

Mechanisms of Left Atrial Enlargement in Obesity



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Left atrial (LA) enlargement is common in obesity. We sought to determine the influence of ventricular (LV) remodeling on LA size in obesity. We studied 50 otherwise healthy obese subjects (body mass index 37.2 ± 4.6 kg/m², 50 ± 6 years) and 58 age and gender-matched nonobese controls (body mass index 26.2 ± 2.9 kg/m², 52 ± 5 years). Diastolic function, relative wall thickness (RWT), and LV mass were assessed using echocardiography. LA and LV volume was measured by 3D-echocardiography. Primary outcome was the ratio of LA volume indexed to LV volume in obese and control subjects. Obese subjects had substantially larger LA volumes compared with control subjects (61.0 ± 16.9 vs 38.9 ± 9.2 ml, $p < 0.0001$). When scaled to body size or lean mass, differences in LA size persisted. However, when indexed to LV end-diastolic volume, LA volumes between control and obese subjects were comparable (obese vs controls: 0.44 ± 0.15 vs 0.42 ± 0.10 , $p = 0.46$). A small subset of obese subjects (26%) had LA volume markedly out of proportion to LV volume (LA/LV volume ratio ≥ 0.5) and displayed concentric LV remodeling with larger RWT and LV mass compared with obese subjects with LA/LV < 0.5 (RWT: 0.46 ± 0.09 vs 0.36 ± 0.06 , $p < 0.0001$; LV mass: 79 ± 18 vs 62 ± 13 g/m² $p < 0.01$). In conclusion, LA enlargement in patients with obesity generally occurs commensurate with LV enlargement and parallels eccentric LV remodeling. LA enlargement out of proportion to LV size is associated with increased RWT and mass. This unique signature may identify obese subjects with pathologic LA remodeling. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:442–447)

Obesity is a risk factor for atrial fibrillation and stroke.^{1,2} The mechanism for this relation is believed to be left atrial (LA) enlargement, however, the causal association is clouded due to confounding co-morbidities common in obesity. There are few mechanistic studies describing the relation between obesity and LA size and whether this enlargement should be considered pathologic. The majority of studies include obese individuals with several co-morbid conditions which are also risk factors for diastolic dysfunction which even in the absence of obesity has been linked to LA enlargement.^{3–6} Lastly, the larger body surface area (BSA) from higher fat mass in obese individuals can confound scaling of LA size, potentially overemphasizing the impact of body size. Therefore, the goal of the present study was to characterize LA size and function in a manner independent of body size and competing co-morbid conditions. As the chamber directly connected to the left atrium, the left ventricle may provide insight into distinguishing pathologic from physiologic adaptations. We hypothesized LA enlargement in obese subjects with minimal co-morbid conditions would not be related to echocardiographic markers of diastolic function per se but rather

reflect differences in ventricular size compared with age-matched nonobese controls.

Methods

Study subjects were recruited from the Dallas Heart Study, a population-based cohort of over 6,000 individuals as previously described.⁷ All study procedures were approved by the Institutional Review Boards of the University of Texas Southwestern Medical Center. After providing informed consent, all subjects underwent testing as outlined below. Inclusion criteria for obese subjects were (1) body mass index (BMI) from 30 to 50 kg/m², and (2) age from 40 to 60 years. Exclusion criteria were the presence of diabetes, obstructive sleep apnea, uncontrolled hypertension, heart failure, severe asthma/COPD, coronary artery disease as evidenced by exertional angina or previous myocardial infarction, or cerebrovascular disease as evidenced by previous transient ischemic attack or stroke. Nonobese control subjects who had no chronic medical conditions were identified from a previous study from our laboratory in a similarly aged population.⁸ Body composition was determined by dual energy x-ray absorptiometry as described previously.⁹ NT-proBNP levels were measured commercially (Quest Laboratories).

