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ORIGINAL RESEARCH

Longitudinal Changes in Cardiac Structure and Function in Severe Obesity: 11-Year Follow-Up in the Utah Obesity Study

Sheldon E. Litwin, MD; Ted D. Adams, PhD; Lance E. Davidson, PhD; Rodrick McKinlay, MD; Steven C. Simper, MD; Lauren Ranson, BS; Steven C. Hunt, PhD

BACKGROUND: Progressive cardiac remodeling and worsening myocardial function over time have been proposed as potential mediators of heart failure in obesity.

METHODS AND RESULTS: We serially assessed cardiac structure and function in 254 subjects participating in a longitudinal study of obesity. Demographic, clinical, laboratory, and echocardiographic features were determined at baseline and 2-, 6-, and 11-year follow-up. We measured body mass index (BMI) exposure as the area under the curve of the BMI at each of the 4 visits. At enrollment, mean age of the subjects was 47 years, 79% were women, mean BMI was 44 kg/m^2, 26% had diabetes mellitus, 48% had hypertension, and 53% had hyperlipidemia. Between baseline and 11 years, BMI increased by 1.1 and 0.3 kg/m^2 in men and women, respectively. There were modest increases in left ventricular (LV) end-diastolic volume, LV mass, and left atrial volume, and significant decreases in early/late mitral diastolic flow velocity ratio and E wave deceleration time. However, there were no significant changes in LV ejection fraction or ratio of early mitral diastolic flow velocity/early mitral annular velocity, whereas right ventricular fractional area change increased. Significant predictors of the change in LV mass were male sex, baseline BMI, BMI area under the curve, and change in LV stroke volume, but not smoking, hypertension, or diabetes mellitus.

CONCLUSIONS: In long-standing, persistent severe obesity, there was evidence of cardiac remodeling over a period of 11 years, but no clear worsening of systolic or diastolic function. Measures of remodeling were most strongly related to BMI. The observed changes might predispose to heart failure with preserved ejection fraction, but are not classic for an evolving dilated cardiomyopathy.

Key Words: heart failure ■ hypertension ■ hypertrophy ■ obesity

Multiple population-based studies have observed that adult subjects with obesity have an increased risk of developing heart failure (HF) over periods of time ranging from 5 to 15 years.[1–9] The risk of HF appears to be directly related to the severity of obesity, whether assessed by body mass index (BMI) or waist circumference.[10] Most studies on this topic have used clinical definitions of HF or diagnoses of HF from administrative databases, and have not distinguished between HF with reduced ejection fraction (EF) versus HF with preserved EF (HFpEF). In several of the studies, the association of obesity with incident HF was attenuated or eliminated when accounting for higher levels of physical fitness[3,11] or conditions that commonly coexist with obesity.[1,2] Thus, it remains uncertain as to whether obesity directly or indirectly contributes to HF risk. One potential link between obesity and the development of HF is the process of cardiac remodeling that occurs in response to obesity and obesity-associated conditions. If progressive, the

Correspondence to: Sheldon E. Litwin, MD, Division of Cardiology, Medical University of South Carolina, 30 Courtenay St, Charleston, SC 29425. E-mail: litwins@musc.edu

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CLINICAL PERSPECTIVE

What Is New?

- These data show that long-standing severe obesity is associated with gradual increases in left ventricular mass and left atrial volume, but no decline in left ventricular ejection fraction.
- The cardiac remodeling represents a potential mechanism that may contribute to the clear association between obesity and an increasing incidence of heart failure with preserved ejection fraction.

What Are the Clinical Implications?

- More aggressive weight management approaches need to be considered on a broader scale than is currently being done.

Nonstandard Abbreviations and Acronyms

BMI	body mass index
E/A	ratio of early/late mitral diastolic flow velocities
E/e'	ratio of early mitral diastolic flow velocity/early mitral annular velocity
EF	ejection fraction
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
LA	left atrial
LV	left ventricular

remodeling could eventually cause or contribute to both systolic and diastolic dysfunction or predispose to HF through other mechanisms.

Increased left ventricular (LV) mass, left atrial (LA) enlargement, and subclinical LV dysfunction have consistently been observed in cross-sectional studies of subjects with obesity compared with subjects of normal weight.[12–15] Interestingly, LV EF has been reported to be in the normal range in most studies.[16–18] Recent studies increasingly suggest that obesity is a stronger risk factor for HFpEF compared with HF with reduced EF.[19] Furthermore, the increasing appearance of HF in younger patients seems to be largely driven by lifestyle-related risk factors, including obesity.[20] Perhaps this is not surprising because changes in cardiac geometry begin with childhood obesity.[21] The duration and severity of obesity have been suggested as important determinants of developing HF.[22] To help define the natural history of cardiac remodeling in obesity, we performed serial echocardiograms over a period of 11 years in a group of subjects with severe obesity who were recruited as a nonsurgical comparison group in a study designed to assess the long-term health effects of bariatric surgery.[23] We attempted to account for the exposure to obesity during the course of the study, although all of the patients have a much longer duration of obesity because BMI was markedly elevated in all patients at the time of enrollment.

METHODS

The Utah Obesity Study was performed from 2000 to 2015.[24] The University of Utah Institutional Review Board approved the study, and all subjects gave informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request. Subjects with severe obesity (n=1156) who met criteria for bariatric surgery (BMI ≥40 or ≥35 kg/m^2 with ≥2 complications of obesity) were recruited into a study examining the cardiovascular and metabolic effects of weight loss achieved by Roux en Y gastric bypass surgery.[24] The subjects consisted of 3 initial groups: (1) subjects undergoing bariatric surgery (n=418; surgery group); (2) subjects seeking surgery, but who did not have it done, generally because the procedure was not covered by their insurance policy (n=417; no surgery group 1); and (3) subjects with severe obesity not seeking gastric bypass surgery who were randomly selected from a population database (n=321; no surgery group 2). Measurements were obtained at 4 time points (baseline, 2 years, 6 years, and 12 years). At each time point, most of the subjects underwent echocardiography, and measurements of resting blood pressure, anthropometric indexes, fasting glucose, glycosylated hemoglobin, and serum lipids were obtained. Prevalence and incidence of diabetes mellitus in the overall study population at 12-year follow-up have recently been reported.[23]

The study group reported herein consisted of 254 subjects with severe obesity who did not undergo bariatric surgery at any point during the follow-up, and had echocardiographic studies at baseline and examination 4. The average follow-up duration for the entire study cohort was 12 years, but the patients in this subset had an average follow-up of 11 years. Comparison of subjects who had a follow-up echocardiogram at the fourth study visit and those who did not are shown in Table S1.

