Effect of Obesity on Left Atrial Strain in Persons Aged 35−55 Years (The Asklepios Study)

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Obesity increases the risk of heart failure and atrial fibrillation. Left atrial (LA) dysfunction is increasingly recognized as a mediator of cardiovascular disease. Early effects of obesity on LA function have not been examined in large population samples. We quantified LA strain and strain rate (SR) through speckle tracking echocardiography in 1,531 middle-aged community-based participants enrolled in the Asklepios study. We compared LA function between individuals with body mass index (BMI) < 25 kg/m^2 (n = 779), 25 to 29.9 kg/m^2 (n = 618) and ≥ 30 kg/m^2 (n = 134). Significant differences in reservoir longitudinal LA strain (BMI < 25 kg/m^2 = 35.3%, BMI 25−29.9 kg/m^2 = 33.1%, and BMI ≥ 30 kg/m^2 = 30.9%; p < 0.00001) strain rate ([SR] BMI < 25 kg/m^2 = 151; BMI 25 to 29.9 kg/m^2 = 141; and BMI ≥ 30 kg/m^2 = 135 %/s; p <0.00001) and expansion index (BMI < 25 kg/m^2 = 1.6, BMI 25 to 29.9 kg/m^2 = 1.4, and BMI ≥ 30 kg/m^2 = 1.4; p <0.00001) were seen, indicating reduced reservoir function with increasing BMI. Obesity was also associated with impaired LA conduit function, including conduit longitudinal LA strain (BMI < 25 kg/m^2 = 21.6%, BMI 25 to 29.9 kg/m^2 = 18.9%, and BMI ≥ 30 kg/m^2 = 16.7%; p <0.00001), SR (BMI < 25 kg/m^2 = −189, BMI 25 to 29.9 kg/m^2 = 166, and BMI ≥ 30 kg/m^2 = 150 %/s; p <0.0001) and passive LA emptying fraction (BMI < 25 kg/m^2 = 40.5, BMI 25 to 29.9 kg/m^2 = 36.5, and BMI ≥ 30 kg/m^2 = 36%, p <0.00001). These differences persisted after adjustment for age, gender and other potential confounders. In contrast to reservoir and conduit function, obesity was associated with increased booster pump function (active LA emptying fraction: BMI < 25 kg/m^2 = 19.4%, BMI 25 to 29.9 kg/m^2 = 20.5%, and BMI ≥ 30 kg/m^2 = 21.5%; p <0.00001). In middle-aged adults, obesity is associated with impaired reservoir and conduit LA function and higher booster function, which may be compensatory. Loss of booster LA function, either because of more advanced LA dysfunction or atrial fibrillation, may play an important role in precipitating heart failure in obese individuals. **© 2018 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;123:854−861)**

Obesity is a strong modifiable risk factor for the development of atrial fibrillation and heart failure.[1] An increased LA size has previously been studied as a marker of obesity-associated LA remodeling.[2−5] Using LA enlargement as a measure of atrial remodeling might not differentiate compensatory LA remodeling (due to increased cardiac output in obesity[6]) from the pathologic remodeling (due to increased LA afterload[7,8] and/or potential myopathic effects of adipokines[9,10] and other neurohormonal pathways). In contrast to LA volume, LA reservoir function increases in states of increased cardiac output, but decreases with increase in LA afterload and stiffness.[11] Therefore, phasic LA dysfunction might better identify adverse atrial remodeling of obesity.[12−14] In this study, we aimed to determine whether overweight and obesity are independently associated with measures of LA dysfunction assessed through volumetric methods and LA longitudinal strain measurements in middle-aged adults from the community enrolled in the Asklepios study.

Methods

The methods and design for the Asklepios study have previously been described. Briefly, the study recruited a cohort of 2,524 community-dwelling apparently healthy volunteers aged 35 to 55 years.[15,16] A complete echocardiographic examination was performed on 2,368 participants using a standardized protocol. None of the participants had apparent cardiovascular diseases (including valvular heart disease) at the time of enrolment (and echocardiography).

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The Ghent University Hospital Ethical Committee approved the study protocol and participants provided written informed consent.