Echocardiography was obtained using traditional views (iE33 Philips Medical Systems, Andover, Massachusetts). Doppler indices were obtained at end-expiration with 4 values averaged. Pulsed-wave Doppler, using a sample volume depth of 2.0 mm placed at the tips of the mitral valve leaflets, was used to determine peak mitral inflow velocities. For tissue Doppler measurements, the septal and lateral walls were highlighted with a sample volume depth of 5.0 mm. Septal

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and lateral values were averaged to obtain TDI e_{mean} which is abbreviated and reported as e' throughout. Isovolumic relaxation time (IVRT) was measured as the time between aortic valve closure and mitral valve opening by placing a 4-mm sample within the LV outflow tract in the 5-chamber view. Relative wall thickness (RWT) and left ventricular mass of obese subjects was measured as previously described.^{10,11}

LA and LV volumes were measured using 3D echocardiography (X-3 probe, IE33 Phillips Medical Systems, Andover, Massachusetts). Left ventricular end-diastolic volumes were analyzed offline (Qlab 9.0 Phillips Medical Systems, Andover, Massachusetts) with identification of 5 points at the apex and mitral annulus in the 2- and 4-chamber views. LA volumes were measured using a similar 5 point system with placement of points on the mitral annulus in 2- and 4-chamber views and the rear most portion of the left atrium. Atrial contours were adjusted manually to align with the atrial walls. The largest LA volume was designated as LA max (LA volume just before atrial contraction) and LA min (the smallest LA volume). All volumes presented are averaged from two 3D measures. Analysis was performed blinded to group allocation and BMI. The interobserver variability in LA volumes was 5%. LA pump function was assessed by LA ejection fraction from 3D echocardiography.

Data were expressed as means \pm standard deviation (SD) unless stated otherwise. Student's *t* test was used to detect differences between obese and nonobese subjects. Subgroup analysis was performed within the obese cohorts in patients with LA volume substantially out of proportion to left ventricular volumes. A LA/LV ratio ≥ 0.5 was chosen as the cut point as this corresponded to 1 standard deviation above the group average of the nonobese control subjects. A one-way ANOVA with post hoc testing (i.e., Bonferroni for homogenous variables or Dunnett T3 for nonhomogenous variables) was used to compare by BMI strata. Mann-Whitney test was used to assess differences between NT-proBNP levels in the subgroup analysis of obese subjects to assess potential baseline differences in cardiac function. Data were analyzed using GraphPad Prism 7 for Windows (San Diego, California). A *p* value < 0.05 was considered statistically significant.

Results

Baseline characteristics are presented for the obese and nonobese groups in Table 1. Total weight and lean body mass were significantly higher in obese subjects relative to

Table 1
Baseline demographic characteristics

Group characteristics	Nonobese n = 58	Obese n = 50	<i>p</i> value
Women, n (%)	30 (52%)	26 (52%)	NS
Age (years)	52 \pm 5	50 \pm 6	0.09
BMI (kg/m ²)	26.2 \pm 2.9	37.2 \pm 4.6	0.001
Height (cm)	170 \pm 10	172 \pm 8	0.33
Weight (kg)	76 \pm 14	110 \pm 19	< 0.001
BSA (m ²)	1.88 \pm 0.23	2.28 \pm 0.23	< 0.001
Lean body mass (kg)	50.8 \pm 10.9	60.1 \pm 11.7	< 0.001

control groups. There were no differences in group heights. Absolute LA end-diastolic volume (LA max) in obese subjects was substantially larger than in nonobese subjects (Figure 1; Table 2). To account for the effects of body size on the atrial remodeling, LA size was indexed to BSA, height and lean body mass. Obese subjects had significantly larger atria indexed to when assessed by any of these anthropomorphic metrics (Figure 1; Table 2). Indexing LA volume to left ventricular volume however eliminated differences between obese subjects and nonobese controls (LA/LV volume fraction: 0.44 ± 0.15 vs 0.42 ± 0.10 $p = 0.46$; Figure 1; Table 2). This trend was persistent across BMI subgroups (Table 3). Despite increasing LA volumes, LA/LV ratio remained constant.

Although the difference was small, obese subjects as a group had a higher early diastolic mitral inflow velocity (E wave) compared with nonobese controls. Obese subjects also had a significantly higher late diastolic mitral inflow velocities (A wave) compared with nonobese controls. Average E/A ratio, tissue Doppler (e' med, e' lat), and IVRT did not differ significantly between groups (Table 2). Obese subjects had a higher E/ e' ratio largely a result of higher E wave (obese group vs control group: 8.7 ± 2.1 vs 7.3 ± 2.0 , $p < 0.001$, Table 2). The difference in E/ e' was largely driven by subjects with BMI > 40 kg/m² (Table 3). No subjects in the study met criteria for diastolic dysfunction with 4 of the obese subjects falling into the indeterminate range.