Diabetes mellitus was defined as blood glucose ≥126 mg/dL measured after an overnight fast, glycosylated hemoglobin ≥6.5%, use of insulin or an oral hypoglycemic agent, or all. Hypertension was defined as a resting blood pressure ≥140/90 mm Hg, the use of antihypertensive medications, or both. Mean arterial

pressure was calculated as two thirds diastolic plus one third systolic blood pressure.

Waist circumference was measured at the umbilicus. Percentage body fat and lean fat mass were calculated from measurement of resistance and reactance to an electrical current using bioelectrical impedance equipment (RJL Systems Analyzer; Quantum II, Clinton, MI) and using an equation developed specifically for severe obesity using hydrostatic weighing as the reference method.[25] Participants were asked to comply with the following criteria before the impedance analysis: fasting overnight or for a minimum of 4 to 5 hours; no exercise for at least 12 hours; no alcohol for at least 24 hours; and balanced hydration. All participants were asked to lie in a supine position for at least 5 minutes before the examination.

Using a variation of a previously validated approach to quantify the aggregate effects of weight over time,[26] we calculated cumulative exposure to obesity as the mean of the BMI at each of 2 consecutive visits (1–2, 2–3, and 3–4) multiplied by the time between the visits, and then summated and standardized by the total follow-up time (area under the curve). Submaximal treadmill exercise tests were performed using a modified Bruce protocol. Exercise was stopped when patients reached 80% of predicted maximum heart rate because of concerns about potential safety with severely obese patients performing treadmill exercise. The total treadmill time in seconds was used as an index of exercise capacity or fitness.

Echocardiography

Two-dimensional images, M-mode, and Doppler recordings were obtained from standard imaging windows (Sequoia 256; Siemens). All of the data were stored in digital format and analyzed off-line in a blinded manner. LV dimensions were determined from 2-dimensional parasternal long-axis images, according to American Society for Echocardiography criteria.[27] LV mass was calculated using the American Society for Echocardiography formula.[27] LV EF was measured using the Teicholz method.[27] LA diameter was measured in the parasternal long-axis view, and LA volume was measured using the method of discs from the apical 4-chamber view. LV mass and LA volumes are reported in absolute values because we tracked serial changes in individuals and compared results over time. Indexing to measures of body surface area may lead to erroneous conclusions about changes in heart chamber sizes when subjects have significant changes in body weight. LV geometry was defined on the basis of indexed LV mass and relative wall thickness.[18,27,28] Right ventricular fractional area change was measured from the apical 4-chamber view. Tricuspid annular plane systolic excursion was not routinely measured at the time this study began in 2000. Tissue Doppler velocities were recorded from the medial (septal) mitral annulus as this provides the most parallel angle of incidence between the ultrasound beam and the direction of longitudinal movement of the LV. Accurate lateral tissue Doppler velocities may be more challenging to obtain in subjects who are obese.

Statistical Analysis

Continuous variables are reported as mean±SD. Paired changes from baseline to 11 years were calculated and adjusted using sex and age as covariates in a general linear model. Unadjusted values are shown in Tables S2 and S3. Multiple linear regression analysis was used to determine the factors (those that were present at baseline, and those that changed during follow-up) that were associated with changes in each of the main echocardiographic parameters that were significantly different at 11-year follow-up versus baseline (change in LV mass index, change in LV end diastolic volume, change in LA volume, change in ratio of early/late mitral diastolic flow velocities [E/A], and change in E deceleration time). All *P* values associated with tests for longitudinal changes were obtained from repeated measure tests. Bonferroni's correction was used to account for multiple comparisons when testing for changes in the 19 clinical variables, changes in the 10 echocardiographic measurements, or the 5 multiple regression equations. The data that support the findings of this study are available from Dr Steven C. Hunt upon reasonable request.

RESULTS

At the baseline examination, participants had clinical characteristics that are relatively typical for patients undergoing bariatric surgery in the United States. The mean age of the subjects was 47±11 years, 79% were women, mean unadjusted BMI was 44±7 kg/m^2, 26% had diabetes mellitus, 48% had hypertension, and 53% had hyperlipidemia.

Over an average follow-up period of 11 years, there were small changes in age-adjusted anthropometric indexes or cardiovascular risk factors (Table 1; unadjusted values shown in Table S2). Mean age-adjusted BMI increased by 1.1±0.8 kg/m^2 in men and 0.3±0.4 kg/m^2 in women (*P*=not significant; Table 1). Body fat percentage increased, whereas fat free mass decreased. There were modest declines in exercise capacity between the baseline and 11-year visits (Table 1). There were more patients diagnosed with hypertension over time, although systolic and diastolic blood pressures did not change

