Asymptomatic left ventricular diastolic dysfunction in diffuse systemic sclerosis patients: conventional echocardiography and left atrial speckle tracking

Ahmed Aboughanima[a,b], Abdelaziz Gomaa[c,d], Gehan El Olemy[a,e]

[a]Department of Rheumatology & Rehabilitation, Faculty of Medicine, Benha University, Benha, Egypt, [b]Department of Internal Medicine, Rheumatology Division, Dallah Hospital, Riyadh, KSA, [c]Department of Cardiololgy, Faculty of Medicine, Zagazig University, Zagazig, Egypt, [d]Department of Cardiology, Dallah Hospital, Riyadh, KSA, [e]Department of Internal Medicine, Rheumatology Division, Al Adan Hospital, Al Adan, Kuwait

Correspondence to Ahmed T. Aboughanima, MD, Dallah Hospital, Fas, An Nakheel, Riyadh 12381, KSA. Tel: +966 563 056 017; fax: 009662995652; e-mail: dr_ahmedtaha73@yahoo.com

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Objective
Our objective was to assess asymptomatic left ventricular diastolic dysfunction (LVDD) in diffuse systemic sclerosis (SSc) patients using both conventional and two-dimensional speckle tracking echocardiography in correlation to disease variables.

Patients and methods
Twenty-two patients with diffuse SSc without symptoms of LVDD and 22 controls were included in a comparative cross-sectional study. Skin fibrosis was assessed by modified Rodnan skin thickness score and disease severity by Medsger's score. Parameters related to diastolic functions of the left ventricle were obtained by conventional echocardiography. Assessment of left atrium (LA) functions was by two-dimensional speckle tracking echocardiography as a predictor of LVDD.

Results
There were significant differences between patients and controls regarding E-wave deceleration time (194.8±27.3 vs. 157.1±20.3; $P<0.001$), E/E' (8.85±1.98 vs. 6.99 ±0.69; $P=0.008$), positive peak LAε (11.4±2.9 vs. 18.8±2.28; $P<0.001$), and sec. positive peak LAε (17.5±3.9 vs. 25.5±2.7; $P<0.001$). All LA strain parameters were significantly correlated with disease duration, disease severity, N-terminal pro b-type natriuretic peptide, E/E', and E-wave deceleration time, while positive peak LAε was correlated with the modified Rodnan skin thickness score. Receiver operating characteristic curve analysis identified a positive peak value of less than or equal to 10.8 and sec. positive peak of less than or equal to 17.5 as predictors for the detection of E/E' more than or equal to 8.

Conclusion
LA reservoir and conduit functions were significantly affected in SSc patients than controls and were associated with longer disease duration and more severe disease, while only reservoir function was associated with more fibrotic skin changes. All LA strain parameters correlated significantly with E/E' ratio, while positive peak LA and sec. positive peak LA were demonstrated as LVDD predictors in patients with diffuse SSc.

Keywords:
diastolic dysfunction, speckle tracking, systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is a rare connective tissue disease characterized by inflammation and progressive fibrosis involving multiple organs, including the skin, lungs, gastrointestinal tract, kidneys, and the heart. Although cardiac involvement is often clinically asymptomatic [1], it is recognized in a significant number of patients [2,3].

The pathogenesis of SSc is not entirely understood but microangiopathy and the extensive accumulation of extracellular matrix are the most characteristic features and the resulting fibrosis disrupts the structure of tissues and frequently leads to dysfunction of the affected organs [4].

Myocardial involvement is one of the leading causes of mortality in SSc, the mechanisms of primary myocardial involvement, including the characteristic vascular lesions and fibrous tissue deposition, which lead to coronary microcirculation and myocardial dysfunction [2,5]. In addition, patients with scleroderma have an increased risk of pulmonary arterial hypertension [6].

Systolic and/or diastolic dysfunction may occur in SSc patients even before any symptoms suggestive of

cardiac involvement discovered and both of them carry bad prognostic signs during the disease course. Early detection of cardiac affection is important in the proper management of the disease [7].

Left atrium (LA) assumes a basic part in left ventricular (LV) filling with LA reservoir, pump, and conduit contractile functions [8,9]. LA functional indices can be assessed by two-dimensional (2D) echocardiography and Doppler echocardiography, such indices is dependent on hemodynamic loading circumstances and geometric hypothesis. Strain imaging employing tissue Doppler imaging (TDI) and two-dimensional speckle tracking echocardiography (2D-SPE) provide better reproducibility in assessing LA function and serve as a good solution to overcome this problem [10]. Therefore 2D strain imaging speckle tracking of LA has been used as a newer tool for assessing LV function [11].

