E/E' ratio is more sensitive than E/A ratio for detection of left ventricular diastolic dysfunction in patients with systemic sclerosis

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ABSTRACT

Objectives. *To investigate the efficiency of early filling (E) and early diastolic mitral annular velocity (E') ratio (E/E' ratio) assessed by tissue Doppler imaging (TDI) on early detection of diastolic left ventricular (LV) dysfunction in systemic sclerosis (SSc) patients without congestive heart failure (CHF) symptoms.*

Methods. *Thirty-five Korean SSc patients without CHF symptoms and 35 healthy, age-sex matched controls were studied. Two-dimensional and M-mode echocardiography including conventional and tissue Doppler imaging was performed and pulmonary function test with diffusing capacity of lung for carbon monoxide was assessed.*

Results. *Mean E and late filling (A) ratio (E/A ratio) showed no significant difference between the two groups, while TDI showed that SSc patients had significantly elevated E/E' ratio (10.6±4.2 vs. 8.8±2.2, p=0.032), in comparison with controls. SSc patients who had taken angiotensin converting enzyme inhibitor or angiotensin II receptor blocker had significantly lower E/E' than those who had not (8.0±2.4 vs. 11.9±4.3, p=0.01).*

Conclusions. *E/E' ratio is more sensitive than E/A ratio for identifying LV diastolic dysfunction in SSc patients without CHF symptoms. Furthermore, SSc patients who had received ACEI or ARB treatment showed significantly better preservation of LV diastolic function than those who had not received these medications.*

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterised by thickening and fibrosis of the skin and by distinctive forms of involvement of internal organs such as heart, lungs, kidneys, gastrointestinal tract and musculoskeletal system (1). Heart involvement of SSc including pericarditis, congestive heart failure (CHF), primary pulmonary hypertension, and conduction abnormality, is one of the fatal organ involvements (1, 2). Primary heart involvement of SSc might be induced by vasospasm of the small coronary arteries or arterioles, which would substantially impair cardiac perfusion and function, but with reversibility at early phase. This would be followed by structural coronary arteriolar lesion leading to irreversible abnormalities including myocardial fibrosis, which could provoke bilateral ventricular contractility and relaxation abnormalities (3). Notably, left ventricle (LV) diastolic dysfunction has been reported to precede systolic dysfunction in patients with SSc (4). It is often difficult to properly detect heart involvement of SSc, because the clinical manifestations caused by heart involvement are frequently indistinguishable from those caused by lung involvement of SSc (4, 5). Considering the confounding effects that lung lesions have on right ventricle (RV), LV function can reflect heart involvement of SSc more sensitively than RV function. Thus, it may be more feasible to assess LV diastolic function rather than RV to detect heart involvement of SSc at an earlier stage (6-8).

Although LV diastolic function impairments have been elucidated in several studies using conventional Doppler echocardiography which are recommended as one of the predictors of outcome of SSc (9), the reliability of peak velocity of early filling (E) and late filling (A), and E/A ratio was not proved to be high enough to reflect diastolic LV function, because of its pre-load dependency (10). A recent study showed that early diastolic mitral annular velocity (E') and E/E' ratio, which were assessed by tissue Doppler imaging (TDI),

can be used to more correctly evaluate myocardial relaxation and filling pressure of LV, because these parameters are independent of pre-load (11).
In this study, we investigated diastolic LV dysfunction using both conventional Doppler echocardiography and TDI in SSc patients without CHF symptoms, compared the indices measured with those in healthy controls, and determined the efficacy of E/E' ratio assessed by TDI on early detection of diastolic LV dysfunction in SSc patients. We also investigated the effect of medications on diastolic LV dysfunction in patients with SSc.

Materials and methods

Subjects

Thirty five patients (26 women, 9 men), who were diagnosed with SSc at Yonsei University Severance Hospital from 2000 to 2005 and did not present with symptoms of CHF, were selected as cases. All subjects fulfilled the American College of Rheumatology 1980 criteria for the classification of SSc (12). We performed conventional echocardiography and TDI in 35 patients. A total of 35 age- and sex-matched individuals (25 women, 10 men) were consecutively selected as controls. Controls had no diseases such as hypertension, underlying cardiovascular disease, diabetes, and they underwent conventional echocardiography and TDI for medical check-up. Medications were defined as those that the patients had received at least 6 months prior to the performance of echocardiography. The institutional review boards approved this study.