Table 1. Age-Adjusted Clinical Parameters at Baseline and 11-Year Follow-Up

Variable	Men (n=53)		Women (n=201)		Both
	Baseline	11 y	Baseline	11 y	*P* Value*
Age, y	49.1±1.5	60.2±1.5	46.7±0.8	57.7±0.8	<0.001
Weight, kg	149.0±2.9	149.5±3.7	117.8±1.5	115.0±1.9	NS
BMI, kg/m^2	45.6±0.9	46.7±1.2	43.5±0.5	43.8±0.6	NS
BMI AUC	N/A	46.3±1.0	N/A	43.3±0.5	N/A
Waist, cm	137.4±2.3	142.3±2.7	129.1±1.2	132.5±1.4	<0.001
% Body fat	44.1±0.6	45.5±0.8	53.2±0.3	54.0±0.4	<0.05
Fat free mass, kg	81.3±1.1	77.5±1.5	54.9±0.6	52.4±0.7	<0.001
LDL, mg/dL	103.8±3.8	103.5±4.4	107.8±1.9	118.8±2.2	<0.001
HDL, mg/dL	37.1±1.3	36.4±1.5	48.2±0.7	49.6±0.8	NS
Triglycerides, mg/dL	175.8±14.7	154.3±10.2	176.8±7.6	145.7±5.2	<0.001
Glycosylated hemoglobin, %	5.98±0.13	6.53±0.22	5.84±0.07	6.32±0.11	<0.001
HOMA-IR	5.05±0.61	6.88±1.5	3.89±0.31	5.88±0.78	NS
Systolic BP, mm Hg	132.6±2.3	122.6±2.4	124.4±1.2	125.0±1.2	NS
Diastolic BP, mm Hg	76.5±1.5	69.5±1.3	70.6±0.7	69.7±0.7	NS
Heart rate, bpm†	73.4±1.8	70.5±1.5	73.8±0.9	70.2±0.8	<0.01
Treadmill time, s	690±26	642±38	540±13	537±16	NS
Hypertension, %	55	72	47	59	<0.05
Diabetes mellitus, %	38	53	23	41	<0.001
Dyslipidemia, %	77	91	46	59	NS

Data are shown as mean±SEM or percentage. AUC indicates area under the curve; BMI, body mass index; BP, blood pressure; bpm, beats per minute; HDL, high-density lipoprotein; HOMA-IR, homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein; N/A, not applicable; and NS, not significant.

**P* value from testing for sex- and age-adjusted 11-year changes for men and women combined, except for age, which was unadjusted. *P* values were adjusted for 19 multiple comparisons by the Bonferroni test.

†Sample size for treadmill time was 49 men and 185 women at baseline and 15 men and 78 women at follow-up.

(Table 1). This likely reflects an increase in use of blood pressure–lowering medications (Table 2). Interestingly, there were only modest declines in the treadmill times between the baseline and 11-year visits (Table 1). When adjusting for baseline variables, fitness (as defined by treadmill time) was only a predictor for E/A and had little influence on the other parameters in the models.

Cardiac Structure

At baseline, mean LV diastolic volumes for both men and women were within the sex-specific normal ranges, as reported in the EchoNormal study (Table 3; unadjusted echocardiographic parameters shown in Table S3).[29] Sex-specific LV masses were near or just above the upper limits of the normal range, as established in the EchoNormal study. The most common LV geometry was concentric remodeling (Figures 1 and 2). LA diameters were also at the upper limits of normal, whereas LA volumes were within normal limits. At 11-year follow-up, there were age-adjusted increases in LV diastolic volumes in both sexes and for the entire group (Table 3). Of note, mean LV end-diastolic volumes at 11-year follow-up were 130 mL in men and 107 mL in women, both of which remained in the normal range despite enlarging over time. There were significant increases in LV mass in both men and women, and the sex- and age-adjusted changes for the entire group were also significant. The magnitude of change in LV mass was greater in men than women. Relative wall thickness was elevated in both sexes at baseline and remained so at follow-up, although there were declines in relative wall thickness over the study period. LV mass/volume did not change over time. There was a shift to a higher proportion of patients with concentric hypertrophy in both sexes (Figures 1 and 2A). Excluding patients with a diagnosis of

Table 2. Blood Pressure Medication Use at Baseline and 11-Year Follow-Up

Class of Drugs	Baseline (n=254)	11 y (n=254)
β Adrenergic blocking agents	3	13*
Calcium channel blocking agents	13	13
Angiotensin-converting enzyme inhibitors	14	21*
Angiotensin receptor blocking agents	10	24*

Data are shown as percentage of patients taking these agents. Patients may have taken >1 class of medications.

**P*<0.05 vs baseline.

Table 3. Age-Adjusted Echocardiographic Parameters at Baseline and 11-Year Follow-Up

Variables	Men (n=53)		Women (n=201)		*P* Values*
	Baseline	11 y	Baseline	11 y	Change
LV end diastolic volume, mL	107±3.8	131±3.9†	94±1.9	107±2.0†	<0.001
LV mass, g	229±6.7	273±7.3†	177±3.4	191±3.7†	<0.001
LV mass/LV end diastolic volume, g/mL	2.27±0.09	2.17±0.06	2.00±0.04	1.84±0.03	0.010
LV mass/height$^{2.7}$, g/m$^{2.7}$	46.1±1.6	57.5±1.9†	46.2±0.8	52.2±1.0†	<0.001
Relative wall thickness	0.54±0.017	0.50±0.013	0.51±0.009	0.47±0.007†	<0.001
LV ejection fraction, %	60.6±1.4	62.8±1.3	61.4±0.7	62.4±0.7	NS
LA diameter, cm	4.1±0.7	4.3±0.6	3.8±0.4	3.9±0.3	0.004
LA volume, mL	65±3.0	85±3.1†	47±1.5	54±1.6†	<0.001
RV fractional area change, %	38±1.4	44±1.3†	42±0.7	45±0.7†	<0.001
E/A	1.27±0.04	1.03±0.04†	1.20±0.2	0.91±0.2†	<0.001
E deceleration time, ms	203±6.3	179±6.2†	203±3.2	190±3.2†	<0.001
E/e'	9.02±0.85	9.45±0.51	9.25±0.44	9.40±0.26†	NS

E indicates early diastolic mitral inflow velocity; E/A, ratio of early/late mitral diastolic flow velocities; E/e', ratio of early mitral diastolic flow velocity/early mitral annular velocity; LA, left atrial; LV, left ventricular; and RV, right ventricular.