This study was carried out to assess asymptomatic left ventricular diastolic dysfunction (LVDD) in SSc patients using both conventional echocardiography and two-dimensional speckle tracking echocardiography (2D-STE) of the LA in correlation to disease variables.

Patients and methods

Twenty-two patients with diffuse SSc were included: 19 women and three men. SSc was diagnosed according to 2013 ACR/EULAR Classification Criteria for scleroderma [12] without history of coronary artery disease, pulmonary hypertension, or reduced ejection fraction (EF %) were collected from the Rheumatology Clinic in Dallah Hospital, Riyadh, KSA. Twenty-two age-matched and sex-matched controls were included. The study protocol was approved by the local ethics committee. All participants provided written consent.

General examination and measurements

Detailed clinical history and physical examination were carried out for all patients. Age, sex, weight, height, body surface area, BMI, blood pressure, and heart rate measurements of the patients and control group were acquired. Modified Rodnan skin thickness score (MRSS) was used to evaluate skin fibrosis; this score consists of an evaluation of patient's skin thickness rated by clinical palpation using a 0–3 scale (0=normal skin; 1=mild thickness; 2=moderate thickness; 3=severe thickness with inability to pinch the skin into a fold) for each of 17 surface anatomic areas of the body: face, anterior chest, abdomen (right and left separately), fingers, forearms, upper arms, thighs, lower legs, and dorsum of hands and feet. These individual values are added and the sum is defined as the total skin score [13]. SSc severity was assessed according to the Medsger scale, which includes a general status of the patient, peripheral vascular, skin, joints, tendon, muscle, gastrointestinal tract, lung, and kidney involvement [14].

All patients underwent laboratory testing including blood cell count, serum creatinine levels, erythrocyte sedimentation rate (ESR), high-sensitive C-reactive protein (hs-CRP), antinuclear antibody (ANA), antiscleroderma 70 (anti scl-70), anti-centromere antibodies, N-terminal pro b-type natriuretic peptide (NT pro-BNP), in addition to diffusion capacity for carbon monoxide (DLCO).

Conventional echocardiography and Doppler measurements

Standard transthoracic echocardiography was performed in the left decubitus position using an ultrasound system (acusonsc2000; Siemens, Siemens Medical Solutions, California, USA) with a 3.4 MHz multifrequency transducer. Parameters related to diastolic functions of the LV were obtained as follows: LA maximal volume index (cm^3/m^2), early (E) and late (A) transmitral flow velocities, the ratio of early to late peak velocities (E/A), and deceleration time (DT) of E velocity were obtained. We followed the update recommendations for the evaluation of LVDD by echocardiography from the American Society of Echocardiography and the European Association of Cardiovascular Imaging to determine the parameters related to LVDD [15].

LA diameters were measured from the apical four-chamber view. LA areas and volumes were measured using the biplane method of disks (modified Simpson's rule), in the apical four-chamber and two-chamber view at end systole (maximum LA size), and the mean values of area and volume were obtained [16]. LA volumes were subsequently indexed to body surface area.

The E/A ratio is measured by placing a pulse wave Doppler across the mitral valve and measuring the velocities across the valve. Conventional pulsed Doppler imaging of mitral inflow was recorded from the apical four-chamber view with the Doppler sample placed between the tips of the mitral leaflets. Peak transmitral flow velocity in early diastole (E), peak transmitral flow velocity in late diastole (A), and E/A ratio were measured. DT was defined as a slope from the maximum E point to the baseline [15].

The E/E' ratio, which has been shown to provide good noninvasive estimates of LV filling pressure, was calculated by dividing the peak E velocity (obtained by pulsed Doppler from the mitral inflow) by the E' that was measured from the septal, lateral mitral annulus by use of pulse wave TDI. In normal individuals, the E/E' ratio is less than 8. In the presence of diastolic dysfunction/impaired relaxation, E' will be rather low, in contrast the E-wave increases with elevated filling pressures. Thus, the E/E' ratio will increase in the presence of diastolic dysfunction [8].

Pulmonary artery systolic pressure (PASP) was estimated from peak tricuspid regurgitation jet velocities, with adding average right atrial pressure [17].

