Evaluation of Left Atrial Function by Real-time 3-D Echocardiography in Patients with Systemic Lupus Erythematosus

Kulin Li, Ruxing Wang, Min Dai, Juan Lu, Yaohong Zou, and Xiangjun Yang

ABSTRACT. ***Objective.*** Left atrial function plays a key role in maintaining an optimal cardiac output. Left ventricular diastolic dysfunction has been reported in systemic lupus erythematosus (SLE), but its effect on left atrial function has been largely overlooked. Our aim was to assess left atrial performance using real-time 3-D echocardiography (RT3DE) technology in patients with SLE.

Methods. Our study included 102 patients with SLE without any cardiac symptoms, and 32 healthy controls. According to the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), all subjects were classified into 3 groups: healthy controls, patients with an SDI = 0, and patients with an SDI ≥ 1.

Results. Left atrial volume indexed to body surface area was dilated in subjects with SLE, whereas the left atrial passive emptying fraction (EF) was lower. Left atrial active EF was significantly higher in the SDI = 0 group than in controls (46.4 ± 9.1% vs 30.0 ± 10.3%, $p < 0.05$); however, it was significantly lower in the SDI ≥ 1 group than in the SDI = 0 group (41.2 ± 9.8% vs 46.4 ± 9.1%, $p < 0.05$). By multivariate linear analysis, the SDI was independently and positively associated with left atrial volume index and inversely associated with left atrial total function.

Conclusion. Our study demonstrated that left atrial mechanical function and volume are impaired in SLE, particularly in patients with an SDI ≥ 1 and disease activity. RT3DE may have better diagnostic value than traditional echo indexes in detecting subclinical cardiac dysfunction in patients with SLE.
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Key Indexing Terms:
REAL-TIME 3-D ECHOCARDIOGRAPHY SYSTEMIC LUPUS ERYTHEMATOSUS
LEFT ATRIUM

Cardiac involvement is one of the major complications and the third leading cause of death in patients with systemic lupus erythematosus (SLE)[1]. Impaired left ventricular (LV) diastolic function has been reported in patients with SLE, which may be the earliest and even the unique manifestation of cardiac involvement. Global and regional Doppler echocardiography variables have been used to evaluate diastolic function in SLE. Among them, the ratio of peak transmitral flow velocity in early diastole to early diastolic mitral annulus velocity (E/E′ ratio) has been suggested as a reliable index and proven to be better than others[2,3]. However, these variables are susceptible to LV preload and only reflect the instantaneous diastolic function[4]; more effective recognition of myocardial dysfunction is imperative.

The left atrium contributes to the maintenance of cardiac output and acts as a reservoir during ventricular systole, a conduit during early ventricular diastole, and an active pump during late ventricular diastole. During ventricular diastole, the left atrium is directly exposed to LV diastolic pressure. Factors causing LV filling pressure to rise will also cause left atrial pressure overload. Thus, left atrial size reflects the duration and severity of LV diastolic dysfunction, not strongly depending on short-term changes in preload[4]. The left atrial size has proven to be a potential indicator of early change and outcome in many cardiac diseases[5]. Despite the importance of these changes, there were few reports on left atrial function in SLE.

Real-time 3-D echocardiography (RT3DE) has been increasingly integrated into clinical application. The RT3DE volumetric analysis has been validated to be well correlated with widely accepted reference techniques, such as magnetic resonance imaging and computed tomography[6,7]. Further, RT3DE measurements are more accurate and more reproducible than 2-dimensional echocardiography imaging because they eliminate the need for geometric assump-

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tions[8,9]. In light of this evidence, our aim was to evaluate left atrial function using RT3DE in patients with SLE in comparison with Doppler-echo variables.