Doppler-echocardiographic examinations were performed using a Vivid-7 ultrasound platform (Vingmed Ultrasound; Horten, Norway) as previously described in detail.[15] Left ventricular (LV) end-diastolic volume and mass were indexed linearly for body surface area. This analysis is based on data from 1,531 participants who had optimal images for LA speckle-tracking (visualizing the entire atrium throughout the cardiac cycle). LA analyses were performed using speckle tracking analyses on EchoPAC (GE Healthcare; Chalfont St. Giles, United Kingdom). LA endocardial borders were manually traced in apical 2- and 4-chamber views using atrial diastasis as the point of reference. An automated tracking algorithm was applied, with manual adjustments performed as needed to optimize wall tracking (Figure 1). Time-resolved numerical values derived from speckle tracking were exported from the echoPAC software for further calculations in custom-designed software written in Python (Python Software Foundation, Wilmington, Delaware). We computed longitudinal atrial strain, defined as the change of atrial myocardial length throughout the atrial cycle (L_1) compared with its resting (or reference) length (L_0) in a relaxed state at diastasis (end of atrial diastole), as $(L_1-L_0)/L_0$. Strain rate (SR) was calculated as the rate of change in longitudinal strain over time (units: %/s). Strain and SR were calculated for reservoir, conduit, and booster phases. Additionally, the maximum (LAmax), minimum (LAmin), and diastatic (LAdias) LA volumes were measured. LA expansion index, passive LA emptying fraction (LAEmF), and active LAEmF were calculated as volumetric measures of reservoir, conduit, and booster phases, respectively. LA expansion index was calculated as (LAmax−LAmin)/LAmin, passive LAEmF as (LAmax−LAdias)/LAmax, and active LAEmF as (LAdias−LAmin)/LAmax. Interobserver

Table 1
General demographic, clinical, and echocardiographic characteristics of normal weight, overweight, and obese participants

Parameter	Normal weight (n = 779) Mean (95%CI) or count (%)	Overweight (n = 610) Mean (95%CI) or count (%)	Obese (n = 142) Mean (95%CI) or count (%)	p value
Age	44.7 (44.3 to 45.1)	46.3 (45.8 to 46.7)	47.2 (46.2 to 48.3)	<0.0001*,#
Male sex	323 (41.46%)	438 (70.87%)	89 (66.42%)	<0.0001
Body mass index	22.3 (22.2 to 22.4)	27 (26.8 to 27.1)	32.7 (32.3 to 33)	<0.0001*,#,$
Systolic blood pressure	123 (122 to 123)	130 (129 to 131)	134 (131 to 136)	<0.0001*,#,$
Diastolic blood pressure	76 (76 to 77)	82 (81 to 82)	87 (86 to 89)	<0.0001*,#,$
Pulse pressure	46 (45 to 47)	48 (47 to 49)	46 (44 to 47)	<0.0001*,$
Heart rate	69 (68 to 69)	68 (68 to 69)	74 (72 to 76)	<0.0001#,$
Current smoker	188 (24.13%)	134 (21.68%)	33 (24.63%)	0.51
Hypertension	127 (16.30%)	215 (34.79%)	78 (58.21%)	<0.0001
Antihypertensive therapy	33 (4.24%)	70 (11.33%)	35 (26.12%)	<0.0001
Diabetes	1 (0.13%)	9 (1.46%)	8 (5.97%)	<0.0001
Medications				
Aspirin	5 (0.64%)	12 (1.94%)	3 (2.24%)	0.0637
Lipid lowering therapy	28 (3.59%)	36 (5.83%)	14 (10.45%)	0.0022
Beta-blocker	19 (2.44%)	36 (5.83%)	12 (8.96%)	0.0002
ACE inhibitor	6 (0.77%)	14 (2.27%)	9 (6.72%)	<0.0001
ARB	8 (1.03%)	11 (1.78%)	4 (2.99%)	0.1736
Calcium channel blocker	3 (0.39%)	7 (1.13%)	0 (0.00%)	0.1399
Laboratory variables				
Total cholesterol	208 (205 to 210)	219 (216 to 221)	217 (210 to 223)	<0.0001*,#
HDL	66.6 (65.4 to 67.8)	57.2 (56 to 58.4)	51.3 (49 to 53.6)	<0.0001*,#,$
Triglycerides	78 (75 to 81)	107 (103 to 112)	135 (123 to 147)	<0.0001*,#,$
Non-HDL cholesterol	137 (135 to 140)	158 (154 to 161)	162 (155 to 169)	<0.0001*,#
Estimated GFR (ml/min)	91.7 (90.6 to 92.8)	91.8 (90.6 to 93)	91 (88.4 to 93.7)	0.8705
Glucose	88.8 (88.2 to 89.5)	91.7 (90.9 to 92.4)	95.7 (94 to 97.4)	<0.0001*,#,$
Echocardiographic variables				
LV end-diastolic volume index	57.3 (56.6 to 57.9)	60.9 (60.1 to 61.7)	59.5 (57.8 to 61.3)	<0.0001*,#
LV ejection fraction	64.4 (63.9 to 65)	65.6 (64.9 to 66.2)	65.5 (64.2 to 66.9)	0.0270*
LV mass index (g/m^2)	74.7 (73.5 to 75.8)	86.4 (84.9 to 87.9)	84.6 (81.4 to 87.8)	<0.0001*,#
LV mass index ($g/^{1.7}$)				
Relative wall thickness	0.359 (0.355 to 0.363)	0.387 (0.382 to 0.392)	0.409 (0.398 to 0.421)	<0.0001*,#,$
Cardiac output, ml/min	4224 (4161 to 4287)	4852 (4770 to 4933)	5322 (5128 to 5516)	<0.0001*,#,$
Cardiac index, ml min^{-1} BSA^{-1}	2428 (2394 to 2462)	2477 (2438 to 2516)	2503 (2418 to 2588)	0.0813

Significant pairwise comparisons:
* Normal weight versus overweight;
\# Normal weight versus obese;
$ Overweight versus obese.

