Evaluation of left atrial volume and function in systemic sclerosis patients using speckle tracking and real-time three-dimensional echocardiography

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Abstract

Objective: The aim of the present study was to evaluate left atrial (LA) volume and functions using real-time three-dimensional echocardiography (RT3DE) and speckle tracking in systemic sclerosis (SSc) patients.

Methods: The study was designed as a cross-sectional observational study. We studied 41 consecutive SSc patients (38 females, mean age: 49.5±11.6 years) and 38 healthy controls (35 females, mean age: 48.5±10.8 years). Patients with evidence or history of cardiovascular disease and patients with risk factors as hypertension, diabetes and chronic renal failure were excluded from the study. All study subjects underwent standard echocardiography; LA speckle tracking and RT3DE was performed to assess LA volume and phasic functions. Differences between numeric variables were tested using the independent sample Student's t-test or Mann-Whitney U test, where appropriate.

Results: There were no significant differences between SSC patients and controls regarding left ventricular (LV) systolic functions and two-dimensional (2-D) atrial diameters. Presence of LV diastolic dysfunction (LVDD) was evaluated and graded according to recommendations of the American Society of Echocardiography. Accordingly, LVDD was observed to be significantly more frequent in SSc patients; 16 SSc patients (39%) and 5 controls (12.8%) were observed to have LVDD (p=0.007). With regard to results obtained from RT3DE, LA maximum, minimum, and before atrial contraction volumes were significantly higher (40.5±14.6 vs. 32.6±8.9, 15.5±8.4 vs. 9.9±3.5 and 28.7±11.7 vs. 21.4±7.0 mL respectively, p<0.05 for all), whereas LA active emptying fraction, LA total emptying fraction, LA expansion index, and passive emptying fraction values were significantly (47.1±12.0 vs. 52.9±10.1%, 62.8±10.5 vs. 69.5±6.7%, 187.5±76.0 vs. 246.6±96.0, 29.6±9.3 vs. 34.4±11.0% respectively, p<0.05 for all) in SSc patients than in controls. In addition, regarding results obtained from speckle tracking echocardiography, atrial peak-systolic longitudinal strain (ε), early negative strain rate (SR), late negative SR, and peak positive SR values were observed to be significantly lower in SSc patients.

Conclusion: LA volumes were significantly increased, and LA reservoir, conduit, and contractile functions were significantly impaired in SSc patients compared with controls. LA volume and functional analyses with RT3DE and speckle tracking may facilitate the recognition of subtle LA dysfunction in SSc patients. *(Anatol J Cardiol 2016; 16: 316-22)*

Keywords: systemic sclerosis, real-time three-dimensional echocardiography, left atrial volume

Introduction

Systemic sclerosis (SSc) is a systemic connective tissue disease characterized by inflammation and fibrosis in various organs. Cardiac involvement in SSc has long been recognized as a common and adverse finding in SSc patients associated with poor prognosis (1). There is ongoing research regarding methods for the early detection of subclinical cardiac involvement, which is important for adequate long-term management of these patients (2, 3). Left atrium (LA) plays a critical role in left ventricular (LV) filling with LA reservoir, conduit, and contractile functions (4, 5). LA structural and functional remodeling has been proposed as a reliable indicator of diastolic pressure burden, and the LA size has been shown to be a predictor of adverse cardiovascular outcome both in general population and in many cardiovascular conditions (6). Although two-dimensional (2D) echocardiography is commonly used for the assessment of LA in clinical practice, the use of real-time three-dimensional echocardiography (RT3DE) has recently been introduced as a reliable and reproducible technique for the assessment of LA volume and function (7-10). There is limited information in the literature about the effect of SSc on LA functions. Although some of these studies have investigated interatrial electromechanical dyssynchrony as the surrogate for LA function, other studies have performed LA volume analysis (11). In the present study, we aimed to evaluate the LA volume and function with

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RT3DE and 2D speckle tracking echocardiography in SSc patients and compare these parameters with healthy controls. We also aimed to evaluate the mechanisms of possible atrial functional alterations in these patients using the information obtained from LA phasic functional analysis.