Two-dimensional SPE measurements

Using 2D-STE of LA software (EchoInsight; Epsilon, Ann Arbor, Michigan, USA), LA endocardial border was traced in the apical four-chamber view, taking care to exclude the appendage and pulmonary veins from the LA cavity. Then, a composite LA longitudinal strain curve throughout the cardiac cycle was generated. This curve comprised six individual atrial segments. If more than 1 atrial segment had to be excluded from the analysis because of suboptimal visualization and tracking, an alternative loop was selected to ensure complete analysis for each participant [18–20].

The tracking settings allow distinguishing three LA strain values. If the reference point is set at the onset of the QRS, we can measure positive peak atrial longitudinal strain (ε pos peak), which corresponds to an LA reservoir function. If the reference point is set at the onset of the P wave, we can measure both negative atrial longitudinal strain (ε neg peak), which mirrors LA pump function and second positive peak atrial strain (sec. ε pos peak), which corresponds to LA conduit function [21–23].

Statistical analysis

Numerical data are presented as mean±SD and were tested for a normal distribution using the Shapiro–Wilk test, assuming normality at a *P* value of more than 0.05. Comparisons between SSc patients and controls were performed using Student's independent *t* tests for parametric variables or by Mann–Whitney *U* test for nonparametric ones. Comparisons between categorical variables were made with χ^2 test. Correlations were tested by Pearson's (*r*) or Spearman's (rho) correlation tests for parametric and nonparametric variables, respectively. Receiver operating characteristic (ROC) curve analysis was used to detect cutoff values of positive peak and sec. positive peak with optimum sensitivity and specificity in the detection of E/E' ratio of less than or equal to 8. All tests were two-sided and *P* values less than 0.05 were considered statistically significant. All analyses were performed using SPSS 20.0.0 (IBM Inc., Chicago, Illinois, USA).

Results

Our study included 22 patients with diffuse SSc (19 women and three men); their age ranged between 25 and 58 years with mean±SD of 37.3±9.3 years and 22 age-matched and sex-matched healthy persons as the control group. The disease duration ranged between 3 and 12 years with a mean±SD of 7.09±2.3 years, MRSS ranged between 3 and 21 with a mean±SD of 11.09±5.5. Medsger disease severity scale ranged between 2 and 13 with a mean±SD value of 7.63±3.2; neutrophil/lymphocyte ratio ranged between 0.62 and 1.3 with a mean±SD value of 0.68±0.14. ESR ranged between 26 and 47 with a mean±SD of 36.9±5.9, the hs-CRP ranged between 10 and 18 with a mean±SD value of 13.2±1.96, all patients had positive ANA, the anti scl-70 antibodies was positive in 18 (81.8%) patients, while anti-centromere antibodies were positive in five (22.7%) patients. The NT pro-BNP ranged between 80 and 230 with a mean±SD of 134.4±42.2 and the DLCO ranged between 70 and 98 with mean±SD of 82.9±8.1 (the demographic, clinical and laboratory parameters of the SSc group are shown in Table 1). Conventional echocardiographic findings are presented in Table 2. There were significant differences between SSc patients and control group regarding mitral E-wave (DT) and E/E' ratio, while there were no significant differences regarding LA maximal volume index, EF %, E/A ratio, and PASP P < (0.05). LA 2D-STE findings are presented in Table 3. There were significant differences between SSc patients and the control group concerning positive peak LAε and sec. positive peak LAε, while there was no significant difference regarding negative peak LAε.

Pearson's correlation analysis showed significant correlations of all LA strain parameters (positive LAε, negative LAε, and sec. positive LAε) with disease duration, Medsger severity scale, NT pro-BNP, mitral E/E' ratio, and E-wave-DT, while only positive peak LAε was correlated with MRSS and sec. positive peak LAε was correlated with ESR. There were no correlations of all LA strain imaging parameters with neutrophil/lymphocyte ratio and hs-CRP (Table 4). ROC curve analysis showed that Sec. positive peak LA value of less than or

Table 1 The demographic, clinical, and laboratory parameters of systemic sclerosis patients (*N*=22)