To determine if LA enlargement in the obese subjects was associated with changes in ventricular structure and function, we stratified the obese group by LA/LV ratio. The range of LA/LV ratios across the total cohort including both obese and controls was from 0.2 to 1.0, with an average of 0.4, and standard deviation was 0.1. A value of 0.5 corresponded to the seventy-fifth percentile of LA/LV ratio of the total cohort and was used as cut off to better characterize obese subjects who had LA enlargement considerably out of proportion to LV volume. Of the 50 obese group subjects, 13 (26% of obese subjects) had LA/LV ratios ≥ 0.5 . There were no significant differences in age or body weight between obese subjects who had LA/LV > 0.5 compared with those < 0.5 (Table 4).

Broken into LA/LV ratio subgroups, average E/ e' was slightly, but statistically higher in the obese subjects in the LA/LV < 0.5 group compared with both obese subjects with LA/LV ≥ 0.5 and controls (Table 4). There were no differences in E/A ratio or IVRT within the 2 obese subgroups. LA pump function as assessed by LAEF did not differ significantly between obese group with LA/LV < 0.5 and the obese group with LA/LV ≥ 0.5 (Table 4).

LV volumes among all 3 groups were significantly different. Obese subjects with LA/LV ratio < 0.5 had the largest LV volumes when compared with obese subjects with LA/LV ratio > 0.5 and nonobese controls. Interestingly, despite larger LV volumes, obese subjects with LA/LV ratio < 0.5 had smaller LA volumes compared with obese subjects with LA/LV ratio ≥ 0.5 . Therefore, the increase in LA/LV ratio in obese subjects with LA/LV > 0.5 was driven by both a significantly larger LA size as well as a smaller LV size compared with obese subjects who had LA/LV ratios similar to non-obese control subjects.

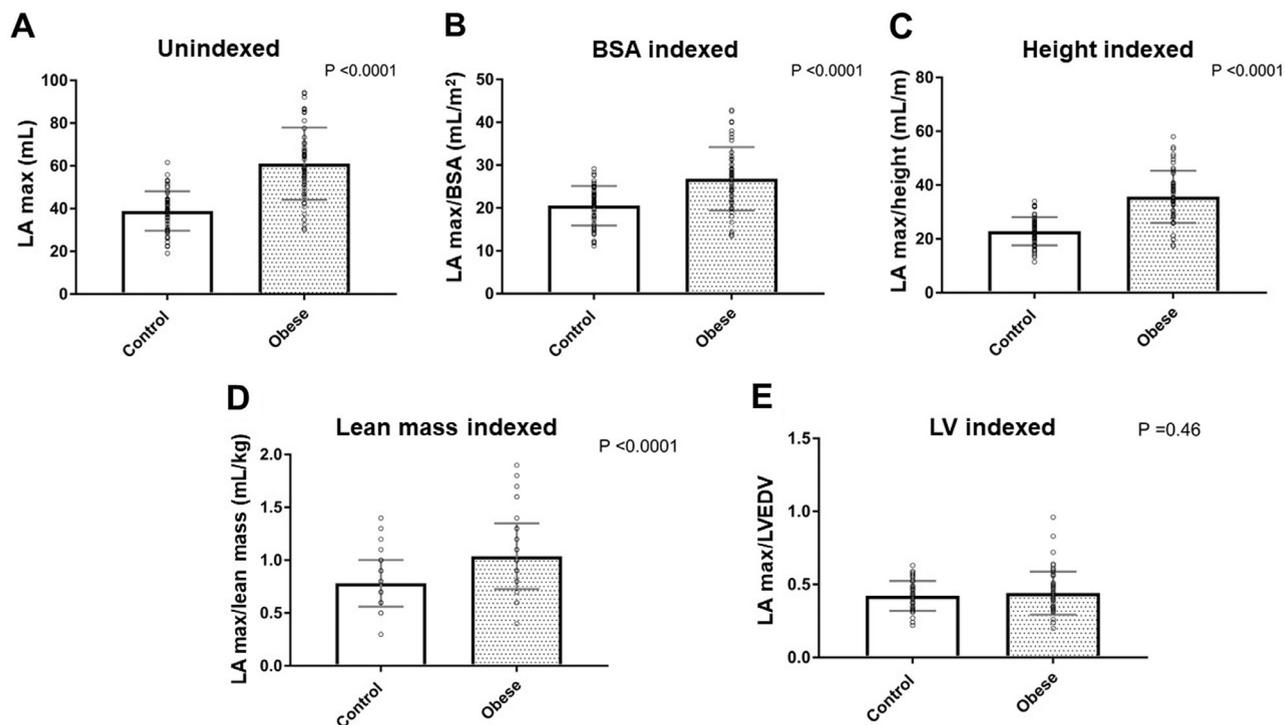


Figure 1. Indexing left atrial volume: various indexing strategies for left atrial volumes in obese and nonobese control subjects. Panel A shows absolute left atrial volumes. Panels B to D show atrial volumes indexed by body surface area (BSA), height, and lean body mass respectively in both groups. Panel E shows atrial volume indexed to left ventricular volume which normalizes differences between obese and nonobese controls. Error bars represent standard deviation.