Methods

Study design and population

Study was designed to be as cross-sectional observational study. Fifty-three consecutive patients followed in the outpatient rheumatology clinic of the Marmara University Hospital with SSc (defined according to the American Rheumatism Association criteria) were enrolled into the study (12). A detailed medical history, physical examination, and 12-lead electrocardiography were obtained from all patients. Patients with evidence of ischemia on electrocardiograms and evidence of LV systolic dysfunction (ejection fraction of <55%), patients with a history of coronary artery disease, severe valvular heart disease, or atrial fibrillation, and patients with poor-quality imaging on performing 2D echocardiography and/or RT3DE were excluded from the study. Other exclusion criteria were history of arterial hypertension, diabetes mellitus, peripheral arterial disease, chronic obstructive pulmonary disease, chronic renal failure, and liver disease. After excluding patients with these criteria, data of remaining 41 SSc patients and 38 healthy controls were used in the analysis. All subjects provided written informed consent, and the institutional Ethical Committee approved the study protocol.

Rheumatologic parameters

The modified Rodnan skin score (MRSS) was assessed by an experienced rheumatologist by the evaluation of the patient's skin thickness rated by palpation using a scale of 0–3 (0=normal skin, 1=mild thickness, 2=moderate thickness, and 3=severe thickness with the inability to pinch the skin into a fold) for each of the 17 surface anatomic areas of the body such as face, anterior chest, abdomen, (right and left individually) fingers, forearms, upper arms, thighs, lower legs, dorsum of hands and feet. These individual values were added and the sum was defined as the total skin score (range, 0–51).

C-reactive protein (CRP) levels were analyzed using the nephelometric method (Date Behring Siemens, Marburg, Germany). Erythrocyte sedimentation rate (ESR) was measured using the Westergren method. Anti-nuclear antibodies were analyzed by the immunofluorescence (Euroimmun) technique using a commercial kit with Mosaic Hep-20-10/liver (monkey; Luebeck, Germany) substrate. Anti-Scl-70 and anti-centromere antibodies were analyzed by the immunoblotting technique.

Echocardiographic evaluation

All echocardiographic examinations were performed by one researcher who was blinded to the clinical data of the study population using a cardiac ultrasound machine capable of performing real-time 3D examination (IE33; Philips Medical Systems, Andover, MA, USA) with a digital storage software for offline analysis. All patients were in sinus rhythm at the time of examination, and all measurements were calculated from three consecutive cycles; an average of the three measurements was recorded. LV end-diastolic (LVEDD) and LV end-systolic (LVESD) diameters were determined by the M-mode echocardiography under 2-D guidance in the parasternal long-axis view. LA diameter, diastolic interventricular septum, and LV posterior wall thickness were also recorded from the same view.

