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Alterations in Left Ventricular Structure and Function in Young Healthy Obese Women

Assessment by Echocardiography and Tissue Doppler Imaging

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OBJECTIVES This study was designed to determine the effects of obesity on left ventricular (LV) structure and function in young obese women.

BACKGROUND Severe prolonged obesity in older adults results in increased plasma volume, eccentric LV hypertrophy, and systolic and diastolic dysfunction. Obese women are at increased risk for the development of heart failure. However, the effects of the obesity on cardiac structure and function in young, otherwise-healthy women are controversial.

METHODS Fifty-one women were evaluated: 20 were obese (body mass index [BMI] $\geq$30 kg/m^2) and 31 were non-obese (BMI $<$30 kg/m^2). Left ventricular structure and systolic and diastolic function were assessed by two-dimensional echocardiography and tissue Doppler imaging, including the load-independent systolic myocardial velocity (Sm global) and early diastolic myocardial velocity (Em global), respectively. The effects of BMI on LV structure and function were assessed using multivariate regression analyses.

RESULTS Obese women had higher end-diastolic septal and posterior wall thickness, LV mass, and relative wall thickness than non-obese women; BMI values showed significant correlations with these variables ($r = 0.58$, $p < 0.0001$; $r = 0.50$, $p < 0.0002$; $r = 0.52$, $p < 0.0001$, and $r = 0.40$, $p < 0.005$, respectively). The Sm global and Em global were lower in obese women, suggesting systolic and diastolic function are decreased; both were negatively correlated with BMI ($r = -0.43$, $p <$. 002 and $r = -0.61$, $p < 0.0001$, respectively). Multivariate analysis showed BMI was the only independent predictor of relative wall thickness, Sm global, and Em global.

CONCLUSIONS Obesity in young otherwise-healthy women is associated with concentric LV remodeling and decreased systolic and diastolic function. These early abnormalities in LV structure and function may have important implications for explaining the myocardial dysfunction that is associated with increased cardiovascular morbidity and mortality caused by obesity. (J Am Coll Cardiol 2004;43:1399–404) © 2004 by the American College of Cardiology Foundation

Obesity affects more than 43 million Americans, and the incidence has been increasing markedly in both men and women in recent years (1). Obesity is an independent risk factor for the development of heart failure (HF), even after accounting for other co-morbid conditions that cluster with it, such as diabetes and hypertension. For reasons that are not completely clear, obese and overweight women are at higher risk than obese and overweight men for developing HF (2). The effects of long-standing obesity on left ventricular (LV) structure and function have been characterized as eccentric LV hypertrophy and diastolic dysfunction and occasionally systolic dysfunction and HF (3,4).

However, controversy exists regarding the effects of obesity on the cardiac structure and function of young obese subjects. One study of adolescents showed obesity to be associated with concentric remodeling rather than the classically described eccentric hypertrophy (5). Regarding the systolic function of young obese people, some studies report that systolic function is normal or increased, whereas others show decreases in systolic function (6–9). These studies of LV systolic function and past studies of LV diastolic function are confounded by the fact that obesity is associated with an increase in plasma volume and that the evaluation of LV function in these studies was assessed using load-dependent indices, such as the left ventricular ejection fraction (LVEF) and mitral inflow velocities (early diastolic and atrial [E/A] ratios). Thus, it is difficult to ascertain how much of the functional abnormalities are due to obesity versus how much had been influenced by differences in loading conditions (6–11). Furthermore, in some of the past studies of obesity, some of the subjects studied have had co-morbid conditions such as hypertension, which also causes abnormalities in ventricular structure and function (12).

