The association of obesity and abnormal cardiac function is not well established. We sought whether body mass index (BMI) and insulin levels were associated with subclinical myocardial disturbances.

Methods and Results—Transthalacic echocardiography, myocardial Doppler-derived systolic (sm) and early diastolic velocity (em), strain and strain rate imaging and tissue characterization with cyclic variation (CVIB), and calibrated integrated backscatter (cIB) were obtained in 109 overweight or obese subjects and 33 referents (BMI <25 kg/m²). BMI correlated with left ventricular (LV) mass and wall thickness (P<0.001). Severely obese subjects (BMI >35) had reduced LV systolic and diastolic function and increased myocardial reflectivity compared with referents, evidenced by lower average long-axis strain, sm, cIB, lower CVIB, and reduced em, whereas LV ejection fraction remained normal. Differences in regional or global strain, sm, and em were identified between the severely obese (BMI >35) and the referent patients (P<0.001). Similar but lesser degrees of reduced function by sm, em, and basal septal strain and increased reflectivity by cIB were present in overweight (BMI, 25 to 29.9) and mildly obese (BMI, 30 to 35) groups (P<0.05). Although tissue Doppler measures were not associated with duration of obesity, they did correlate with fasting insulin levels and reduced exercise capacity. BMI was independently related to average LV strain (β=0.40, P=0.02), sm (β=−0.36, P=0.002), and em (β=−0.41, P<0.001).

Conclusions—Overweight subjects without overt heart disease have subclinical changes of LV structure and function even after adjustment for mean arterial pressure, age, gender, and LV mass. (Circulation. 2004;110:3081-3087.)

Key Words: obesity ▪ systole ▪ diastole ▪ echocardiography

The prevalence of obesity (a body mass index [BMI] >30) is increasing in both the developed and developing worlds, with >20% of the US adult population being reported as obese. Obesity has been associated with heart failure, and individuals with severe obesity have long been recognized to have a form of cardiomyopathy attributed to chronic volume overload, characterized by left ventricular (LV) dilation, increased left ventricular wall stress, and compensatory (eccentric) left ventricular hypertrophy. Impairment of cardiac function has been reported to correlate with BMI and duration of obesity, with most studies reporting abnormal diastolic function without consistent association with systolic dysfunction. Indeed, obesity has been linked to a spectrum of more minor cardiovascular changes, ranging from a hyperdynamic circulation to subclinical cardiac structural changes. These early manifestations may be important, because treatment to reverse the process is most likely to be effective earlier in the disease.

The association of obesity and abnormal cardiac function is not supported by firm pathological evidence of an obesity-related cardiomyopathy. Moreover, the reported changes may reflect the role of comorbidities that contribute to LV dysfunction (eg, hypertension, diabetes, coronary artery disease, and obstructive sleep apnea), as well as altered loading—especially as conventional measures such as mitral inflow velocities, isovolumetric ventricular relaxation times, and ejection fraction are load dependent. Direct measurement of myocardial properties with newer echocardiography techniques such as tissue Doppler may be less load dependent. We therefore sought to define the preclinical effects of obesity on the cardiovascular system, independent of other factors, by examining left ventricular performance using sensitive new echocardiographic techniques including tissue Doppler imaging, myocardial strain imaging, and integrated backscatter in healthy subjects with excess body weight. We also sought the associations of these changes with insulin levels, duration of obesity, and exercise capacity.

Methods

Patient Selection
We studied 142 healthy subjects of either gender across a spectrum of body mass. Obese subjects were recruited from general practice.
and specialist clinics as well as self-referral from ambulatory clinics for management of overweight and obesity, based at a tertiary hospital and university. The referent group (BMI, 18.5 to 24.9 kg/m²) was recruited from healthy volunteers in the community. Four groups were identified: severely obese (BMI >35 kg/m²; n=46), mildly obese (BMI, 30 to 34.9 kg/m²; n=37), overweight (BMI, 25 to 29.9 kg/m²; n=26), and healthy referent subjects (BMI <25 kg/m²; n=33).

