on heart involvement in systemic sclerosis.

Limitations

This study has several limitations. It was a single-facility study, which made it difficult for us to follow patients to the terminal stage and to assess the survival rate because of the type of facility. We examined the longitudinal change in hemodynamic function in a small number of patients, but the stroke volume may be affected by other factors after further functional decline. Long-term follow-up is necessary to demonstrate a correlation between stroke volume and mortality. In addition, the small number of follow-up patients is not suitable for multiple regression analysis to detect independent factors affecting stroke volume, but simple regression analyses suggested a candidate among the factors.

Abbreviations

E/E' ratio: early filling to early diastolic mitral annular velocity ratio; E/A ratio: early to late mitral peak velocity ratio; 6MWT: the 6-minute walk test; EF: left ventricular ejection fraction; FVC: forced vital capacity; DLCO: diffusion capacity of the lung for carbon monoxide.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Kanazawa University according to the principles in the Declaration of Helsinki and written informed consent to participate in the study was received from all patients (No. 812).

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and analyzed during the current study are available.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

FS was the lead for the study and designed the methodology. MN evaluated the data and analyzed the study results. FS and NM drafted the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Stroke volumes in each patient. Black lines are values at rest and red lines are those after walking. The lines represent the data of the first evaluation and re-evaluation of 17 patients.