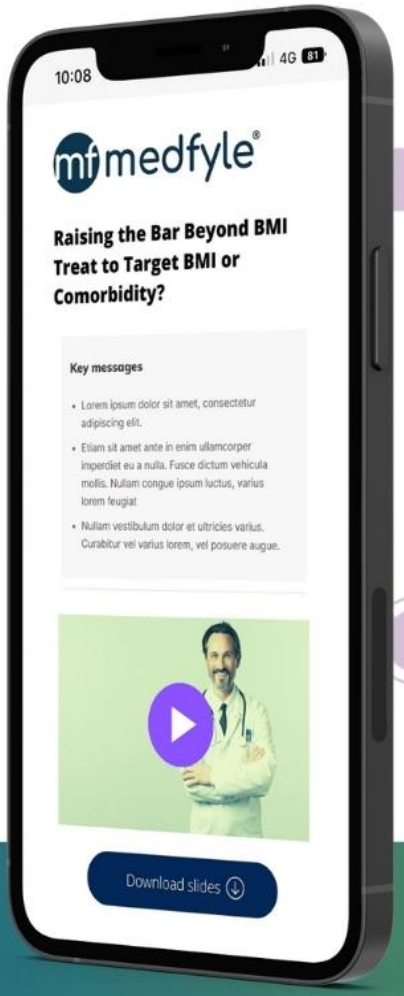
Medfyle Conference Coverage from ObesityWeek® 2022

Discover a new way to catch up with the latest advances in obesity research and care presented at ObesityWeek® 2022.

- Medfyle summaries
- Expert interviews
- Expert presentations
- Posters



CLICK TO ACCESS NOW

This activity is supported by an educational grant from Lilly

Echocardiographic Abnormalities in Normotensive Obese Patients: Relationship with Visceral Fat

Lelio Morricone, Alexis Elias Malavazos,* Calin Coman,† Cristina Donati,* Tamin Hassan,‡ and Francesco Caviezel**

Abstract

MORRICONE, LELIO, ALEXIS ELIAS MALAVAZOS, CALIN COMAN, CRISTINA DONATI, TAMIN HASSAN, AND FRANCESCO CAVIEZEL. Echocardiographic abnormalities in normotensive obese patients: relationship with visceral fat *Obes Res.* 2002;10:489–498.

Objective: To evaluate the relationship of echocardiographic characteristics and visceral adipose tissue (VAT) distribution in normotensive obese patients.

Research Methods and Procedures: Echocardiographic parameters were assessed in 28 normotensive obese patients [7 men, 21 women, mean age, 43.2 years; mean body mass index (BMI), 37.2 kg/m^2; 10 with impaired glucose tolerance (IGT); 6 with type 2 diabetes] and 18 sex- and age-matched healthy, normal-weight controls (4 men, 14 women; mean age, 45.8 years; mean BMI, 22.4 kg/m^2) by an M-mode, color-doppler videofluoroscope. VAT in the obese patients was assessed by computed tomography (at L4 level).

Results: The obese patients had a significantly larger internal diastolic left ventricular (LV) diameter ($p < 0.05$), a thicker end-diastolic septum ($p < 0.001$) and posterior wall ($p < 0.001$), a greater indexed (g/m$^{2.7}$) LV mass ($p < 0.001$), a higher atrial diastolic filling wave velocity ($p < 0.001$), a lower ratio between early and atrial diastolic filling wave velocities ($p < 0.01$), and a prolonged isovolumic relaxation time ($p < 0.05$). End-diastolic septum and posterior wall thickness and the LV mass were significantly greater in patients with a VAT area >130 cm^2 than with <130 cm^2. In the multivariate regression analysis, only VAT ($p < 0.0001$), waist-to-hip ratio ($p < 0.001$), and sex ($p < 0.001$) were associated with the most important echocardiographic alterations.

Discussion: The morphological and functional echocardiographic alterations usually found in normotensive obese patients closely correlate with the amount of intra-abdominal fat deposition, even in the presence of diabetes or IGT.

Key words: visceral adipose tissue, echocardiographic abnormalities, computed tomography, diabetes

Introduction

The results of various studies demonstrate that obese subjects are prone to a number of complications, such as diabetes, hypertension, stroke, and coronary heart disease (1,2). More importantly, obesity has long been recognized as an independent risk factor for cardiovascular disease (3). With regard to heart morphology and function, left ventricular (LV) hypertrophy and abnormal diastolic filling have been observed in obese patients with mild hypertension (4–6). The remarkable increase in heart volume particularly observed in morbid obesity is caused by true myocellular hypertrophy and not fatty infiltration (7).

Cardiac abnormalities of obese people include the echocardiographically revealed early and preclinical LV or septal hypertrophy, and left or right ventricular dysfunction, even in the absence of hypertension (8–10). Most of these abnormalities, which are usually more pronounced in patients with morbid obesity, can be partially reversed after weight loss (11,12), regardless of a concomitant change in blood pressure (13).

There is considerable evidence indicating the crucial importance of central adipose tissue distribution in favoring cardiovascular and metabolic abnormalities in obesity (2,14–17). Most of the studies addressing this issue have assessed visceral fat distribution by means of anthropometric indexes, such as the waist-to-hip ratio (WHR), the waist-to-thigh ratio (WTR),

Submitted for publication September 25, 2001.
Accepted for publication in final form March 5, 2002.
*Department of Endocrinology, †Echocardiography Unit, and the ‡Radiology Unit, Institute of Medical and Surgical Sciences, S. Donato Hospital, University of Milan, Milan, Italy.
Address correspondence to Dr. Lelio Morricone, Department of Endocrinology, Istituto di Scienze Medico-Chirurgiche, Università di Milano, Via Morandi 30, 20097 S. Donato Milanese (MI), Italy.
E-mail: lelio.morricone@libero.it

waist circumference alone, or abdominal sagittal diameter. However, in addition to the relatively good, but questioned, results obtained using ultrasound techniques (18–20), computed tomography (CT), DXA, and magnetic resonance imaging are currently considered the best methods of measuring regional adipose tissue distribution (18).