To exclude organic heart disease, patients underwent a clinical history and examination as well as resting and stress ECG and transthoracic echocardiography. We excluded subjects with ischemic heart disease, hypertension, and diabetes mellitus on the basis of previous history (including treatment). Subjects with a history or examination findings of congestive heart failure were excluded. Ischemic heart disease was excluded on the basis of clinical assessment and resting and stress ECG. Written informed consent for participation was obtained, and the hospital ethics committee approved the protocol.

Clinical Assessment
Demographic details of age, gender, clinical status, and blood pressures were obtained from standard measurements and questionnaires. A detailed history and physical examination was conducted to exclude obesity-related and cardiovascular comorbitides. Arterial pressure was measured after subjects had rested for >5 minutes, in a supine position in a quiet room. Anthropometric measurements (weight, height) were obtained, and BMI was calculated (body weight divided by height in meters squared). Fat mass and fat-free mass were estimated with the use of a tetrapolar bioelectrical impedance analyzer.

Biochemistry
Blood samples were taken for biochemical analysis of renal function, electrolytes, fasting insulin, total cholesterol, triglycerides, and HDL cholesterol. Insulin was assayed on the nonreferent groups by 2-site immunoenzymometric assay with fluorescence detection using the Tosoh ALI-600 semiautomated immunoassay analyzer. Cholesterol and HDL cholesterol were assayed by enzymatic colorimetric assays with the Roche Modular Chemistry Analyzer.

Metabolic Exercise Testing
Exercise testing was performed on obese subjects with treadmill exercise, using an exercise protocol individualized to the exercise capacity of the patient. Measured peak VO₂ was obtained by breath-by-breath analyses of expired gas (V29C Sensorimedics).

Echocardiographic Image Acquisition and Analysis
Images were gathered with a standard ultrasound machine (Vivid 7, GE Vingmed) with a 2.5-MHz phased-array probe.1

Conventional Doppler Echocardiography
Images were obtained in the standard tomographic views of the LV (parasternal long- and short-axis and apical 4-chamber, 2-chamber, and long-axis views). Using pulsed-wave Doppler, mitral inflow velocities, peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, and isovolumetric relaxation time (IVRT) were measured. LV diameter and wall thickness were measured from the 2-dimensional targeted M-mode echocardiographic tracings in the parasternal long axis, according to the criteria of the American Society of Echocardiography. LV end-diastolic (LVEDV) and end-systolic volumes (LVESV) and the LV ejection fraction (LVEF) at rest were computed from 2- and 4-chamber views, using a modified Simpson’s biplane method. Each representative value was obtained from the average of three measurements. LV mass was determined by Devereux’s formula and indexed to height to the power of 2.7.2

Myocardial Tissue Characterization
Processing of ultrasound and tissue Doppler signals provides a number of sensitive parameters of systolic and diastolic function that are less sensitive to loading and correlate with structural change, such as myocardial fibrosis.10 Tissue Doppler measurements have also been used to derive myocardial strain and strain rate, which are well-validated descriptors of shortening and lengthening that reflect the compressibility of tissue. Strain rate (SR; ΔV/Δt) is derived between two points, where ΔV is the difference in velocity separated by a distance Δt. Strain, the dimensionless relative change in length of the contracting (or relaxing) muscle, is obtained by integration of strain rate with respect to time f(ΔV/Δt)dt (ie, the temporal integral of the spatial differential of velocity). Although the problem of signal noise remains a limitation, this has been reduced by recent modifications in acquisition and analysis. We have recently applied the techniques to global myocardial problems, including assessment of LVH and diabetic heart disease.11 and found it to be a sensitive indicator of myocardial performance.