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. Deceleration time (DT) was defined as slope from the peak the zero velocity E wave. Pulsed wave tissue Doppler imaging (TDI) was performed to assess LV longitudinal functions. In the apical four-chamber view, a 5-mm pulsed Doppler sample volume was placed on the mitral annulus at the septal and lateral sites. To minimize the angle between the beam and the direction of annular motion, care was taken to keep the ultrasound beam perpendicular to the plane of the annulus. Peak systolic (S′) as well as early and late diastolic myocardial velocities (E′ and A′) were recorded. The mean E′ value of LV was calculated using E′ velocities obtained from septal and lateral mitral annular sites. The mean E′ value of LV was used for the calculation of left ventricle E/E′ ratio. Systolic pulmonary artery pressure (sPAP) was derived from continuous Doppler interrogation of tricuspid regurgitation. Estimate of right atrial pressure was added to the right ventriculoatrial gradient based on peak tricuspid regurgitation velocity. Right atrial pressure was estimated from the size of the inferior vena cava and inspiratory collapse according to the recommendations of the American Society of Echocardiography (13). Presence of LV diastolic dysfunction (LVDD) was evaluated and graded according to the recommendations of the American Society of Echocardiography (14) using 2D and tissue-Doppler echocardiography. Patients with lateral mitral annular E′ velocity and/or septal mitral annular E′ velocity values lower than the predefined reference range for various age groups (E′ values lower than the 95% confidence interval range of normal assumption) and/or patients with left atrial volume index (LAVI) values of ≥34 mL/m^2 were deemed to have LVDD in the presence of a normal (i.e., ≥50%) LV ejection fraction (14). LVDD was graded according to the ratio of transmitral early (E) and late (A) flow velocities (E/A ratio), mitral DT, and E/E′ ratio (14). Accordingly, patients with an E/A ratio of <1 (<0.8 for patients over 50 years of age), mitral DT of >200 ms, and/or E/E′ ratio of ≤8 were assumed to have grade 1 LVDD. Patients with E/A ratios between 1 and 1.5 (between 0.8 and 1.5 for patients aged >50 years), mitral DTs between 160 and 200 ms, and/or E/E′ ratios between 9 and 12 were accepted to have grade 2 LVDD. Grade 3 LVDD was assumed to be present if the E/A ratio was ≥1.5, mitral DT was <160 ms, and/or E/E′ ratio was ≥13.

RT3DE was performed using an X5-1 matrix-array transducer (1–3 MHz) for acquisition of ''full-volume'' pyramidal volumetric data sets along four consecutive cardiac cycles. Images were recorded during breath holding, and 3-D echocardiographic images were coupled with electrocardiographic recordings. Apical two-chamber and four-chamber views were generated from the pyramidal data set during expiration. LA cavity was included in the pyramidal scan volume. The RT3DE recordings were digitally stored and analyzed using an analysis software (QLab-Philips version 9.1; Philips Medical systems, Andover, MA, USA). The following anatomical landmarks were manually pointed out to calculate LA volumes: lateral, septal, anterior, and inferior points of the mitral annulus as well as the fifth point at the atrial superior dome point opposite the annulus (theoretical ''apex'' of the left atrium) (15). Regions assumed to be within the pulmonary vein ostia or LA appendix were excluded from the analysis. The software automatically defined the LA internal endocardial border using the manually placed points. Mitral annular plane was accepted to be the limit for the LA base, and manual adjustments were performed accordingly. From these data, a 3D model of LA volume was generated (Fig. 1). The narrowest possible image sector angle including the LA was used to achieve the maximum frame rate, which was 28±6 /s in our study.

All stored digital data were analyzed by an observer blinded to both SSc and controls. The software automatically generated Vmax, Vmin, LA total stroke volume (TSV), and LA total emptying fraction (TEF). Pre-atrial contraction volume (VpreA) was manually generated from the automatically generated volume-time curve at the last frame before the mitral valve opening or at the beginning of the P wave on electrocardiogram (Fig. 1). The following measurements were selected as surrogates of LA function and were calculated manually by the following predefined formulae: LA active stroke volume (ASV): VpreA-Vmin; LA active emptying fraction (AEF): ASV/VpreA×100; LA expansion index (EI): TSV/Vmin×100; and LA passive emptying fraction (PEF): (Vmax-VpreA)/Vmax×100 (16).

TEF and EI have been assumed to reflect LA reservoir function, AEF has been assumed to reflect LA pump function, and PEF has been assumed to reflect LA conduit function (17). LVEF calculated by RT3DE via the evaluation of apical four-chamber and two-chamber views using the pyramidal 3D data set.

