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Left atrial volume and function in patients with cardiac syndrome X assessed by real time three-dimensional echocardiography

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Objective: The aim of this study was to evaluate left atrial (LA) volume and function using real time three-dimensional echocardiography (RT3DE) in patients with cardiac syndrome X (CSX).

Methods: Fifty patients with CSX (28 females; mean age 50.9±10.9 years) and 50 age- and gender-matched healthy controls (30 females; mean age 52.3±9.8 years) who had negative treadmill exercise test and normal coronary arteries on invasive coronary angiography were included in the study. Comprehensive two-dimensional (2D), pulsed and tissue Doppler, speckle tracking echocardiography, and RT3DE for the assessment of LA dynamics were performed in all study participants.

Results: Cardiac syndrome X and control groups have similar clinical characteristics regarding age, sex, body mass index, hypertension, diabetes, and smoking habit. 2D echocardiographic parameters were also similar between groups. Pulsed- and tissue Doppler parameters, IVRT, A, and A_m values, were higher in CSX group, while E_m, E/A, and E_m/A_m ratios were higher in the control group reflecting mild diastolic dysfunction. Regarding RT3DE parameters, LA maximum volume, minimum volume, volume before atrial contraction, LA maximum volume index, total and active stroke volumes were found to be increased in CSX patients. However, LA total stroke fraction, passive stroke volume, passive stroke fraction, peak systolic, and diastolic longitudinal strains were found to be lower in CSX patients.

Conclusion: The main finding of this study was that CSX patients had altered LA booster pump, reservoir, and conduit functions. This finding may have clinical implications for early detection of abnormal LA dynamics in CSX patients.

KEYWORDS
left atrial volume, myocardial ischemia, three-dimensional transthoracic echocardiography

1 | INTRODUCTION

Cardiac syndrome X (CSX) is a clinical entity characterized by angina-like chest pain with a positive noninvasive stress test and angiographically normal coronary arteries.[1,2] The exact pathophysiological mechanisms underlying CSX have not been completely understood. However, endothelial dysfunction leading to microvascular angina and impaired coronary flow reserve has been proposed as the main causative factors.[3] Intravascular ultrasound studies of coronary arteries demonstrated that patients with CSX had coronary arteries with atheromatous plaques and intimal thickening, which conventional coronary angiography did not detect.[4] Indeed, between 10% and 20% of patients who underwent coronary angiography for the evaluation of chest pain were found to have normal or near normal coronary

arteries.[5] These findings prompted clinicians to consider CSX as an early phase of atherosclerosis. With increasing interest in this syndrome, the latest European guidelines included treatment options for these patients who continue to report symptoms.[6]

Left atrium (LA) plays a critical role in left ventricular filling with LA reservoir, conduit, and contractile functions.[7,8] Changes in LA size and function are associated with major adverse cardiovascular events such as atrial arrhythmias, heart failure with preserved ejection fraction, stroke, and death.[9–13] Abnormal LA function is considered as an early finding in atherosclerosis, which usually accompanies with CSX. Previous studies have well documented this association using conventional pulsed and tissue Doppler echocardiographic measurements.[2,14,15] However, there are not much data with regard to utilization of other advanced techniques such as real-time three-dimensional echocardiographic (RT3DE) imaging in determining LA dynamics, which is a recently developed technique that allows the quantitative assessment of function and volume of any cardiac chamber. This technique is considered a feasible and reproducible method for its clinical application.[16,17] So, we hypothesized that left atrial function would be impaired within the patient group with CSX.

2 | METHODS

We recruited subjects from the cardiology outpatient clinic of our university hospital. Fifty patients with newly diagnosed CSX (28 females and 22 males, mean age 50.9±10.9 years) were enrolled in the study. The diagnosis of CSX was based on the presence of typical anginal chest pain, positive treadmill exercise test, and angiographically normal coronary arteries. Fifty healthy control subjects (30 females and 20 males, mean age 52.3±9.8 years), who had atypical chest pain, negative treadmill exercise test and angiographically no evidence of coronary artery disease, matched for age and sex, represented the control group.