ACE = angiotensin convertase enzyme; ARB = angiotensin receptor blocker; HDL = high density lipoprotein; GFR=glomerular filtration rate; LV = left ventricle; CI = confidence intervals.

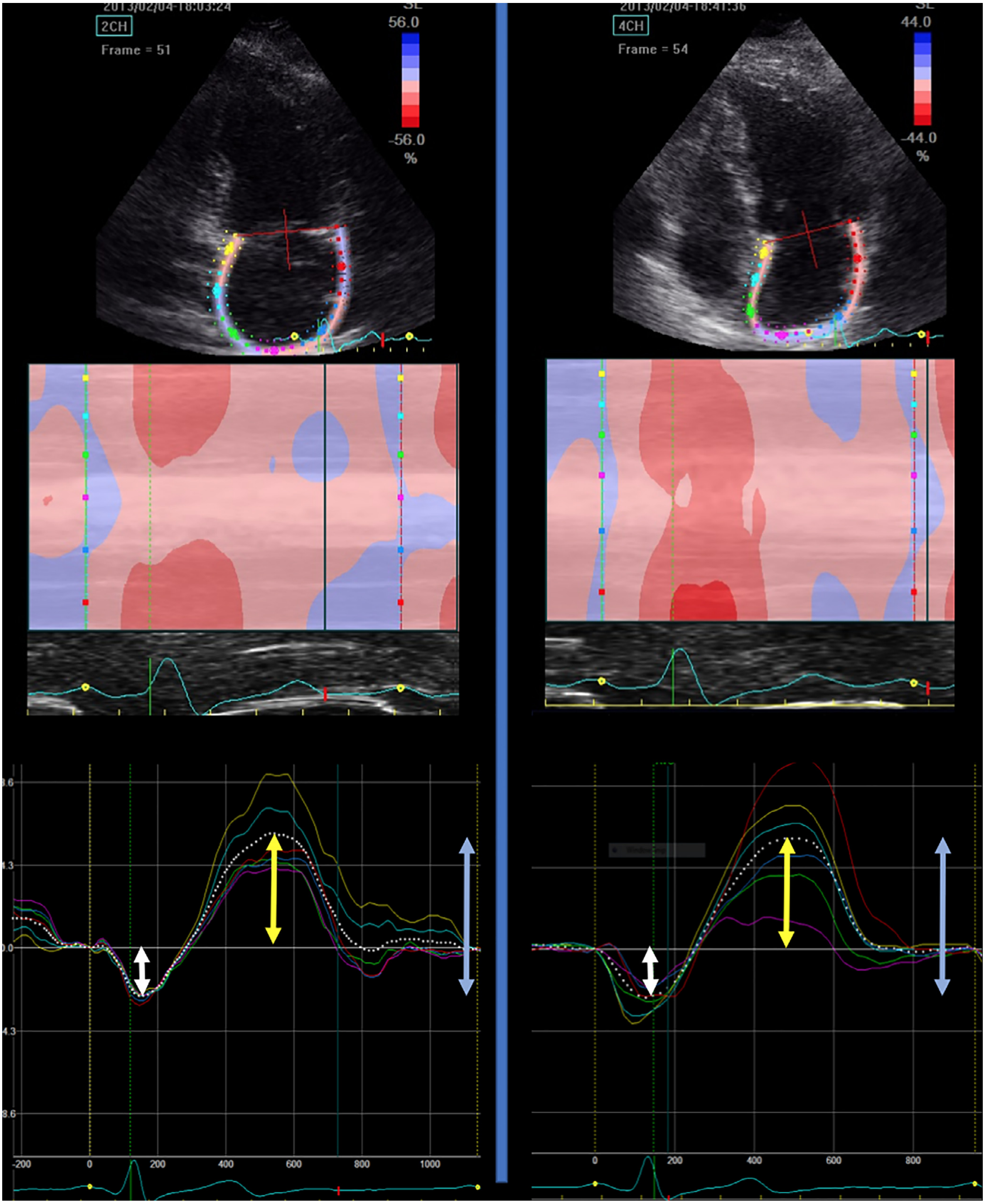

Figure 1. Representative example of LA strain measurements. The upper panels demonstrate the region of interest, corresponding to the left atrial wall in apical 4-chamber and 2-chamber views. The middle panels demonstrate a color-coded map of atrial wall deformation over time. The lower panels demonstrate the LA strain curve. Notice that the diastatic phase (end of atrial diastole) is used as the reference phase for LA strain computations. The white arrows demonstrate the amplitude of booster pump strain (atrial kick). The yellow arrows demonstrate the amplitude of conduit strain. The blue arrows demonstrate the amplitude of reservoir strain. (Color version of figure is available online.)

coefficients of variation were 3.2% for maximum LA volume, 6.7% for minimum LA volume, 2.5% for diastatic LA volume, 4.9% for conduit strain, 4.4% for conduit strain rate, 6.7% for booster strain, 6% for booster strain rate, 4.5% for reservoir strain, and 6.5% for reservoir strain rate. Intraobserver coefficients of variation for all volume and strain measures were < 6%.