Clinical manifestations, autoimmune antibodies, and major organ involvement

Clinical manifestations were investigated at the time of diagnosis of SSc. Clinical manifestations included proximal and distal skin thickening, fingertip ulceration, telangiectasia, Raynaud's phenomenon, and bibasilar infiltration of the lungs on chest x-ray or chest CT scans. Major organ involvements of SSc were evaluated at the time of echocardiographic performance, and defined as below: Lung = forced vital capacity (FVC) or single-breath diffusing capacity for carbon monoxide (DLCO) less than 70% predicted, rales, fibrosis on CT scan, and pulmonary hypertension; heart = ECG conduction defect, arrhythmia, RV enlargement, LV ejection fraction (LVEF) less than 50%, regional wall motion abnormality, RV pressure >30 mmHg without evidence of lung involvement, and E/E' over 15; gastro-intestine (GI) = requirement of antireflux medication or antibiotics for bacterial overgrowth, abnormal small bowel series, malabsorption syndrome or pseudo-obstruction, and total parental nutrition required; kidney = creatinine over 1.3 mg/dl, urine protein on dip stick over 2+, and dialysis required; nerve = abnormal findings on nerve conduction study; muscle = proximal muscle weakness (11, 13, 14).

Echocardiography

Two-dimensional and M-mode echocardiography, conventional Doppler echocardiography and TDI data were obtained from all patients and controls at Yonsei University Cardiovascular Center. Two-dimensional and Doppler echocardiography was performed with a commercially available echocardiography unit equipped with an imaging transducer having pulsed-wave and TDI capability. LVEF was calculated by two-dimensional echocardiography using the multiple diameter method (15). From the mitral inflow velocities, peak velocity of E and A, and deceleration time (DT) of E-wave velocity were measured. When possible, estimation of pulmonary artery systolic pressure was obtained with the tricuspid regurgitant velocity (16). For TDI, the filter setting was lowered, and the Nyquist limit was adjusted to a range of 15 to 20 cm/s. Gain was minimised to allow for a clear tissue signal with minimal background noise. E' wave was measured from the apical four-chamber view with a 2- to 5-mm sample volume placed at the septal corner of mitral annulus. Measurements were recorded with simultaneous electrocardiography at a sweep speed of 50 to 100 mm/s. The following measurements were made from the TDI recordings: peak systolic velocity (S'), early (E') and late (A') diastolic velocities. E/E' ratio was also calculated. Measurements were made for three to five cardiac cycles and averaged.

Pulmonary function tests

All patients underwent pulmonary function tests (PFT) including FVC, forced expiratory volume in 1 second (FEV1), and DLCO.

Statistical analysis

All statistical analyses were conducted using the SPSS package for Windows version 13.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean±SD. Differences between patients and controls were examined by the Mann-Whitney U-test. Comparison of E/E' ratio in SSc patients according to medications taken was done using the Mann-Whitney U-test. For all statistical evaluation of the results, p-values <0.05 were considered significant.

Results

Characteristics of the study subjects

Table I shows the clinical manifestations, major organs involved, medications, and PFT results of patients with SSc. Mean age of the patients was 49.2±12.8 years old, and mean disease duration from the diagnosis of SSc to the performance of echocardiography was 9.8±2.2 months. The most common clinical manifestation belonging to disease entity of SSc was proximal skin thickening (82.9%), followed by Raynaud's phenomenon (74.3%). Also, the frequent major organ involvement of SSc was lung (48.6%) and heart (37.1%). Twenty-four patients (68.6%) received calcium channel blocker (CCB) for hypertension or Raynaud's phenomenon, and twelve patients (34.3%) received angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) for hypertension. Mean values in PFT showed relatively preserved lung functions.

Comparison of cardiac functions between SSc patients and controls

Table II shows the indices measured by echocardiography. Two-dimensional and M-mode echocardiography revealed no significant differences in parameters including LVEF between patients and

Table I. Characteristics of the patients with systemic sclerosis.