Obese subjects with $LA/LV \geq 0.5$ had a significantly higher RWT than obese subjects with $LA/LV < 0.5$ (Figure 2; Table 4). In addition, obese subjects with $LA/LV \geq 0.5$ also had significantly higher LV mass when compared with $LA/LV < 0.5$. NT-proBNP was significantly higher in the obese group with $LA/LV < 0.5$ (67 ± 62 pg/ml) when compared with the obese group with $LA/LV \geq 0.5$ (34 ± 30 pg/ml; $p < 0.01$; Table 4) and likely reflected lower myocardial wall stress and higher RWT and mass seen in the latter group.

Discussion

In this study we demonstrate that (1) LA volumes of obese subjects are larger than nonobese controls; (2) scaling

Table 2
Echocardiographic parameters between obese and control subjects

Variable	Nonobese	Obese	p value
LA _{max} (ml)	38.9 ± 9.2	61.0 ± 16.9	<0.001
LA EF (%)	52 ± 10	50 ± 13	0.40
LA _{max} /BSA (ml/m ²)	20.6 ± 4.6	26.9 ± 7.4	<0.001
LA _{max} /height (ml/m)	22.9 ± 5.2	35.7 ± 9.7	<0.001
LA _{max} /lean body mass (ml/kg)	0.78 ± 0.22	1.04 ± 0.31	<0.001
LV end diastolic volume (ml)	93 ± 21	142 ± 26	<0.001
LA _{max} /LVEDV ratio	0.42 ± 0.10	0.44 ± 0.15	0.46
e' (cm/sec)	9.9 ± 1.9	9.1 ± 2.0	0.61
E/e'	7.3 ± 2.0	8.7 ± 2.1	<0.001
E wave (cm/sec)	70 ± 16	77 ± 15	0.03
A wave (cm/sec)	51 ± 11	61 ± 16	<0.001
E/A ratio	1.41 ± 0.33	1.33 ± 0.40	0.23
Isovolumic relaxation time (msec)	72 ± 18	72 ± 13	0.80

of LA to LV volume eliminates differences in LA size between obese and nonobese controls; and (3) obese subjects with LA/LV volume ratio > 0.5 have higher LV masses, lower NT-proBNP levels, and more concentric hypertrophic remodeling than obese subjects with LA/LV volume ratio < 0.5 . Our results highlight LA size in obesity must be understood in the context of LV remodeling rather than absolute atrial volumes, and that only a small subset of obese subjects have atrial enlargement that may be considered pathologically abnormal driven by a concentrically thickened ventricle.

Although many studies have shown that obese patients have LA enlargement, atrial size is typically quantified by indexing to height or BSA relative to nonobese controls.¹² Indexing strategies relying on anthropomorphic measures may not accurately characterize physiologic or pathologic remodeling. Particularly in obesity, indexing to body mass may over-adjust LA volumes and potentially mask maladaptive remodeling. The impact of obesity associated comorbid conditions can also influence cardiovascular remodeling and isolating the independent impact of obesity can be challenging.¹³ By focusing on a cohort of middle-aged obese subjects free from diabetes, sleep apnea, coronary artery disease, heart failure, and renal dysfunction, we have reduced the risk of possible residual confounding factors that could affect atrial remodeling.

Consistent with previously reported studies, our study did show that LA volume in obese patients is approximately 50% larger than nonobese controls. Scaling to left ventricular end-diastolic volumes normalized differences between groups suggesting that LA enlargement for most obese patients reflects an overall increase in cardiac size. To our