The relationships between the echocardiographic abnormalities of obesity and CT measurements of intra-abdominal fat have so far only been studied by Nakajima et al. (21). In Japanese patients with uncomplicated obesity, they found that the echocardiographic alterations were more pronounced in patients with upper-body obesity (i.e., the patients with a CT-measured visceral/subcutaneous [V/S] ratio of >0.4) (22) than in those with lower-body obesity. Because the cutoff point of the V/S ratio proposed for the Japanese population is low for an Italian obese population in relationship to a number of cardiovascular risk factors, especially in men (17), and because the V/S ratio may not exactly reflect the level of abdominal visceral adipose tissue (VAT) associated with cardiovascular or metabolic disease, we preferred to correlate the subclinical echocardiographic abnormalities of our white obese subjects with the absolute amount of visceral fat accumulation regardless of, or in addition to, the V/S ratio. Particular attention was paid to the amount of intra-abdominal fat, which is currently considered a risk factor for cardiovascular complications. The aims of this study were to evaluate a number of cardiac ultrasonographic parameters in normotensive obese patients whose visceral fat deposition was measured by means of CT and to analyze the relationship of echocardiographic parameters with visceral fat distribution.

Research Methods and Procedures

Twenty-eight obese patients [7 men and 21 women, mean age 43.2 $\pm$ 2.2 years (range, 24 to 64 years), mean body mass index (BMI) of 37.2 $\pm$ 1 kg/m^2] were recruited from the Metabolic Ward of our Department. None of the subjects had ischemic or valvular heart disease, hypertension (blood pressure $\geq$140/90 mm Hg) and arrhythmias; those with hepatic, pulmonary, renal, or endocrine diseases were excluded, as were those with neoplastic disease. None of the patients were taking medications that interfere with heart function. The patients were compared with 18 healthy sex-, age-, and height-matched normotensive and normal-weight control subjects only for the echographic study [4 men and 14 women, mean age 45.1 $\pm$ 2.2 years (range, 24 to 62 years), mean BMI of 22.6 $\pm$ 0.4 kg/m^2] belonging to the medical and nursing staff of our Department. The study was performed in accordance with the Declaration of Helsinki (amended edition, Sonmerset West, 1996), and the subjects entered the study after giving informed consent to a routine examination, echocardiography, and (only obese subjects) single abdominal CT scanning.

Clinical Data

Blood pressure was measured in the right arm using a mercury sphygmomanometer with the subject in a sitting position after a 15-minute rest; the mean of three determinations performed at 5-minute intervals was recorded. A cuff of appropriate size was used in the obese subjects. Anthropometric measurements included height (to the nearest 0.5 cm), weight (to the nearest 0.5 kg), waist circumference (midway between the lower limb margin and the iliac crest on the midaxillary line), hip circumference (at the level of the greater trochanter), thigh circumference (measured just below the gluteal fold), and abdominal sagittal diameter (measured with the subject in a supine position using a suitable abdominal caliper applied $\sim$5 cm above the umbilicus and the distance between the lumbar plane and upper caliper bar was measured in centimeters).The WHR and WTR were calculated. BMI was calculated as weight (in kilograms) divided by height (in square meters). Fat mass and fat-free mass (FFM) were determined by means of bioelectrical impedance (BIA 101-S; Akern, Florence, Italy). Smoking habits and alcohol intake were assessed using appropriate questionnaires. Ex-smokers were considered nonsmokers if they had not smoked for 5 years.

Biochemical Data

All of the subjects underwent an oral glucose tolerance test (OGTT) with 75 g of glucose; the results were interpreted on the basis of the World Health Organization (WHO) criteria. Fasting blood samples were obtained from the obese patients to measure plasma insulin; hemoglobin; blood cells; total, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) cholesterol; apolipoprotein A and B; creatinine; uric acid; and fibrinogen. Plasma glucose levels were determined using a glucose analyzer (glucose-oxidase method; Instrumentation Laboratory, Milan, Italy), insulin levels using a commercial immunoradiometric assay (IRMA) kit, total and HDL cholesterol by means of a modified version of Allain's method (Instrumentation Laboratory), LDL and VLDL cholesterol using the Friedewald equation, triglycerides by means of bichromatic analysis, and apolipoprotein A and B using an immunodiffusion method.

Echocardiographic Measurements

The echocardiographic recordings were made using an M-mode color-doppler VSF (Vingmed-System Five; General Electric, Horten, Norway) with a 2.5- to 3.5-MHz transducer probe by a physician experienced in echocardiography who was unaware of the patients' biochemical characteristics. The subjects were examined in the left lateral decubitus position after 10 minutes of supine rest. M-Mode tracings were obtained from the parasternal LV short-axis view and at a paper speed of 50 mm/s. The internal size of the LV in diastole and systole and the

Table 1. Clinical characteristics of the study population

Variable	Controls ($n = 18$)	Obese individuals ($n = 28$)	p value
Age (years)	45.8 ± 9.5	43.2 ± 11.9	0.41
Sex (male/female)	4/14	7/21	0.82
Weight (kg)	61 ± 9.5	99.0 ± 13.2	<0.001
Height (cm)	165.4 ± 10.1	163.2 ± 7.5	0.47
BMI (kg/m^2)	22.4 ± 1.7	37.2 ± 5.4	<0.01
Waist circumference (cm)	78.9 ± 7.5	108.3 ± 13.8	<0.001
Waist-to-hip ratio	0.81 ± 0.05	0.91 ± 0.14	<0.001
Waist-to-thigh ratio	1.73 ± 0.22	1.81 ± 0.45	0.45
Abdominal sagittal diameter (cm)	19.6 ± 1.88	27.28 ± 3.7	<0.0001
Fat mass (kg)	17.1 ± 4.2	39.5 ± 10.3	<0.001
Fat-free mass (kg)	44.2 ± 9.3	58.8 ± 7.1	<0.001
Systolic BP (mm Hg)	117.6 ± 5.7	119.4 ± 4.9	0.24
Diastolic BP (mm Hg)	78.0 ± 4.2	79.02 ± 2.9	0.40
Normal glucose tolerance	18	12	
Impaired glucose tolerance		10	
Type 2 diabetes		6	
Duration of obesity (years)		21.4 ± 11.5	
Current smokers	5 (33%)	14 (50%)	0.13
Alcohol consumers	9 (50%)	12 (43%)	0.35

Data are expressed as mean values ± SD.
BMI, body mass index; BP, blood pressure.

thickness of the ventricular septum and posterior wall were measured according to the American Society of Echocardiography (23). LV mass was calculated using the Penn convention (24) and normalized for height (in meters) to the 2.7 power to take into account the independent effect of obesity on LV geometry (25).