The demographic, clinical, and laboratory parameters	
Age (years) [mean±SD (range)]	37.3±9.3 (25–58)
Sex (female/male ratio)	19/3
Disease duration (years) [mean±SD (range)]	7.09±2.3 (3–12)
MRSS [mean±SD (range)]	11.09±5.5 (3–21)
Medsger scale [mean±SD (range)]	7.63±3.2 (2–13)
Hemoglobin (g/dl) [mean±SD (range)]	11.8±1.21 (9.5–14)
White blood cell count (mm^3) [mean±SD (range)]	10.2±2.66 (4.5–15)
Neutrophil count (mm^3) [mean±SD (range)]	1.85±0.4 (1.3–2.8)
Lymphocyte count (mm^3) [mean±SD (range)]	2.14±0.26 (1.8–2.8)
Neutrophil/lymphocyte ratio	0.68±0.14 (0.62–1.3)
Platelet count (mm^3)	248.6±65.2 (150–410)
Blood urea (mg/dl) [mean±SD (range)]	15.2±6.08 (7–28)
Creatinine (mg/dl) [mean±SD (range)]	1.02±0.14 (0.7–1.3)
ESR (mm/h)	36.9±5.9 (26–47)
hs-CRP (mg/l) [mean±SD (range)]	13.2±1.96 (10–18)
ANA positive [*n* (%)]	22 (100)
Anti Scl-70 antibodies positive [*n* (%)]	18 (81.8)
Anti-centromere antibodies [*n* (%)]	5 (22.7)
NT pro-BNP (pg/ml)	134.4±42.2 (80–230)
DLCO (%)	82.9±8.1 (70–98)

ANA, antinuclear antibody; anti Scl-70, antiscleroderma 70; DLCO, diffusion capacity for carbon monoxide; ESR, erythrocyte sedimentation; hs-CRP, high-sensitive C-reactive protein; MRSS, modified Rodnan skin thickness score; NT pro-BNP, N-terminal pro b-type natriuretic peptide.

Table 2 Comparison of conventional and Doppler parameters between systemic sclerosis and control groups

	SSc group (*N*=22) (mean±SD)	Control group (*N*=22) (mean±SD)	ZMWU	*P*
LA maximal volume index (cm^3/m^2)	25.04±2.96	24.5±3.93	0.33	0.74
EF %	61.9±5.2	63.3±5.1	Student's *t*=0.93	0.35
Doppler mitral E-wave (DT) (ms)	194.8±27.3	157.1±20.3	4.4	<0.001*
E/A ratio	1.06±0.16	1.15±0.14	Student's *t*=2.0	0.052
PASP (mmHg)	26.4±2.59	27.5±1.81	Student's *t*=1.62	0.11
E/E' ratio	8.85±1.98	6.99±0.69	2.66	0.008*

DT, deceleration time; EF, ejection fraction; LA, left atrium; PASP, pulmonary artery systolic pressure; SSc, systemic sclerosis. *Significant ($P<0.05$).

equal to 10.8 has a sensitivity of 90.9%, specificity of 81.8%, positive predictive value of 83.3%, and negative predictive value of 90% for the detection of E/E' ratio of more than or equal to 8 (area under the curve=0.897, 95% confidence interval=0.76–1.0; $P=0.002$) and Sec. positive peak LA of less than or equal to 17.5 has a sensitivity of 90.9%, specificity of 90.9%, positive predictive value of 90.9%, and negative predictive value of 90.9% for the detection of E/E' ratio of more than or equal to 8 (area under the curve=0.95, 95% confidence interval=0.85–1.0; $P<0.001$) (Fig. 1 and Table 5).

Table 3 Comparison of left atrium two-dimensional speckle tracking echocardiography parameters between systemic sclerosis and control groups

ECHO variables	SSc group (*N*=22) (mean±SD)	Control group (*N*=22) (mean ±SD)	ZMWU	*P*
Positive peak LAε (%)	11.4±2.9	18.8±2.28	5.29	<0.001*
Negative peak LAε (%)	–6.72±2.78	–7.31±2.64	0.88	0.37
Sec. positive peak LAε (%)	17.5±3.9	25.5±2.7	Student's *t*=7.85	<0.001*