MATERIALS AND METHODS

Study population. A total of 102 consecutive patients with SLE and 32 healthy participants were enrolled in our study from our hospital between July 2012 and November 2013. All patients fulfilled the diagnostic criteria of SLE according to the American College of Rheumatology (ACR)[10]. Exclusion criteria included coexisting hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, pericardial disease, and atrial fibrillation. Clinical and demographic characteristics of all subjects were documented, such as age, disease duration, and so on. Blood samples were obtained from all participants and laboratory tests were performed as follows: hemoglobin, fasting glucose, low-density lipoprotein cholesterol, triglyceride, and N-terminal pro-brain natriuretic peptide (NT-proBNP). Antibodies for antiphospholipid, antinuclear, dsDNA, and anti-Smith antibodies were also examined in patients with SLE. The SLE Disease Activity Index (SLEDAI) and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) were used to determine disease activity and SLE-related organ damage, respectively[11,12]. Subjects were categorized into 3 groups based on the determined SDI: control group (n = 32), SDI = 0 group (n = 58), and SDI ≥ 1 group (n = 44). Azathioprine, methotrexate, and cyclophosphamide were used and recorded as immunosuppressive therapy.

The final protocol was approved by the Research Ethics Committee of Wuxi People's Hospital affiliated to Nanjing Medical University, and the written informed consent of all patients was obtained prior to our study.

Echocardiographic evaluation. All study participants were evaluated by 2-dimensional echocardiography. Two-dimensional measurements were taken with M-mode echocardiography and LVEF was calculated by the Simpson method[13]. LV mass (LVM) was calculated using the Devereux formula:

$$LVM = 0.8 \{1.04 [(LVID_d + PWT_d + SWT_d)^3 - (LVID_d)^3]\} + 0.6 \text{ g}$$

where LVID is the end-diastolic dimension, PWT is the posterior wall thickness, SWT is the septal wall thickness, and $_d$ represents the end diastole. LVM was indexed to body surface area (BSA)[13]. Peak transmitral flow velocity in early diastole (E), late diastole (A), and the deceleration time of the E-wave velocity were measured by pulse-wave Doppler. Tissue Doppler imaging at the septal side of the mitral annulus specified early diastolic (E′) and late diastolic (A′) mitral annular velocities. The E/E′ ratio was subsequently calculated. The E/E′ ratio < 8 suggested normal LV filling pressure, and the E/E′ ratio > 15 indicated abnormal diastolic function[2,3].

RT3DE was performed using Philips IE33 ultrasound machine (Philips Medical Systems) attached to a matrix-array X3-1 transducer (2–4 MHz). The 3-D images were acquired in full volume mode within 4–7 cardiac cycles. The 3-D datasets were transferred and analyzed offline using the QLAB 8.0 software (Philips Medical Systems). The apical 4-chamber and 2-chamber views were considered as fundamental planes. Tracing was performed by marking 5 atrial points: the anterior, inferior, lateral, septal mitral annuli, and the left atrial roof. Then left atrial volumes were automatically calculated by the software and resulted in left atrial volume-time curves (Figure 1). The left atrial maximum volume (LAVmax) just prior to mitral valve opening, the left atrial minimum volume (LAVmin) at mitral valve closure, and the left atrial volume before left atrial contraction (LAVpreA), defined as the volume at P-wave onset on the electrocardiogram, were calculated and indexed to BSA. Phasic left atrial volumes and fractions were calculated as follows:

$$\text{left atrial total emptying fraction (EF)} = (\text{LAVmax} - \text{LAVmin}) \div \text{LAVmax}$$
$$\text{left atrial passive EF} = (\text{LAVmax} - \text{LAVpreA}) \div \text{LAVmax}$$
$$\text{left atrial active EF} = (\text{LAVpreA} - \text{LAVmin}) \div \text{LAVpreA}$$
$$\text{left atrial expansion index} = (\text{LAVmax} - \text{LAVmin}) \div \text{LAVmin}$$

Passive atrial EF was defined as index for conduit function, active atrial EF for pump function, and expansion index for reservoir function[6,8,14].