2-D Speckle tracking strain imaging

LA speckle tracking analysis was performed using LA-focused images in apical four-chamber view. A minimum frame rate of 40 frames per second was required for the reliability of the analysis. A line was manually drawn along the LA endocardial border when the LA was at its minimum volume using the point-and-click approach. The software then automatically generated additional lines on the region of atrial epicardium and mid-myocardial line within the narrowest region of interest (ROI). The ROI then included the entire LA myocardial wall, and a click feature increased or decreased the width between the endocardial and epicardial lines depending on the thickness of the myocardial wall. The LA myocardium was divided into six segments (basal segment, mid-segment, and apical segment of both the atrial septum and atrial lateral wall). The software generated peak longitudinal strain (ε), late negative strain rate (A-SR, LA contraction), peak positive SR (S-SR, LV systole), and early negative SR (E-SR, LV early diastole) curves for each atrial segment, and average ε and SR values were used in the analysis. S-SR has been assumed to be an index of LA reservoir function; E-SR and A-SR have been assumed to be indices of LA conduit function and LA contractile function, respectively (17).

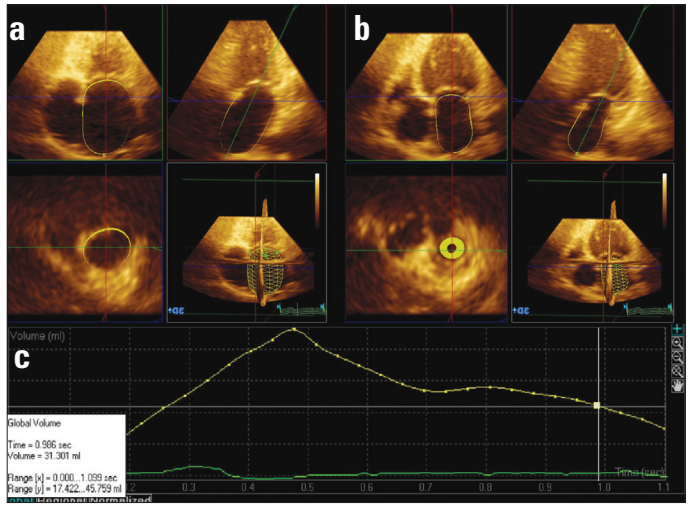

Figure 1. a–c. Real-time three-dimensional tracings of maximum (a) and minimum (b) left atrial volumes and time–volume curve displayed before left atrial contraction volume (VpreA) (c)

Statistical analysis

Statistical analyses were performed using the SPSS 20.0 statistical package for Windows (IBM Corporation Software Group, New York, USA). Distribution of data was assessed using the one-sample Kolmogorov–Smirnov test. Values displaying normal distribution were expressed as the mean±SD, and values not displaying normal distribution were expressed as median (quartiles). Differences between numeric variables were tested using the independent sample Student's t-test or Mann–Whitney U test, where appropriate. Chi-square test was used for the comparison of categorical variables. Correlation was tested with Pearson's or Spearman's correlation tests, where appropriate. For the evaluation of the intra- and interobserver reliability, 20 randomly selected recordings were reanalyzed by the same operator and by another operator blinded to the previously measured data. Intra- and interobserver variability for Vmax, Vmin, and VpreA were assessed by calculating the absolute difference between two observations divided by the mean of the two observations and expressed as percentages. Intra- and intraobserver variability for the LA peak longitudinal systolic ε and S-SR were also examined. A value of $p<0.05$ was considered as statistically significant.

Table 1. Clinical characteristics of SSc patients (n=41)

	SSc patients
Time since diagnosis, years	6.3±4.7
Time since onset of Raynaud phenomenon, years	9.4±4.9
Limited/diffuse cutaneous SSc, n	28/13
Modified Rodnan skin thickness score	14.8±6.2
Raynaud's phenomenon, n (%)	40 (97.6)
Interstitial lung disease, n (%)	21 (51.2)
Pulmonary hypertension, n (%)	6 (14.6)
Digital ulcer, n (%)	21 (51.2)
Esophageal involvement, n (%)	22 (53.7)
ESR, mm/h	30.3±18.5
CRP, mg/L	5.86±5.89
Active disease†, n (%)	7 (17.1)
Immune markers, n (%)	
Antinuclear antibodies	40 (97.6)
Anti-SCL 70 antibodies	12 (29.3)
Anti-centromere antibodies	6 (14.6)
Lung function, % predicted	
FVC	90.9±18
DLCO	74.7±18.1