	Total (n=35)
Age (years old)	49.2 ± 12.8
Female/Male	26 / 9
Disease duration (months)	9.8 ± 2.2
Clinical manifestations, n (%)	
Proximal skin thickness	29 (82.9)
Raynaud's phenomenon	26 (74.3)
Sclerodactyly only	23 (65.7)
Bibasilar pulmonary fibrosis	17 (48.6)
Finger tip ulceration	15 (42.9)
Telangiectasia	3 (8.6)
Major organ involvement, n (%)	
Lung	17 (48.6)
Heart	13 (37.1)
Gastrointestine	6 (17.1)
Nerve	3 (3.8)
Kidney	1 (2.9)
Muscle	1 (2.9)
Medications, n (%)	
Calcium channel blocker	24 (68.6)
D-penicillamine	12 (34.3)
ACEI or ARB	12 (34.3)
Astrix	9 (25.7)
NSAIDs	8 (22.9)
Prostaglandin E1	3 (8.6)
Pulmonary function test	
FVC (%)	74.5 ± 13.9
FEV1 (%)	77.0 ± 19.1
DLCO (%)	77.9 ± 19.9

ACE: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; NSAIDs: non-steroidal anti-inflammatory drugs; FCV: forced vital capacity; FEV1: forced expiratory volume 1 second; DLCO: single-breath diffusing capacity for carbon monoxide. Continuous variables are expressed as mean ± standard deviation.

Table II. Comparison of cardiac functions between the patients with systemic sclerosis and controls.

	Patients (n=35)	Controls (n=35)	*p*-value
Age (years)	49.2 ± 12.8	51.6 ± 8.3	NS
Female / Male	26 / 9	25 / 10	NS
Systolic blood pressure (mmHg)	129.2 ± 7.2	118.2 ± 10.3	NS
Diastolic blood pressure (mmHg)	71.2 ± 9.3	68.1 ± 11.2	NS
Two-dimensional and M-mode echocardiography			
LA dimension (mm)	34.8 ± 6.6	34.4 ± 5.3	0.357
LV end-systolic dimension (mm)	32.2 ± 7.4	30.5 ± 3.7	0.232
LV end-diastolic dimension (mm)	48.1 ± 6.8	47.8 ± 3.7	0.845
Septal end-systolic thickness (mm)	12.1 ± 1.5	12.3 ± 1.8	0.672
Septal end-diastolic thickness (mm)	9.1 ± 1.6	9.1 ± 1.3	0.934
Posterior wall end-systolic thickness (mm)	12.7 ± 2.1	12.8 ± 1.8	0.901
Posterior wall end-diastolic thickness (mm)	8.7 ± 2.0	8.7 ± 1.3	1.000
LV ejection fraction (%)	66.3 ± 7.5	69.1 ± 5.6	0.082
Conventional Doppler echocardiography			
Mitral peak E velocity (m/sec)	0.7 ± 0.3	0.6 ± 0.2	0.066
Mitral peak A velocity (m/sec)	0.7 ± 0.2	0.5 ± 0.1	0.001
Mitral E/A ratio	1.1 ± 0.4	1.2 ± 0.3	0.294
Mitral deceleration time (msec)	195.0 ± 41.6	202.4 ± 38.4	0.457
Tricuspid regurgitating velocity (m/sec)	2.4 ± 0.4	2.1 ± 0.2	0.001
RV Pressure (mmHg)	28.7 ± 8.4	23.2 ± 3.4	0.001
Tissue Doppler imaging (TDI)			
TDI S' velocity (cm/sec)	7.5 ± 2.1	6.9 ± 1.3	0.146
TDI E' velocity (cm/sec)	7.2 ± 2.1	7.3 ± 2.3	0.807
TDI A' velocity (cm/sec)	8.8 ± 2.6	7.6 ± 1.8	0.042
TDI E/E' ratio	10.6 ± 4.2	8.8 ± 2.2	0.032
TDI E/E' ratio >15	6	0	0.001

LA: left atrium; LV: left ventricle; RV: right ventricle; NS: not significant. Continuous variables are expressed as mean ± standard deviation. For all statistical evaluations, $p<0.05$ was considered statistically significant.