CT Measurements of VAT

Abdominal fat deposition was assessed by CT according to Sjöström et al. (26). The areas of total adipose tissue, VAT, and subcutaneous adipose tissue (SAT) were measured using a single scan at the L4 level, with the subjects being centered using an L4 lateral topogram. The visceral/subcutaneous adipose tissue area ratio (V/S ratio) was calculated. The adipose tissue areas were examined with attenuation values of between −150 and −50 Hounsfield Units.

Statistical Analysis

The data were expressed as means ± SD. The groups were compared using Student's two-tailed t test for unpaired data or the χ^2 test, as appropriate. Pearson's correlation coefficient and stepwise regression analysis were used to evaluate the association between the echocardiographic parameters and selected variables. Any differences were considered significant at $p < 0.05$. The statistical analyses were performed using the STATISTIX 4.1 statistical package (Analytical Software, Tallahassee, FL).

Results

The clinical and anthropometric characteristics of the obese and healthy control subjects are shown in Table 1. According to the OGTT and the WHO criteria, 10 obese patients (35.7%) had impaired glucose tolerance (IGT), and 6 (21.4%) had type 2 diabetes. Most of the blood chemical variables of the obese patients were within the normal range, with only plasma insulin and triglyceride levels being slightly higher (Table 2).

The obese patients were divided into two groups depending on whether their VAT values were <130 cm^2 ($n = 9$) or >130 cm^2 ($n = 19$), because this cutoff point has been recognized as the threshold of a true risk for cardiovascular and metabolic diseases among patients with increased intra-abdominal fat deposition, especially postmenopausal women (27–29).

Table 2. Biochemical characteristics of the obese patients ($n = 28$)

Variable	Concentration	
	mg/dL	mM
Fasting plasma glucose	92.1 ± 15.3	5.15 ± 0.84
Cholesterol	206.4 ± 41.5	5.33 ± 1.07
HDL—cholesterol	42.8 ± 13.8	1.11 ± 0.35
LDL—cholesterol	131.7 ± 39.6	3.40 ± 0.99
VLDL—cholesterol	36.32 ± 19.42	0.94 ± 0.50
Triglycerides	181.6 ± 97.1	2.06 ± 1.10
Apolipoprotein A	116 ± 43	3.04 ± 1.11
Apolipoprotein B	128 ± 58	3.35 ± 1.49
Fibrinogen	321.5 ± 105	
Uric acid	4.9 ± 0.7	
Fasting plasma insulin concentration	15.5 ± 7.6 μU/mL	
	111.2 ± 53.9 pM	

Data are expressed as mean values ± SD.
HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

All the biochemical parameters in the group of obese patients with VAT values >130 cm^2 were comparable with those of the obese subjects with VAT values <130 cm^2, except for higher fibrinogen (341.9 ± 27.3 vs. 273.2 ± 11.5 mg/dL, $p < 0.001$) and lower apolipoprotein A concentrations (110 ± 7 vs. 130 ± 2 mg/dL, $p < 0.001$).

The echocardiographic characteristics of the study population are shown in Table 3. Compared with the healthy controls, the obese patients had a larger internal diastolic LV diameter ($p < 0.05$), greater end-diastolic septum and posterior wall thicknesses ($p < 0.001$), a larger absolute and indexed LV mass ($p < 0.001$), and a larger end-systolic left atrium diameter ($p < 0.001$). With regard to the functional parameters, the obese patients showed a prolonged isovolumic relaxation time ($p < 0.05$), an increased atrial diastolic filling wave velocity ($p < 0.001$), and a lower E/A ratio [i.e., the ratio between the early (E) and the atrial diastolic filling wave velocities (A); $p < 0.01$).

The echocardiographic variables of the two groups of obese subjects with different areas of VAT (<130 or >130 cm^2) are compared in Table 4. The end-diastolic septum and posterior wall thickness, as well as the indexed LV mass, were significantly more pronounced in the patients with the greatest amount of visceral fat accumulation ($p < 0.001$; Figure 1). The other morphological and functional echocardiographic parameters were comparable in the two groups.

The Pearson correlation analysis data are shown in Table 5. Only the echocardiographic parameters that were significantly different from those of the normal controls were

Table 3. Echocardiographic characteristics of the study population

Variable	Controls ($n = 18$)	Obese ($n = 28$)	p value
Internal diastolic LV diameter (cm)	4.73 ± 0.4	5.06 ± 0.5	<0.05
End-diastolic LV volume (mL)	86.7 ± 22.1	100.8 ± 27.2	0.06
Ejection fraction (%)	60.8 ± 7.3	61.5 ± 5.8	0.73
End-diastolic septum thickness (cm)	0.92 ± 0.13	1.18 ± 0.20	<0.001
End-diastolic posterior thickness (cm)	1.02 ± 0.11	1.18 ± 0.2	<0.001
LV mass (g)	163.1 ± 37.5	240.1 ± 85.3	<0.001
Indexed LV mass ($g/m^{2.7}$)	41.6 ± 6.4	63.8 ± 21.2	<0.001
Fractional shortening (%)	37.8 ± 7.3	36.1 ± 7	0.44
End-systolic left atrium (cm)	3.1 ± 0.5	3.8 ± 0.4	<0.001
Isovolumic relaxation time (ms)	75.5 ± 8.9	81.1 ± 17.8	<0.05
E (m/s)	0.82 ± 0.2	0.85 ± 0.17	0.71
A (m/s)	0.63 ± 0.17	0.83 ± 0.18	<0.001
E/A ratio	1.35 ± 0.30	1.06 ± 0.29	<0.01

Data are expressed as mean values ± SD.
LV, left ventricle; E, early diastolic filling wave velocity; A, atrial diastolic filling wave velocity.