* *P*-value from testing for gender- and age-adjusted 11-year changes for males and females combined.

† *P*<0.01 for gender-specific 11-year changes. All *P*-values were adjusted for 10 multiple comparisons by the Bonferroni test.

hypertension at either visit showed similar changes in the pattern of LV geometry (Figure 2B), suggesting that hypertension was not the sole cause of changes in LV remodeling. LA anterior-posterior diameter and LA volume both increased over time in the sex- and age-adjusted analysis. Absolute increase in LA volume was larger in men than women.

Cardiac Function

LV EF and right ventricular fractional area change were both within normal limits at baseline. There were no changes in LV EF in either sex or for the entire group over the period of follow-up (Table 3). Right ventricular fractional area change increased between baseline and 11-year follow-up. Mitral inflow patterns at baseline showed E wave predominance with normal E deceleration times and septal ratio of early mitral diastolic flow velocity/early mitral annular velocity (E/e') <10. Over the course of the study, there was a decrease in the mitral E/A ratio, as expected with aging, and a mild shortening of E wave deceleration time in both men and women. However, E/e', a reported index of LV filling pressures,[30] was normal at baseline and did not change over the 11-year follow-up in either sex.

Predictors of Change

The only baseline characteristics that predicted the change in the key echocardiographic variables were sex and baseline BMI, both of which were predictive of the change in LV mass (Table 4). The cumulative effect of BMI over the follow-up period, assessed by BMI area under the curve, significantly predicted the

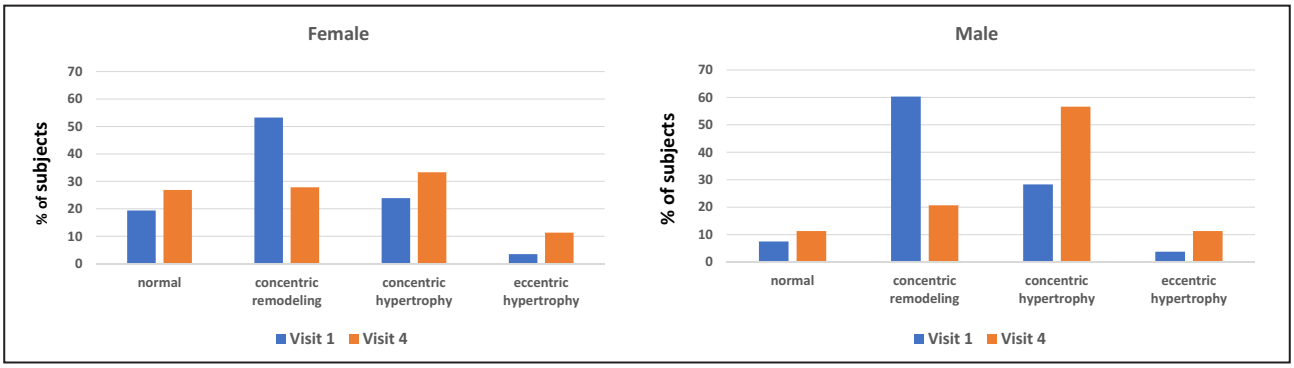

Figure 1. Changes in patterns of left ventricular (LV) geometry over time.

LV geometry was classified into 1 of 4 categories based on LV mass index (LV mass/height$^{2.7}$) and relative wall thickness. At baseline, concentric remodeling was the most common pattern in both sexes. After 11 years of follow-up, there was a shift toward less concentric remodeling and more concentric hypertrophy in both men and women.