Intraobserver and interobserver variation. A total of 15 randomly selected subjects were independently assessed by 2 echocardiologists to identify variability between and within observers in the measurement of RT3DE variables.

Statistical analysis. Numerical values were presented as the mean ± SD, and categorical variables were provided as absolute numbers. Independent-samples Student t test was used for comparing continuous variables and the chi-square test was used for categorical variable comparison. Correlations of RT3DE derived left atrial variables with E/E′ were evaluated by Pearson correlation coefficient. Multivariate linear regression analyses were performed to determine the independent effect of SLE-related clinical markers on left atrial variables. Intraobserver and interobserver reliability for RT3DE measurements were determined using the correlation coefficient. For all tests, a p value < 0.05 was considered significant. All statistical analyses were performed using SPSS 15.0 statistical software (SPSS Inc.).

RESULTS

Clinical findings. Table 1 summarizes the demographic and clinical characteristics for all subject groups. The mean age of the 102 patients with SLE was 33.0 years (± 8.5) with a mean SLE disease duration of 2.0 years (± 0.5). The majority in both groups was female (88.2%). The SLEDAI ranged from 0 to 5; a total of 17 patients (26.4%) had active disease characterized by the SLEDAI ≥ 3. Upon admission, the most frequent clinical manifestation of SLE was proteinuria in the SDI = 0 group (49.9%) and arthritis in SDI ≥ 1 group (71.4%); however, there was no significant difference in the percentage of damage items. No significant differences in age, sex distribution, BSA, and heart rate were identified between groups. The average disease durations, SLEDAI, and SDI were higher in the SDI ≥ 1 group compared with the SDI = 0 group; however, other clinical variables were similar between the 2 SLE groups.

Two-dimensional echocardiographic variables. Left atrial dimension and LVEF were comparable between groups (Table 2). Compared with the control group, the frequency of E/E′ ratio > 15 was higher in the SDI = 0 group, although E velocity, A velocity, E/A ratio, E′ velocity, A′ velocity, E/E′ ratio, LVM index, and deceleration time were nearly identical. In contrast, the SDI ≥ 1 group exhibited elevated E/A ratio, E/E′ ratio, and LVM index versus the other groups.

RT3DE data of the study population. Compared with the control group by RT3DE, the SDI = 0 group showed significantly higher LAVmax, LAVmin, and LAVpreA indexes, and lower left atrial passive EF ($p < 0.05$). Also, the SDI ≥ 1 group presented significantly higher LAVmax, LAVmin, and LAVpreA indices, and lower left atrial passive EF than the SDI = 0 group ($p < 0.05$; Table 3). The left atrial active EF was higher in the SDI = 0 group than in the control group, and significantly lower in the SDI ≥ 1 group than in the SDI = 0 group. Left atrial expansion index and total EF

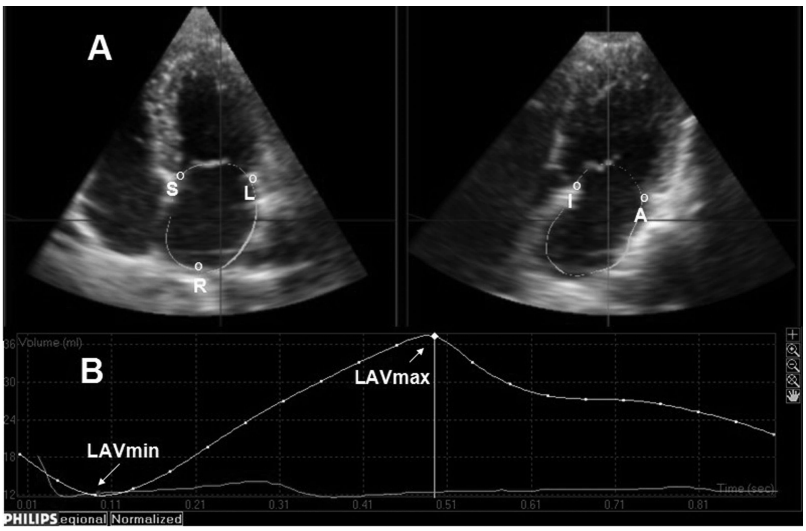

Figure 1. Offline analysis of the left atrial volume. A. Anatomic landmarks used to calculate left atrial volumes by marking 5 points at A, I, L, S, and R. B. Reconstruction of the left atrial time-volume curve. A: anterior; I: inferior; L: lateral; S: septal annuli; R: roof; LAVmax: left atrial maximum volume; LAVmin: left atrial minimum volume.