Continuous variables were presented as means and 95% confidence intervals. Categorical variables were shown as total counts with percentages and were compared using the chi-square test or the Fisher's exact test. We stratified participants into 3 groups based on the body mass index (BMI): < 25 kg/m^2 (n = 779), 25 to29.9 kg/m^2 (n = 618) and >30 kg/m^2 (n = 134). Continuous variables were compared between the groups using analysis of variance. Adjusted comparisons between the groups were made with analysis of covariance. Models were adjusted for age and gender. Additional adjustments were performed for history of hypertension, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, and antihypertensive medication use. A 2-sided p value of 0.05 was used to define statistical significance. Post hoc pairwise comparisons were made with Bonferroni correction for alpha error. Statistical significance was defined as a 2-tailed $p < 0.05$. Analyses were performed using SPSS v24 for Mac (IBM, Chicago, Illinois) and the Statistics and Machine Learning Toolbox in Matlab v2016b (The Mathworks; Natick, Massachusetts).

Results

A comparison of general characteristics of Asklepios study participants who were included in the analyses (n = 1531) versus those not included (n = 993) is shown in **Supplemental Table 1**. Included participants had a greater proportion of men and a slightly lower average BMI (24.9 vs 26.3 kg/m^2) and burden of cardiovascular risk factors. Table 1 shows demographic, clinical, and echocardiographic

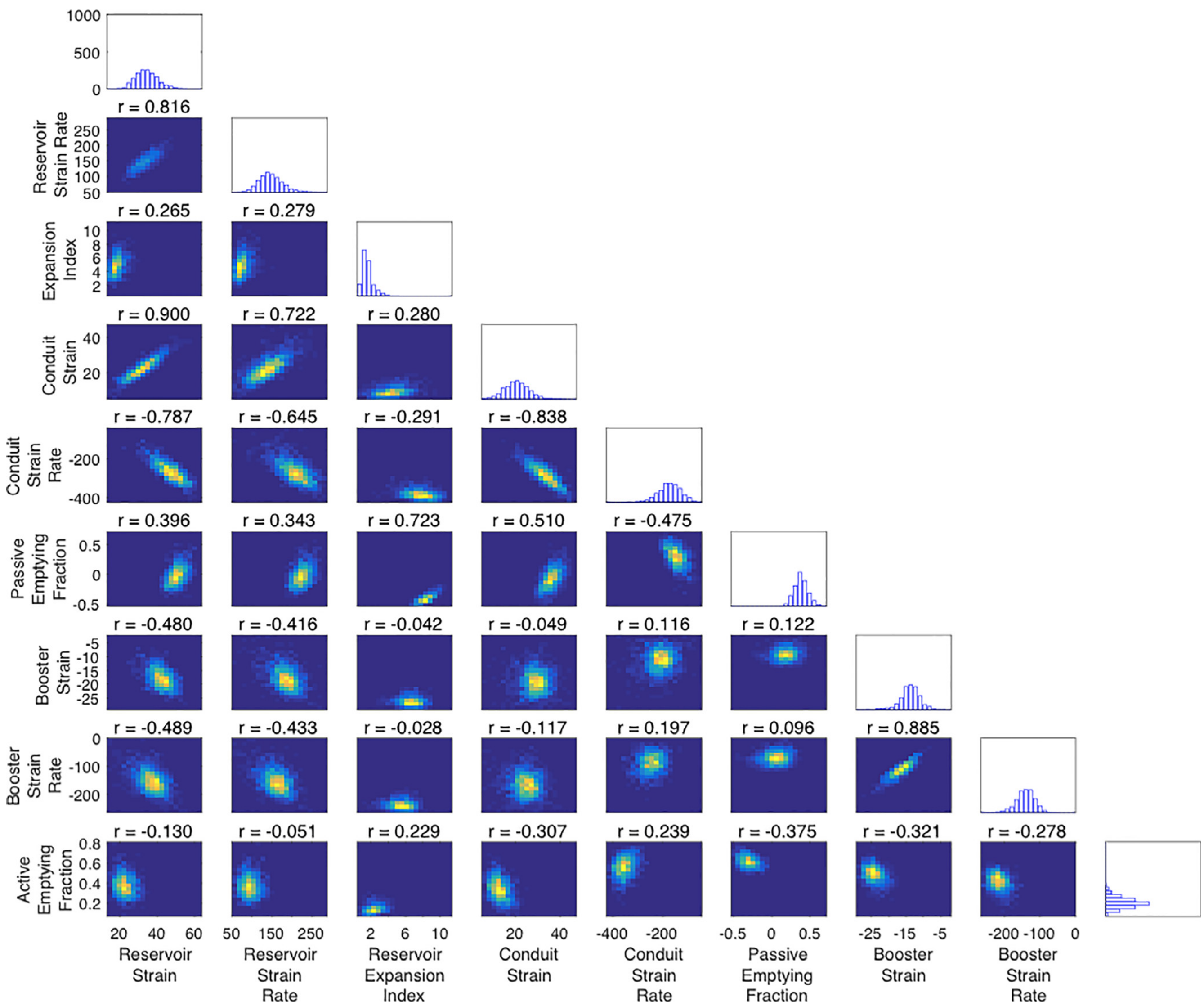

Figure 2. Panel A shows a matrix of density plots depicting correlation of various measures of LA size and function for the sample. Panel B shows a color correlation map between these measures. Correlation coefficients are shown in each cell of the color map. (Color version of figure is available online.)

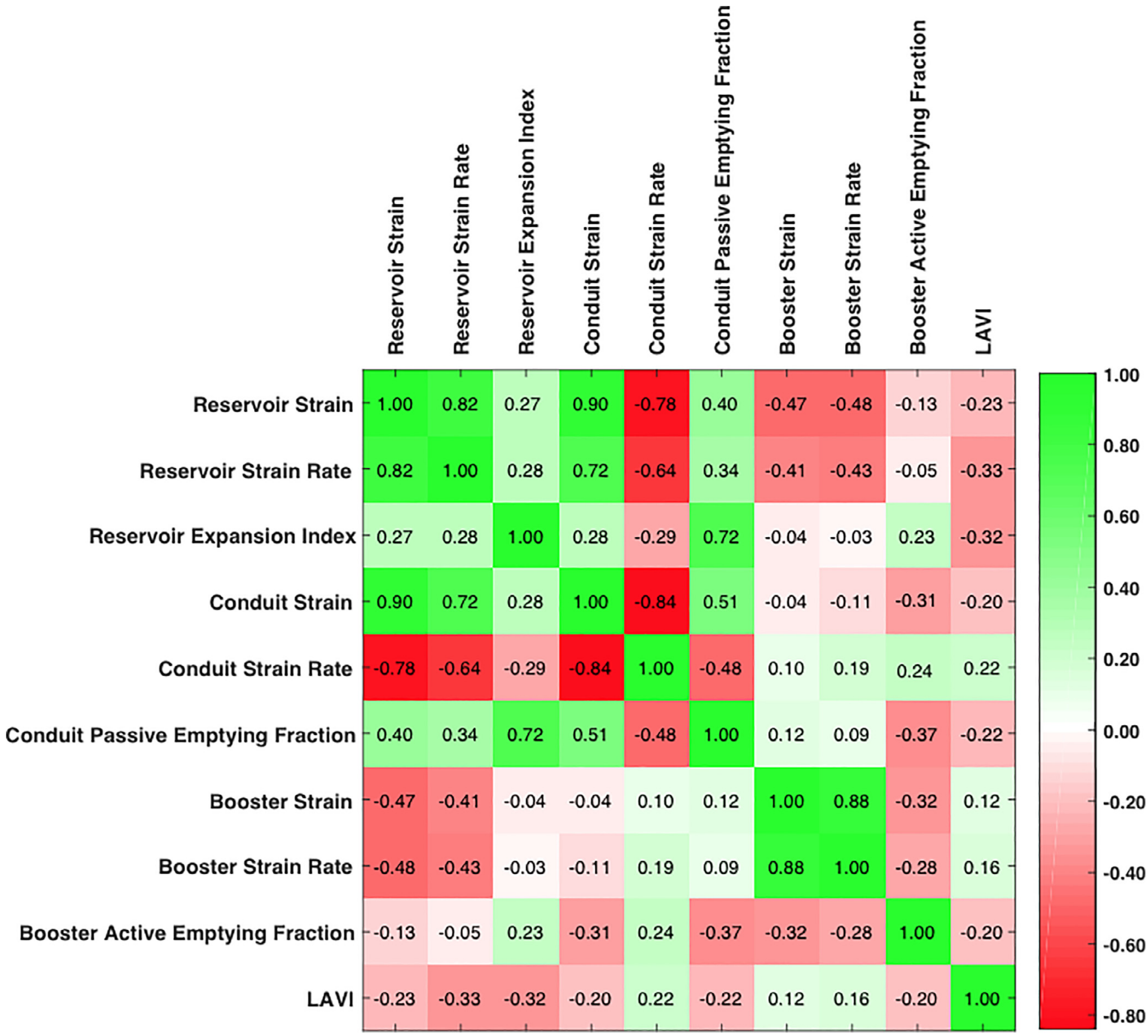

Figure 2 Continued.

Table 2
Unadjusted comparison of LA measures between the BMI groups

LA parameter	Normal weight Mean (95%CI)	Overweight Mean (95%CI)	Obese Mean (95%CI)	p Value
Reservoir strain	35.3 (34.8 to 35.7)	33.1 (32.6 to 33.6)	30.9 (29.9 to 31.8)	<0.00001*,#,$
Reservoir strain rate	151 (149 to 153)	141 (139 to 143)	135 (130 to 139)	<0.00001*,#,$
Reservoir expansion index	1.6 (1.5 to 1.6)	1.4 (1.4 to 1.5)	1.4 (1.3 to 1.5)	<0.00001*,#
Conduit strain	21.6 (21.1 to 22)	18.9 (18.5 to 19.3)	16.7 (15.9 to 17.5)	<0.00001*,#,$
Conduit strain rate	−189 (−193 to −185)	−166 (−171 to −161)	−150 (−161 to −139)	<0.00001*,#,$
Conduit passive emptying fraction	40.5% (39.8% to 41.1%)	36.5% (35.8% to 37.2%)	36% (34.5% to 37.6%)	<0.00001*,#
Booster strain	−13.9 (−14.1 to −13.6)	−14.3 (−14.6 to −14.1)	−14.1 (−14.7 to −13.5)	0.03060*
Booster strain rate	−144 (−147 to −141)	−148 (−151 to −145)	−145 (−151 to −138)	0.22551
Booster active emptying fraction	19.4% (19.1% to 19.8%)	20.5% (0.20048 to 0.20938)	21.5% (20.5% to 22.5%)	0.00001*,#
Left atrial volume index	21.3 (20.9 to 21.8)	23.4 (22.8 to 23.9)	22.6 (21.5 to 23.9)	<0.00001*

Significant pairwise comparisons:
* Normal weight versus overweight;
# Normal weight versus obese;
$ Overweight versus obese.
LA = left atrium; BMI = body mass index; CI = confidence intervals.