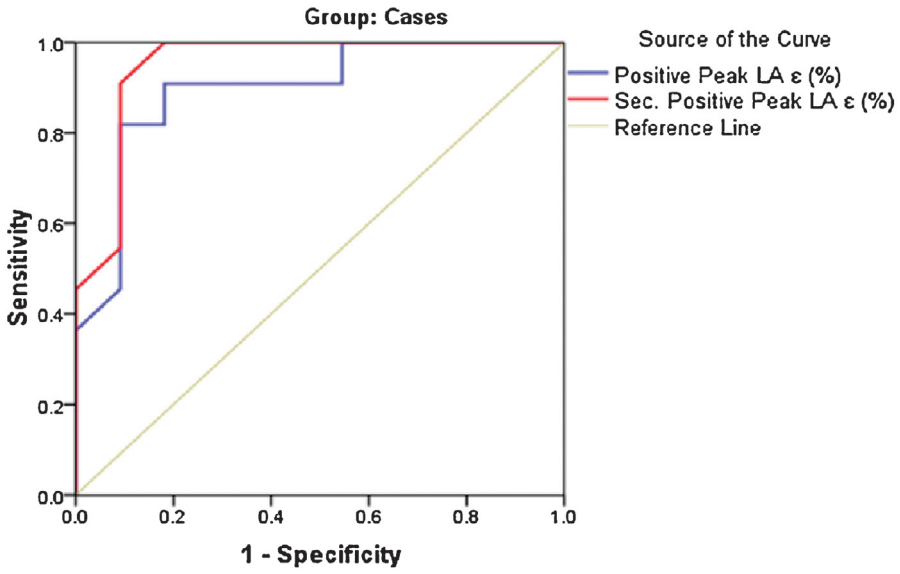
LA, left atrium; SSc, systemic sclerosis. *Significant ($P<0.05$).

Table 4 Correlation of left atrium two-dimensional speckle tracking echocardiography parameters with systemic sclerosis disease-related variables and conventional echocardiographic findings

	Positive peak LAε (%)	Negative peak LAε (%)	Sec. positive peak LAε (%)
Disease duration	Rho=–0.464	Rho=0.471	*r*=–0.430
	P=0.029*	*P*=0.027*	*P*=0.046*
Medsger scale	Rho=–0.523	Rho=0.553	*r*=–0.445
	P=0.012*	*P*=0.002*	*P*=0.038*
MRSS	Rho=–0.516	Rho=0.89	*r*=–0.086
	P=0.014*	*P*=0.69	*P*=0.70
Neutrophil/ lymphocyte ratio	Rho=–0.365	Rho=0.253	*r*=–0.092
	P=0.069	*P*=0.26	*P*=0.68
NT pro-BNP	Rho=–0.429	Rho=496	*r*=–0.550
	P=0.046*	*P*=0.019*	*P*=0.008*
ESR	Rho=–0.149	Rho=0.253	*r*=–0.543
	P=0.51	*P*=0.26	*P*=0.009*
hs-CRP	Rho=–0.085	Rho=0.130	*r*=–0.032
	P=0.71	*P*=0.56	*P*=0.88
E/E' ratio	Rho=–0.527	Rho=0.525	Rho=–0.454
	P=0.01*	*P*=0.011*	*P*=0.034*
Doppler mitral E-wave (DT)	Rho=0.572	Rho=–0.662	Rho=0.556
	P=0.005*	*P*≤0.001*	*P*=0.007*

r, Pearson's correlation coefficient; rho, Spearman's correlation coefficient. DT, deceleration time; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitive C-reactive protein; LA, left atrium; MRSS, modified Rodnan skin thickness score; NT pro-BNP, N-terminal pro b-type natriuretic peptide. *Significant ($P<0.05$).

Figure 1



ROC curve analysis to sensitivity and specificity of positive peak LAε and sec. positive peak LAε in detection of E/E' ratio. ROC, receiver operating characteristic.

Table 5 Statistical analysis of receiver operating characteristic curve assessing the ability of positive peak left atrium ε and sec. positive peak left atrium ε to predict E/E' ratio more than or equal to 8

Variables	Cutoff	Sensitivity %	Specificity %	PPV%	NPV%	AUC	95% CI	*P*
Positive peak LA	≤10.8	90.9	81.8	83.3	90	0.897	0.76–1.0	0.002*
Sec. positive peak LA	≤17.5	90.9	90.9	90.9	90.9	0.950	0.85–1.0	<0.001*

AUC, area under the curve; CI, confidence interval; LA, left atrium; NPV, negative predictive value; PPV, positive predictive value.
*Significant ($P<0.05$).

Discussion

In our study, there were only highly significant differences between SSc patients and control group regarding mitral E-wave (DT) and E/E' ratio while there were no significant differences regarding LA maximal volume index, EF %, E/A ratio, and pulmonary artery systolic pressure and this can be explained by the fact that all our patients included in the study were asymptomatic and no gross cardiac abnormalities was detected in conventional echocardiographic study and the aim of our study to detect early cardiac involvement in SSc patients.

Mele *et al.* [24] showed that TDI-derived E/E' ratio are a valuable approach to detecting cardiac involvement in asymptomatic SSc patients. Also Ataş *et al.* [25] reported no significant differences between groups regarding LVEF and LA diameter values; however, they noted higher E/E' ratio and DT in SSc patients than in controls.