The exclusion criteria for the study were poor image quality on echocardiography, hypertrophic, ischemic or dilated cardiomyopathy, moderate-to-severe valvular heart disease, heart failure with reduced or preserved ejection fraction, history of myocarditis or pericarditis, left ventricular hypertrophy of any origin (LV mass >104 g/m^2 on echocardiography), arrhythmias, renal and hepatic failure, acute and chronic inflammatory diseases, Tietze's syndrome, and history of cardiac surgery. All study participants underwent a comprehensive physical examination and routine laboratory tests before participation. The study was approved by the local institutional ethics committee, and informed consent was obtained from each study participant.

2.1 | Laboratory analysis

Venous blood samples were obtained by venipuncture at morning after an 8-hour overnight fasting. Glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were measured by enzymatic methods using an autoanalyzer (Beckman Coulter AU5800, Fullerton, CA, USA). Low-density lipoprotein cholesterol (LDL-C) level was calculated with the Friedewald equation.[18]

2.2 | Treadmill exercise stress test

Treadmill exercise test was performed according to the modified Bruce protocol (T600 Treadmill; Spacelabs Burdick Inc., Deerfield, WI, USA) after the participants had been requested to avoid from food, alcohol, caffeine, or smoking at least 4 hours before the test. Heart rate, 12-lead electrocardiography (ECG), and blood pressure were recorded during and after the exercise. Horizontal or a downsloping ST-segment depressions greater than 1 mm or upsloping ST-segment depressions greater than 2 mm after the J point in two or more contiguous leads were considered to be a positive stress test for myocardial ischemia.

2.3 | Echocardiographic evaluation

All the study participants underwent comprehensive echocardiographic examinations using an iE33 Philips echocardiography unit equipped with broadband S5-1 and X3 matrix-array transducers (Philips Medical Systems, Bothell, WA, USA). M-mode, two-dimensional, pulsed-wave Doppler, tissue Doppler imaging, and RT3DE were performed by two experienced cardiologists blinded to the study population. Two-dimensional and Doppler examinations were performed in accordance with the American and European Societies of Echocardiography recommendations.[19,20]

The following 2DE parameters were measured; left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), aortic root, LA diameter, interventricular (IVST), and posterior wall thicknesses in diastole (PWT). LV ejection fraction (LVEF) was calculated using Simpson's method.

The following pulsed-wave and tissue Doppler parameters were measured; mitral inflow velocities of the early diastolic (*E*)-wave, late systolic (*A*)-wave, the *E*/*A* ratio, E-wave deceleration time (DT), isovolumetric relaxation time (IVRT), myocardial systolic (S_m), peak early diastolic (E_m), and peak late diastolic (A_m) velocities. E/E_m and E_m/A_m ratios were subsequently calculated. Sample volume was placed on septal mitral annulus in the apical four-chamber view.

For the LA speckle tracking analysis, a line was manually adjusted along the LA endocardial border from the apical four-chamber view after atrial contraction when the atrial volume at its nadir before mitral valve closure. The software then automatically generated additional lines near the atrial epicardium and mid-myocardial line, with the narrowest region of interest (ROI). The ROI then included the entire LA myocardial wall and was adjusted for thickness. The software generated strain curves for each atrial segment. The values of peak early and late diastolic longitudinal strain were measured.

Real time three-dimensional echocardiography was performed by the same two cardiologists. RT3DE images were obtained from apical four-chamber view with the study participants in breath-hold, and views were gated with electrocardiographic tracing. At least four consecutive cardiac cycles were analyzed, and an average was obtained. Full-volume mode was used, and entire LV and LA cavities were included within the pyramidal scan volume. The RT3DE volumes were digitally stored and analyzed off line later

using QLab software (QLab, Philips version 9.1; Philips Medical Systems). LA models were created using 5-point method with automatic border definition on the atrial face of the mitral annulus (anterior, inferior, lateral, and septal) and midpoint of the LA roof (bottom border of LA in the apical four-chamber view). Pulmonary vein ostia or LA appendage were excluded from the measurements because of complex and variable shape of the LA appendage and difficulty of obtaining a clear image of LA appendage on 2D echocardiography. From these data, a 3D model of the LA volume was generated (Figure 1A and B). The following volumetric measurements were determined;

1. maximum LA volume at end systole (LAVmax), the time at which the atrial volume was the largest just before the mitral valve opening. The resulting maximum LA volume index (LAVI) was calculated by dividing LAVmax to body surface area.
2. minimum LA volume at end diastole (LAVmin), the time at which the atrial volume at its nadir before mitral valve closure,
3. LA volume before atrial contraction (LAVpreA): the last frame before mitral valve reopening (Figure 2).

From above volumes, the following parameters were measured according to previous studies as parameters of LA function[8,17];

1. LA reservoir function:
   LA total stroke volume=LAVmax−LAVmin
   LA total stroke fraction=(LAVmax−LAVmin)/LAVmax×100
2. LA conduit function:
   LA passive stroke volume=LAVmax−LAVpreA
   LA passive stroke fraction=(LAVmax−LAVpreA)/LAVmax×100
3. LA booster pump function:
   LA active stroke volume=LAVpreA−LAVmin
   LA active stroke fraction=(LAVpreA−LAVmin)/LAVpreA×100.

2.4 | Coronary angiography

Coronary angiography was performed using standard Judkins technique in all subjects (Philips Medical Systems Integris H 3500 ve 5000). Normal coronary arteries were defined as no visible luminal narrowing or irregularity. All patients underwent a hyperventilation test to exclude the possibility of coronary artery vasospasm, which was performed by asking the patients to breathe quickly and deeply for 5 minutes.

2.5 | Statistical analysis

Statistical analyses were performed using SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate whether the variables were normally distributed. Continuous variables were presented as means with standard deviations or medians with 25th–75th percentiles. Categorical variables were given as numbers with percentages. Continuous data were analyzed by Student's *t* test for normally distributed variables and Mann–Whitney *U* test for nonnormally distributed variables. Categorical data were analyzed using chi-square test or Fisher's exact test. Inter-rater reliability was assessed using kappa value of agreement to determine that researchers consistently assigned subjects to appropriate groups. Inter-rater reliability using intra-class correlation coefficient (ICC) was also assessed to determine that researchers provided consistency in their measurements of left atrial volumes. All

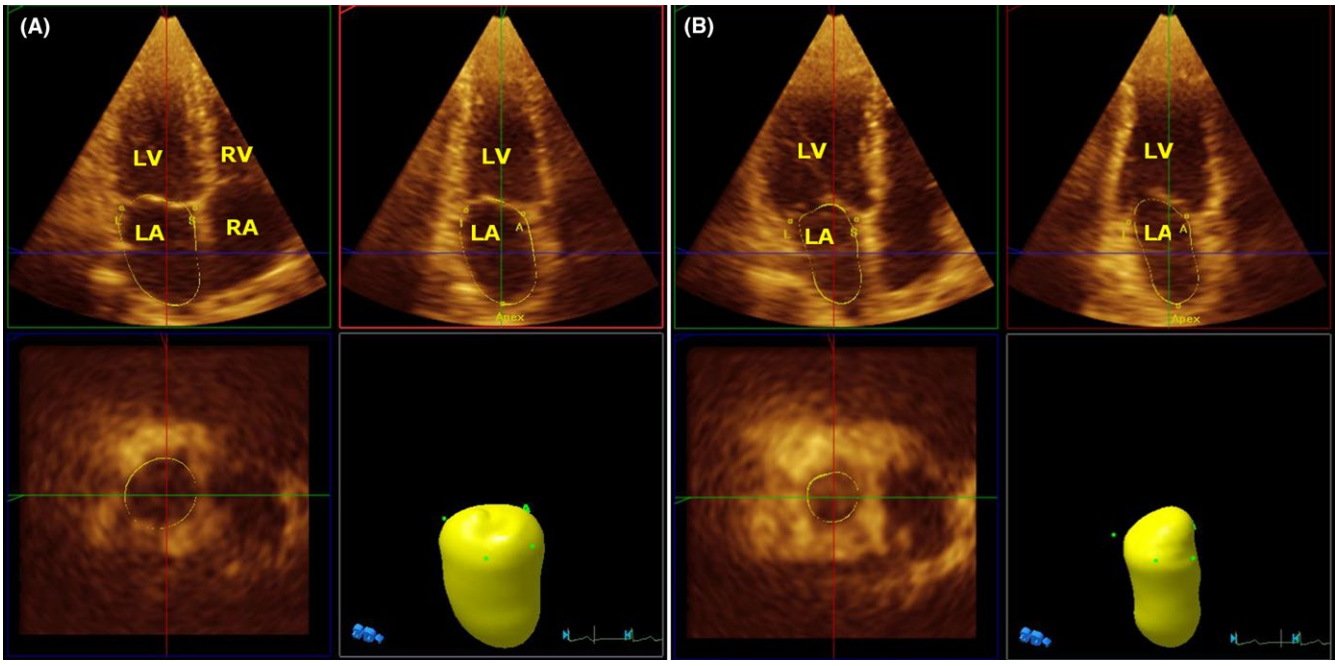

FIGURE 1 Real time three-dimensional echocardiography recordings of (A) maximum left atrial volume and (B) minimum left atrial volume. LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle

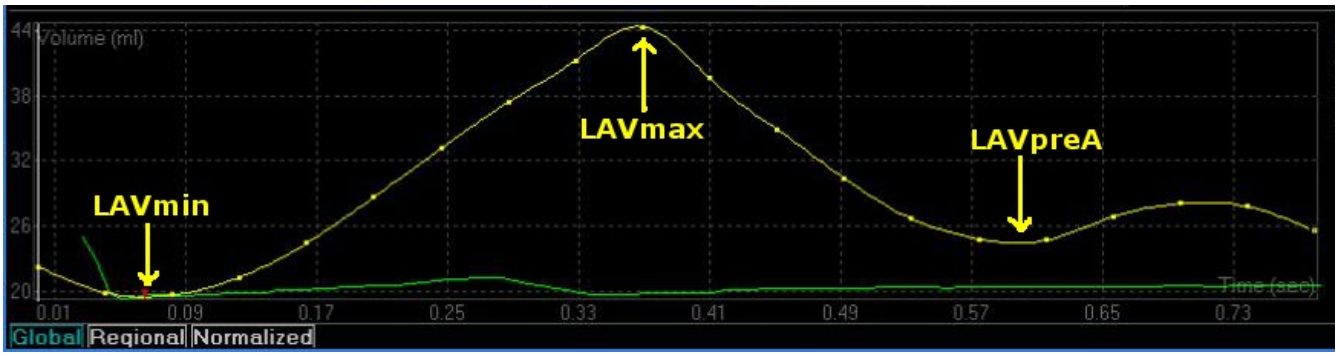

FIGURE 2 Time-volume curve with indicating maximum (LAVmax) and minimum (LAVmin) left atrial volumes and before left atrial contraction volume (LAVpreA)

P-values were two-tailed, and values of less than .05 were considered to indicate statistical significance.

3 | RESULTS

Baseline clinical characteristics and laboratory findings of the study population are presented in Table 1. There was no statistically significant difference between CSX and the control group with regard to age, sex, body mass index, smoking, diabetes, systolic and diastolic blood pressures, glucose, creatinine, total cholesterol, HDL-C, LDL-C, triglycerides levels. The resulting kappa indicated perfect agreement, κ=0.96. The resulting ICC for LAVmax, LAVmin, and LAVpreA was 0.97, 0.95, and 0.94, respectively, indicating that echocardiologists had a very high degree of agreement.

TABLE 1 Clinical characteristics and laboratory findings of the CSX and control groups

	CSX group n=50	Control group n=50	*P*-value
Age, years	50.9±10.9	52.3±9.8	.51
Female, n (%)	28 (56)	30 (60)	.83
BMI, kg/m^2	27.9±4.0	27.1±4.2	.33
Smokers, n (%)	12 (24)	15 (30)	.65
Diabetes, n (%)	4 (8)	1 (2)	.36
SBP, mm Hg	124±13	121±15	.38
DBP, mm Hg	77±10	74±13	.16
Fasting blood glucose, mg/dL	99.9±15.7	100.1±15.3	.94
Creatinine, mg/dL	0.82±0.16	0.78±0.17	.22
Total cholesterol, mg/dL	200.3±39.8	191.7±37.6	.28
LDL-C, mg/dL	125.0±31.6	120.5±33.8	.50
HDL-C, mg/dL	41.7±9.1	43.3±9.3	.43
Triglycerides, mg/dL	159.2±75.1	140.6±66.6	.21

BMI=body mass index; CSX=cardiac syndrome X; DBP=diastolic blood pressure; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; SBP=systolic blood pressure.

The results of two-dimensional and Doppler echocardiographic measurements are demonstrated in Table 2. Regarding two-dimensional echocardiographic parameters, there was no significant difference between groups with regard to LVEF, LVEDD, LVESD, LA diameter, PWT, and IVST. Regarding pulsed and tissue Doppler echocardiographic indices, DT, ET, *E*, $S_{m,}$ and E/E_m ratio were not different between groups. However, IVRT, *A*, and A_m values were increased in CSX group, while E_m value, E/A, and E_m/A_m ratios increased in the CSX group when compared to the control group. Speckle tracking echocardiography showed that LA peak systolic and diastolic longitudinal strain values were decreased in CSX patients when compared to the control subjects (Table 2).

The results of RT3DE measurements are shown in Table 3. LA volumes, LAVmax, LAVmin, LAVpreA were found to be increased in CSX patients. LA stroke volumes, both total and active, also enhanced in CSX patients in comparison with controls. However, LA passive stroke volume was lower in CSX patients. In addition, LA total and passive stroke fraction were also decreased in CSX patients.

4 | DISCUSSION

To the best of our knowledge, the present study is the first in which LA volumes and LA mechanical functions were assessed by RT3DE in CSX patients. The main finding of this study is that LA functions are altered in CSX patients. To describe in detail, LA function basically plays three main physiologic roles in the presence of sinus rhythm: (1) acting as a contractile pump (booster) that provides up to one-third of the left ventricular volume, which are represented by LA active stroke volume and fraction in RT3DE, (2) acting as a reservoir that collects pulmonary venous return during ventricular systole, which are represented by LA total stroke volume and fraction in RT3DE, peak systolic and diastolic longitudinal strain by speckle tracking echocardiography; and (3) acting as a conduit for passing stored blood from the LA to the LV during early diastolic phase which are represented by LA passive stroke volume and fraction in RT3DE and peak diastolic longitudinal strain by speckle tracking echocardiography.[8,17] Actually in our study, LA active stroke volume and fraction were increased in CSX patients reflecting enhanced booster pump function. In addition, LA total stroke volume increased while LA total stroke fraction and peak systolic and diastolic longitudinal strain decreased in CSX patients reflecting impaired

TABLE 2 Two-dimensional Doppler and two-dimensional speckle tracking echocardiographic parameters of the CSX and control groups

	CSX group n=50	Control group n=50	*P*-value
LVEF, %	61.1±3.4	61.5±2.0	.55
LA diameter, mm	35.2±2.9	34.2±2.6	.08
LVEDD, mm	46.9±2.4	46.0±1.7	.03
LVESD, mm	28.6±2.8	27.7±1.6	.06
IVST, mm	10 (10–11)	10 (10–10)	.10
PWT, mm	10 (9–10)	9 (8–10)	.11
DT, ms	179 (162–230)	180 (170–189)	.75
IVRT, ms	85.0±12.6	79.4±10.4	.01
ET, ms	279±31	291±45	.14
E, cm/s	78.3±17.4	82.3±13.7	.20
A, cm/s	80.5±18.1	61.6±9.6	<.0001
S_m, cm/s	9.0 (8.2–10.4)	9.4 (8.5–11.2)	.42
E_m, cm/s	10.4±2.8	11.6±1.5	.01
A_m, cm/s	10.2±1.5	8.5±1.5	<.0001
E/*A*	0.85 (0.79–1.24)	1.30 (1.22–1.44)	<.0001
E/E_m	7.8±1.8	7.2±1.9	.15
E_m/A_m	1.03±0.28	1.37±0.21	<.0001
LA peak systolic longitudinal strain, %	45.2±11.1	54.5±8.5	<.0001
LA peak diastolic longitudinal strain, %	17.2±5.3	20.2±5.2	.006

A=late mitral diastolic velocity; A_m=peak late mitral tissue Doppler diastolic velocity; CSX=cardiac syndrome X; DT=mitral E-wave deceleration time; *E*=mitral early diastolic velocity; E_m=peak early mitral tissue Doppler diastolic velocity; ET=ejection time; IVRT=isovolumetric relaxation time; IVST=interventricular septal thickness; LA=left atrium; LVEDD=left ventricular end-diastolic diameter; LVEF=left ventricular ejection fraction; LVESD=left ventricular end-systolic diameter; PWT=posterior wall thickness; S_m=peak early systolic myocardial velocity.

reservoir function. Finally, LA passive stroke volume and fraction and peak diastolic longitudinal strain decreased in CSX patients also reflecting impaired conduit function. Thus, LA dynamics were altered in CSX patients when compared healthy individuals.

The underlying mechanisms that contribute to the aforementioned changes may be; when left ventricular dysfunction begins to develop due to subclinical atherosclerosis or impaired coronary flow reserve, the LA may preserve adequate cardiac output by altering booster pump and reservoir functions.[21,22] As LV diastolic dysfunction further impairs, LA pressure increases to overwhelm the left ventricular pressure. Thus, left atrial dilatation and increased left atrial reservoir function develop because of enhanced left ventricular stiffness. During early diastole, impaired diastolic relaxation, and increased left ventricular stiffness together with increased intraventricular pressure cause a decrease in left atrial passive emptying leading to decreased conduit volume, thus negatively affecting conduit function.[8,23–25]

Several imaging methods have been used to assess LA volume and function such as two-dimensional and Doppler echocardiography, speckle tracking echocardiography, cardiac computed tomography, cardiac magnetic resonance, and angiography.[16] Each technique has its own limitation. Administration of contrast medium, radiation exposure, higher costs, low temporal resolution, and invasiveness of the method are some of the problems. In addition, two-dimensional measurements may inherently carry miscalculations due to oblique position of interatrial septum, shape of the left atrial appendage, and asymmetric LA enlargement. Nowadays, a novel imaging technique, RT3DE, has recently been introduced as a reliable and reproducible technique for the assessment of cardiac chambers. RT3DE provides an accurate measurement of the left atrial volume and function and could be considered a feasible and reproducible method for its clinical application. 3D measurements were also found to be comparable to magnetic resonance imaging (MRI) and are superior to current 2D echocardiographic techniques in assessing LA volumes.[17,26–28] Indeed, in our study, two-dimensional echocardiographic parameters were similar between groups. Only a few pulsed- and tissue

TABLE 3 Three-dimensional echocardiographic parameters of the CSX and control groups

	CSX group n=50	Control group n=50	*P*-value
LA maximum volume, mL	41.6±8.7	36.0±3.6	<.0001
LA minimum volume, mL	16.9±3.9	13.6±2.4	<.0001
LA maximum volume index, mL/m^2	22.5±5.1	19.6±2.8	<.001
LA volume before atrial contraction, mL	28.2±6.3	21.3±3.3	<.0001
LA total stroke volume, mL	24.7±5.5	22.4±3.0	.01
LA total stroke fraction	59.7±4.8	62.2±5.7	.02
LA active stroke volume, mL	11.2±2.9	7.7±2.2	<.0001
LA active stroke fraction	39.8±4.5	36.1±8.0	.005
LA passive stroke volume, mL	13.5±3.3	14.7±2.5	.03
LA passive stoke fraction	32.4±5.0	40.8±6.2	<.0001

CSX=cardiac syndrome X; LA=left atrium.

Doppler parameters were different in CSX group reflecting a mild diastolic dysfunction at most. However, all RT3DE parameters were abnormal in CSX group. This may be due to the fact that RT3DE may detect early changes in LA dynamics before two-dimensional, pulsed- and tissue Doppler echocardiographic techniques could detect.

4.1 | Limitations

We accept that our study had some limitations. Firstly, our study had a relatively small sample size. Another limitation was that the possibility of any underlying coronary artery spasm in our patients with CSX was ruled out by a hyperventilation test despite the superiority of the ergonovine test. Additionally, LA appendage plays an important role in the LA reservoir function, especially during increase in LA pressure or volume. However, we did not include LA appendage for the calculation of LA volume and function. Lastly, we did not evaluate left ventricular strain/strain rate and natriuretic peptides together with RT3DE.

5 | CONCLUSION

We demonstrated alterations of LA volume and functions by RT3DE in CSX patients. However, only mild LA diastolic dysfunction was present in this group of patients when traditional methods were used. These findings may be indicative of subclinical cardiac involvement in CSX, which may cause directly or indirectly functional and structural changes in the LA. This finding may also have clinical implications for early detection of abnormal LA dynamics in CSX.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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