Table 3
Echocardiographic parameters by BMI group

Variable	<25 kg/m ² n = 21	25 to 29.9 kg/m ² n = 37	30 to 34.9 kg/m ² n = 18	35 to 39.9 kg/m ² n = 19	>40 kg/m ² n = 13	p value —
LAmax (mL)	33.5 ± 7.3	43.1 ± 11.8	51.9 ± 13.1 †	67.7 ± 16.8 †	59.4 ± 17.0 †	< 0.001
LAmax/BSA (ml/m ²)	18.8 ± 4.7	22.1 ± 5.7	25.0 ± 6.3 *	29.0 ± 7.1 †	24.5 ± 7.2	< 0.001
LV end diastolic volume (mL)	79.7 ± 15.7 **	100.9 ± 20.9 **	129.2 ± 23.1 **	145.4 ± 26.5	150.0 ± 29.0	< 0.001
LAmax/LVEDV ratio	0.42 ± 0.09	0.43 ± 0.11	0.41 ± 0.14	0.48 ± 0.17	0.39 ± 0.11	0.30
e' (cm/sec)	10.3 ± 1.9	9.7 ± 1.9	9.1 ± 2.1	9.4 ± 1.7	8.6 ± 2.0	0.17
E/e'	7.5 ± 2.7	7.2 ± 1.6	7.7 ± 1.8	8.9 ± 2.1	9.7 ± 2.1 †	0.002
E wave (cm/sec)	74 ± 17	67 ± 13	67 ± 15	81 ± 13 †	81 ± 15	0.002
A wave (cm/sec)	55 ± 14	52 ± 10	56 ± 16	62 ± 17	66 ± 16	0.04
E/A ratio	1.38 ± 0.22	1.34 ± 0.32	1.30 ± 0.49	1.36 ± 0.34	1.29 ± 0.35	0.58
Isovolumic relaxation time (msec)	65 ± 14	73 ± 20	68 ± 17	73 ± 11	75 ± 12	0.51

* p < 0.05 compared with <25 kg/m².

** p < 0.05 compared with all groups.

† p < 0.05 compared with <25 and 25 to 29.9 kg/m².

‡ p < 0.05 compared with 25 to 29.9 and 30 to 34.9 kg/m².

knowledge, this study is the first to demonstrate that LA enlargement in obese patients occurs in the absence of clinically significant LV dysfunction. Our findings are strengthened using 3D echocardiography to accurately measure LA and LV volumes compared with traditional echocardiographic volumetric techniques.

Not all obese subjects displayed eccentric atrial remodeling. We identified a subgroup representing approximately 25% of the obese cohort who had LA enlargement out of proportion to LV size (LA/LV ratio >0.5). The LVs in this subgroup remodeled in a concentric manner with a smaller LV chamber, increased relative wall thickness and concentricity

Table 4
Obesity subgroup analysis by left atrial and ventricular volume ratios

Group characteristics	Obese LA/LV <0.5 n = 37	Obese LA/LV >0.5 n = 13	p value —
	Female, n (%)	21, (57%)	
LA/LV Ratio	0.37 ± 0.07	0.63 ± 0.13	<0.01
Age (years)	50 ± 6	49 ± 6	NS
BMI (kg/m ²)	37.2 ± 4.6 *	37.0 ± 4.6 *	NS
Height (cm)	172 ± 9	172 ± 7	NS
Weight (kg)	110 ± 19 *	109 ± 18 *	NS
Lean body mass (kg)	59.5 ± 11.8 †	61.5 ± 12.0 †	NS
BSA (m ²)	2.3 ± 0.2 *	2.3 ± 0.2 *	NS
NT-proBNP (pg/mL)	67 ± 62	34 ± 30	<0.01
e' (cm/sec)	9.1 ± 2.1	9.4 ± 1.7	0.14
E (cm/sec)	78 ± 16 *	72 ± 13	0.63
A (cm/sec)	63 ± 18 *	54 ± 7	<0.01
E/e'	8.9 ± 2.2 *	7.9 ± 1.4	<0.01
E/A	1.32 ± 0.43	1.36 ± 0.31	0.46
Iso-volume relaxation time (msec)	72 ± 12	74 ± 15	0.9
Relative wall thickness ratio	0.36 ± 0.06	0.46 ± 0.09	<0.001
LA max volume (ml)	54.9 ± 13.0	78.6 ± 14.3	<0.001
LA EF (%)	50 ± 14	50 ± 10	0.92
LV end diastolic volume (ml)	147 ± 26	127 ± 23	<0.001
LV mass (g/m ²)	62 ± 13	79 ± 18	<0.01

† p < 0.01 Compared with controls (values from Table 2).