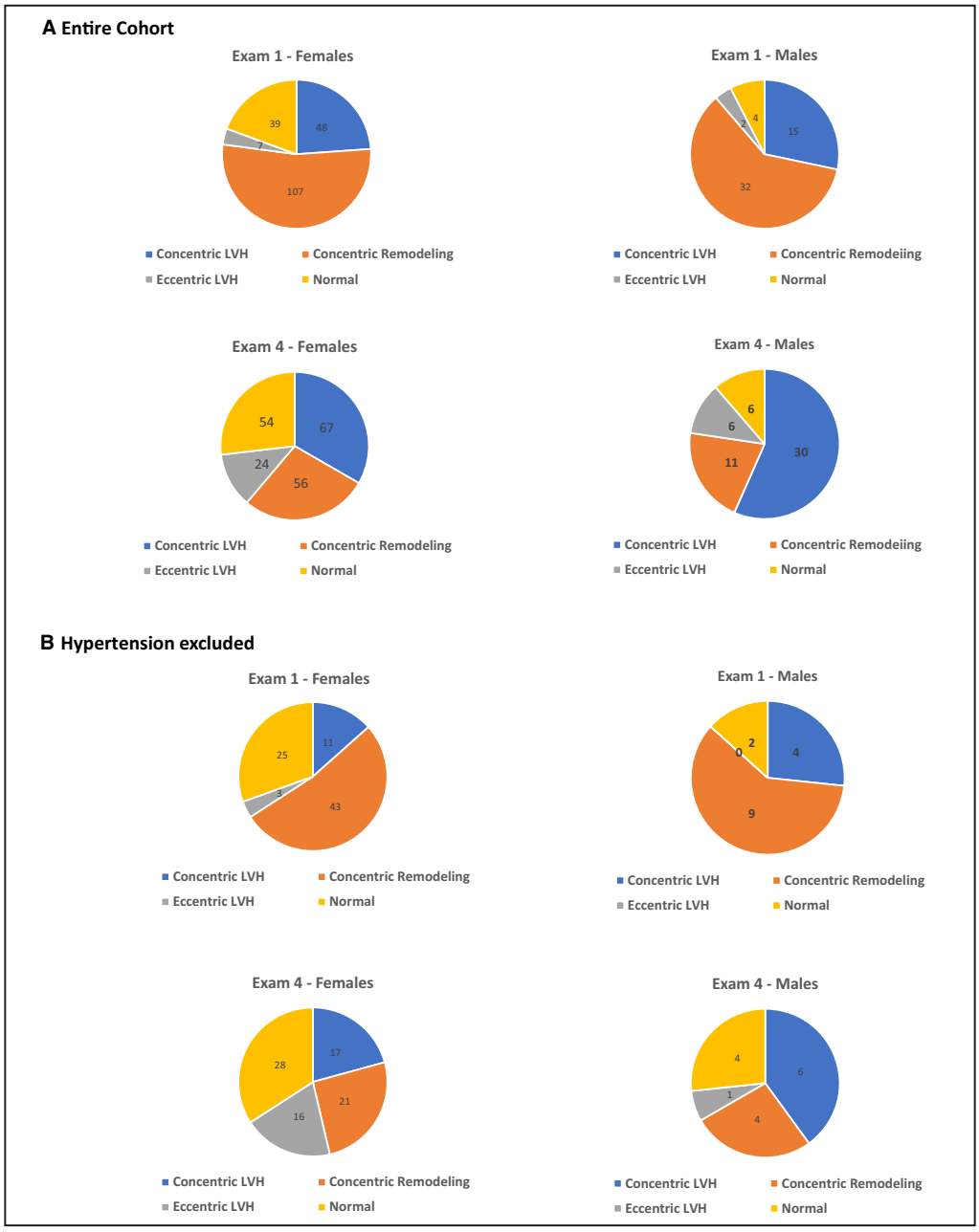

Figure 2. Changes in patterns of left ventricular (LV) geometry between baseline and 11 years in overall cohort (A) and the subgroup of patients without a diagnosis of hypertension at either visit (B).
Absolute numbers of patients in each category are shown. LVH indicates LV hypertrophy.

changes in LV mass. Change in LV stroke volume was also associated with the change in LV mass. Diagnoses of hypertension or diabetes mellitus and changes in these diagnoses (yes/no) between visit 1 and visit 4 were not predictive of changes in any of the main echocardiographic parameters. Likewise, change in mean arterial pressure between visit 1 and 4 were not predictive of the change in LV mass. Findings were similar when change in waist circumference rather than BMI area under the curve was placed into the model, with waist change predicting change in LV mass ($P<0.0001$) but not predicting change in LA volume ($P=0.53$).

We considered the possibility that the sample in this analysis was biased because we only included subjects who had an echocardiogram at both time points (baseline and 11 years), and thus were alive and healthy enough to attend the 11-year follow-up visit. To test this possibility, we compared LV mass in 3 separate groups: (1) those subjects included in this analysis (no surgery,

Table 4. Predictors of Changes in Cardiac Structure and Function Over Time

Baseline Variable Predictors of Change			Δ LV Mass*	Δ LVdV	Δ RWT	Δ LA Diameter	Δ LA Volume	Δ E/A	Δ E Decel Time	Δ RV Fractional Shortening
Sex			<0.001†	0.06	0.69	0.70	0.01	0.37	0.35	0.14
Age			0.77	0.54	0.79	0.79	0.37	0.41	0.10	0.90
BMI			0.001†	0.04†	0.54	0.34	0.93	0.53	0.55	0.23
Smoking status			0.14	0.17	0.23	0.95	0.94	0.96	0.75	0.87
Change in Variable Predictors	**Mean Change±SD**	***P* Value**								
BMI AUC			<0.001†	0.01	0.93	0.05†	0.04†	0.27	0.69	0.20
Δ Mean BP	−1.96±15.1	0.04	0.37	0.83	0.65	0.14	0.69	0.90	0.70	0.10
Δ Heart rate	−3.4±14.6	<0.001	0.19	0.89	0.45	0.50	0.008†	0.01†	0.18	0.46
Δ HbA1c	0.49±1.44	<0.001	0.18	0.03	0.09	0.08	0.74	0.03†	0.67	0.97
Δ LV stroke volume	23.0±33.2	<0.001	0.005†	0.02†	0.32	0.27	0.02†	0.54	0.38	0.72
Hypertension			0.31	0.08	0.20	0.69	0.71	0.36	0.57	0.39
Diabetes mellitus			0.36	0.73	0.29	0.84	0.33	0.25	0.52	0.64

AUC indicates area under the curve; BMI, body mass index; BP, blood pressure; E Decel time, E wave deceleration time; E/A, ratio of early/late mitral diastolic flow velocities; HbA1c, glycosylated hemoglobin; LA, left atrial; LV, left ventricular; LVdV, LV diastolic volume; RV, right ventricular; and RWT, relative wall thickness.

*Changes are defined as examination 4 minus examination 1. *P* values are unadjusted for multiple comparisons, but should be <0.006 to adjust for 8 dependent variables using the Bonferroni adjustment.

†*P*<0.05.

echocardiogram at visit 1 and 4); (2) patients initially in the nonsurgery group but who subsequently crossed over to surgery (not included in this analysis); and (3) patients not undergoing surgery, but missing an echocardiogram at either visit 1 or visit 4. We found no difference in LV mass in the 3 groups at baseline, and no differences between groups 1 and 3 at follow-up. As expected, there was lower LV mass in group 2 (those who crossed over to surgery) versus groups 1 and 3 at the 10-year follow-up. These data suggest that our findings are not related to bias or sampling error related to the study design. Table S1 shows demographic, anthropomorphic, and echocardiographic parameters in the groups with (n=254) and without an echocardiogram (n=483) at visit 4. Only BMI and waist circumference were different in these groups. There were 2 cases of incident HF over the 11 years of follow-up in the 254 patients included in this analysis (0.8%) compared with 4 of 484 (0.8%) patients without a follow-up echocardiogram at 11 years.

DISCUSSION

Data obtained from population studies provide convincing evidence that increasing levels of obesity are associated with the development of clinically diagnosed HF over time.[1,2,31] The mechanisms by which this occurs are less certain. Data from the FHS (Framingham Heart Study) suggest that a reduced EF was common in the subjects with incident HF,[1] whereas more recent studies have often not clearly distinguished whether incident cases of HF occurred with reduced or preserved EF.[2,3] In the past 2 decades, there has been a shift in the epidemiological characteristics of HF, with a higher proportion of HFpEF and fewer cases of HF with reduced EF, likely because of reductions in ischemic heart disease burden.[32,33] The increase in prevalence of HFpEF seems to be related, at least in part, to the increasing prevalence of obesity.[20] The current study allowed us to track changes in cardiac geometry and function over a long period of time in patients with persistent, severe obesity, and thus to gain some insights into the natural history of cardiac remodeling and function as it relates to adiposity. Studies such as this are needed as the severity and duration of obesity have been proposed as key factors in the development of HF.[22,34]

Obesity and Risk of HF

Although it is clear that obesity, defined by either BMI or waist circumference, is associated with incident HF,[10] existing literature is mixed as to whether this association is independent of other obesity-related conditions. In the FHS (n=5881), higher BMI at enrollment was associated with an increased risk of incident HF over a mean follow-up period of 14 years in both sexes, and this risk was graded across categories of increasing BMI.[1] In models with stepwise selection of covariates, age, history of myocardial infarction, valve disease, and systolic blood pressure all entered the model ahead of BMI as predictors of

HF. Among 6809 subjects in the MESA (Multicenter Study of Atherosclerosis) without cardiovascular disease at baseline, BMI and waist circumference were significantly associated with incident HF over a median follow-up of 7.6 years.[2] However, in that study, the associations became nonsignificant after adjustment for obesity-related comorbidities (hypertension, hypercholesterolemia, dysglycemia, LV hypertrophy, kidney disease, and inflammation), suggesting that these other disorders, rather than obesity itself, were more closely related to the development of HF. In the CCLS (Cooper Center Longitudinal Study) (n=19 485), higher midlife BMI was associated with greater risk of HF hospitalization.[3] This association was substantially attenuated after adjusting for cardiorespiratory fitness levels. These findings imply that low fitness may have impacted the risk of developing HF, perhaps more so than obesity. Other studies support low levels of physical activity as a major risk factor for HF.[6] We did not find a relationship between baseline levels of fitness and change in LV geometry or function (except for E/A). However, our population had a low incidence of clinical HF. This is likely related, at least in part, to the relatively low burden of comorbid conditions in our population. Thus, multiple factors appear to contribute to the risk of HF in subjects with obesity.

Obesity-Related Cardiac Remodeling

With the increasing prevalence of obesity in the past few decades,[35] obesity-related cardiac remodeling may be impacting the types of cardiovascular disease encountered in modern practices. In addition to the apparent increased proportion of patients with HFpEF, atrial fibrillation is increasingly common and associated with obesity.[36–38] The likely causal nature of this relationship may be inferred from recent data showing that weight loss achieved through bariatric surgery reduces the incidence of new atrial fibrillation.[39] Notably, atrial fibrillation is extremely common in patients with HFpEF and likely is a contributing factor to the development of HF.[40] The findings from this longitudinal study of patients with >11 years of severe obesity (with a low burden of comorbidities) show significant, but relatively small, increases in LV volume, LV mass, and LA volume over time with no significant changes in LV EF or estimated LV filling pressures. Such changes could predispose to development of HFpEF. However, the changes we observed are not characteristic of an evolving dilated cardiomyopathy. As there were only 2 incident cases of clinically diagnosed HF in this subgroup of patients during the course of follow-up, we cannot evaluate whether changes in cardiac geometry or function were related or potentially contributory to the development of clinical HF. The incidence of new-onset HF (2/254) in the nonsurgical control group of our study (ie, those with persistent obesity) appears to be lower than that in some published studies.[1,2,41] However, other studies also report a low incidence of new HF in populations similar to ours.[8] The expected incidence of HF in subjects with obesity is not well defined and likely varies in different populations, particularly if there are differences in age, race, sex, severity of obesity, and the prevalence of obesity-related coexisting conditions.

Potential Mechanisms of Obesity-Related Cardiac Remodeling

In 1985, Alexander appears to have coined the term, "cardiomyopathy of obesity."[22] He proposed that increased total blood volume, high cardiac output, systemic hypertension, pulmonary hypertension, and depressed ventricular function may collectively lead to HF in some individuals with obesity. He also suggested that circulatory congestive symptoms rarely occurred unless the degree of obesity was extreme (body weight >135 kg) and was present for at least 10 years. Presciently, he also observed that many obese patients with HF had preserved contractile function. The patients in our study all had BMI >35 kg/m^2 with mean body weight of 149 kg in men and 118 kg in women at the time of enrollment, and they were followed up for 11 additional years. Thus, they had cumulative lifetime durations of severe obesity much more than 10 years. To further quantify the cumulative effects of obesity, we calculated exposure to obesity as the area under the curve of BMI over follow-up time. This approach of assessing the cumulative BMI burden over time may be particularly useful in longitudinal studies because it is straightforward and may facilitate comparison of results in different patient cohorts. Although the incidence of HF was low in our population, the changes in LV geometry (particularly the increased prevalence of concentric hypertrophy) and LA volume might predispose to more HF and atrial fibrillation with an even longer duration of follow-up.[42,43]