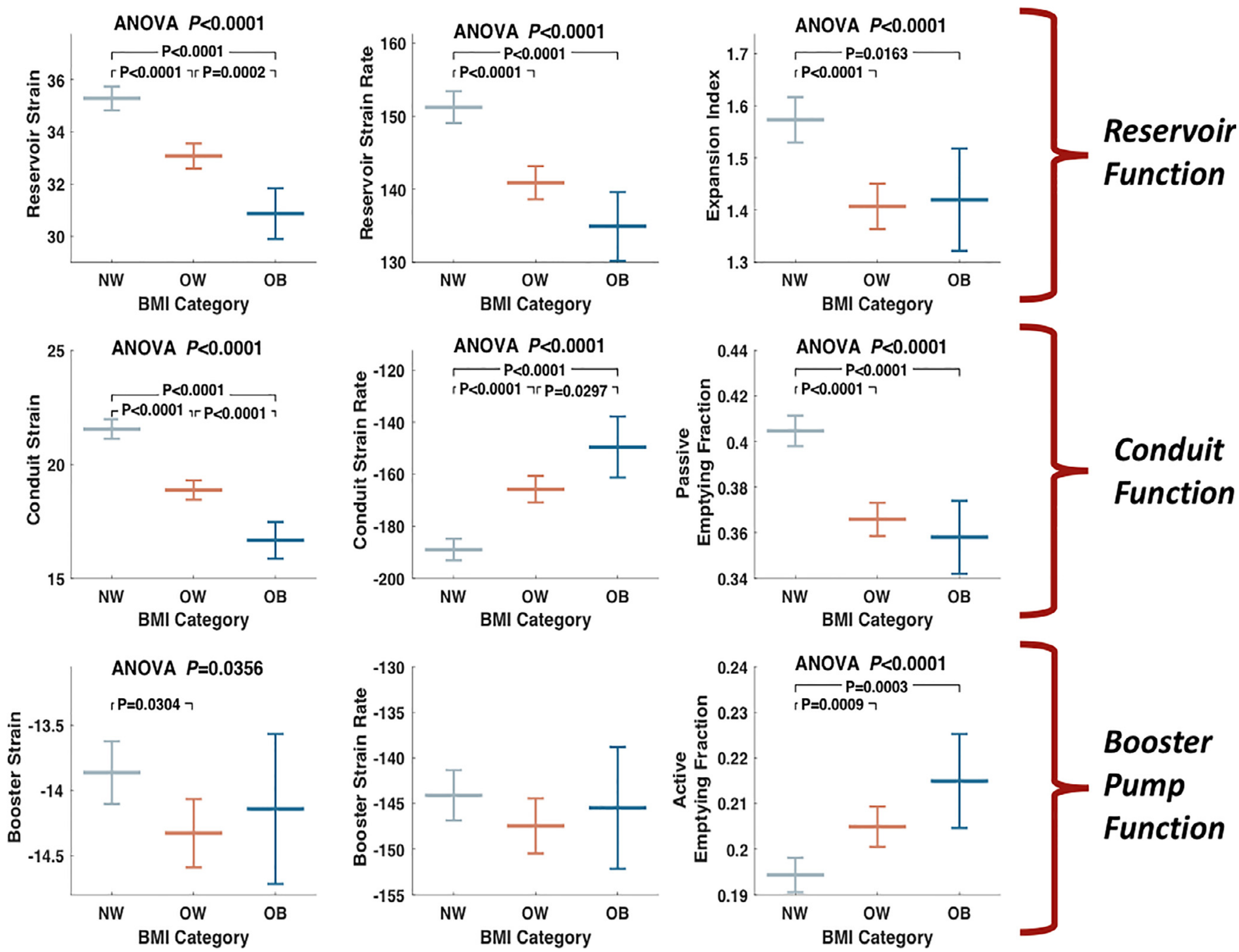

Figure 3. Unadjusted comparisons of reservoir, conduit, and booster function between participant with BMI < 25 kg/m^2, 25 to 29.9 kg/m^2, and >30 kg/m^2. BMI = body mass index; ANOVA = analysis of variance.

characteristics of participants included in this analysis, stratified by BMI. Nearly half of the included participants had BMI > 25 kg/m^2 (n = 752, 49%). Overall, the BMI groups 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 included slightly older participants, with a higher proportion of men. The BMI groups 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 also included a higher proportion of participants with hypertension, diabetes, and dyslipidemia.

Figure 2A and B depicts the distribution and correlation various measures of phasic LA function and LA size in relation to each other. Measures of reservoir function demonstrated strong correlations with conduit function and moderate correlations with booster function; however, conduit and booster function demonstrated very weak correlations. Interestingly, volumetric and longitudinal strain-based measures correlated weakly, even within domains of LA function, suggesting that transverse contraction accounts for an important proportion of the variability in LA volumetric phasic measures. Finally, LA volume index (LA maximum volume linearly indexed to body surface area) correlated weakly with all measures of phasic LA function.

Table 2 and Figure 3 show unadjusted analyses comparing measures of LA size and phasic LA function in various BMI groups. Reservoir function was lower for participants in the BMI 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 groups as compared with BMI < 25 kg/m^2 group, as indicated by lower average reservoir strain (35.3% vs 33.1% vs 30.9% in BMI < 25 kg/m^2, 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 groups respectively, p <0.00001), SR (151%/s vs 141%/s vs 135%/s, p <0.00001) and expansion index (1.6 vs 1.4 vs 1.4, p <0.00001). In these analyses, participants with BMI ≥ 30 kg/m^2 demonstrated lower reservoir longitudinal strain compared with those with BMI 25 to 29.9 kg/m^2, whereas no significant differences were found in reservoir SR and expansion index between BMI 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 participants.

Conduit function was lower in the BMI 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 groups, as indicated by lower conduit strain (21.6% vs 18.9% vs 16.7%, p <0.00001), SR (−189%/s vs −166%/s vs −150%/s, p <0.00001), and passive LAEmF (40.5% vs 36.5% vs 36%, p <0.00001). In these analyses, longitudinal conduit strain and SR, but not the passive

LAEmF, were significantly different between the BMI 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 groups.

In contrast to conduit and reservoir LA function, the active LAEmF was significantly greater in the BMI 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 groups compared with the BMI < 25 kg/m^2 group (19.4% vs 20.5% vs 21.5%, p <0.00001). Longitudinal booster strain was significantly greater (i.e., more negative) in participants with BMI 25 to 29.9 kg/m^2 (−13.9%, −14.3% and −14.1% in the BMI < 25 kg/m^2, 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 groups respectively, p = 0.03). In pairwise comparisons, the difference between the BMI < 25 kg/m^2 and 25 to 29.9 kg/m^2 groups was significant.

Supplemental Table 2 shows age- and gender-adjusted comparisons of measures of phasic LA function and LA volume index across BMI groups. Overall, the results were similar to those found in unadjusted models, that is, reservoir and conduit functions were decreased, whereas the active LAEmF was increased in the BMI 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 groups when compared with the < 25 kg/m^2 group. **Supplemental Table 3** shows the results from models that were further adjusted for history of hypertension, diabetes, antihypertensive medication use, total cholesterol, HDL-cholesterol, triglycerides, and glomerular filtration rate. In these comparisons, participants with a BMI ≥ 30 kg/m^2 demonstrated significantly lower reservoir strain and conduit strain compared with participants in with BMI < 25 kg/m^2 and 25 to 29.9 kg/m^2. Between-group differences in booster function and LA volume index became nonsignificant in these models.