* p < 0.001 Compared with controls (values from Table 2).

index. NT-proBNP levels were also lower reflecting lower ventricular wall stress as a function of LaPlace' law. Low BNP levels have previously been shown to be linked to concentric ventricular remodeling in obesity, specifically in patients with increased visceral adiposity.¹⁴ Our data suggest that LA enlargement out of proportion to LV volumes may be driven by increased ventricular stiffness from a concentrically thickened ventricle.¹⁵ Other studies have shown similar findings in nonobese populations. In a study of 30 subjects with isolated systolic hypertension, LA size was best correlated with LV wall thickness.¹⁶

Surprisingly, diastolic function was not worse in obese subjects with LA/LV volume ratio >0.5. Although ventricular hypertrophy is often linked to diastolic dysfunction, the relation between these 2 factors is complex.^{17,18} Previous studies have a relation between BMI and worsening diastolic function.¹⁹ We did observe a linear relation between BMI and E/e' but no subjects met criteria for diastolic dysfunction, likely reflecting the low co-morbidity burden in our cohort. Traditional echocardiographic measures of diastolic function are influenced by age, co-morbid conditions as well as hemodynamic parameters including

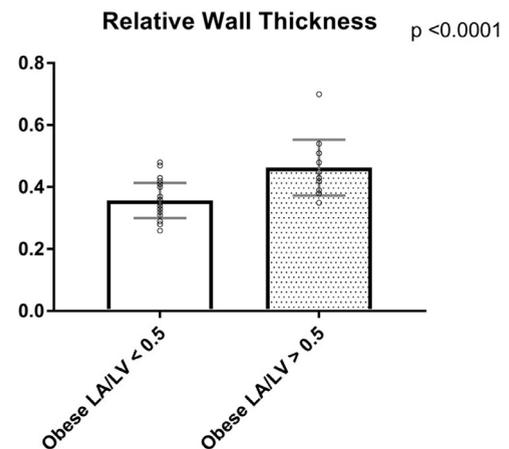


Figure 2. Relative wall thickness by obesity subgroup: relative wall thickness in obese subjects stratified by left atrial to ventricular volume ratio. Obese subjects with LA/LV ≥ 0.5 display significantly higher relative wall thickness than those with LA/LV < 0.5.

afterload, preload, heart rate, and pericardial constraint to name a few.²⁰ In obesity, expansion of plasma volume and higher heart rate influences atrioventricular filling, manifesting as faster mitral inflow, and myocardial tissue velocities. It should be emphasized that the lack of differences in Doppler echocardiography criteria for diastolic dysfunction between the 2 obese subgroups in our study does not necessarily imply that other aspects of ventricular diastolic function are similar in both groups. Rather LV stiffness and distensibility – mechanical properties that dictate ventricular diastolic pressure responses to a given hemodynamic stressor, and a measure not readily captured by echo – may be significantly higher in patients with concentric hypertrophy.²¹

There are few studies examining the relation between LA enlargement and ventricular remodeling. In a retrospective analysis of 4,444 elderly patients, age, LA size, and decreased LV ejection fraction were the strongest determinants of atrial fibrillation.²² Increased LA size was associated with lower EF and eccentric hypertrophy suggesting a role for systolic dysfunction and increased LA pressure. In contrast, whereas we observed LA enlargement in subjects with eccentric remodeling, LA enlargement was much more pronounced in subjects with concentric remodeling. Differences between studies can likely be attributed to exclusion of patients with LV systolic dysfunction in addition to careful controlling for age, gender, or other co-morbidities in our cohort.

LA size in nonobese patients is an important risk factor for development of atrial fibrillation, stroke, and heart failure.^{12,23} Our study highlights the importance of understanding the relation between ventricular remodeling and its parallel effects on atrial size. Reductions in LA size may provide a simple and effective marker in predicting improvements in ventricular compliance.^{24,25} Particularly in obesity where the risk for future heart failure is high, LA enlargement out of proportion to left ventricular size could serve as a longitudinal prognostic tool, potentially tracking rates of progression or regression in ventricular hypertrophic remodeling.

Our study was limited in that our participants were highly screened to be healthy without co-morbid conditions. Although this approach allowed for the study of the isolated effects of obesity on cardiac structure and function, generalizing these findings to the general obese population should be done with caution. In conclusion, LA enlargement and remodeling in obese subjects with minimal cardiovascular co-morbidities closely tracks changes in left ventricular structure and not echocardiographic markers of diastolic function. Obese subjects with LA size out of proportion to LV volume (>50%), displayed concentric LV remodeling with increased relative wall thickness, LV mass, and lower serum NT-proBNP levels.

Disclosures

The authors have no financial and personal relations with other people or organizations that could inappropriately influence (bias) their work. This includes employment, consultancies, stock ownership, honoraria, paid expert testimony, and patent applications/registrations.

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