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Echocardiographic Epicardial Adipose Tissue Is Related to Anthropometric and Clinical Parameters of Metabolic Syndrome: A New Indicator of Cardiovascular Risk

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Metabolic syndrome is related to multiple cardiovascular risk factors. Visceral adipose tissue (VAT) plays a key role in metabolic syndrome. Easy detection of VAT could be an important tool to increase knowledge of metabolic syndrome. The objective of this study was to study the relationship of echocardiographic epicardial adipose tissue to anthropometric and clinical parameters of metabolic syndrome. We selected 72 consecutive subjects, 46.5 ± 17.4 yr of age, with a body mass index between 22 and 47 kg/m^2. Each subject underwent transthoracic echocardiogram to measure epicardial fat thickness on right ventricle and magnetic resonance imaging to calculate visceral adipose tissue. Anthropometric, metabolic, and cardiac parameters were also evaluated. Echocardiographic epicardial adipose tissue showed a very good correlation with magnetic resonance imaging abdominal VAT and epicardial fat measurement (Bland-Altman plot and linear regression). Multiple regression analysis showed that waist circumference ($r^2 = 0.428$; $P = 0.01$), diastolic blood pressure ($r^2 = 0.387$; $P = 0.02$), and fasting insulin ($r^2 = 0.387$; $P = 0.03$) were the strongest independent variables correlated with epicardial adipose tissue. Echocardiographic epicardial adipose tissue could be applied as an easy and reliable imaging indicator of VAT and cardiovascular risk. (*J Clin Endocrinol Metab* 88: 5163–5168, 2003)

METABOLIC SYNDROME IS related to multiple cardiovascular risk factors (1–3). There are no well-accepted criteria for the diagnosis of metabolic syndrome. Nevertheless, it is identified by the presence of three or more metabolic alterations, such as abdominal obesity, hypertension, impaired fasting glucose or glucose intolerance, high levels of triglycerides, low levels of high-density lipoprotein cholesterol, and insulin resistance (4). Plasma adiponectin and C-reactive protein (CRP) have also been proposed to be related to central adiposity and cardiovascular risk (5–7).

Visceral obesity seems to play a key role in the development of all features of metabolic syndrome (8–15). Hence, detection of visceral adipose tissue (VAT), the fat deposited around the internal organs, might be important for risk stratification of metabolic syndrome. Nevertheless, it is difficult to obtain an accurate measurement and characterization of VAT. Several methods are applied as surrogates for estimation of VAT. Anthropometric measurements are the most used, but are frequently imprecise. However, waist circumference is widely accepted as a good predictor of intraabdominal fat mass (16, 17). Imaging techniques are certainly more precise and reliable than anthropometric measurements. Magnetic resonance imaging (MRI), the gold standard technique, estimates VAT accurately, but unfortunately it is costly (18). Recently, we have proposed and validated a new method to estimate VAT by echocardiographic epicardial adipose tissue measurement (19). Epicardial adipose tissue is a true visceral fat deposited around the heart with characteristics of a high insulin-resistant tissue. Epicardial adipose tissue measurement could be an important tool to increase knowledge of metabolic syndrome on epidemiological basis.

The aim of this work was to study the relationship of echocardiographic epicardial adipose tissue to anthropometric, metabolic, and cardiac parameters of metabolic syndrome.

Subjects and Methods

Subjects

We selected 72 consecutive subjects (Caucasian; 36 females and 36 males), 46.5 ± 17.4 yr of age, with a body mass index (BMI) between 22 and 47 kg/m^2 (median, 34). Echocardiographic measurements were performed in all subjects during routine examinations. Metabolic syndrome was identified by the presence of three or more of the following parameters: BMI greater than 30 kg/m^2, predominant truncal/abdominal fat distribution (value of waist circumference >88 cm in women and >102 cm in men), impaired fasting glucose (fasting glucose >110 mg/dl), hypertension (systolic arterial blood pressure >130 mm Hg and diastolic >85 mm Hg for at least three measurements), high plasma lipids (serum level of total cholesterol >220 mg/dl, HDL cholesterol <40 mg/dl for men and <50 mg/dl for women, LDL >130 mg/dl, and serum level of triglycerides >150 mg/dl). This study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki and has been approved by review committee of La Sapienza University. All subjects gave informed consent before the study began.