Table 1. Clinical characteristics in both groups and controls. Values are mean ± SD or n (%) unless otherwise specified.

Characteristics	SDI = 0, n = 58	SDI ≥ 1, n = 44	Controls, n = 32
Age, yrs	34.2 ± 8.4	33.8 ± 8.6	34.8 ± 8.1
Male/female, n/n	7/51	5/39	3/29
Heart rate, beat/min	72.6 ± 9.6	73.8 ± 8.7	71.5 ± 9.8
Body surface area, m^2	1.76 ± 0.33	1.78 ± 0.37	1.81 ± 0.35
Systolic BP, mmHg	120.3 ± 7.4	123.1 ± 7.0	121.1 ± 7.8
Diastolic BP, mmHg	78.3 ± 5.9	76.1 ± 5.3	78.5 ± 6.2
Triglyceride, mg/dl	147.2 ± 16.8	148.6 ± 16.3	146.0 ± 14.2
LDL cholesterol, mg/dl	112.5 ± 16.8	107.0 ± 12.7	113.3 ± 17.3
Hemoglobin, mg/dl	132.2 ± 11.2	132.8 ± 11.0	134.3 ± 11.1
Glucose, mg/dl	99.7 ± 9.3	101.0 ± 11.8	98.8 ± 11.4
NT-proBNP, pg/ml	133.4 ± 67.2	141.9 ± 75.9	110.0 ± 67.3
Malar rash	16 (27.5)	17 (38.6)	—
Discoid rash	17 (29.3)	14 (31.9)	—
Photosensitivity	9 (15.5)	7 (15.9)	—
Oral ulcers	14 (24.1)	7 (15.9)	—
Arthritis	33 (56.8)	31 (71.4)	—
Serositis	7 (12.1)	9 (20.4)	—
Renal	25 (43.1)	22 (52.3)	—
Neurologic	5 (8.6)	7 (15.9)	—
Hematologic	18 (31.1)	16 (36.4)	—
Disease duration, yrs	2.0 ± 0.4	2.2 ± 0.5†	—
SLEDAI	0.6 ± 1.4	2.6 ± 1.3†	—
SDI	0	1.7 ± 1.2†	—
aPL+	11 (18.9)	10 (22.7)	—
ANA+	58 (100)	44 (100)	—
Anti-dsDNA antibody+	43 (74.1)	37 (84.1)	—
Anti-Sm antibody+	10 (17.2)	12 (27.3)	—
Glucocorticoid	25 (43.1)	23 (52.3)	—
Hydroxychloroquine	58 (100)	44 (100)	—
Immunosuppressant	22 (37.9)	24 (54.5)	—

† $p < 0.05$, comparison between the 2 SLE groups. SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; BP: blood pressure; LDL: low-density lipoprotein; NT-proBNP: N-terminal pro-brain natriuretic peptide; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ANA: antinuclear antibody; SLE: systemic lupus erythematosus; aPL: antiphospholipid antibodies.

Table 2. Two-dimensional echocardiographic variables in the study population. Comparison between patients with SLE and control subjects. Values are mean ± SD unless otherwise specified.