The hypothesis of this study is that in the absence of co-morbid conditions, young healthy women exhibit early alterations in LV structure and function that have been

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JACC Vol. 43, No. 8, 2004
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Abbreviations and Acronyms

BMI	= body mass index
BP	= blood pressure
DBP	= diastolic blood pressure
Ded	= left ventricular mid-cavity dimensions at end-diastole
Des	= left ventricular mid-cavity dimensions at end-systole
E/A ratio	= early diastolic and atrial velocity ratio
Em	= early diastolic myocardial velocity
%FS	= percent fractional shortening
HF	= heart failure
LV	= left ventricle/ventricular
LVEF	= left ventricular ejection fraction
LVM	= left ventricular mass
MAP	= mean arterial pressure
RWT	= relative wall thickness
SBP	= systolic blood pressure
Sm	= systolic myocardial velocity
TDI	= tissue Doppler imaging
Vcf	= velocity of circumferential fiber shortening

associated in other conditions with the development of myocardial dysfunction and HF. This study was conducted as part of a larger study of the cardiovascular effects of obesity in young women. The effects of obesity on LV structure and function was evaluated by use of new echocardiographic techniques that have been shown to be relatively load-independent, reliable, and reproducible (13,14). Characterization of ventricular structure and function in young obese subjects may help elucidate the mechanisms responsible for the increased cardiovascular morbidity and mortality associated with this condition.

METHODS

Subjects. Fifty-one young (21 to 37 years old) healthy women were recruited to participate by advertisement or through the Center for Human Nutrition at Washington University School of Medicine, and they were grouped according to their body mass index (BMI) as: obese (BMI $\geq$30 kg/m^2, n = 20), and non-obese (BMI $<$30 kg/m^2, n = 31). All subjects underwent a history and medical evaluation to exclude co-morbid conditions (other than obesity). Measurements included height and weight and blood pressure (BP); all obese subjects underwent a 2-h glucose tolerance test, a lipid panel, and a routine chemistry panel including electrolytes and creatinine. Subjects were excluded if they had any of the following: 1) a history of hypertension, were on antihypertensive medication, or if their sitting BP was elevated (systolic blood pressure [SBP] $\geq$140 mm Hg and/or diastolic blood pressure [DBP] $\geq$90 mm Hg); 2) diabetes mellitus (fasting glucose $>$126 mg/dl or a glucose level $>$200 mg/dl 2 h after a 75-g glucose load); 3) any history or findings of cardiovascular disease, including HF, congenital heart disease, and/or had undergone any cardiovascular procedures; 4) hyperlipidemia (total cholesterol $>$260 mg/dl and/or triglyceride levels $>$400 mg/dl); 5) major systemic disease (e.g., cancer, lupus); 6) engaged in smoking within 12 months of the study; 7) were pregnant; and 8) were taking any vasoactive medications. All subjects signed an informed consent, which was approved by the Institutional Review Board at Washington University School of Medicine.

Echocardiography. All subjects underwent a complete two-dimensional and Doppler echocardiographic examination by use of a commercially available ultrasound system (Sequoia-C256, Acuson-Siemens, Mountain View, California) equipped with second harmonic imaging software. Two-dimensional echocardiographic measurements included the LV end-diastolic and end-systolic volumes using the method of discs, and the LVEF was calculated by the modified Simpson's method. The LV percent fractional shortening (%FS) was obtained from the parasternal short-axis view and calculated as: %FS = [(Ded − Des)/Ded] × 100, where Ded and Des are the left ventricular mid-cavity dimensions at end-diastole and end-systole, respectively. The velocity of circumferential fractional shortening (Vcf) was calculated as: Vcf = %FS/LVET, where LVET is the left ventricular ejection time, a measurement derived (in ms) from the opening to the closing of the aortic valve. The left ventricular mass (LVM) was determined using the area-length method; the LVM index and LVM/height were calculated by dividing the LVM by the body surface area and by the height, respectively. The relative wall thickness (RWT) was calculated as: RWT = [2 × PWth]/[Ded], where PWth = posterior wall thickness at end-diastole. All measurements were performed according to the recommendations of the American Society of Echocardiography (15).