Data are presented as mean±standard deviation or median (interquartile range)
CRP - C-reactive protein; DLCO - diffusing capacity for carbon monoxide; ESR - erythrocyte sedimentation rate; FVC - forced vital capacity; SSc - systemic sclerosis.
†Active disease is defined as the European Scleroderma Study Group activity index score of higher than 3.

Results

Data of 41 patients (38 females, mean age: 49.5±11.6) with SSc and 38 healthy controls (35 females, mean age: 48.5±10.8) were included in the analysis. There were no significant differences between SSc patients and healthy controls regarding age, gender, and body mass index (BMI) values. Clinical characteristics of SSc patients are presented in Table 1. Six patients (14.6%) had a diagnosis of SSc-associated pulmonary hypertension (PHT) at the time of enrollment into the study. sPAP values could be measured from 30 SSc patients, and the average sPAP was 30.5±7.1 mm Hg. Comparison of 2D echocardiographic parameters and demographic characteristics between two groups is shown in Table 2. There were no significant differences between groups regarding LVEDD, LVESD, LVEF, and LA diameter values. However, Em/Am ratio was lower and E/E′ ratio and DT were higher in SSc patients than in controls. LVDD was significantly more frequent in SSc patients; 16 SSc patients (39%; eight patients with grade 1, six patients with grade 2, and two patients with grade 3 LVDD) and five controls (12.8%; all with grade 1 LVDD) were observed to have LVDD (p=0.007). Results of the RT3DE parameters are shown in Table 3. Vmax, Vmin, and VpreA values were significantly higher; TEF, PEF, AEF, and EI were significantly lower in SSc patients than in controls. There were no significant differences between groups regarding TSV, ASV, and PSV values (Table 3). LVEF was similar in both groups by R3TDE (Table 3). Results of ε and SR parameters are shown in Table 3. Peak longitudinal systolic ε, S-SR, E-SR, and A-SR were significantly lower in SSc patients than in controls (Table 3). Majority of 3D echocardiographic parameters reflecting left atrial phasic functions were found to be significantly correlated with sPAP. Peak longitudinal systolic ε and ESR values were also negatively correlated with sPAP (Table 4). However, linear regression analysis revealed that none of these parameters were independently associated with sPAP. There were no significant correlations between parameters obtained from LA RT3DE or speckle tracking analysis and parameters reflecting the activity of SSc as MRSS, ESR, or CRP. SSc patients were sub-grouped according to the presence of LVDD to observe the contribution of LVDD for altered LA volume and phasic functions. There were no sig-

Table 2. Baseline demographic characteristics and two-dimensional echocardiographic parameters of patients and controls

	SSc Patients	Controls	*P*
Age, years	49.5±11.6	48.8±10.8	0.5
Female	38 (92.7%)	35 (92.1%)	0.5
Body mass index, kg/m^2	26.1±3.9	25.3±5.7	0.4
Two-dimensional echocardiography			
LVEDD, mm	44.7±3.6	45.1±4.0	0.1
LVESD, mm	27.5±3.9	27.4±4.2	0.8
LVEF, %	67.8±5.5	68.8±5.9	0.9
Left atrial diameter, mm	34.1±4.6	33.1±2.9	0.5
IVS, mm	9.5±0.9	9.2±0.8	0.1
PW, mm	9.1±0.9	8.8±0.8	0.2
LV mass, g	146.9±25.3	143.0±33.7	0.5
LV mass index, g/m^2	86.1±13.3	83.6±17.2	0.4
Doppler and tissue Doppler echocardiography			
Em, m/sn	0.7±0.15	0.66±0.16	0.1
Am, m/sn	0.71±0.17	0.67±0.16	0.5
DT, m/sn	191.7±42.1	177.8±30.2	0.08
Em/Am	1.1±0.34	1.3±0.33	0.01
Lateral E′, m/sn	12.1±3.4	16.6±4.5	<0.001
Lateral A′, m/sn	11.7±4.0	11.4±4.0	0.8
Lateral S, cm/sn	9.7±2.0	10.4±2.4	0.1
Septal E′, m/sn	9.0±2.3	11.7±3.4	<0.001
Septal A, m/sn	9.8±2.5	10.5±3.0	0.2
Septal S, cm/sn	8.2±1.3	8.5±1.0	0.3
E/E′	7.8±2.7	6.2±1.4	0.003

DT - deceleration time; IVS - interventricular septum thickness; LVEDD - left ventricle end diastolic dimension; LVEF - left ventricle ejection fraction; LVESD - left ventricle end systolic dimension; PW - posterior wall thickness
Data are presented as mean±standard deviation or median (quartiles). Independent sample Student's t-test and chi-square

Table 3. Three-dimensional, left atrial strain, and strain rate parameters of SSc patients and controls

	SSc Patients	Controls	*P*
LA maximum volume, mL	40.5±14.6	32.6±8.9	0.005
LA minimum volume, mL	15.5±8.4	9.9±3.5	<0.001
Pre-atrial contraction volume, mL	28.7±11.7	21.4±7.0	0.001
LA total stroke volume, mL	25.1±35.1	22.7±6.7	0.2
LA total emptying fraction, %	62.8±10.5	69.5±6.7	0.001
LA active stroke volume, mL	13.2±5.6	11.5±4.6	0.1
LA active emptying fraction, %	47.1±12.0	52.9±10.1	0.02
LA expansion index	187.5±76.0	246.6±96.0	0.003
LA passive stroke volume, mL	11.9±5.5	11.2±4.9	0.5
LA passive emptying fraction, %	29.6±9.3	34.4±11.0	0.03
LV ejection fraction	63.8±4.4	64.4±6.3	0.6
Peak systolic longitudinal strain, %	42.7±12.9	59.8±10.4	<0.001
Peak diastolic longitudinal strain, %	17.7±6.3	20.8±7.4	0.10
Systolic strain rate, s^{-1}	2.6±0.8	3.7±1.0	<0.001
Early diastolic strain rate, s^{-1}	-2.8±0.8	-4.7±1.0	<0.001
Late diastolic strain rate, s^{-1}	-2.8(1.2)	-3.5(1.2)	0.009

LA - left atrial; SSc - systemic sclerosis
Data are presented as mean±standard deviation or median (quartiles). Independent sample Student's t-test

nificant differences regarding 3D LA volume parameters between the two groups. Only E-SR was found to be significantly lower in SSc patients with LVDD than in those without LVDD (Table 5). Mean values of intraobserver variability for Vmax, Vmin, and VpreA were 4.0%±5.8%, 5.4%±5.6%, and 4.1%±4.9%, respectively. Corresponding values for interobserver variability were 7.0%±5.4% for LAVmax, 6.2±5.2% for LAVmin, and 5.0±6.2% for LApreA. The mean values of intraobserver variability for peak systolic ε and S-SR were 6.4±4.8% and 7.2±4.4%, respectively. Corresponding values for interobserver variability were 7.5±5.2% and 7.3±4.6%, respectively.

Discussion

The principal finding of the study is that there are significant alterations in LA volumes and phasic functions in SSc patients. To the best of our knowledge, LA volume and functional analyses with RT3DE have been explored in SSc patients for the first time in our study. Compared with other modalities such as cardiac CT or magnetic resonance imaging (MRI), RT3DE is the most suited for measuring LA volumes and mechanical functions because it allows the assessment of phasic LA functional components and LA pathophysiology in various disease states. LA volumes derived from RT3DE show good agreement with CMR-derived volumes (9) and have a lower intraobserver variability than 2D echocardiography (18). LVDD is an expected finding in SSc patients, and it has been demonstrated in a number of studies with different techniques (19). Significantly more patients in the

Table 4. Bivariate correlation analysis of sPAP and parameters reflecting LA volumes and phasic functions

Variables	R	P
LA maximum volume	0.48	0.001
LA minimum volume	0.48	0.001
LA total emptying fraction	-0.23	0.06
Pre-atrial contraction volume	0.53	<0.0001
LA active emptying fraction	-0.25	0.04
LA passive emptying fraction	-0.26	0.09
LA expansion index	-0.27	0.09
Peak systolic longitudinal strain	-0.44	0.04
Peak diastolic longitudinal strain	-0.30	0.1
Systolic strain rate	-0.37	0.07
Early diastolic strain rate	-0.52	0.01
Late diastolic strain rate	-0.36	0.1

LA - left atrial; sPAP - systolic pulmonary artery pressure

Table 5. Differences in three-dimensional and speckle parameters in SSc patients based on diastolic dysfunction

Variables	SSc Patients with LVDD n=16	SSc Patients without LVDD n=25	*P*
LA maximum volume, mL	38.4 (17.7)	40.4 (19.6)	0.60
LA minimum volume, mL	13.5 (12.3)	13.3 (12.0)	0.60
Before LA contraction volume, mL	25.9 (17.5)	28.2 (15.5)	0.70
LA total stroke volume, mL	24.2 (11.7)	26.1 (10.9)	0.28
LA total emptying fraction,%	65.9 (15.9)	65.2 (14.2)	0.84
LA active stroke volume, mL	12.1 (5.4)	14.2 (7.7)	0.42
LA active emptying fraction	48.6 (13.7)	50.9 (14.6)	0.88
LA expansion index	193.3 (113.1)	187.2 (105.6)	0.84
LA passive stroke volume, mL	11.1 (7.5)	11.4 (7.1)	0.52
LA passive emptying fraction, %	29.5 (13.9)	30.4 (10.0)	0.98
Peak systolic strain, %	44 (19)	42.5 (15.8)	0.40
Peak diastolic strain,%	16 (9)	20 (11.3)	0.50
Systolic strain rate, s^{-1}	2.6 (1.5)	2.9 (1.0)	0.26
Early diastolic strain rate, s^{-1}	-2.7(1.7)	-3.6 (1.4)	0.02
Late diastolic strain rate, s^{-1}	-2.8 (1.1)	-3 (1.3)	0.47

LA - left atrial; LVDD - left ventricular diastolic dysfunction; SSc - systemic sclerosis
Data are presented as median (quartiles). Mann-Whitney U test

SSc group than in the control group had LVDD in our study. LA mechanical functions comprise reservoir, conduit, and contractile functions at different stages of cardiac cycle. The reservoir function takes effect during ventricular systole, passive conduit function during early diastole, and contractile function during late ventricular diastole (17). In our study, LA volumes were significantly higher in SSc patients than in controls. Regarding LA phasic functional parameters derived from RT3DE, AEF, PEF, and TEF were observed to be significantly reduced in SSc patients.