Table 4. Echocardiographic and clinical characteristics of the obese patients by amount of VAT*

Variable	VAT < 130 cm^2 (range, 37.2 to 127; n = 9)	VAT > 130 cm^2 (range, 138 to 378; n = 19)	p value
Sex (female/male)	9/0	12/7	<0.05
Weight (kg)	94 ± 5.9	101.5 ± 15.06	0.07
BMI (kg/m^2)	34.7 ± 3.09	38.4 ± 6.03	<0.05
Internal diastolic LV diameter (cm)	5.12 ± 0.36	5.03 ± 0.57	0.61
End-diastolic LV volume (mL)	95.0 ± 18.7	103.5 ± 30.4	0.37
Ejection fraction (%)	62.4 ± 5.52	61.1 ± 6.10	0.57
End-diastolic septum thickness (cm)	1.11 ± 0.07	1.26 ± 0.18	<0.001
End-diastolic posterior thickness (cm)	1.0 ± 0.07	1.26 ± 0.20	<0.001
LV mass (g)	199.2 ± 31.46	379.2 ± 93.7	<0.01
Indexed LV mass (g/m$^{2.7}$)	50.13 ± 8.9	70.36 ± 22.4	<0.01
Fractional shortening (%)	36.23 ± 7.56	36.06 ± 6.92	0.95
End-systolic left atrium (cm)	3.64 ± 0.37	3.90 ± 0.48	0.13
Isovolumic relaxation time (ms)	80.36 ± 18.4	81.44 ± 18	0.88
E (m/s)	0.80 ± 0.16	0.88 ± 0.17	0.28
A (m/s)	0.76 ± 0.17	0.87 ± 0.17	0.13
E/A ratio	1.13 ± 0.4	1.03 ± 0.19	0.50

Data are expressed as mean values ± SD.

VAT, visceral adipose tissue; BMI, body mass index; LV, left ventricle; E, early diastolic filling wave velocity; A, atrial diastolic filling wave velocity.

* VAT measured as area (square centimeters) by means of computed tomography scanning at level L4 to L5.

included and explored for their possible correlation with all of the variables reflecting fat distribution, to which age, body weight and height, FFM, blood pressure, and the duration of obesity were added because of their importance in relationship to cardiac dimension and function. The major echocardiographic volume abnormalities closely correlated with VAT: in particular, the end-diastolic septum thickness ($p < 0.0001$), diastolic posterior wall thickness ($p < 0.0001$), and indexed LV mass ($p < 0.0001$). They also correlated with waist circumference ($p < 0.0001$), the WHR and WTR ($p < 0.001$), abdominal sagittal diameter ($p < 0.001$), and the V/S ratio ($p < 0.01$) as well as age and FFM ($p < 0.001$ and $p < 0.01$, respectively). The indexed LV mass, internal diastolic LV diameter, and isovolumic relaxation time also correlated with the duration of obesity ($p < 0.01$). The E/A ratio only associated with diastolic blood pressure ($p < 0.01$). No correlations were found between all echographic variables studied and body weight and height, BMI, SAT, or systolic blood pressure.

Table 6 shows the multiple stepwise regression analysis of the echocardiographic parameters that correlated with the indexes of fat distribution in the Pearson analysis as dependent variables and a number of clinical and anthropometric parameters as independent variables, to which diabetes and IGT were added as important categorical variables (the two pathologies were considered as one, because both reflect a derangement in carbohydrate metabolism that has substantially similar consequences on the cardiovascular system) (30,32). End-diastolic posterior wall thickness and the indexed LV mass most closely correlated with VAT ($p < 0.0001$), whereas the end-diastolic septum thickness was associated with waist circumference ($p < 0.001$) and the WHR did with the internal diastolic LV diameter ($p < 0.001$). Moreover, sex correlated with the end-diastolic septum thickness and end-systolic left atrium ($p < 0.001$). In our obese patients, BMI, FFM, blood pressure, age, the duration of obesity, and diabetes-IGT status did not enter the model.

When the obese patients of the diabetes-IGT group ($n = 16$) were compared with those with normal glucose tolerance ($n = 12$), the former had a larger indexed LV mass (70.7 ± 6.3 vs. 54.6 ± 2.4 g/m$^{2.7}$, $p < 0.01$) and a thicker end-diastolic posterior wall (1.25 ± 0.05 vs.1.09 ± 0.04 cm, $p < 0.05$). These two subgroups, which were comparable in terms of age, BMI, fasting plasma insulin levels, and VAT, did not differ in the other echocardiographic parameters.