Characteristics	SDI = 0, n = 58	SDI ≥ 1, n = 44	Controls, n = 32
LA dimension, mm	35.2 ± 4.3	34.7 ± 3.9	33.3 ± 4.1
LV end-diastolic dimension, mm	46.3 ± 4.1	47.6 ± 4.5	45.9 ± 3.5
LV end-systolic dimension, mm	29.2 ± 2.1	29.4 ± 2.4	28.5 ± 2.1
Septal thickness, mm	8.4 ± 0.7	8.5 ± 0.7	8.2 ± 0.8
Posterior wall thickness, mm	8.3 ± 0.7	8.4 ± 0.7	8.0 ± 0.8
Left ventricular mass, g	125.4 ± 24.0	133.6 ± 23.3*†	119.2 ± 20.8
Left ventricular mass index, g/m^2	73.0 ± 20.9	77.6 ± 18.5*	68.8 ± 15.9
LV emptying fraction, %	65.1 ± 4.7	67.0 ± 6.5	66.5 ± 5.9
E, m/s	0.79 ± 0.31	1.02 ± 0.33*†	0.70 ± 0.18
A, m/s	0.65 ± 0.33	0.48 ± 0.16*†	0.56 ± 0.18
E/A ratio	1.28 ± 0.12	2.23 ± 0.17*†	1.30 ± 0.23
E′, cm/s	9.0 ± 1.4	8.3 ± 1.4	9.2 ± 2.3
E/ E′ ratio	8.5 ± 3.5	13.0 ± 3.4*†	7.6 ± 0.3
Frequency of E/ E′ ratio > 8, n (%)	15 (25.8)*	32 (72.7)*†	2 (6)
Frequency of E/ E′ ratio > 15, n (%)	7 (12.0)*	12 (27.2)*	0 (0)
Deceleration time, ms	171.2 ± 24.2	178.2 ± 32.3	169.1 ± 30.5

* $p < 0.05$, comparison between SLE and control subjects. † $p < 0.05$, comparison between the 2 SLE groups. SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; LA: left atrial; LV: left ventricular; E: mitral early diastolic velocity; A: mitral late diastolic velocity; E′: early diastolic mitral annular velocity; SLE: systemic lupus erythematosus.

Table 3. 3-D echocardiographic variables in the study population. Values are mean ± SD.

Characteristics	SDI = 0, n = 58	SDI ≥ 1, n = 44	Controls, n = 32
LA maximum volume, ml	37.3 ± 7.4*	48.6 ± 9.4*†	27.1 ± 5.2
LA maximum volume index, ml/m^2	20.8 ± 0.8*	26.9 ± 0.8*†	15.5 ± 1.0
LA minimum volume, ml	12.4 ± 2.1*	19.3 ± 2.7*†	9.3 ± 2.3
LA minimum volume index, ml/m^2	7.0 ± 0.7*	10.8 ± 1.1*†	5.3 ± 0.4
LA volume before LA contraction, ml	23.7 ± 5.0*	33.7 ± 7.6*†	13.7 ± 4.5
LA volume index before LA contraction, ml/m^2	13.3 ± 1.2*	18.6 ± 1.6*†	7.7 ± 1.3
LA total emptying fraction, %	65.3 ± 2.8	59.8 ± 3.7*†	66.0 ± 4.9
LA passive emptying fraction, %	36.1 ± 7.6*	30.6 ± 7.5*†	50.2 ± 10.1
LA active emptying fraction, %	46.4 ± 9.1*	41.2 ± 9.8*†	30.0 ± 10.3
LA expansion index, %	196.6 ± 29.5	151.3 ± 25.8*†	198.7 ± 41.4

* $p < 0.05$, comparison between SLE and control subjects. † $p < 0.05$, comparison between the 2 SLE groups. SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; LA: left atrial; SLE: systemic lupus erythematosus.

were similar between the SDI = 0 group and controls, and lower in the SDI ≥ 1 group versus SDI = 0 group.

Significant correlations were found between several left atrial variables and E/E′ ratio, as shown in Figure 2, among which the LAVmax index presented the highest correlation coefficient ($r = 0.60$, $p < 0.01$).