Anthropometric measurements

Weight (to the nearest 0.1 kg) and height (to the nearest 0.5 cm) were measured while the subjects were fasting and wearing only their undergarments. BMI was calculated as body weight divided by height squared and was used as a marker of degree of obesity. Minimum waist circumference (in centimeters; minimum circumference between the

Abbreviations: BMI, Body mass index; CI, confidence interval; CRP, C-reactive protein; CV, coefficient of variation; 2D, two-dimensional; LDL, low-density lipoprotein; LVM, left ventricular mass; MRI, magnetic resonance imaging; SAT, sc adipose tissue; TAT, total adipose tissue; VAT, visceral adipose tissue.

lower rib margin and the iliac crest, midwaist) and maximum hip circumference (in centimeters; the widest diameter over the greater trochanters) were measured while the subjects were standing with their heels together.

Impedensitometry measurements

Fat mass and fat-free mass were estimated using a bioelectrical impedance analyzer (BIA-103; Akern, Florence, Italy) following the manufacturer's equations, which included data from obese and lean subjects (20).

Analytical procedures

Plasma glucose was determined by the glucose oxidase method [Autoanalyzer, Beckman Coulter, Inc., Fullerton, CA; coefficient of variation (CV), 1.9 ± 0.2%]. Plasma total cholesterol (CV, 3.4 ± 0.2%), high-density lipoprotein cholesterol (CV, 3.7 ± 0.4%), low-density lipoprotein (LDL) cholesterol (CV, 3.8 ± 0.4%), and triglycerides (CV, 3.1 ± 0.5%) concentrations were measured using enzymatic kits (Ortho-Clinical Diagnostic, Milan, Italy). High sensitivity CRP was measured with the use of latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring, Newark, DE; CV, 4.5 ± 0.5%). Blood samples for plasma hormone measurements were collected in heparinized tubes. After centrifugation, plasma insulin (Sorin Biomedical, Milan, Italy; CV, 3.0 ± 0.3%) and leptin (Linco Research, Inc., St. Charles, MO; CV, 3.7 ± 0.5%) concentrations were determined by RIA. To evaluate day by day plasma leptin variations, we measured the plasma leptin concentration at 24-h interval in all subjects. Plasma leptin concentrations had a very small interday variation (mean variation, 3.4 ± 0.6%). The plasma adiponectin concentration were measured by RIA (Linco Research, Inc.; CV, 4.7 ± 0.4%). Samples were diluted 500 times before assay.

Echocardiographic study

Each subject underwent transthoracic two-dimensional (2D) guided M-mode echocardiogram. Echocardiograms were performed with a SONOLINE instrument (Siemens, New York, NY) by standard techniques with subjects in the left lateral decubitus position. Echocardiograms were recorded on videotape. The echocardiographic study required the recording of 10 or more cycles of 2D parasternal long- and short-axis views and 10 or more cycles of M-mode with optimal cursor beam orientation in each view (21, 22). Echocardiograms were preliminarily read by a first reader and subsequently reread by highly experienced reader. Both readers were blinded to the subjects' anthropometric features. The CV between the two different sonographers was 2.8%, indicating good reproducibility of the echocardiographic measurements We excluded 2 subjects from 74 initially selected because of nonoptimal technically satisfactory view.

We measured epicardial fat thickness on the free wall of right ventricle from both parasternal long- and short-axis views. We used imaging constraints to make sure that the epicardial fat thickness was not measured obliquely. Measurements on M-mode strips obtained from both 2D views with longitudinal cursor beam orientation in each view were also performed. The maximum values at any site were measured, and the average value was considered. In any case, a very good reliability of epicardial fat thickness measurement from different views occurred (intraclass correlation coefficient, 0.92). Epicardial adipose tissue appears as an echo-free or a hyperechoic space, if it is massive. The measurement of epicardial fat on the right ventricle was chosen for two reasons: 1) this point is recognized as the highest absolute epicardial fat layer thickness (23), and 2) parasternal long- and short-axis views allow the most accurate measurement of epicardial adipose tissue on the right ventricle, with optimal cursor beam orientation in each view.

Hypertrophy of the right ventricle trabecula and moderator band, even if it occurred, did not confound epicardial adipose tissue calculation (23).

Left ventricular mass (LVM) was estimated by using the anatomically validated formula of Devereux *et al.* (24). The index that adjusted LVM was obtained as LVM/height$^{2.7}$ (LVMh$^{2.7}$) (25, 26). If the 2D-guided M-mode beam could not be optimally oriented, 2D long-axis views were used to obtain linear measurements of LV cavity (LV end-diastolic diameter and LV end-systolic diameter) and walls (interventricular septum and posterior wall) according to the recommendations of American Society of Echocardiography (22).

MRI measurements

Each subject underwent MRI of VAT to assess the correlation between echocardiographic epicardial fat and MRI VAT. The MRI studies were performed with a 1.5-T system (Gyroscan ACS-NT 1000, