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Assessment of left atrial volume and function by real time three-dimensional echocardiography in obese patients

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Objective: To evaluate left atrial (LA) volume and functions in obese subjects using real time three-dimensional echocardiography (RT3DE) and also the relationship between LA mechanical functions and N-terminal pro-atrial natriuretic peptide (NT-proANP).

Methods: This study included 40 obese (26 females and 14 males, mean age 51.9 years) and 40 normal weight subjects (23 females and 16 males, mean age 53.5 years) with normal coronary angiograms. All the study participants underwent RT3DE to assess LA volume and mechanical function. Plasma NT-proANP was determined by ELISA method.

Results: There was no significant difference between groups in left ventricular (LV) diameters and ejection fraction, which reflect LV systolic function. However, transmitral deceleration time, isovolumetric relaxation time, and peak late diastolic tissue Doppler velocity values, which reflect LV diastolic function, were found to be significantly higher in obese subjects when compared with controls. LA maximum volume (LAVmax), LAVmax index (LAVI), LA minimal volume (LAVmin), before atrial contraction volume (LAVpreA), LA active emptying volume, LA total emptying volume, and LA active emptying fraction, which reflect LA reservoir and pump functions, were also higher in obese subjects when compared with controls. LA passive emptying fraction was significantly lower in obese subjects than in controls. NT-proANP levels were similar between groups. There were positive correlations between NT-proANP level and LAVI, LAVmax, LAVmin, LAVpreA, and LA total and active emptying volumes.

Conclusions: Left atrial mechanical functions and volumes are impaired in obese subjects. These findings may be regarded as early markers of subclinical cardiac failure in obese subjects who have not yet exhibited any clinical evidence of cardiovascular disease.

KEYWORDS
echocardiography, left atrial volume, obesity

1 | INTRODUCTION

Obesity constitutes a major public health problem, and its prevalence continues to increase sharply in worldwide. It has a substantial clinical, social, and economic burden, notably due to being a major risk factor for the development of cardiovascular disorders such as atrial fibrillation (AF), diastolic dysfunction, and cardiac failure.[1,2] Previous studies have demonstrated a variety of minor cardiovascular changes ranging from hyperdynamic circulation to subclinical cardiac structural changes in obese subjects.[3–5] However, conventional noninvasive

imaging modalities fail to document a detailed picture of cardiac structural changes and detect subtle and early functional alterations associated with obesity.[6] Currently, left atrial (LA) size measurement appears to be one of the most commonly used methods to estimate the amount of atrial remodeling. LA volumes and LA mechanical functions have been shown to be associated with several major adverse cardiovascular outcomes such as atrial arrhythmias, cardiac failure, stroke, and death.[7–10] In addition, many studies have demonstrated that real time three-dimensional echocardiography (RT3DE) is able to provide an accurate measurement of LA volume and function and can be considered a feasible and reproducible method for its clinical utility.[11,12] Nowadays, the development of cardiac imaging techniques such as RT3DE enabled us to identify obesity-related preclinical damage at earlier stages. However, there are not much data regarding the effects of obesity in LA volume and functions in obese subjects. Therefore, we aimed to evaluate the effects of obesity on LA volume and mechanical functions using RT3DE in a population of obese subjects free of overt cardiovascular disease. In addition, the relationship between LA mechanical function and NT-proANP was examined.

2 | METHODS

We included 40 obese (mean age 51.9±9.0 years, mean body mass index [BMI] 35.5±4.3 kg/m²) and 40 normal weight control subjects (mean age 53.5±6.7 years, mean BMI 25.7±1.6 kg/m²). The study participants were selected from consecutive patients who underwent coronary angiography within 6 months before study enrollment in our center and found to have angiographically normal coronary arteries. A careful history was taken, and a complete physical examination was performed in all subjects. A resting 12-lead electrocardiography was obtained. The demographic parameters of all patients were recorded. To avoid confounding factors that affect the LA volume, individuals having the following conditions from both groups were excluded from the study: systemic hypertension (blood pressure ≥140/90 mm Hg or ongoing antihypertensive treatment), diabetes mellitus (fasting serum glucose level ≥126 mg/dL or ongoing diabetes treatment), history of coronary artery disease (≥30% luminal diameter narrowing of ≥1 coronary artery shown on angiography), antiarrhythmic drug use, valvular heart diseases, obstructive sleep apnea, chronic inflammatory diseases, atrial fibrillation, cardiomyopathies, renal failure, liver disease, and poor-quality imaging on two-dimensional (2D) echocardiography and/or RT3DE.

Using standard laboratory methods, blood samples were drawn after an overnight 12-hour fasting to determine levels of blood glucose, electrolytes, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides. Plasma NT-proANP level was studied by ELISA method with a commercially available kit (Enzyme Immunoassay For In Vitro Quantitative Measurement of NT-ProANP, SEA484Hu, 96 tests). The protocol was approved by the local research ethics committee, and the written informed consents from all subjects were obtained.

2.1 | Echocardiographic evaluation

All the study participants underwent a detailed 2DE examination in accordance with the recommendations of the American Society of Echocardiography, followed by RT3DE, which was carried out by two experienced echocardiologists. Inter-observer variability was comparable between two echocardiologists. A commercially available machine (iE33, Philips Medical Systems, Bothell, WA, USA) equipped with broadband S5-1 transducer—with digital storage software for offline analysis—was utilized. Another two echocardiologists performed offline analysis, and they were blinded to the recordings of both obese and nonobese subjects. The following 2DE parameters were measured: left ventricular end-diastolic diameter (LVEDD, mm), left ventricular end-systolic diameter (LVESD, mm), LA diameter (mm), diastolic interventricular septal thickness (IVST, mm), and diastolic posterior wall thickness (PWT, mm). Transmitral pulsed-wave Doppler velocities were recorded from the apical four-chamber view with Doppler sample placed at the level of the mitral valve leaflet tips both at rest and during the Valsalva maneuver. Early (E-wave) and late (A-wave) diastolic flow velocities, E/A ratio, E-wave deceleration time (DT), and isovolumic relaxation time (IVRT) were measured. Tissue Doppler imaging of septal anulus motion was undertaken for measuring peak early systolic (Sm), peak early diastolic (Em), and peak late diastolic (Am) velocities. The E/Em and Em/Am ratios were subsequently calculated.

RT3DE was performed with an X3 matrix-array transducer (1-3 MHz). Individuals were instructed to hold their breath, and images were synchronized with electrocardiographic tracing. For measurements, four consecutive cardiac cycles were analyzed and an average was obtained. Apical two-chamber and four-chamber views were derived from the pyramidal dataset during expiration. Both left ventricle (LV) and LA cavities were included in the pyramidal scan volume. Anatomic landmarks were used to calculate LA volumes and manually identified by marking five points on the atrial surfaces of the mitral annulus: at the anterior, inferior, lateral and septal annuli, and the fifth point at the apex of LA. Points deemed to represent the pulmonary vein ostia or LA appendage were excluded from the measurement. The LA internal endocardial contour of each frame was detected by automated processing. From these data, a 3D model of the LA volume was generated (Figure 1). The RT3DE datasets were digitally stored and analyzed using analysis software (QLab-Philips version 7.1; Philips Medical Systems). All the stored digital data were analyzed by two independent echocardiologists blinded to the clinical data of the study participants. The following volumetric measurements have been performed:

- LA maximum volume at end-systole (LAVmax), the time at which the atrial volume was the largest just before the mitral valve opening,
- LA minimum volume at end-diastole (LAVmin), the time at which the atrial volume at its nadir before mitral valve closure,
- LA volume before atrial contraction (LAVpreA), the last frame before mitral valve reopening or at time of P-wave on electrocardiogram (Figure 2).

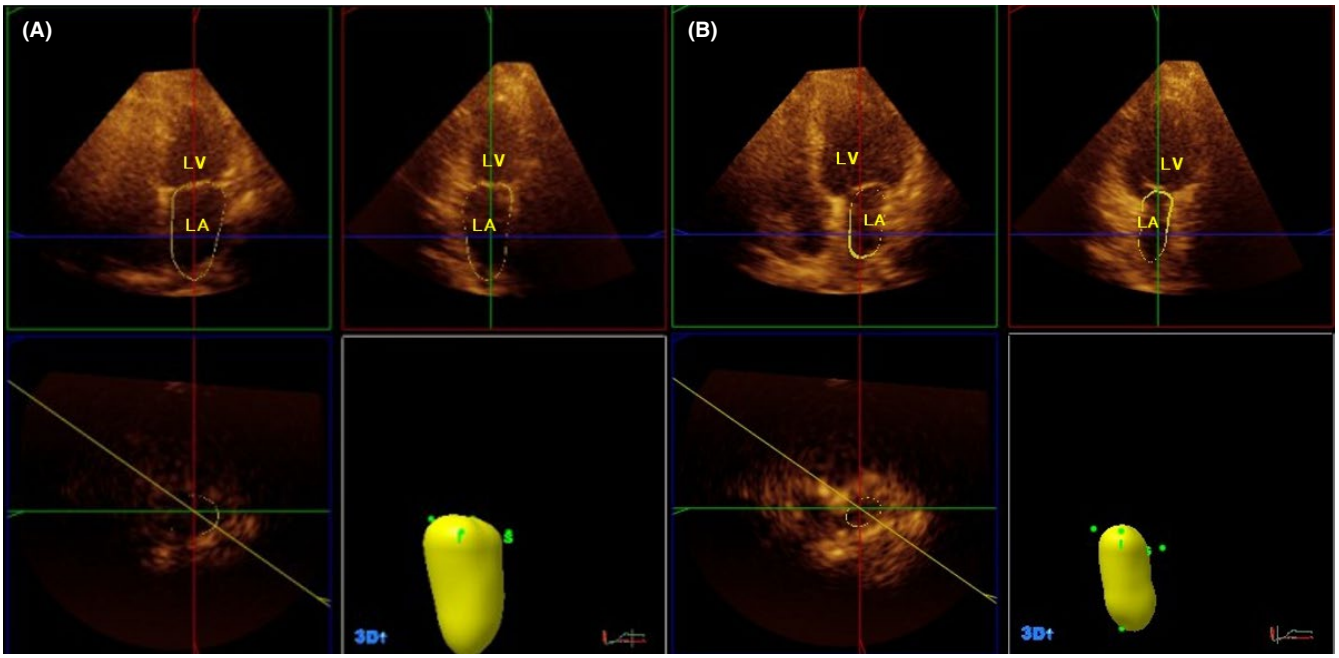

FIGURE 1 Real time three-dimensional echocardiography recordings of (A) maximal left atrial volume and (B) minimal left atrial volume. LA=left atrium; LV=left ventricle

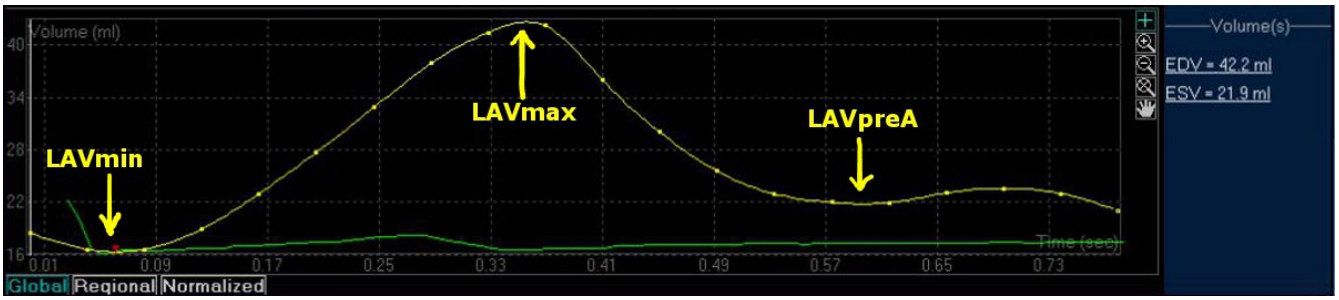

FIGURE 2 Time–volume curve showing left atrial maximal volume (LAVmax), left atrial minimal volume (LAVmin), and before left atrial contraction volume (LAVpreA). EDV=end-diastolic volume; ESV=end-systolic volume

From the three volumes, the following measurements were selected as indices of LA function and calculated according to previous studies.[13,14]

- LA reservoir function:
  LA total emptying volume = LAVmax – LAVmin
  LA total emptying fraction = (LAVmax – LAVmin)/LAVmax. × 100
- LA conduit function:
  LA passive emptying volume = LAVmax – LAVpreA
  LA passive emptying fraction = (LAVmax – LAVpreA)/LAVmax×100.
- LA booster pump function:
  LA active emptying volume = LAVpreA – LAVmin
  LA active emptying fraction = (LAVpreA−LAVmin)/LAVpreA×100

The LV ejection fraction (LVEF) was also assessed by RT3DE via evaluation of apical four-chamber and two-chamber views using the pyramidal 3D dataset.[15] Inter-observer variability was assessed by analysis of the RT3DE data from 20 randomly selected subjects from each group by two independent observers, each blinded to the results obtained by the other.

2.2 | Statistical analysis

Statistical analysis was performed using SPSS for Windows version 17.0 software (SPSS, Chicago, IL, USA). All continuous variables were expressed as means±SD, and categorical variables as numbers and percentages. Differences between groups were assessed with the chi-square test for categorical variables and the Student's *t* test or Mann-Whitney U test for continuous variables, depending on whether they distributed normally or did not, as tested by Kolmogorov-Smirnov test. Pearson's correlation analysis was used to estimate the relationship between NT-proANP and RT3DE parameter. *P* value <.05 was considered to be statistically significant.

TABLE 1 Clinical characteristics and laboratory findings of the study population

	Obese subjects n=40	Controls n=40	*P*-value
Age (years)	51.93±9.05	53.54±6.75	NS
Female, n (%)	26 (65)	23 (57.5)	NS
BMI (kg/m^2)	35.54±4.31	25.75±1.63	<.0001
Systolic BP (mm Hg)	112.25±11.65	109.25±11.74	NS
Diastolic BP (mm Hg)	64.00±11.61	62.37±10.68	NS
Smokers, n (%)	13 (32.5)	11 (27.5)	NS
Total cholesterol (mg/dL)	192.55±19.54	187.87±44.15	NS
LDL cholesterol (mg/dL)	122.82±22.98	118.87±30.25	NS
HDL cholesterol (mg/dL)	41.42±7.11	40.53±8.39	NS
Triglycerides (mg/dL)	160.05±64.90	150.78±53.17	NS
Fasting blood glucose (mg/dL)	100.45±28.67	102.16±41.13	NS
NT-proANP (nmol/L)	1.32±0.73	1.08±0.50	NS
Creatinine (mg/dL)	0.79±0.35	0.73±0.13	NS

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, nonsignificant; NT-proANP, N-terminal pro-atrial natriuretic peptide.

3 | RESULTS

Clinical characteristics and laboratory data of 40 obese and 40 normal weight subjects are showed in Table 1. Mean BMI for the obese and the control groups was 33.35±3.37 and 22.91±1.58 kg/m^2 respectively (*P*<.0001). Obese subjects and the controls were similar regarding age, gender, smoking, dyslipidemia, smoking, blood sugar, blood pressure, LDL-C, and HDL-C. There was no significant difference regarding plasma levels NT-proANP between groups (1.32±0.73 vs 1.08±0.50 mg/L, *P*=.10).

The findings of two-dimensional and Doppler echocardiographic measurements are demonstrated in Table 2. There was no significant difference between groups regarding left atrial diameter, LVEDD, LVESD, PWT, IVST, and LVEF. In addition, Em, Sm, E/A, E/Em, and Em/Am ratios were not different between groups. However, DT, IVRT, and Am were significantly higher in obese subjects when compared with controls (223.32±36.46 vs 186.40±36.15, *P*<.0001; 94.17±10.61 vs 80.57±15.50, *P*<.0001; 9.77±1.30 vs 8.90±1.69, *P*<.001, respectively).

The findings of RT3DE measurements are shown in Table 3. LAVmax and LAVmax indexed, LAVpreA, LA active and total emptying volumes, and active emptying fraction were significantly higher in

TABLE 2 Echocardiographic parameters of the study population

	Obese subjects n=40	Controls n=40	*P*-value
LV ejection fraction (%)	65.35±3.93	65.00±4.84	NS
Left atrial diameter (mm)	35.48±2.68	34.20±2.91	NS
LVEDD (mm)	47.37±2.36	46.42±2.68	NS
LVESD (mm)	29.67±2.65	28.47±3.18	NS
IVST (mm)	10.02±0.07	10.05±1.01	NS
PW thickness (mm)	9.95±0.79	9.33±0.97	NS
E/A	1.32±0.27	1.29±0.24	NS
DT (ms)	223.32±36.46	186.40±36.15	<.0001
IVRT (ms)	94.17±10.61	80.57±15.50	<.0001
Sm (cm/s)	10.88±1.87	11.82±1.75	NS
Em/Am	1.22±0.20	1.33±0.29	NS
E/Em	7.54±1.41	7.26±2.01	NS
Em	11.80±1.95	11.51±1.83	NS
Am	9.77±1.30	8.90±1.69	.012

A, late mitral diastolic velocity; Am, peak late mitral tissue Doppler diastolic velocity; DT, mitral E-wave deceleration time; E, mitral early diastolic velocity; Em, peak early mitral tissue Doppler diastolic velocity; IVRT, isovolumetric relaxation time; IVST, interventricular septal thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; PWT, posterior wall thickness; Sm, peak early systolic myocardial velocity.