controls. SSc patients had significantly higher mean A velocity than those in controls, however, mean E/A ratio was not significantly different between the two groups. TDI showed that SSc patients had significantly elevated mean E/E' ratio (10.6±4.2 *vs*. 8.8±2.2, p=0.032), in comparison with controls. E/E' >15 was found in 6 out of 35 SSc patients, but not in controls. Mean RV pressure in SSc patients was significantly higher than that in any of controls (28.7±8.4 mmHg *vs*. 23.2 ± 3.4 mmHg, p=0.001). When patients were divided into two groups according to the lung involvement of SSc, patients with lung involvement had significantly decreased DLCO and increased RV pressure compared with those without lung involvement. However there was no difference in E/E' ratio between patients with and without lung involvement (Fig. 1A).

Comparison of cardiac functions between SSc patients receiving and not receiving medications

We divided the SSc patients into two groups according to the medications (ACEI or ARB and CCB) that they had taken (receiving and not receiving groups) and compared cardiac functions. There were no differences in age, sex distribution, disease duration, body surface area, hypertension frequency, or mean systolic blood and diastolic blood pressure between the two groups (data not shown). There were no significant differences in mean E/A ratio between patients receiving and not receiving ACEI or ARB as well as CCB (Fig. 1B). However, patients who had taken ACEI or ARB had significantly lower mean E/E' ratio than patients who had not taken (8.0±2.4 *vs*. 12.0±4.3, p=0.01) (Fig. 1C). Mean E/E' ratio was not significantly different between those patients receiving and not receiving CCB (Fig. 1C).

Discussion

Heart involvement in patients with SSc is one of the fatal risk factors to increase the mortality and morbidity (17). Since the clinical symptoms of SSc are, however, occult and indistinguishable due to other SSc complications, such as vascular or interstitial lung involvement, esophageal dysfunction, and chest wall disorders, the incidence and prevalence of SSc heart involvement might have been underestimated, to date (18-20). CHF is, moreover, a rare manifestation of SSc in early phase, so it is difficult to make an early detection of cardiac dysfunction correctly (21, 22). In this study, even though most patients exhibited relaxation abnormalities, there was no patient who was presenting overt CHF symptoms including dyspnea on exertion or at rest at the time of either diagnosis of SSc or echocardiographic performance. However, considering diastolic LV dysfunction with preserved systolic