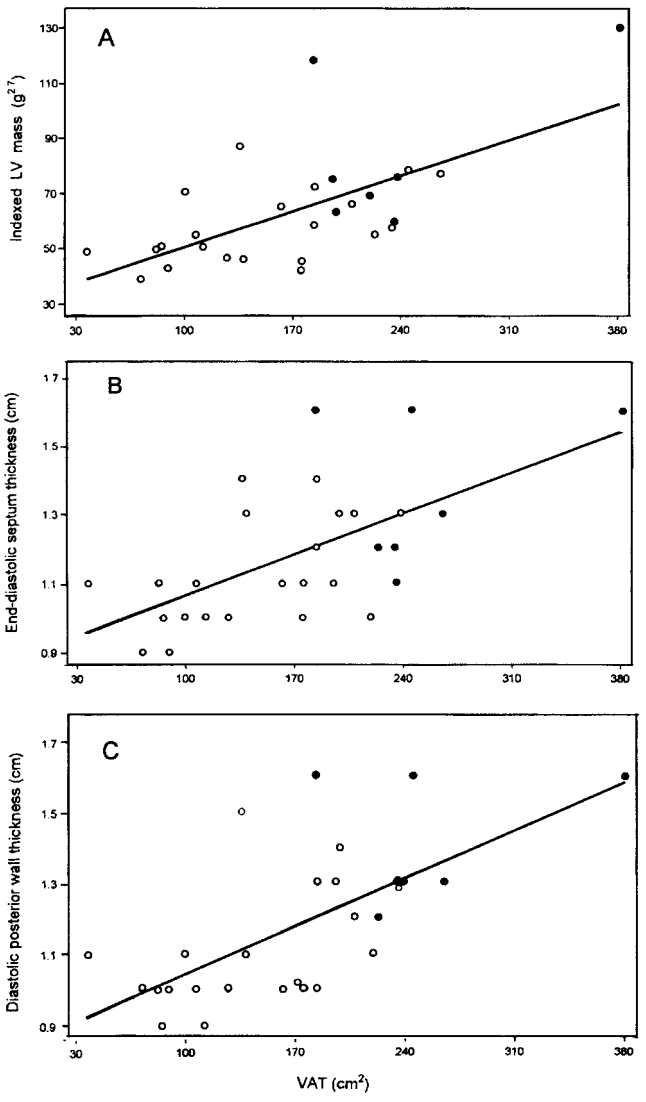


Figure 1: The relationship between visceral adipose tissue [(VAT) in square centimeters] and indexed left ventricular (LV) mass (A; $r = 0.65$, $p < 0.0001$), end-diastolic septum thickness (B; $r = 0.64$, $p < 0.0001$), and diastolic posterior wall thickness (C; $r = 0.65$, $p < 0.0001$) of normotensive obese men (●) and women (○).

Discussion

The results of this study show that normotensive obese patients with no apparent clinical manifestations of heart disease may have echocardiographic abnormalities, mainly represented by LV hypertrophy, a thicker septum and posterior wall, a larger internal diastolic LV and end-systolic left atrium diameter, a prolonged isovolumic relaxation time, and a lower atrial diastolic filling wave velocity. These findings are in accordance with those of previous studies of obese patients (8–10,12,13,33–35).

Given the well-established importance of visceral fat distribution as a risk factor for cardiovascular and metabolic disease, the distribution of central adipose tissue in our obese population was studied using CT to obtain more objective and reliable data concerning intra-abdominal fat deposition. The main result of this study is the remarkable relationship between some echocardiographic abnormalities and the amount of intra-abdominal fat: the greater the visceral fat deposition, the greater a given cardiac abnormality. Our data are substantially comparable with those of the Japanese study in which intra-abdominal adipose tissue deposition was measured using an identical CT technique (21). In the Japanese study, the VAT of the patients with visceral obesity (a V/S ratio of >0.4) was significantly greater than that of the patients with subcutaneous obesity (i.e., a V/S ratio of <0.4). Furthermore, the patients with visceral obesity had diastolic size and stroke indexes that were significantly greater than those of the patients with subcutaneous obesity.

Classifying visceral and subcutaneous obesity on the basis of the V/S ratio is limited because the variety of combinations between the two fat compartments means that many obese subjects may have mixed obesity. Because absolute visceral fat deposition is particularly important pathophysiologically and it is difficult to obtain a reliable V/S cutoff point distinguishing visceral and subcutaneous obesity in white people, especially in men (17), we concentrated on VAT per se rather than waist circumference alone and other parameters reflecting body fat distribution.

In addition, because cardiovascular and metabolic diseases mainly develop in people whose intra-abdominal fat deposition corresponds to an area of >130 cm^2 as measured by means of a single CT scan at the L4 to L5 level regardless of BMI and the WHR (27–29), we evaluated the echocardiographic and metabolic parameters on the basis of a VAT cutoff point of 130 cm^2. It is interesting to note that our normotensive obese patients with the greatest amount of VAT (i.e., >130 cm^2) had a thicker end-diastolic septum and posterior wall and a larger indexed LV mass than those with VAT <130 cm^2. The abnormalities of the parameters reflecting cardiac performance (e.g., isovolumic relaxation time or the E/A ratio) were similar in the two groups.

The finding of cardiac wall and LV mass hypertrophy, even in the absence of hypertension, especially in patients with a marked visceral fat deposition, is not easy to explain. A number of possibilities have been proposed. First, changes in LV volume may at least partially depend on the hemodynamic changes accompanying obesity, particularly an increase in total blood volume and flow together with an increase in cardiac output and stroke volume (12,36–38). Second, it has been suggested that the hyperinsulinemia and insulin resistance frequently found in obesity may induce heart hypertrophy, because of the growth-stimulating effect of insulin due to activation of IGF-1 receptors (39–41), or modification in the intra- and extracellular calcium balance that may induce cardiomyocyte hypertrophy (42). Hyperinsulinemia may

Table 5. Pearson correlation coefficients between echocardiographic parameters and selected variables in the obese patients ($n = 28$)