Pulsed-wave Doppler-derived transmitral inflow measurements. Pulsed-wave Doppler-derived transmitral inflow velocities were obtained with the transducer in the apical four-chamber view and the sampling volume at the mitral valve leaflet tips. The early diastolic (E) and atrial (A) velocities were measured, and the E/A ratio was calculated. The deceleration time (in ms) and the isovolumic relaxation time (in ms) were measured according to the recommendations of the American Society of Echocardiography (16).

Tissue Doppler imaging (TDI). Tissue Doppler imaging was used to measure myocardial tissue velocities. These velocities were obtained with the transducer in the apical four- and two-chamber views and the sampling volume at the lateral, septal, anterior, and inferior mitral annular regions. Measurements included the systolic myocardial velocity (Sm) and early diastolic (Em) myocardial velocity at the mitral annulus; Sm velocities from the four sites were averaged to derive a global measurement of systolic function (Sm global). Similarly, Em velocities from the four mitral annular regions were averaged to derive Em global as a measurement of diastolic function as described by Alam et al. (17).

All reported measurements are the averages derived from three consecutive cardiac cycles. The echocardiographic measurements were repeated in 10% of the cases by a second observer to determine the inter-observer correlations. For

Table 1. Subject Characteristics and Hemodynamics

	Non-Obese (n = 31)	Obese (n = 20)	p Values
Age (yrs)	30 ± 5	32 ± 4	0.14
BMI (kg/m^2)	24 ± 4	37 ± 5	**< 0.0001**
Heart rate (beats/min)	70 ± 11	73 ± 9	0.21
SBP (mm Hg)	107 ± 10	117 ± 12	**< 0.005**
DBP (mm Hg)	71 ± 7	71 ± 9	0.78
MAP (mm Hg)	83 ± 7	86 ± 9	0.21

Significant p values are in **bold**.
BMI = body mass index; DBP = diastolic blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure.

measurements of pulsed-wave Doppler-derived transmitral E-wave velocity, TDI-derived Em global, and for LVM, these were 0.98, 0.95, and 0.88, respectively.

Hemodynamics. Heart rate was recorded from the electrocardiogram during the echocardiographic examination. The SBP and DBP were recorded after 10 to 15 min of rest in the supine position. Mean arterial pressure (MAP) was calculated as: MAP = [(2 × DBP) + (SBP)]/3.

Statistical analysis. The SAS software (SAS Institute, Cary, North Carolina) was used for the statistical analyses. All variables are expressed as mean ± 1 standard deviation. Student *t* tests were performed to compare the continuous variables describing the two groups. Chi-square analysis was used to compare the racial composition of the two groups. Pearson correlation coefficients were calculated for BMI and measurements of LV structure and function. Stepwise multivariate regression analyses were performed to determine the independent predictors of LV RWT, of systolic function, as described by the Sm global, and of diastolic function, as described by the Em global; independent variables in the multivariate model included BMI, SBP, DBP, heart rate, and age. A p value <0.05 was considered statistically significant.

RESULTS

Patient characteristics. The baseline characteristics of the groups are shown in Table 1. By definition, the BMI was significantly higher in the obese group; the average duration of obesity was 12 ± 6 years (range 6 to 22 years). Although the SBP was normal in both groups according to the standard definition, it was significantly higher in the obese group ($p < 0.005$); the heart rate, DBP, and MAP were similar between the groups. There were 12 white and 8 non-white subjects in the obese group and 25 white and 6 non-white subjects in the non-obese group (p = NS).

LV structure. The LV volumes at both end-diastole and end-systole were similar in both groups (Table 2). Although the LVM index was similar in both groups, the posterior and septal wall thickness, the LVM, and the LVM/height were all significantly higher in the obese group than in the non-obese group. Furthermore, the RWT, an index of LV remodeling, was significantly higher in the obese women ($p < 0.005$). In fact, the RWT showed concentric LV remodeling, a pattern that has been associated with adverse prognosis in patients with hypertension (18).