In addition, systolic, early, and late diastolic SR values were also significantly lower in SSc patients. Based on these results, it may be suggested that when compared with controls, LA dysfunction is present in SSc patients with significant impairment in all parameters reflecting phasic functions and increase in volumes. Our observations are partially in agreement with the findings of Agoston et al. (20). They have recently reported that LA reservoir and conduit function were impaired, but contractile function and Vmax were similar between SSc patients and healthy controls on using 2D echocardiography and speckle tracking. The cause of inconsistency regarding contractile function and Vmax may be related to different echocardiographic techniques used in these studies. Coexisting LVDD may be thought to be responsible for observed alterations in our study; however, impairment in LA pump function is not an expected finding for impaired LV diastolic compliance, in which compensatory increase in LA contractility is expected. In addition, there were no significant differences regarding RT3DE and speckle tracking parameters (except E-SR) reflecting LA volume and phasic functions between SSc patients with and without LVDD. Decreased E-SR of SSc patients with LVDD may indicate some degree of impairment in LA conduit function, which is an expected finding related to impaired LV diastolic compliance. Previous studies have found LA peak systolic longitudinal strain as the parameter that is more closely related with LVEDD pressure and serum N-terminal pro-brain natriuretic peptide levels (21, 22). In our study, there were no significant differences between SSC patients with and without LVDD regarding LA peak systolic or LA peak diastolic strain values. The reason for the discrepancy between our study and other abovementioned studies is not clear. Difference regarding patient population characteristics may be a contributing factor because our patient population comprised SSc patients without overt cardiovascular disease. Based on our observations, it may be suggested that intrinsic LA function is also altered in SSc patients besides the possible volume alterations associated with impairment in LV diastolic function in them. Previous studies showed that myocardial involvement in SSc is characterized by patchy fibrosis secondary to both repeated ischemia and/or immunoinflammatory damage, leading to LVDD (23). Based on our observations, it may be speculated that these structural changes are influential on atrial myocardium in SSc patients. However, evaluation with additional diagnostic modalities such as cardiac MRI with late gadolinium enhancement may have better clarified the relationship between LV fibrosis and LA mechanical function. There were no significant correlations between LA phasic volumes and parameters reflecting the activity of SSc such as MRSS, ESR and CRP. Heterogeneity regarding disease activities at the time of enrollment may be a contributing factor for this observation. 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 and the possible effect of SSc on LA functions (24). There were also significant correlations between sPAP and LA phasic volume parameters in our study, although no independent association could be demonstrated between sPAP and these parameters. Fisher et al. (25) reported that LA dimensions were significantly larger in SSc patients with PHT than in idiopathic PHT patients and suggested that this observation is a reflection of increased prevalence of LVDD in SSc patients. Dimitroulas et al. (26) has also recently reported that Vmax is a strong independent predictor of the presence of PHT at rest in a small cohort of SSc patients using 2D echocardiography. The etiology of PHT in SSc patients seems to be multifactorial, and it has been reported that there is a high incidence of postcapillary PHT in SSc patients (27). In our study, the vast majority of SSc patients did not have advanced PHT. In addition, the multifactorial etiology of PHT in SSc may also be a contributing factor for the absence of independent association between sPAP and LA volume or for functional parameters in our study. The clinical relevance of our findings is not clear at the moment. However, our findings may constitute an impetus for future studies investigating the prognostic value of subtle LA dysfunction in SSc patients. RT3DE may be a valuable tool for detecting subclinical cardiac involvement in SSc. It may also be interesting to evaluate the association between subtle LA dysfunction and incidence of supraventricular arrhythmias in these patients.

Study limitations

The major limitation of this study was the small sample size. Secondly, LA appendage has an important role in the function of LA, but we did not include appendage volume for the calculation of LA function. Software (Q lab Philips version 9.1) used for the analysis of 3D volumetric data is originally designed for the evaluation of LV volumes. However, use of this software for the evaluation of LA volumes also seems to be prudent as it has been used by many other studies in the literature. Investigating a correlation between LA volume parameters obtained by 3D echocardiography and another imaging modality as MR would also have been more informative. Results of further prospective studies are needed to elucidate the prognostic role of RT3DE LA volumes in SSc patients.

Conclusion

In our study, LA volume and function analyses by 2D speckle tracking and RT3DE demonstrated significant alterations in LA phasic volumes and functions in SSc patients compared with controls. Results of further studies are needed to elucidate the prognostic significance of subtle LA dysfunction observed in SSc patients.

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