	End-diastolic septum thickness	Diastolic posterior wall thickness	Indexed LV mass ($g/m^{2.7}$)	End-systolic left atrium (cm)	Internal diastolic LV diameter (cm)	A (m/s)	E/A ratio	Isovolumic relaxation time (ms)	Fractional shortening (%)
VAT	0.64*	0.65*	0.63*	0.43†	0.29	0.25	−0.16	−0.02	−0.04
Waist	0.64*	0.60‡	0.57‡	0.02	0.18	0.27	−0.14	−0.09	0.05
WHR	0.52‡	0.57‡	0.52‡	0.47‡	0.42†	0.06	−0.14	0.01	−0.18
WTR	0.52‡	0.37†	0.29	0.02	−0.08	0.21	−0.15	0.10	−0.04
A. diam	0.48†	0.48†	0.56‡	0.36†	0.30	0.22	−0.17	−0.13	−0.02
SAT	−0.3	−0.31	−0.23	−0.25	−0.1	−0.1	0.02	0.05	0.22
VAT/SAT	0.43†	0.43†	0.48†	0.27	0.2	0.19	−0.13	−0.04	−0.15
Weight	0.26	5.02	4.48	0.13	5.16	1.40	4.19	−0.27	0.43
BMI	0.11	0.13	0.23	−0.14	−0.01	0.13	0.08	−0.18	0.18
FFM	0.47†	0.52‡	0.40†	0.41†	0.40†	0.21	−0.05	−0.14	−0.16
Duration of obesity	0.22	0.22	0.35†	0.004	0.34†	0.22	−0.05	−0.35†	−0.01
Age	0.50‡	0.58‡	0.53‡	0.46†	0.31	0.31	−0.36	−0.05	−0.02
Height	0.15	0.14	−0.05	0.22	0.21	−0.12	0.13	−0.12	−0.27
SBP	−0.01	0.03	0.00	0.07	0.16	0.05	0.01	0.01	−0.04
DBP	−0.20	0.17	0.14	−0.18	0.09	0.03	−0.43†	0.29	0.13

LV, left ventricle; A, atrial diastolic filling wave velocity; E, early diastolic filling wave velocity (m/s); VAT, visceral adipose tissue; WHR, waist-to-hip ratio; WTR, waist-to-thigh ratio; A. diam, abdominal sagittal diameter; SAT, subcutaneous adipose tissue; BMI, body mass index; FFM, fat-free mass; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.
* $p < 0.0001$.
† $p < 0.01$.
‡ $p < 0.001$.

also indirectly contribute to heart hypertrophy in obese subjects by increasing blood volume as a result of its effect on sodium reabsorption in the kidney (43). Patients with visceral obesity frequently are characterized by higher plasma insulin concentrations under both fasting and postglucose load conditions than those with subcutaneous obesity (17,44). However, studies of the influence of insulin and insulin resistance on cardiac diameters, wall thickness, and LV mass have led to conflicting results, mainly due to nonhomogeneous study populations and different methods (10,34,45–48). With regard to our study population, the fasting plasma insulin levels of obese patients with the greatest amount of intra-abdominal fat levels were slightly but not significantly higher than those of the patients with less VAT deposition.

It is worth noting that the stepwise multivariate analysis showed that only VAT and waist circumference closely and almost exclusively correlated with diastolic septum thickness. Our findings are substantially in keeping with those of Nakajima et al. (21), those reported in elderly obese subjects whose ultrasound-measured VAT values significantly correlated with LV mass (34), and those of a study of a mixed population in which LV mass was associated with WHR in women but not in men (49).

Age may be of some importance in justifying some myocardial dysfunctions (49,50), but we did not found this correlation in the multivariate regression analysis. In contrast, none of our patients was older than 64 years and all of them were normotensive.

The absence of any correlation between echocardiographic abnormalities and body weight and BMI has been reported in other studies (31,34,47,49), albeit with some exception (21,51). This finding underlines the primary importance of VAT deposition, rather than body weight or BMI, in explaining some of the echocardiographic abnormalities observed in obesity.

Another interesting finding of this study is the fact that >50% of the patients had impaired carbohydrate metabolism: although 35% had IGT and 21% diabetes, the IGT-

Table 6. Stepwise regression analysis (T value) of the association between selected independent variables and echocardiographic parameters in the obese patients ($n = 28$)

	Independent variables											
	VAT	Waist	WHR	SBP	DBP	BMI	FFM	Duration of obesity	Age	Diabetes-IGT	Sex	Model R^2
End-diastolic septum thickness (cm)	−0.01	4.08*	−1.58	−1.06	1.07	−0.23	0.65	−0.12	0.66	0.77	−3.13*	0.57
Constant value: 0.47198												
β		0.007									−0.190	
SE β		0.001									0.006	
Diastolic posterior wall thickness (cm)	4.46†	1.26	0.04	−0.05	1.62	−0.71	1.45	0.05	1.91	1.32	−1.96	0.43
Constant value: 0.85258												
β	0.001											
SE β	4.3^{-4}											
Indexed LV mass ($g/m^{2.7}$)	4.22†	1.22	0.27	0.01	0.25	0.24	0.42	1.15	1.48	1.40	−0.15	0.40
Constant value: 32.3065												
β	0.18											
SE β	0.04											
End-systolic left atrium (cm)	1.02	1.16	0.06	0.45	−1.47	0.24	0.99	−0.74	1.49	−0.46	−3.09*	0.26
Constant value: 4.22857												
β											−0.54	
SE β											0.17	
Internal diastolic LV diameter (cm)	−0.39	−0.51	2.34*	0.21	−0.49	−0.30	1.51	1.33	0.74	−0.82	−0.87	0.17
Constant value: 3.69711												
β			1.48									
SE β			0.65									

VAT, visceral adipose tissue; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; FFM, fat-free mass; IGT, impaired glucose tolerance; β, estimated regression coefficient; SE β, SE of the estimated regression coefficient; LV, left ventricle.

* $p < 0.001$.

† $p < 0.0001$.

diabetes category in the stepwise regression model did not correlate with all of the echocardiographic abnormalities. The obese population studied by Nakajima et al. (21) was considered to be free from complications, but some of the subjects were found to have IGT or diabetes on the basis of an OGTT: like ours, the Japanese study did not find any correlation between diabetes or IGT and echocardiographic abnormalities. No relationship between diabetic status and LV mass was found in the multivariate analysis of the data coming from the large American Indian population belonging to the Strong Heart Study (49). Diabetes or IGT may certainly promote some cardiac abnormalities in wall thickness and performance, probably because of hyperinsulinemia, increased cardiac stroke, or other unclear mechanisms, even without hypertension (37,38,52). Some of the echocardiographic abnormalities that we studied have been found to be more pronounced in obese subjects with IGT-diabetes than in normotolerant obese ones. However, the correlation with IGT and diabetes in our study could have been masked by the greater statistical power of VAT and the other indicators of visceral fat distribution included in the stepwise regression model as independent variables. Furthermore, the relatively small number of patients in our study and in the Japanese study may have contributed to minimizing the importance of diabetes or IGT as cofactors in heart abnormalities. Recently, it was reported that, among the 1345 participants in the Strong Heart Study, those with IGT had a greater LV mass and thicker LV wall than the

group of normally tolerant subjects; however, the IGT subjects had slightly higher blood pressure values (32).