TABLE 3 Measurements of left atrial volumes and mechanical functions by RT3DE in the study groups

	Obese subjects n=40	Controls n=40	*P*-value
LAVmax (mL)	43.11±7.05	36.82±4.81	<.001
LAVmin (mL)	18.34±4.31-5	14.52±4.04	<.001
LAVpreA (mL)	29.85±6.52	22.36±5.32	<.001
LA total emptying volume (mL)	24.77±4.50	22.29±3.49	.007
LA total emptying fraction	57.65±6.24	60.81±7.73	NS
LA active emptying volume (mL)	11.50±2.95	7.83±2.33	<.001
LA active emptying fraction	38.64±4.89	35.14±7.41	.015
LA passive emptying volume (mL)	13.26±4.18	14.45±3.48	NS
LA passive emptying fraction	30.96±8.86	39.61±9.13	<.001
LAVmax index (mL/m)	22.55±4.86	20.47±2.96	.013
LVEF (%)	64.14±3.41	65.21±2.24	NS

LA, left atrium; LAVmax, LA maximum volume at end-systole; LAVmin, LA minimum volume at end-diastole; LAVpreA, LA volume before atrial contraction; LVEF, left ventricular ejection fraction.

obese subjects than in controls. LA passive emptying fraction was significantly lower in patients with obesity than in controls. There were positive correlations between NT-proANP level and LAVI, LAVmax, LAVmin, LAVpreA, and LA active and total emptying volumes (Table 4).

4 | DISCUSSION

To the best of our knowledge, this is the first study that assessed LA volumes and LA mechanical functions using RT3DE in obese subjects, who are free from overt epicardial coronary artery disease. RT3DE parameters such as LAVmax, LAVmin, LAVpreA, and LA active and total emptying volumes were found to be increased in obese subjects, which reflect impaired LA reservoir and booster pump functions. Furthermore, another RT3DE parameter, LA passive emptying fraction, was found to be decreased in obese subjects, which indicates altered LA conduit function. The present study showed that LA volume was increased and LA mechanical function was impaired in obese subjects.

Obesity is a major risk factor for the development of atrial fibrillation (AF).[16] In a recent population-based cohort study, it has been pointed out that obese individuals have an associated 49% increased risk of developing AF compared to nonobese individuals, and the risk arises in conjunction with increased BMI.[15] The Framingham Heart Study showed that heart failure had developed in 8.4% of their study population and that the risk of heart failure development increased approximately twofold for people with obesity in comparison with nonobese population.[1] More recently, the Framingham investigators provided convincing data that obesity is indeed linked with excess risk of AF and that the risk is likely mediated through LA enlargement. LA enlargement was proposed as the mediating factor for obesity, and it was a risk factor for AF in the Framingham Study.[16] There are several other possible mechanisms responsible for the development of AF in obesity, and LA enlargement seems to be the main causative factor.[3,16]

TABLE 4 Correlations between NT-proANP and RT3DE parameters in the study group

Parameter	r	*P*-value
LAVI	.519	.001
LAVmax	.506	.001
LAVmin	.395	.012
LAVpreA	.447	.004
LA total emptying volume	.409	.009
LA total emptying fraction	−.087	.592
LA active emptying volume	.403	.01
LA active emptying fraction	.047	.77
LA passive emptying volume	.156	.33
LA passive emptying fraction	−.141	.40

LA, left atrium; LAVI, LA volume index; LAVmax, LA maximum volume at end-systole; LAVmin, LA minimum volume at end-diastole; LAVpreA, LA volume before atrial contraction; NT-proANP, N-terminal pro-atrial natriuretic peptide; RT3DE, real time three-dimensional echocardiography.