Tissue characterization may also be performed by analysis of integrated backscatter (IB) of ultrasound.12 IB parameters reflect function (cyclic variation, CVIB) as well as reflectivity (calibrated, CIB)—the latter being abnormal in pathological hypertrophy, suggesting that IB changes are related to fibrosis. Changes in backscatter measures precede overt functional changes in hypertensive LVH, in renal failure, and in the aging heart.13

Tissue Doppler Imaging
Myocardial velocities were recorded by using color tissue Doppler to record low-velocity, high-intensity myocardial signals at a high frame rate (120 MHz), giving a temporal resolution of 8 ms. The imaging angle was adjusted to ensure a parallel alignment of the beam with the myocardial segment of interest. Three cycles of tissue Doppler imaging data were acquired in each apical view to assess myocardial longitudinal function. The basal septal segment was used for myocardial peak systolic velocity (sm) and early diastolic velocity (em). Pulsed-wave tissue Doppler of the septal annulus was used for the measurement of early peak diastolic mitral annular velocity (‘e’). Left ventricular filling pressures were approximated from the relationship of E/e’, and A duration > pulmonary venous flow a wave duration (PVA).

Strain and Strain Rate Data Analysis
Strain and strain rate curves were extracted from color tissue Doppler images by using standard software (Echopac, GE Vingmed). Strain and strain rate were derived from strain and strain rate curves obtained by placing a sample bar (12 mm) on 6 walls in the 3 apical views.13 Sampling in the midmyocardial layer was performed in each segment and maintained at the same position during the cardiac cycle by manually tracking wall motion, but data were excluded if we were unable to obtain a smooth strain curve or the angle between the scan-line and wall was >20°. Peak strain was defined as the greatest value on the strain curve, and peak strain rate was measured from the strain curve, as previously validated.13,14 Results are expressed both as the average strain for all segments, the inferior, and the septal strain; our recent work has shown a single sepal measurement to be the most robust strain measures, probably because of minimal cardiac motion and a parallel alignment with the Doppler beam in most patients.

Calibrated Integrated Backscatter
The IB curves were extracted in the parasternal long-axis and apical views, using standard software (Echopac, GE Vingmed). Measurements were obtained by placing a 9×9-pixel sample volume in the basal septum, posterior wall, and other basal segments in apical views and pericardium in end-diastole. The position of the sample volume was checked and adjusted in each frame to keep the sample volume within the same region during the whole cardiac cycle. Calibrated IB was obtained by subtracting average pericardial IB intensity from average myocardial IB intensity of the septum or posterior wall.12 Myocardial cyclic variation of IB (CVIB) was determined as the difference between the minimal and maximal values in a cardiac cycle. Results are expressed the average CVIB for all segments.
analyses were used,\textsuperscript{15} including Pearson’s correlation analysis to estimate correlations between BMI, insulin, and echocardiographic variables. ANOVA was used to assess linear trend of parameters in the 4 groups, and post hoc testing was undertaken, using the Dunnett’s multiple comparison test. Multivariate stepwise linear regression analysis was performed to assess the adjusted correlations between echocardiography variables and BMI. Data were analyzed with the use of using standard statistical software (SPSS version 10, SPSS). Values of $P<0.05$ were considered significant.

**Interobserver and Intraobserver Variability**

Variability in the measurement of peak strain, strain rate, and calibrated IB from a single acquisition was evaluated in 15 randomly selected subjects by 2 independent observers for interobserver and intraobserver variability. To determine reproducibility, the same observer who was blinded to the former results measured peak strain, strain rate, and calibrated IB for each of the selected patients again at a separate time (at least 2 weeks later). To test interobserver variability, another observer (unaware of patient identity and first observer’s results) analyzed the same patients’ data in the same way.

**Clinical Characteristics**

Table 1 summarizes the clinical and echocardiographic characteristics of the 4 groups. Differences in weight, BMI, and fat mass reflect categorization, based on the BMI. Although none of the subjects had a prior diagnosis of hypertension, there were significant differences in mean arterial pressure between the severely obese group and the referent group. There was close relation between the fasting insulin level, with BMI ($r=0.72$, $P<0.001$) in overweight and obese subjects.

![Table 1. Clinical and Echocardiographic Characteristics in the 4 Groups, Compared by ANOVA](image-url)
Echocardiographic Findings

Left Ventricular morphology
LV wall thickness, diameters, volumes and LV mass indexed to height\(^{5,7,16}\) increased with increasing BMI. These morphologic measures, except for LVEDD, were significantly different in mildly and severely obese groups as compared with the referents (Table 1). Both the indexed LV mass and wall thickness were correlated with insulin levels \((r=0.24, P<0.05\) and \(r=0.29, P<0.01\), respectively) (Table 2). However, these associations were accounted for by the linear relation of the insulin levels with BMI.

Left Ventricular Systolic Function
Ejection fraction did not differ significantly across the BMI subgroups. However, there were significant differences between obese and referent groups with regard to septal, inferior, and average regional strain and systolic myocardial tissue velocity sm (Table 3 and Figure 1). On subgroup analysis, all LV systolic measures of function except EF reached significance in the overweight and obese subgroups when compared with the referents. There were also significant differences between the obese subgroups for both the averaged global and regional LV strain (Figure 1). A similar linear relation with BMI was not observed for strain rate due to wide standard deviation.

Insulin was significantly associated with systolic function, including strain \((r=-0.33, P<0.01)\) and sm \((r=-0.30, P<0.01)\) (Table 2). However, even after adjusting for age, mean arterial pressure, LV mass index, and insulin level in a multivariate stepwise regression model, BMI remained independently related to average LV strain \((\beta=-0.40, P=0.001)\) and sm \((\beta=-0.36, P=0.002)\) (Table 4).

Left Ventricular Diastolic Function
Increasing degrees of obesity were associated with a significant increment of IVRT and nonlinear changes in E and the E/A ratio, probably reflecting the impact of loading conditions. However, the findings on tissue Doppler measures were consistent with an association between diastolic dysfunction and obesity, evidenced by reduced mitral annular velocity (e\(^{'\}\)), myocardial early diastolic velocity (em), and elevated filling pressures, approximated by E/e\(^{'\}\). (Table 1) Diastolic myocardial velocity (em) was significantly reduced in all the obese subgroups compared with the referents as well as between the subgroups (Figure 2A).

Insulin levels were significantly associated with diastolic function, including em and e\(^{'\} \ (r=-0.29, P=0.01)\) (Table 2). BMI remained as a significant predictor even after adjusting for age, mean arterial pressure, LV mass index, and insulin level \((\beta=-0.41, P<0.001)\) (Table 4). Using e\(^{'\}<7\), the categoric diagnosis of diastolic dysfunction was linearly associated with BMI (Figure 2B). Echocardiographic indexes of diastolic dysfunction (a combination of e\(^{'\} with the E/A, E deceleration time, duration pulmonary venous a wave reversal > duration of mitral inflow A wave and E/e\(^{'\}) were present in 24% of the severely obese subgroup (Figure 2B).

Of those undergoing metabolic exercise testing, sm \((r=-0.43, P=0.001)\), em \((r=-0.39, P=0.001)\), and E/e\(^{'\} (r=-0.29, P=0.01)\) were the echocardiographic measures that correlated best with reduced exercise capacity measured by V\(_{O2}\)max.

Tissue Characterization
The cyclic variation index CVIB and cIB (of both the septum and posterior wall), which are the expression of the intrinsic myocardial contractility and acoustic properties, are also altered with increased BMI. Increases in cIB(s) were apparent even in the overweight group and became even more significantly prominent in the more obese subgroups (Table 3 and Figure 3).

The interobserver and intraobserver variability of tissue characterization parameters is summarized in Table 5.

Discussion
The results of this study show changes in the LV structure and function in healthy subjects with excess weight who have no other clinically appreciable cause of heart disease. These changes appear to be related to the degree of obesity, and some are even present with less severe obesity. Moreover, these echocardiographic changes are shown to contribute to reduced exercise capacity. BMI remains an independent correlate of cardiac function, even after adjusting for age, mean arterial pressure, LV mass index, and insulin.

LV Morphology and Systolic Function
Subgroups of patients with increasing levels of obesity show differences myocardial velocity, and strain index, even when conventional 2D echo still gives normal values of ejection fraction. The decrement of these measures with increasing BMI are all the more impressive, given that they are preload sensitive\(^{13}\)—and hence would be expected to increase with increased load, evidenced by changes in LVEDD, LA size, and LV mass. These findings challenge the previous findings that LV systolic function is preserved in those with milder degrees of obesity\(^{5,7,16}\) and support a smaller body of literature identifying subclinical depression of LV function.\(^{17–19}\)

The reason for this discrepancy probably relates to the techniques used for the assessment of systolic function. Previous smaller studies have focused on conventional methods such as LVEF and fractional shortening, which are relatively insensitive and thus unable to detect early preclinical changes. The more sensitive, newer echo techniques have been used to demonstrate the presence of subclinical LV changes in young obese women in a recent study.\(^{19}\)

These functional changes are matched by changes in LV morphology. In addition to alterations in chamber size, obese

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TABLE 2. Pearson’s Correlations of LV Echocardiography Measures With Fasting Insulin

<table>
<thead>
<tr>
<th></th>
<th>Insulin r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>sm</td>
<td>-0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Average strain</td>
<td>-0.33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>em</td>
<td>-0.29</td>
<td>0.01</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RWT</td>
<td>0.29</td>
<td>0.01</td>
</tr>
</tbody>
</table>
patients demonstrate increased tissue density, evidenced by increased calibrated myocardial backscatter. Previous studies with this modality have shown that this reflects underlying myocardial fibrosis.\textsuperscript{10,20} Indeed, moderate and severe myocardial fibrosis is a frequent autopsy finding in obese subjects.\textsuperscript{21}

**LV Diastolic Function**

Previous reports of diastolic function in obese subjects have given variable results. Our findings of changes in IVRT are similar to previous studies on moderate and severely obese subjects.\textsuperscript{8,22} However, earlier studies of transmitral flow patterns in obese individuals have reported inconsistent changes in LV filling indexes.\textsuperscript{5} Such disparities in simple flow measures may reflect the sensitivity of transmitral flow indexes to loading conditions as well as the influence of increased LV mass.\textsuperscript{4,7,8,22} The interpretation of transmitral flow in relation to tissue diastolic velocity (em) may be a better means of assessing diastolic function—especially given the intravascular volume expansion of obese subjects.\textsuperscript{19} Indeed, the association of LA enlargement with reduced diastolic function is more consistent with current understanding of the left atrium as a biomarker of filling pressure than are previous findings of isolated LA enlargement without diastolic changes using less sensitive conventional methods.\textsuperscript{23}

**Potential Mechanisms**

This study provides observational findings that link obesity, insulin levels (and thereby insulin resistance), and myocardial

---

**TABLE 3. Association of New Echocardiographic Parameters With BMI**

<table>
<thead>
<tr>
<th>Correlation With BMI</th>
<th>Pearson’s $r$</th>
<th>Significance (2 Tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal peak strain</td>
<td>$-0.44$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Inferior peak strain</td>
<td>$-0.33$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Average peak strain</td>
<td>$-0.39$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Average peak strain rate</td>
<td>$-0.20$</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>Myocardial systolic peak velocity (sm)</td>
<td>$-0.59$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Myocardial early peak velocity (em)</td>
<td>$-0.46$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Septal wall cyclic integrated backscatter</td>
<td>$-0.23$</td>
<td>0.009</td>
</tr>
<tr>
<td>Posterior wall calibrated integrated backscatter</td>
<td>$-0.33$</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

---

**TABLE 4. Multivariate Stepwise Linear Regression Models With sm, LV Strain, and em as Dependent Variables in Overweight and Obese Patients**

<table>
<thead>
<tr>
<th>sm $R^2$, 0.13</th>
<th>LV Strain $R^2$, 0.20</th>
<th>em $R^2$, 0.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>$p$</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Age</td>
<td>$-0.05$</td>
<td>0.67</td>
</tr>
<tr>
<td>BMI</td>
<td>$-0.36$</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Other independent variables (mean arterial pressure, LVM index, insulin) initially included in the stepwise model failed to demonstrate independent association with sm, strain or em.
disturbances. A number of putative mechanisms may underlie these morphological changes. First, increased stroke volume and cardiac output leads to dilatation of the heart chambers with eccentric left ventricular hypertrophy. However, the mechanical advantage conferred by the compensatory reduction of myocardial fiber shortening is offset by a concomitant increase in myocardial oxygen consumption and ventricular wall stress. Second, insulin resistance may mediate the increased LVM in obese subjects. Our study demonstrates some correlation of LV systolic and diastolic measures to fasting insulin level, consistent with previous studies suggesting an association of LV diastolic function with hyperinsulinemia and glucose intolerance. A recent study on young obese women further supported the notion that insulin resistance and alterations in myocardial substrate metabolism lead to myocardial contractile dysfunction associated with obesity. It has been proposed that insulin may also exercise its influence on cardiac geometry due to its growth-stimulating, sodium retention and other neuroendocrine effects. Third, adipose tissue may contribute to circulating angiotensin II, which promotes myocardial tissue growth as well as influencing aldosterone, which may mediate myocardial fibrosis. Fourth, obstructive sleep apnea is common in obese persons and may contribute to heart failure through several mechanisms. In the general community, obstructive sleep apnea is associated with hypertension, although such patients were excluded from our study. Increases in afterload and wall stress associated with generation of negative intrathoracic pressure during episodes of obstructive apnea, as well as inflammatory cytokines and sympathetic activation are potential mechanisms. Further work is needed to clarify the links between these alterations in the LV characteristics with insulin resistance, volume overload, changes in respiratory workload, and other metabolic mechanisms such as renal sodium retention, oxidative stress, and inflammatory cytokines.

Limitations

Although the duration of obesity has previously been shown to be a determinant of cardiac changes from obesity, we were unable to demonstrate such a relation in our study. This may reflect dependence on patient recall and the lack of objective measurement of BMI during subjects’ earlier life. However, our obese group had an average age of 44 years, a relatively young group in terms of the risk of other causes of heart failure. Finally, we did not have complete data on sleep apnea and measurements for insulin resistance. Further studies are required to clarify the association of these factors with cardiac performance.

Conclusions

Obesity is an independent risk factor for subclinical LV dysfunction. Better understanding of the pathophysiology of obesity related LV characteristics will enable us to modify the disease process resulting in regression of subclinical LV changes. Newer echocardiographic techniques used in this study could provide a robust tool for early detection of subclinical cardiac functional and structural changes and to
evaluate their natural history and the efficacy of therapeutic interventions over time.

Acknowledgments

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References


TABLE 5. Mean Absolute Differences and Range of Measures of Strain, SR, and Calibrated IB of Repeated Measures by the Same Observer and Two Observers

<table>
<thead>
<tr>
<th></th>
<th>Intraobserver</th>
<th>Interobserver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak strain, %</td>
<td>1.6±1.2 (0.1–4.6)</td>
<td>1.8±1.2 (0–4.3)</td>
</tr>
<tr>
<td>Strain rate, s⁻¹</td>
<td>0.1±0.1 (0–0.3)</td>
<td>0.1±0.1 (0–0.3)</td>
</tr>
<tr>
<td>Calibrated IB, dB, septum</td>
<td>−3.1±2.8 (−0.3 to −9.5)</td>
<td>−3.3±2.7 (−0.2 to −9.3)</td>
</tr>
<tr>
<td>Calibrated IB, dB, posterior wall</td>
<td>−3.2±2.7 (−0.1 to −9.7)</td>
<td>−3.7±2.7 (−0.1 to −10.0)</td>
</tr>
</tbody>
</table>
Alterations of Left Ventricular Myocardial Characteristics Associated With Obesity
Chiew Y. Wong, Trisha O'Moore-Sullivan, Rodel Leano, Nuala Byrne, Elaine Beller and Thomas H. Marwick

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