In conclusion, most of the echocardiographic abnormalities that can be observed in normotensive obese patients with or without diabetes or IGT are mainly associated with the amount of visceral fat. The presence of diabetes or IGT does not interfere with this relationship. Because echocardiographic changes in obese patients can be reversed by weight loss, therapeutic interventions aimed at reducing overweight and excess visceral fat may allow other advantages; subclinical LV hypertrophy is an independent predictor of cardiovascular morbidity and mortality even in the absence of hypertension (53).

Acknowledgments

This work was supported in part by a grant (60%) from the Italian Ministry for the Universities and Scientific and Technical Research, Rome, Italy. Presented in part at the 10th European Congress on Obesity, Antwerp, Belgium, June 24–27, 2000.

References

1. **Gordon T, Kannel WB.** Obesity and cardiovascular disease: the Framingham Study. *J Clin Endocrinol Metab.* 1976;5: 367–75.
2. **Björntorp P.** Classification of obese patients and complications related to the distribution of surplus fat. *Am J Clin Nutr*. 1987;45:1120–5.
3. **Hubert HB, Feinleib M, McNamara PM, Castelli WP.** Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Study. *Circulation.* 1983;67:968–83.
4. **Garavaglia GE, Messerli FH, Nunez BD, Scmieder RE, Grossman E.** Myocardial contractility and left ventricular function in obese patients with essential hypertension. *Am J Cardiol.* 1988;62:594–7.
5. **Lauer MS, Anderson KM, Kannel WB, Levy D.** The impact of obesity on left ventricular mass and geometry. The Framingham Heart Study. *JAMA.* 1991;266:231–6.
6. **de Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH.** Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. *Hypertension.* 1994;23:600–6.
7. **Warners CA, Roberts WC.** The heart in massive (more than 300 pounds or 136 kilograms) obesity: analysis of 12 patients studied at necroscopy. *Am J Cardiol.* 1984;45:1087–90.
8. **Zarich SW, Kowalchuk GJ, McGuire MP, Benotti PN, Mascioli EA, Nesto RW.** Left ventricular filling abnormalities in asymptomatic morbid obesity. *Am J Cardiol.* 1991;68: 377–81.
9. **Mureddu GF, de Simone G, Greco R, Rosato GF, Contaldo F.** Left ventricular filling pattern in uncomplicated obesity. *Am J Cardiol.* 1996;77:509–14.
10. **Mureddu GF, Greco R, Rosato GF, et al.** Relation of insulin resistance to left ventricular hypertrophy and diastolic dysfunction in obesity. *Int J Obes Relat Metab Disord.* 1998;22: 363–8.
11. **Alpert MA, Lambert CR, Terry BE, et al.** Effect of weight loss on left ventricular diastolic filling in morbid obesity. *Am J Cardiol.* 1995;76:1198–201.
12. **Karason K, Wallentin I, Larsson B, Sjöström L.** Effects of obesity and weight loss on cardiac function and valvular performance. *Obes Res.* 1998;6:422–9.
13. **Karason K, Wallentin I, Larsson L, Sjöström L.** Effects of obesity and weight loss on left ventricular mass and relative wall thickness: survey and intervention study. *Br Med J.* 1997;315:912–6.
14. **Larsson B, Svardsudd K, Welin L, Wilhekmsen L, Björntorp P, Tibblin G.** Abdominal adipose tissue distribution, obesity and risk of cardiovascular disease and death: 13 year follow-up of participants in the study of men born in 1913. *Br Med J.* 1984;288:1401–4.
15. **Ohlsson LO, Larsson B, Svardsudd K, et al.** The influence of body fat distribution on the incidence of diabetes mellitus: 13.5 years of follow-up of participants in the study of men born in 1913. *Diabetes*. 1985;34:1055–8.
16. **Després J-P, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C.** Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis.* 1990;10:497–511.
17. **Enzi G, Pavan M, Digito M, et al.** Clustering of metabolic abnormalities and other risk factors for cardiovascular disease in visceral obesity. *Diab Nutr Metab.* 1993;6:47–55.
18. **van der Kooy K, Seidell JC.** Techniques for the measurement of visceral fat: a practical guide. *Int J Obes Relat Metab Disord.* 1993;17:187–96.
19. **Armellini F, Zamboni M, Rigo M, et al.** Sonography detection of small intra-abdominal fat variations. *Int J Obes Relat Metab Disord.* 1991;15:847–52.
20. **Tornaghi G, Raiteri R, Pozzato C, et al.** Anthropometric or ultrasonic measurements in assessment of visceral fat? A comparative study. *Int J Obes Relat Metab Disord.* 1994;18: 771–5.
21. **Nakajima T, Fujioka S, Tokunaga K, Matsuzawa Y, Tarui S.** Correlation of intraabdominal fat accumulation and left ventricular performance in obesity. *Am J Cardiol.* 1989;64: 369–73.
22. **Matsuzawa Y, Fujioka S, Tokunaga K, Tarui S.** A novel classification: visceral fat obesity and subcutaneous fat obesity. In: Berry EM, ed. *Recent Advances in Obesity Research*. London, UK: John Libbey; 1987, pp. 92–6.
23. **Sahn DJ, Demaria A, Kisslo J, Weyman A.** The Committee on M-Mode Standardization of the American Society of Echocardiography: recommendations regarding quantitation in M-Mode echocardiography: results of a survey study of echocardiographic measurements. *Circulation.* 1978;58:1072–83.
24. **Devereux RB, Reichek N.** Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. *Circulation.* 1977;55:613–8.
25. **de Simone G, Daniels SR, Devereux RB, et al.** Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol.* 1992;20:1251–60.