In our study, LA function was used as an early predictor of LV diastolic dysfunction in concordance with the study of Abhayaratna *et al.* [26] who stated that LA function and volumes are useful parameters of LV diastolic and systolic function and are independent predictors of cardiovascular outcomes. Moreover, increase in LV end-diastolic pressure as a consequence of LV systolic and/or diastolic function may lead to structural and functional changes in the LA [27].

The relation between LA function and LV systolic and diastolic function is explained by the following mechanism; in ventricular systole, the filling of the LA from the pulmonary veins is increased by longitudinal shortening of the ventricular base while during diastole, the filling of the LV is granted by active and passive emptying of LA. Additionally, LV diastolic properties may influence the LA emptying function via direct interaction of ventricular pressures by mitral valve opening during diastole [26,28,29].

Doppler parameters alone do not give an ideal understanding into defective LV relaxation, and subsequently leading to inaccurate assessment of diastolic dysfunction in SSc patients. Also, abnormal Doppler parameters can be reported in patients with constrictive pericarditis without myocardial association [8].

In the present study, atrium strain imaging parameters of SSc patients were highly significantly different than controls regarding positive peak LAε and sec. positive peak LAε, while there was no significant difference regarding negative peak LAε. Our observations are in full agreement with Agoston *et al.* [30] who reported that LA reservoir and conduit function were impaired, but contractile function and LA V_{max} were similar between SSc patients and healthy controls. In the same context, Ataş *et al.* [25] observed significantly lower atrial peak-systolic longitudinal strain (ε), early negative strain rate (SR), late negative SR, and peak positive SR values in SSc patients.

Several studies demonstrated that employing 2D strain technique showed an early reduction in longitudinal function in patients with SSc, where the parameters of conventional echocardiography were not suitable to highlight the systolic function impairment [31–33]. This is on grounds that the myocardial subendocardial layer, primarily in charge of the longitudinal function and more prone to ischemia and fibrosis, is involved before the subepicardial layer [34].

In our study, all LA strain parameters were significantly correlated with disease duration, Medsger severity score, NT pro-BNP, E-wave-DT, and mitral E/E' ratio; however, only positive peak LAε was correlated with MRSS and sec. positive peak LAε was correlated with ESR. On the other hand, all LA strain parameters were neither correlated with neutrophil/lymphocyte ratio nor hs-CRP.

In agreement with our results, previous studies demonstrated prevalent diastolic dysfunction in SSc patients that was significantly correlated with disease duration [35–37]. In partial agreement with our results, Ataş *et al.* [25] found no significant correlations between LA phasic volumes and parameters reflecting the activity of SSc such as MRSS, ESR, and CRP and contributed that to the heterogeneity regarding disease activities at the time of enrollment. Similarly, Appleton *et al.* [38] stated that ESR and CRP are known to reflect the severity of inflammatory activation at the time of measurement, whereas findings obtained during LA volume and function analyses reflect the chronic effect of LVDD.

In normal individuals, the E/E' ratio is less than 8. In the presence of diastolic dysfunction/impaired relaxation, E' will be rather low. In contrast, the E-wave increases with elevated filling pressures. Thus, the E/E' ratio will increase in the presence of diastolic dysfunction [8].

In our study, ROC curve analysis showed that positive peak LA of less than or equal to 10.8 and sec. positive peak LA of less than or equal to 17.5 were predictors of LV dysfunction (defined by E/E' ratio ≥8). Previous cohort study by Singh *et al.* [39] has identified LA stain as a predictor of early diastolic dysfunction, additionally they reported that cutoff values for peak LA strain can be used for the classification of diastolic dysfunction with good to excellent diagnostic utility (area under the curve, 0.86–0.91).

Finally, it is important to have a newer, noninvasive and precise tool like 2D-SPE to identify early impairment of LV function in SSc patients which may lead to increased risk of death, in order to overcome inaccurate findings that may be obtained from conventional echocardiographic assessment. In this regard, we recommend combining 2D-SPE with conventional echocardiography during studying cardiac abnormalities in SSc patients.

Conclusion

LA reservoir and conduit functions were significantly affected in SSc patients than controls and were associated with longer disease duration and more severe disease, while only reservoir function was associated with more fibrotic skin changes. All LA strain parameters correlated significantly with E/E' ratio while positive peak LA and sec. positive peak LA were demonstrated as LVDD predictors in patients with SSc.

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Conflicts of interest

There are no conflicts of interest.

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