Following the multivariate linear analyses (Table 4), the SLEDAI, SDI, and E/E′ ratio were positively associated with the LAVmax, LAVmin, and LAVpreA indexes; however, they were inversely associated with left atrial total EF.

Interobserver and intraobserver variation. The interobserver correlation coefficients (95% CI) were good for LAVmax (0.93, 0.93–0.99), LAVpreA (0.97, 0.91–0.99), and LAVmin (0.97, 0.91–0.99). The intraobserver correlation coefficients (95% CI) were also good for LAVmax (0.98, 0.95–0.99), LAVpreA (0.98, 0.95–0.99), and LAVmin (0.96, 0.89–0.98).

DISCUSSION

To our knowledge, our study is the first to use RT3DE to assess changes in left atrial mechanical function in patients with SLE. In our study, RT3DE analysis showed increased left atrial volume and impaired left atrial function in patients with SLE. Further, SDI was associated with the development of the left atrial dilation and mechanic dysfunction.

Most patients with SLE experience increased oxidative stress, increased levels of proinflammatory cytokines, and immune cell activation resulting from the chronic inflammatory state of SLE, which result in myocarditis, microvascular diseases, or epicardial coronary arteritis[1,15]. SLE may

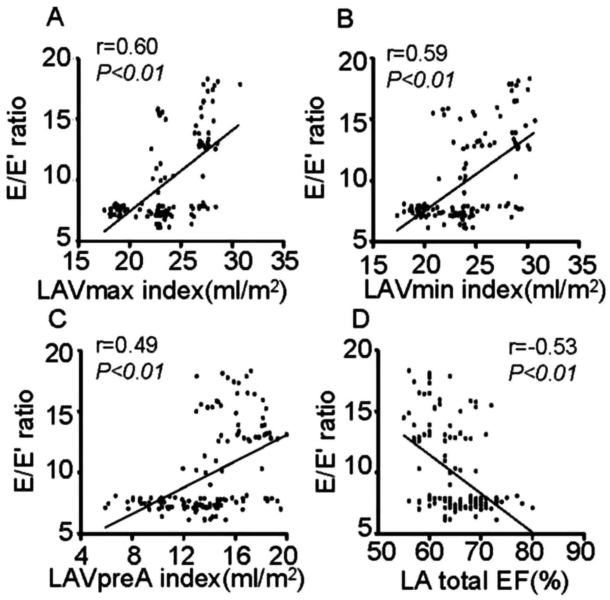

Figure 2. Correlation between real-time 3-D echocardiographic variables and E/E′ ratio. A. LAVmax. B. LAVmin. C. LAVpreA. D. EF. LAVmax: left atrial maximum volume; LAVmin: left atrial minimum volume; LAVpreA: left atrial volume before contraction; EF: left atrial total emptying fraction.

alter atrial myocardium by causing LV diastolic dysfunction and directly affecting atrial myocardium. The SDI not only reflects organ damage, but also indicates longterm inflammatory burden and consequent cumulative cardiac damage[15]. Our study also reflected a trend toward more serious left atrial injuries in patients with SLE with higher SDI.

The most important factor determining left atrial performance is the LV diastolic function[8,14]. Therefore, our results showed that RT3DE-derived left atrial variables were correlated with the conventional diastolic Doppler-echo index E/E′. LV diastolic dysfunction is common and persistent in SLE[1,15] and leads to elevated left intraventricular pressure during diastole, which therefore result in left atrial dilatation and decreased left atrial conduit function[16]. In addition, SLE might directly affect the left atrium, exacerbating left atrial dilatation and stiffness[17].

The impairment of conduit function also results in a larger LAVpreA. According to the Frank-Starling mechanism, the left atrial active function rises in response to moderately elevated LAVpreA because of fiber length increase and compensates for the increased hemodynamic load[14]. Thus, the left atrial total EF was maintained in the SDI = 0 group. After the initial compensatory phase, the further increase of left atrial volume leads to reduction in contractility[14]. Therefore, further deterioration in SLE may lead to the decrease in both left atrial active and total function[17].

The left atrial reservoir function is determined by the LV diastolic function and left atrial myocardial relaxation. Left atrial reservoir function deteriorates with aggravation of SLE because of the increase in left atrial damage and LV diastolic dysfunction[18].

Inflammatory activity, indicated by the SLEDAI, may accelerate the development of cardiac dysfunction. Besides the SDI, SLEDAI has been described as another independent risk factor for cardiovascular events[1,19]. Our results also showed that the SLEDAI was independently associated with left atrial variables, which might reflect the promoting effect of inflammatory activity on left atrial impairment.

In our present study, we reduced confounding risks by excluding patients presenting with traditional cardiovascular risk factors, and limited the sensitivity of our findings. Left atrial diameter, E/A ratio, and E/E′ were similar between the SDI = 0 group and healthy controls when evaluated by traditional methods. The low frequency of E/E′ ratio > 15 and no significant increase in the plasma NT-proBNP signified mild LV diastolic dysfunction in patients with SLE[13]. However, significant changes in the left atrial performance between groups were revealed following RT3DE evaluation. RT3DE may have much better diagnostic value than traditional echo indices in detecting subclinical cardiac dysfunction in patients with SLE, earlier than E/E′ ratio. In our study, the impaired left atrial performance reflected early cardiac

Table 4. Correlation with 3-D echocardiographic variables using multivariate linear regression analyses.

Characteristics	LA Maximum Volume Index		LA Minimum Volume Index		LA Volume Index Before LA Contraction		LA Total Emptying Fraction	
	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p	B (95% CI)	p
Age	0.01 (–0.02–0.04)	0.51	0.01 (–0.03–0.03)	0.76	0.01 (–0.04–0.05)	0.66	0.01 (–1.11–0.12)	0.57
Sex	–0.54 (–1.36–0.28)	0.20	–0.44 (–1.18–0.30)	0.25	–0.90 (–2.10–0.30)	0.14	2.04 (–0.93–5.02)	0.18
Disease duration	0.73 (0.12–1.43)	0.02	0.32 (–0.23–0.87)	0.04	0.44 (–0.44–1.34)	0.32	–0.99 (–3.21–1.22)	0.38
Heart rate	0.01 (–0.02–0.02)	0.78	0.02 (–0.01–0.09)	0.69	–0.01 (–0.02–0.02)	0.68	0.01 (–0.03–0.04)	0.23
E/ E′ ratio	0.19 (0.11–0.27)	0.00	0.13 (0.06–0.20)	0.00	0.16 (0.04–0.28)	0.01	–0.56 (–0.85 – –0.26)	0.00
SLEDAI	0.40 (0.20–0.60)	0.00	0.21 (0.04–0.39)	0.02	0.08 (–0.20–0.37)	0.04	–0.92 (–1.62 – –0.22)	0.01
SDI	0.76 (0.46–1.06)	0.00	0.56 (0.29–0.83)	0.00	0.74 (0.30–1.18)	0.00	–2.53 (–3.63 – –1.43)	0.00

LA: left atrial; E′: early diastolic mitral annular velocity; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

abnormalities that could be attributed to the thinness of the left atrial walls, which might be affected earlier and more seriously than the LV walls.

Some limitations of our study should be noted. Limited patient number and a lack of patient followup lessen the power and interpretation of our findings; thus, longterm followup and large-scale prospective studies are necessary to determine the predictive value of the left atrial mechanical volume and functional assessment in patients with SLE. Further, we did not collect strain and strain rate measurements that could yield more information on early atrial involvement in our study population[8].

Patients with SLE have increased volume and impaired function of the left atrium, especially those patients with higher SDI and disease activity. The RT3DE markers seem to be more sensitive compared to the traditional echo indices in detecting subclinical cardiac involvement in SLE.

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