The present study showed that obesity contributes to impaired LA mechanical function. The precise pathophysiological mechanism for the observed myocardial dysfunction in our obesity group is unknown. Despite the fact that various mechanisms may play a role in the pathogenesis of cardiac dysfunction in obesity, early detection of these myocardial abnormalities may be important in the management of the patients. Elevated plasma volume, ventricular diastolic dysfunction, and enhanced neurohormonal activation often accompany obesity and may contribute to LA enlargement and electrical instability.[17–19]

Left atrial mechanical functions contain reservoir, and passive emptying and active emptying functions at different stages of the cardiac cycle. The reservoir function works during ventricular systole, passive emptying function during early diastole, and active emptying function during late diastole. When left ventricular dysfunction begins to develop, the LA may possibly preserve adequate cardiac output by adjustment of reservoir and booster pump functions. Diastolic heart failure in particular was shown to have a strong impact on LA function. As LV diastolic dysfunction deteriorates, LA pressure increases to overwhelm the intra-ventricular pressure and provide adequate LV filling.[13,20,21] Thus, left atrial dilatation and increased left atrial reservoir function occur due to increased left ventricular stiffness. During early diastole, increased left ventricular stiffness and impaired diastolic relaxation cause a decrease in left atrial passive emptying. Conduit volume from left atrium to left ventricle decreases due to increased intra-ventricular pressure during ventricular diastole. The atrial emptying fraction increases due to increased left atrial volumes according to the Frank-Starling law during diastole. Thus, the Frank-Starling mechanism was also operative in the LA.[22]

Several methods have been used to assess LA function by measuring changes of LA volumes, such as nuclear scintigraphy, 2D echocardiography, pulsed-wave Doppler, tissue Doppler imaging, and angiography.[23,24] However, these techniques have their own limitations, such as higher costs, invasive natures, low temporal resolution, lacking enough information about the volume of LA, and the need for contrast or radiopharmaceutical agents.[23] Nowadays, 3D echocardiography is able to recognize early atrial dysfunction before clinical manifestations and earlier than standard echocardiographic parameters. Indeed, in our study, most two-dimensional pulse and tissue Doppler measurements were within normal range. In contrast, most RT3DE parameters were abnormal. Previous studies have shown that 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.[11,12,14] RT3DE is also a potentially superior tool for the assessment of complex-shaped chambers, which exhibit dynamic changes such as LA and LV. Until recently, 2D volume calculation (area-length and the biplane Simpson's method) has been considered as standard method for left atrial volume assessment. However, 2D measurements may inherently carry miscalculations because of the following reasons: (1) oblique position of the interatrial septum, (2) the LA and LV long axes do not appear in the same cutting plane; (3) it is not always guaranteed that apical four- and apical two-chamber views are exactly 90 perpendicular to each other; and 4) the 2D cutting plane obtained often does not bisect the center of the LA short-axis view.[25] For these reasons, observer variabilities of

LAV by 2D measurements were reported to be larger than those by 3D measurements [14,25] and 3D echocardiographic technique is superior to current 2D echocardiographic techniques. Three-dimensional echocardiography is also comparable to magnetic resonance imaging and multidetector computerized tomography.[26,27]

NT-proANP plays a key role in the regulation of renal sodium and water retention. Obesity is also associated with sodium and water retention, which would be expected to result in elevated natriuretic peptide levels. In the contrary, obese and overweight individuals have been shown to have lower levels of NT-proANP than individuals with normal BMI.[28] It has been speculated that it may be due to enhanced clearance of natriuretic peptide receptors by adipose tissue, diminished myocardial secretion, and decreased synthesis.[28,29] In our study, NT-proANP levels were similar between groups. This may seem to be contradictory at first. However, it may be due to lower numbers of participants in our study. In addition, there were moderate positive correlations between serum NT-proANP levels and RT3DE parameters, LA total and active emptying volumes, showing impaired LA reservoir and booster pump functions.

4.1 | Limitations

We accept that there are some limitations, one of which is the small sample size. We did not have long-term follow-up data. Further large-scale studies with long-term follow-up will help us to define the eventual role of RT3DE in the determination of LA functions in obese subjects. Another limitation is that LA appendage has an important role for the function of LA, but we did not include appendage volumes for the calculation of LA function. In addition, software (QLab-Philips version 9.1) used for the analysis of 3D volumetric data is originally designed for evaluation of left ventricular volumes. However, it was also validated in the assessment of LA volumes and functions.[30] Lastly, LA volumes and functions were not evaluated by another method such as cardiac magnetic resonance imaging or computerized tomography.

5 | CONCLUSION

We demonstrated a deterioration of LA volume and functions by RT3DE in obese subjects. These findings show that LA volume and functions deteriorate in obese individuals and these parameters may have potential to be a preclinical marker of disease pathogenesis, which may also have clinical implications in the management of the patients before developing overt heart failure or any atrial arrhythmias.

DISCLOSURE

The authors declared no conflict of interest.

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