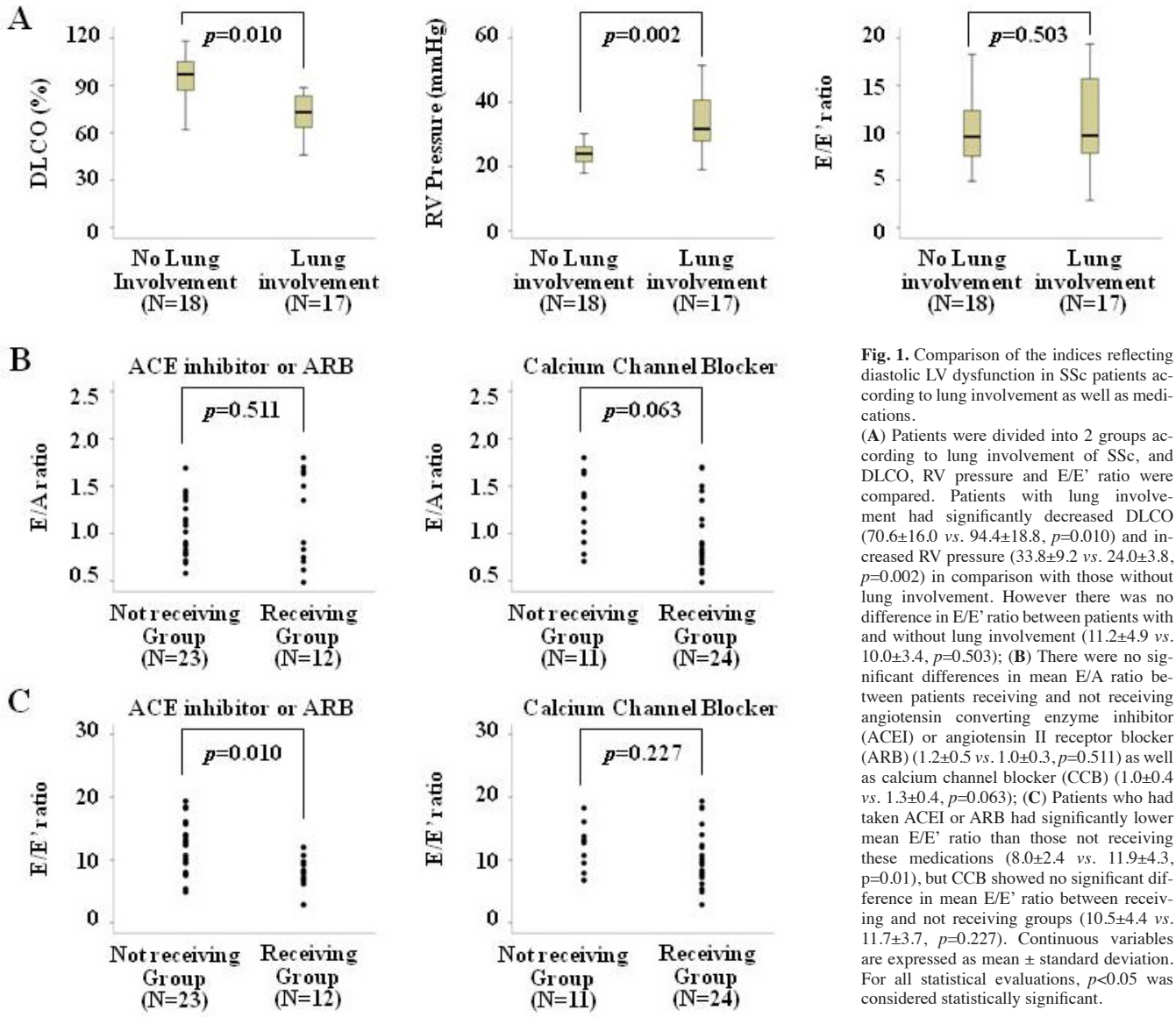

Fig. 1. Comparison of the indices reflecting diastolic LV dysfunction in SSc patients according to lung involvement as well as medications.
(**A**) Patients were divided into 2 groups according to lung involvement of SSc, and DLCO, RV pressure and E/E' ratio were compared. Patients with lung involvement had significantly decreased DLCO (70.6±16.0 *vs*. 94.4±18.8, p=0.010) and increased RV pressure (33.8±9.2 *vs*. 24.0±3.8, p=0.002) in comparison with those without lung involvement. However there was no difference in E/E' ratio between patients with and without lung involvement (11.2±4.9 *vs*. 10.0±3.4, p=0.503); (**B**) There were no significant differences in mean E/A ratio between patients receiving and not receiving angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) (1.2±0.5 *vs*. 1.0±0.3, p=0.511) as well as calcium channel blocker (CCB) (1.0±0.4 *vs*. 1.3±0.4, p=0.063); (**C**) Patients who had taken ACEI or ARB had significantly lower mean E/E' ratio than those not receiving these medications (8.0±2.4 *vs*. 11.9±4.3, p=0.01), but CCB showed no significant difference in mean E/E' ratio between receiving and not receiving groups (10.5±4.4 *vs*. 11.7±3.7, p=0.227). Continuous variables are expressed as mean ± standard deviation. For all statistical evaluations, p<0.05 was considered statistically significant.

function (diastolic heart failure) was reported up to a 5-year mortality rate of 28%, and isolated diastolic LV dysfunction also could increased the rate of morbidity including CHF as high as 45%, (this results were not limited to SSc), the standardised and optimised evaluation methods for diastolic LV dysfunction is needed to improved the rate of mortality as well as morbidity in patients with SSc (23, 24).