LV Hypertrophy and LA Enlargement in Obesity

The presence of LV hypertrophy seems to be a central and perhaps essential component of obesity-associated cardiovascular disorders. With regard to the development of LV hypertrophy in patients with obesity, daytime or nocturnal hypertension can certainly be contributing factors. However, it is evident that LV hypertrophy can occur in the absence of hypertension in subjects with obesity.[14] In the current study, neither the diagnosis of hypertension nor change in mean arterial pressure over time was related to changes in LV mass. In the subgroup without

a diagnosis of hypertension at either visit, we still saw a shift from concentric remodeling to concentric hypertrophy over time (Figure 2B). Other factors, such as intermittent nocturnal hypoxemia attributable to sleep disordered breathing,[12,44] inflammation,[45] and altered cardiac metabolism,[46,47] have all been posited as potential mediators of LV hypertrophy and HF. In most studies, the severity of LV hypertrophy is proportional to the severity of obesity.[12,22,48] This implies that the hemodynamic load driven by metabolic needs of the body may be a major determinant of cardiac size. Increased blood volume and chronically elevated cardiac output[22] are thought to be the key components of obesity-induced overload. Our current findings are consistent with this general hypothesis as BMI at baseline, cumulative BMI exposure, and changes in LV stroke volume were all related to changes in LV mass. Although volume overload was once thought to be the primary stimulus for hypertrophy in obesity,[34] the findings of this study and others indicate that concentric LV geometries are more common.[12,13] The physiological reasons for this are still uncertain.

Once the LV is hypertrophied, particularly with concentric geometry, even relatively small shifts in intravascular volume may lead to rapid increases in LV diastolic pressures because of the low compliance of the chamber.[49] Because blood volume is already high in obese individuals, small additional increases may exert relatively large effects on the vasculature and heart. Thus, patients with obesity may be particularly prone to having fairly normal hemodynamics at rest, but elevated filling pressures or even acute pulmonary edema during exercise or under various types of stress.[49] The presence of subclinical LV systolic and diastolic dysfunction in obesity likely exacerbates this problem.[50,51] We found a reduction in E/A over time in both men and women, a finding that is expected with increasing age. Interestingly, E wave deceleration time shortened at 11-year follow-up. We speculate that this may reflect a decrease in LV compliance associated with progression of LV hypertrophy.

LA enlargement is a risk factor for atrial fibrillation and overall mortality.[42,52] Interestingly, the significant increase in LA volume over time was accompanied by only modest changes in parameters of LV diastolic filling (ie, no change in E/e'). This is compatible with the idea that obesity itself is a driver of cardiac remodeling, and the effect may be partially independent of changes in blood pressure or other hemodynamic alterations.

Limitations

The population in our study was mostly white and women, with only a moderate burden of coexisting conditions that were generally well controlled. Although this profile may differ from that in many patients with chronic, severe obesity, it offers the advantage of allowing us to more precisely study the direct effects of obesity with less confounding by the other conditions. The issue of how to best define adiposity continues to be debated. In some populations, waist circumference is a better predictor of cardiovascular events or outcomes than is BMI.[53] However, in most large studies, the 2 measures are highly correlated and equally predict outcomes.[2,10,54,55] In patients with severe obesity, major discrepancies in classification based on BMI or waist circumference are unusual. In our population, similar results were found using either BMI or waist circumference in the statistical models. Even using adjusted models, the potential for residual confounding by the presence of known or unmeasured comorbidities is a cause of uncertainty when performing multivariable modeling. Therefore, it is not possible to ascribe causality based simply on associations. Given the known effects of race (especially within blacks) on LV mass and geometry, the question of whether there is racial variation in cardiac adaptation to obesity is an important topic for continued investigation. Because this study started in 2001, not all currently used echocardiographic parameters are available (ie, lateral annulus tissue Doppler measurements were not obtained, and speckle tracking was not available for assessment of strain).

CONCLUSIONS

This longitudinal study of a moderate-sized cohort of subjects with long-standing, severe obesity offers unique insights into the effects of adiposity on the heart. Our results show significant, but relatively modest, changes in cardiac geometry over time, the most important being increased LV mass and increased LA volume. Functional changes were less prominent, and interestingly, Doppler estimates of LV filling pressures did not change over time. These findings are consistent with the notion that prolonged exposure to obesity is more likely to lead to HFpEF, rather than a specific obesity-induced dilated cardiomyopathy.

ARTICLE INFORMATION

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Affiliations

From the Department of Internal Medicine, Medical University of South Carolina, Charleston, SC (S.E.L.); Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC (S.E.L.); Division of Epidemiology, University of Utah School of Medicine, Salt Lake City, UT (T.D.A., L.E.D., S.C.H.); Intermountain Health Corporation, Salt Lake City, UT (T.D.A.); Department of Exercise Sciences, Brigham Young University, Provo, UT (L.E.D.); Rocky Mountain Associated Physicians Inc, Salt Lake City, UT (R.M., S.C.S.); Division of Cardiology, Augusta University, Augusta, GA

(L.R.); and Department of Genetic Medicine, Weill Cornell Medicine, Doha, Qatar (S.C.H.).

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Disclosures

None.

Supplementary Materials

Tables S1–S3

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Supplemental Material

Table S1. Comparison of patients who had a follow-up echocardiogram at 11 years vs. those who did not.