26. **Sjöström L, Kvist H, Cederblad A, Tylen U.** Determination of total adipose tissue and body fat in women by computed tomography, ^{40}K, and tritium. *Am J Physiol.* 1986;250: E736–E45.
27. **Després J-P, Lamarche B.** Effects of diet and physical activity on adiposity and body fat distribution: implications for the prevention of cardiovascular disease. *Nutr Res Rev.* 1993; 6:137–59.
28. **Hunter GR, Snyder SW, Kekes-Szabo T, Nicholson C, Berland L.** Intra-abdominal adipose tissue values associated with risk of possessing elevated blood lipids and blood pressure. *Obes Res.* 1994;2:563–8.
29. **Williams MJ, Hunter GR, Kekes-Szabo T, et al.** Intra-abdominal adipose tissue cut-points related to elevated cardiovascular risk in women. *Int J Obes Relat Metab Disord.* 1996;20:613–7.
30. **Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H.** Coronary-heart-disease risk and impaired glucose tolerance. *Lancet.* 1980;i:1373–6.
31. **Jarrett RJ, McCartney P, Keen H.** The Bedford Survey: ten year mortality rates in newly diagnosed diabetes, borderline diabetics and normoglycaemic controls and risk indices for coronary heart disease in borderline diabetics. *Diabetologia.* 1982;22:79–84.
32. **Ilercil A, Devereux RB, Roman MJ, et al.** Relationship of impaired glucose tolerance to left ventricular structure and function: the Strong Heart Study. *Am Heart J.* 2001;141: 992–8.
33. **de la Maza MP, Estevez A, Bunout D, Klenner C, Oyonarte M, Hirsch S.** Ventricular mass in hypertensive and normotensive obese subjects. *Int J Obes Relat Metab Disord.* 1994;18:193–7.
34. **Vetta F, Cicconetti P, Ronzoni S, et al.** Hyperinsulinaemia, regional adipose tissue distribution and left ventricular mass in normotensive, elderly, obese subjects. *Eur Heart J.* 1998;19: 326–31.
35. **de Simone G, Devereux RB, Mureddu GF, et al.** Influence of obesity on left ventricular midwall mechanics in arterial hypertension. *Hypertension.* 1996;28:276–83.
36. **de Divitiis O, Fazio S, Petitto M, Maddalena G, Contaldo F, Mancini M.** Obesity and cardiac function. *Circulation.* 1981;64:477–82.
37. **Messerli FH, Sundgaard-Riise K, Reisin E, Dreslinski G, Dunn FG, Frohlich E.** Disparate cardiovascular effects of obesity and arterial hypertension. *Am J Med.* 1983;74:808–12.
38. **de Simone G, Devereux RB, Daniels SR, et al.** Stroke volume and cardiac output in normotensive children and adults: assessment of relations with body size and impact of overweight. *Circulation.* 1997;95:1837–43.
39. **Ito H, Hiroe M, Hirata Y, et al.** Insulin-like growth factor-I induces hypertrophy with enhanced expression of muscle specific genes in cultured rat cardiomyocytes. *Circulation.* 1993; 87:1715–21.
40. **Ohya Y, Abe I, Fujii K, et al.** Hyperinsulinemia and left ventricular geometry in a work-site population in Japan. *Hypertension.* 1996;27:729–34.
41. **Verdecchia P, Reboldi G, Schillaci G, et al.** Circulating insulin and insulin growth factor-1 are independent determinants of left ventricular mass and geometry in essential hypertension. *Circulation.* 1999;100:1802–7.
42. **Marban E, Koretsune Y.** Cell calcium, oncogenes, and hypertrophy. *Hypertension.* 1999;15:652–8.
43. **De Fronzo RA.** The effect of insulin on renal sodium metabolism: a review with clinical implications. *Diabetologia.* 1981;21:165–71.
44. **Pouliot MC, Després J-P, Nadeau A, et al.** Visceral obesity in men: association with glucose tolerance, plasma insulin, and lipoprotein levels. *Diabetes.* 1992;41:826–34.
45. **Sasson Z, Rasooly Y, Bhesania T, Rasooly I.** Insulin resistance is an important determinant of left ventricular mass in the obese. *Circulation.* 1993;88:1431–6.
46. **Sharp SD, Williams RR.** Fasting insulin and left ventricular mass in hypertensive and normotensive controls. *Cardiology.* 1992;81:207–12.
47. **Galvan AQ, Galetta F, Natali A, et al.** Insulin resistance and hyperinsulinemia: no independent relation to left ventricular mass in humans. *Circulation.* 2000;102:2233–8.
48. **Malmqvist K, Isaksson H, Ostergren J, Kahan T.** Left ventricular mass is not related to insulin sensitivity in never-treated primary hypertension. *J Hypertension.* 2001;9:311–7.
49. **Bella JN, Devereux RB, Roman M, et al.** Relations of left ventricular mass to fat-free and adipose body mass. The Strong Heart Study. *Circulation.* 1998;98:2538–44.
50. **de Simone G, Devereux RB, Kimball TR, et al.** Interaction between body size and cardiac overload: influence on left ventricular mass during body growth and adulthood. *Hypertension.* 1998;31:1077–82.
51. **Dannenberg AL, Levy D, Garrison RJ.** Impact of age and echocardiographic left ventricular mass in a healthy population (the Framingham Study). *Am J Cardiol.* 1989;64:1066–8.
52. **Liu JE, Palmieri V, Roman MJ, et al.** The impact of diabetes on left ventricular filling pattern in normotensive and hypertensive adults: the Strong Heart Study. *J Am Coll Cardiol.* 2001;37:1943–9.
53. **Vakili BA, Okin PM, Devereux RB.** Prognostic implications of left ventricular hypertrophy. *Am Heart J.* 2001;141:334–41.