The main pathogenesis of heart involvement in SSc is myocardial fibrosis, thus diastolic LV dysfunction is more commonly found than systolic LV dysfunction in the early stage of SSc (1). To date, E/A ratio or DT according to mitral inflow pattern based on conventional Doppler echocardiography has been used to assess diastolic LV dysfunction (5, 10). However, there are several limitations of E/A ratio determined from conventional Doppler echocardiography to reflect diastolic LV function accurately: i) as LV filling pressure increases, mitral peak E velocity also increases up to E/A ratio>1, ii) E/A ratio depends upon HR and conduction abnormalities, iii) Mitral inflow pattern could be influenced by the severity of regurgitation. E/A ratio can therefore not reflect diastolic LV function accurately (25-27).

In contrast, E/E' ratio has been proposed as a useful index to evaluate diastolic LV function. E/E' ratio is more reliable index than E/A ratio to assess relaxation abnormality of LV. E/A ratio is under the influence of pre-load alteration, but E/E' ratio is not affected, and E' velocity remains stable despite altered mitral inflow patterns during the course of the disease, suggesting that it might be a good and stable estimate of filling pressure of LV (11, 28, 29). In this study, although there were no differences in mean E/A ratio between patients and controls, mean E/E' ratio in patients with SSc was significantly higher than that in controls. Furthermore, E/E' ratio <8 suggests normal LV filling pressure, whereas E/E' ratio >15 indicates elevated filling pressure and predicts the development of diastolic heart failure (30). In the present study, E/E' >15 was found in 6 out of 35 patients with SSc, but in none of

controls. In addition, patients with lung involvement exhibited significantly decreased DLCO and increased RV pressure, but showed no difference in E/E' ratio compared to those without lung involvement, suggesting that E/E' ratio can reflect heart involvement of SSc independently of lung involvement.

Although no large clinical trials have evaluated the efficacy of ACEI, ARB and CCB on diastolic LV dysfunction in patients with SSc, there is consensus that those vasodilators could improve both myocardial perfusion and function abnormalities (31). Also ACEI and ARB treatment at the early stage of diastolic dysfunction has been shown to prevent the development of LV fibrosis and the transition to overt diastolic heart failure independent of anti-hypertensive effects (32). In this study, patients who had received ACEI or ARB had significantly better-preserved LV diastolic function than those who had not received ACEI or ARB. CCB, however, did not appear to influence LV diastolic function, in contrast with a recent report that CCB might play a protective role in heart function of SSc patients (33). Our results suggest that the use of ACEI and ARB might reduce the frequency of LV diastolic dysfunction in SSc patients.

Since eight patients received both CCB and ARB or ACEI, we also divided the subjects in four subgroups (subgroup 1 = CCB only, subgroup 2 = ARB or ACEI only, subgroup 3 = both CCB and ARB or ACEI and subgroup 4 = no medication), and compared E/E' ratio as well as E/A ratio, to clarify the independent influence of each drug on LV diastolic dysfunction in SSc. The number of patients who received only CCB, only ARB/ACEI, both CCB and ARB/ACEI, and no medication were 16, 4, 8 and 7 respectively. Patients in subgroups 2 and 3 (8.0±1.9 and 7.9±2.7, respectively) had significantly low E/E' ratio compared to those in subgroup 4 (13.8±2.8) (p=0.014 and 0.003, respectively), while, there was no significant difference in E/E' ration between subgroup 1 (11.1±4.7) and subgroup 4. We could find no significant differences in E/A ration among subgroups. This result of subgroup analysis might support our suggestion of the role of ARB or ACEI on early change in LV diastolic function in SSc. However, since the number of subjects in each subgroup was relatively small, it might require a leap in the logic to assert that all SSc patients should receive ARB or ACEI as patients with lupus nephritis take ARB or ACEI to reduce the amount of proteinuria. Thus, in order to elucidate the clinical implication of the use of ARB or ACEI in SSc patients, the large-sized, prospective study will be necessary.

In conclusion, E/E' ratio is more sensitive than E/A ratio for identifying LV diastolic dysfunction in patients with SSc who did not presented with symptoms of CHF. Thus, we suggest that not only conventional echocardiography but also TDI should be performed in SSc patients when they are diagnosed. Furthermore, SSc patients who had received ACEI or ARB treatment showed significantly better preservation of LV diastolic function than those who had not received these medications.

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