	No follow-up echo			Follow-up echo			
Baseline Variable	N	Mean	SD	N	Mean	SD	p
Age	254	47.2	11.1	483	45.0	11.8	0.013
BMI	254	43.9	6.7	484	45.8	7.5	**0.001**
BMIAUC	254	44.0	7.5	434	43.3	8.1	0.30
Waist	254	130.8	16.6	484	134.0	16.6	**0.014**
HbA1c	253	5.9	1.0	478	6.0	1.3	0.14
Glucose	254	105.7	31.4	484	107.8	39.4	0.47
HOMA-IR	243	4.1	4.5	482	4.4	3.9	0.34
SBP	254	126.1	18.1	484	127.5	18.5	0.34
DBP	254	71.8	10.8	484	72.3	10.6	0.60
LV Mass	254	188.1	53.4	301	181.3	50.7	0.12
LV Mass Index	254	111.5	29.2	301	107.6	28.2	0.11
LV Mass index 2.7	254	46.2	11.7	301	44.7	11.6	0.13
LV diastolic volume	254	96.4	28.3	301	97.4	30.1	0.69
LV ejection fraction	254	0.7	0.1	301	0.6	0.1	0.05
relative wall thickness	254	0.5	0.1	301	0.5	0.1	0.33
LV mass/volume	254	2.1	0.7	301	2.0	0.7	0.34
LV EF 4 chamber	254	0.6	0.1	295	0.6	0.1	0.12
LADs	253	3.9	0.5	298	3.9	0.6	0.58
LAv4cs	254	50.9	23.1	296	51.8	15.8	0.66
RV fractional area change	253	40.8	10.1	297	41.3	10.6	0.59
E	247	78.0	17.3	293	78.7	16.7	0.61
E deceleration time	247	203.3	45.4	293	200.3	44.3	0.45
A	247	68.1	21.1	292	68.0	18.7	0.96
E/A	247	1.2	0.4	292	1.2	0.4	0.66
E/e' septal	154	9.2	5.0	191	9.0	3.0	0.58
e' septal	154	9.5	3.5	191	9.9	6.7	0.51
stroke volume	237	70.5	24.3	270	70.1	34.6	0.88
cardiac output	237	5.2	1.7	270	5.4	3.0	0.43

Table S2. Unadjusted (raw) data showing characteristics of participants at baseline and mean follow-up of 11 years.

Unadjusted data Table 1	Male (N=53)				Female (N=201)			
	Baseline		11 years		Baseline		11 years	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (y)	49.1	9.2	60.2	9.4	46.7	11.6	57.7	11.6
Weight (kg)	148.3	26.0	147.8	39.0	118.0	20.3	115.5	24.7
BMI (kg/m2)	45.5	7.1	46.3	11.1	43.5	6.5	43.9	8.1
BMI AUC	N/A	N/A	46.0	8.7	N/A	N/A	43.4	7.2
Waist (cm)	137.3	15.2	141.8	21.5	129.1	16.6	132.6	19.2
Body fat (%)	44.2	5.8	45.3	7.7	53.2	3.3	54.0	4.3
Fat free mass (kg)	81.2	10.7	77.0	14.6	54.9	7.2	52.6	9.5
LDL (mg/dl)	103.8	25.3	102.1	32.5	107.7	27.6	119.2	32.7
HDL (mg/dl)	37.6	5.8	36.7	6.9	48.1	10.3	49.6	11.8
Triglycerides (mg/dl)	176.7	74.6	153.5	82.6	176.5	113.7	145.9	71.6
Hemoglobin A1C (%)	6.03	1.06	6.57	1.61	5.83	0.95	6.31	1.59
HOMA-IR	5.0	5.3	7.1	12.1	3.9	4.2	5.8	10.7
Systolic BP (mmHg)	133.5	18.3	122.9	19.1	124.2	17.5	125.0	16.6
Diastolic BP (mmHg)	76.6	9.7	69.2	9.8	70.6	10.8	69.8	9.7
Heart Rate (bpm)	73.0	15.8	70.4	10.5	73.9	12.8	70.2	10.9
Treadmill time (sec)	675	190	604	177	544	207	545	164
Next two not in adj T1								
Glucose	114.0	37.7	124.8	50.1	103.5	29.3	104.8	45.3
Fat mass (kg)	65.7	18.4	65.5	21.3	63.4	14.5	62.7	16.2

BMI (body mass index); AUC (area under the curve); LDL (low density lipoprotein); HDL (high density lipoprotein); HOMA-IR (Homeostatic Model Assessment of Insulin Resistance); BP (blood pressure)

Table S3. Unadjusted (raw) data showing echocardiographic parameters at baseline and at mean follow-up of 11 years.

Unadjusted data Table 2	Male (N=53)				Female (N=201)			
	Baseline		11 years		Baseline		11 years	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
LV Mass (g)	230.8	59.2	274.3	62.7	176.9	45.7	190.8	50.0
LV mass index (height)	127.5	32.2	154.1	36.0	107.3	26.9	117.8	30.1
LV mass index (height^2	46.6	12.0	58.1	15.1	46.1	11.7	52.1	13.5
LV diastolic volume	106.5	31.0	129.7	34.8	93.7	27.1	107.3	27.2
LV ejection fraction (linea	0.65	0.09	0.68	0.07	0.66	0.08	0.68	0.07
LV ejection fraction (MOD	0.61	0.10	0.63	0.10	0.61	0.10	0.62	0.09
LA volume	65.1	28.3	85.0	37.7	47.2	20.0	53.7	16.7
Relative wall thickness	0.55	0.15	0.51	0.11	0.51	0.13	0.46	0.10
LA diametere	4.15	0.56	4.30	0.49	3.80	0.52	3.92	0.43
LV mass/volume	2.31	0.81	2.20	0.55	1.99	0.63	1.83	0.47
E	71.9	13.8	73.1	20.8	79.5	17.8	73.6	19.1
A	61.8	18.1	79.0	28.1	69.8	21.6	83.9	19.8
E/A	1.23	0.35	1.00	0.39	1.21	0.36	0.92	0.30
E decelertion time	204	50	181	57	203	44	190	44
E/e' septal	9.10	3.42	9.55	4.89	9.23	5.36	9.37	3.29
e' septal	8.54	3.08	8.51	2.61	9.76	3.52	8.24	2.31
stroke volume	82.2	27.1	107.6	33.6	67.2	22.4	89.7	23.5
CO	5.96	1.82	7.38	2.68	4.97	1.67	6.14	1.74
RV fractional area chang	37.6	10.5	44.2	9.5	41.6	9.8	45.0	9.4

LV (left ventricular); LA (left atrial); E (early mitral flow velocity); A (late mitral flow velocity); e’ (mitral annular tissue Doppler velocity); CO (cardiac output); RV (right ventricular)