Discussion

In this study, which included a large community-based sample of middle-aged adults, we assessed the impact of obesity on volumetric and longitudinal strain-based measures of phasic LA function. We demonstrate that obesity is characterized by reduced reservoir and conduit LA function, with an increase in booster LA function. Our findings suggest that LA booster function may compensate for reduced LA conduit function in uncomplicated obesity in middle-age. These findings contrast with more advanced stages of cardiac dysfunction, which are typically characterized by loss of conduit and booster pump LA function, suggesting that loss of compensatory booster pump function accompanies the progression from uncomplicated obesity to heart failure.

LA enlargement is seen early in the course of obesity.[2−5] Various mechanisms for obesity-related LA enlargement have been postulated, including increased stroke volume/total blood volume in response to the increase in metabolic demands,[6] increased LA afterload due to impaired LV lusitropy and/or abnormal LA-LV-aortic coupling,[7,8] atrial remodeling related to systemic inflammation and adipokines,[10] and paracrine effects from epicardial adipose tissue.[9] LA enlargement associated with an increased stroke volume in athletes is considered a compensatory response, and is not associated with adverse coutcomes.[17] In the setting of uncomplicated obesity, using LA enlargement as a measure of atrial remodeling might not differentiate expected compensatory responses from the adverse LA remodeling and dysfunction. Recent studies suggest that phasic LA function is prognostic of adverse outcomes independent of LA size[12−14]; however, the ability of measures of phasic LA function to characterize obesity-related atrial remodeling and dysfunction has not been previously assessed.

In age- and gender-adjusted analyses, we observed that measures of LA conduit and reservoir function were reduced, whereas booster active emptying fraction was increased in participants in a BMI 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2. In 386 middle-aged to older participants without structural heart disease, Abou et al. observed that reservoir LA strain was inversely associated with BMI.[18] However, they did not assess conduit and booster function. Similar to our findings, in a small sample of 70 community-based healthy participants, Erdem et al. observed significantly lower passive LAEmF and higher active LAEmF in participants with BMI ≥ 30 kg/m^2 compared with participants with BMI < 30 kg/m^2.[19] Similar findings were reported in sample samples of participants with hypertension and diabetes with concomitant obesity.[20,21] On the contrary, Tugcu et al. did not identify an association between BMI and volumetric measures of reservoir function in community-based elderly adults, although reservoir function was associated with abdominal obesity.[22] In comparison to previous studies, we studied phasic LA function using both volumetric and longitudinal LA strain-based measures in a large sample of community-dwelling middle-aged participants. Our findings indicate that obesity is associated with a functional LA phenotype characterized by reduced conduit and reservoir function, with an increase in booster function, which may be compensatory. Interestingly, the progressive reduction in reservoir function in individuals with BMI 25 to 29.9 kg/m^2 and BMI ≥ 30 kg/m^2 was more apparent from longitudinal strain-derived measures, whereas the increase in booster pump function was more apparent from volume-based measures of LA function. These findings suggest that transverse contraction of the LA may be important in maintaining LA phasic function with obesity, whereas LA longitudinal reservoir strain may be a more sensitive indicator of LA dysfunction and abnormal LA-LV coupling in early stages of obesity-related myocardial disease.

Cardiac output is a major determinant of LA reservoir function, with increased cardiac output being associated with increased reservoir strain.[11] In our analyses, participants with BMIs 25 to 29.9 kg/m^2 and ≥ 30 kg/m^2 demonstrated lower reservoir LA strain despite higher cardiac output compared with participants with a BMI < 25 kg/m^2. This suggests that LA longitudinal strain can identify obesity-associated LA dysfunction. A similar phenotype of LA remodeling (i.e., lower reservoir/conduit function with higher booster function) has been observed in adults with mild hypertension.[23] With the progression of hypertensive heart disease, booster function also decreases and is associated with heart failure symptoms.[24] It is plausible that a similar reduction of booster function in asymptomatic participants with obesity precedes the onset heart failure symptoms or other complications of obesity (such as atrial fibrillation), although this needs to be assessed in future studies.

Our study is the largest study regarding the effect of obesity of LA phasic function, and is derived from a large community-based sample of middle-aged adults, thus preventing confounding by referral bias. Our study has various limitations. Our study sample was primarily composed of Caucasian individuals of European ancestry, and further studies in racially diverse populations are warranted. Second, ours was a cross-sectional analysis and causality cannot be determined, nor can residual confounding be excluded based on our findings. Not all of our subjects had analyzable LA images, which introduced modest selection bias within our general Asklepios study sample.

In conclusion, in this cross-sectional analysis of a large middle-aged community-based sample, we identified an association between higher BMI and reduced reservoir and conduit LA function, with a compensatory increase in booster function. Our findings suggest that longitudinal LA strain measured using speckle-tracking echocardiography is a sensitive indicator of adverse functional LA remodeling in obesity. Future studies should investigate the role of aggressive risk factor modification in middle-aged adults with obesity and LA dysfunction to reduce the risk of obesity-related cardiovascular comorbidities, specifically heart failure and atrial fibrillation.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.11.035.

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