To determine the potential role of obesity in the pathogenesis of abnormalities of LV structure and function,

Table 2. Left Ventricular Structure and Systolic and Diastolic Function

	Non-Obese (n = 31)	Obese (n = 20)	p Values
Structure			
LVED volume (ml)	85 ± 17	94 ± 17	0.08
LVES volume (ml)	30 ± 8	33 ± 10	0.17
Posterior wall thickness (mm)	79 ± 11	92 ± 10	**< 0.0005**
Septal wall thickness (mm)	78 ± 9	93 ± 11	**< 0.0001**
LV mass (g)	128 ± 32	161 ± 26	**< 0.0005**
LVMI (g/m^2)	78 ± 10	79 ± 13	0.57
LV mass/height (g/m)	80 ± 12	99 ± 17	**< 0.0001**
Relative wall thickness	0.34 ± 0.05	0.40 ± 0.06	**< 0.005**
Systolic function			
LVEF (%)	65 ± 5	65 ± 6	0.69
%FS	38 ± 5	37 ± 5	0.47
Vcf (circ/s)	1.31 ± 0.28	1.32 ± 0.16	0.8
Sm global (mm/s)	10.5 ± 1.2	9.4 ± 1.0	**< 0.005**
Diastolic function			
E-wave (cm/s)	79 ± 17	72 ± 13	0.12
E/A ratio	2.01 ± 0.55	1.76 ± 0.51	0.12
Deceleration time (ms)	191 ± 22	201 ± 33	0.2
IVRT (ms)	88 ± 11	92 ± 13	0.26
Em global (mm/s)	18 ± 2	15 ± 3	**< 0.0005**
Em/Am	1.7 ± 0.3	1.5 ± 0.3	**0.005**
E/Em	5.2 ± 1.4	5.8 ± 1.0	0.09

Significant p values are in **bold**.
E/A = early diastolic and atrial ratio; %FS = percent fractional shortening; IVRT = isovolumic relaxation time; LVED = left ventricular end-diastolic; LVEF = left ventricular ejection fraction; LVES = left ventricular end-systolic; LVMI = left ventricular mass index; Vcf = velocity of circumferential fractional shortening;

JACC Vol. 43, No. 8, 2004
April 21, 2004:1399–404

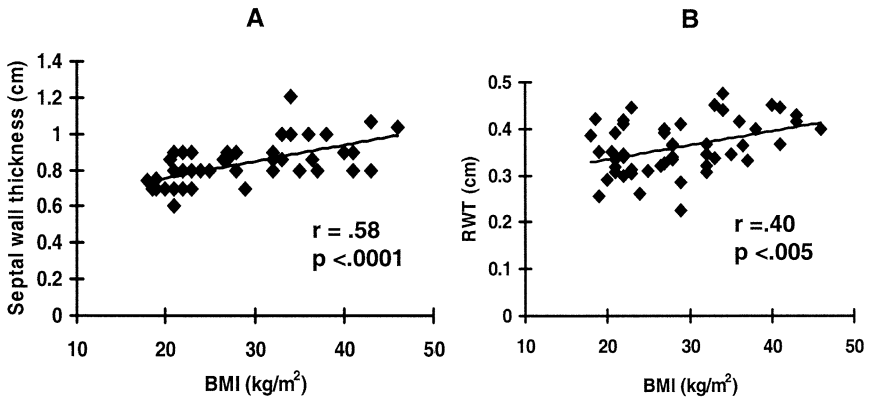

Figure 1. (A) The relationship between septal wall thickness (cm) at end-diastole and body mass index (BMI) (kg/m^2). **(B)** The relationship between relative wall thickness (RWT) and BMI (kg/m^2).

correlations between BMI and the echocardiographically determined variables were performed. The BMI showed a robust correlation with the septal wall thickness ($r = 0.58$, $p < 0.0001$), the posterior wall thickness ($r = 0.50$, $p < 0.0002$), RWT ($r = 0.40$, $p < 0.005$), and LV mass ($r = 0.52$, $p < 0.0001$) (Figs. 1A and 1B). Furthermore, multivariate analysis showed BMI as the only independent predictor of RWT, a measure of LV concentric remodeling ($p = 0.0003$).

LV systolic function. The TDI-derived global Sm, a load-independent index of systolic myocardial contractility, was significantly lower in the obese group ($p < 0.005$). A robust inverse correlation was found between Sm global and BMI ($r = -0.43$, $p < 0.002$) (Fig. 2A), suggesting that myocardial contractility decreases as the severity of obesity increases. Multivariate analysis showed that BMI was the only independent predictor of contractile function, measured by the Sm global ($p = 0.02$). Conventional, load-dependent echocardiographic indices of LV systolic function, such as LVEF, %FS, and Vcf, were similar between the groups.

LV diastolic function. The TDI-derived Em global, a load-independent index of diastolic function, was significantly lower in the obese group ($p < 0.0005$). A robust inverse correlation was found between Em global and BMI ($r = -0.61$, $p < 0.0001$) (Fig. 2B), suggesting that diastolic function worsens as the BMI increases. Multivariate analysis showed that BMI was the only independent predictor of Em global ($p < 0.0001$). Conventional load-dependent indices of LV diastolic function, such as the E-wave, the E/A ratio, deceleration time, and isovolumic relaxation time, were similar between the groups.

DISCUSSION

This cross-sectional study shows that young obese women exhibit abnormalities in LV structure and function, including a pattern of LV concentric remodeling and decreased systolic and diastolic function, as determined by load-independent indices. Furthermore, BMI was found to be a robust, independent predictor of adverse LV remodeling and of systolic and diastolic dysfunction. In these young obese women, LV concentric remodeling was evidenced by increased LVM, increased LVM indexed for height, increased LV wall thickness, increased RWT, and normal LV chamber size. These findings are important because for the

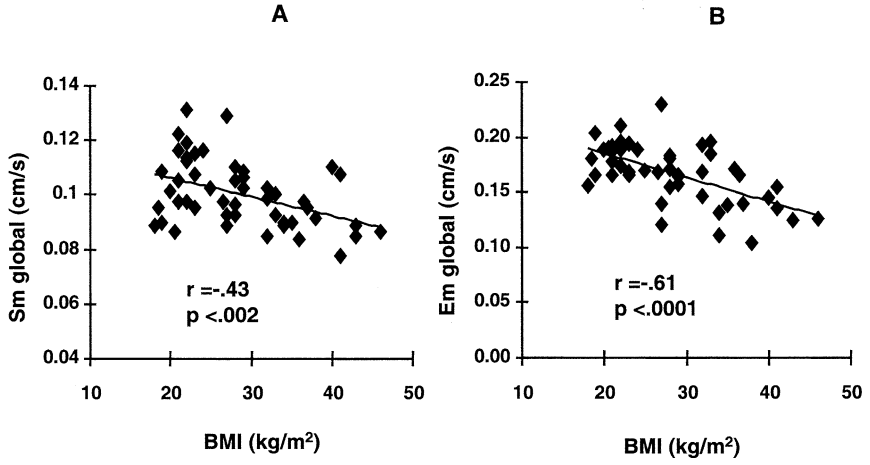

Figure 2. (A) The relationship between systolic myocardial velocity (Sm global) (cm/s) and body mass index (BMI) (kg/m^2). **(B)** The relationship between early diastolic myocardial velocity (Em global) (cm/s) and BMI (kg/m^2).

first time it is shown that young obese women who are otherwise healthy have LV structural and load-independent functional abnormalities similar to those that have been associated in other diseases, such as hypertension, with adverse cardiovascular outcomes and prognosis.

The finding of concentric remodeling in the present study is supported by a study in healthy adolescents in which adiposity indexes significantly correlated with increased LVM and RWT (5). However, this finding is in contrast with those of another study in which obesity was associated with eccentric rather than concentric LV remodeling (19). These seemingly contradictory results may be explained by differences between studies. In the present study the subjects were younger and had a generally shorter duration of obesity (19). Also, it is unlikely that second harmonic imaging was used in the echocardiographic determination of LV structure in the previous study. In the present study, because increased BMI was predictive of LV functional abnormalities (by use of load-dependent techniques), there may be alterations intrinsic to the myocardium in obesity. Hormonal factors, such as high insulin levels, which are common in obese subjects, may also contribute to LV hypertrophy (20,21). The LV concentric remodeling in otherwise-healthy obese young women is of concern because of the association between concentric LV remodeling and increased cardiovascular morbidity and mortality that has been shown in both normal and hypertensive populations (18,22,23).

Perhaps equally intriguing is the subclinical systolic dysfunction observed in the present study. Epidemiologic studies have shown that obesity is an independent risk factor for the development of HF, even after accounting for co-morbid conditions, such as diabetes, and that obese and overweight women are at higher risk of developing HF than obese and overweight men (2). The findings of the present study help to explain the findings of these epidemiologic studies. Specifically, early in the course of obesity there is an increase in blood volume, which leads to increased BP, increased LV wall stress, and compensatory LV hypertrophy. Furthermore, we hypothesized and demonstrated that this LV remodeling is initially concentric in nature and is accompanied by subclinical systolic and diastolic dysfunction. As obesity becomes more chronic, continual volume and/or pressure overload causes eventual LV enlargement, eccentric LV hypertrophy, and progressive systolic and diastolic dysfunction; the later stages are characterized by dilated cardiomyopathy and HF (3,4). This deterioration of LV function from subclinical dysfunction to HF may partly explain why various previous studies of obese subjects who may be at different stages of this deterioration have yielded mixed results on LV systolic function (6–11,24–26). In addition, there are particular challenges common to many non-invasive echocardiographic studies of LV function in obesity: 1) The ideal way to index ventricular function to body size remains unknown. Some studies have shown that in obesity cardiac output is increased; however, when indexed to body size, the cardiac index is decreased (27). 2) Commonly used indices to assess LV function, such as LVEF and mitral valve inflow velocities, are influenced by preload (i.e., the increased plasma volume of obesity) and by afterload (i.e., increased BP and/or ventricular wall stress) (28); thus, abnormalities in these indices may be more indicative of changes in LV loading conditions rather than true alterations in myocardial contractile function. The present study circumvented this issue by using TDI-derived indices of both systolic and diastolic function, which have been shown to be relatively load-independent (14,17). 3) Obese subjects have a high incidence of co-morbid conditions that also affect function, such as hypertension. A previous study of obese subjects showed that a relatively load-independent index of contractility, the end-systolic wall stress/end-systolic volume, was decreased in obese subjects compared with normal subjects (12). However, obese subjects in that study also had hypertension, and thus it is uncertain whether the abnormalities in LV contractility were due to hypertension, obesity, or both.

The findings of altered LV structure and systolic and diastolic function in the present study were obtained by use of second harmonic imaging and TDI, a novel, highly sensitive and specific echocardiographic technique. Second harmonic imaging enhances the detection of the LV cavity-endocardial border and has been shown to be of particular benefit to the imaging of obese subjects (13). The TDI-derived Sm and Em velocities used in the present study have been shown to correlate more robustly with LV function than those observed with pulsed-wave Doppler-derived transmitral indices in subjects with normal LV function (28). Also, a recent study showed the important prognostic value of TDI-derived Em to predict mortality in patients with cardiac disease (29). Our study is the first, to our knowledge, to use TDI to derive load-independent measures of function, which may have prognostic value, to show that increasing BMI in the absence of co-morbidities is an independent predictor of worsening LV systolic and diastolic function.

Study limitations. This is a small observational study of women and, as such, other variables that could potentially predict alterations in LV structure and function, such as male gender or race, could not be evaluated.

Conclusions. Obesity is an independent risk factor for HF, particularly in women. In this study we found that young, otherwise-healthy obese women exhibit alterations in LV structure and function manifested by concentric LV remodeling and decreased systolic and diastolic function. These early abnormalities in LV structure and function may have important implications in explaining the myocardial dysfunction associated with obesity and the associated increased cardiovascular morbidity and mortality.

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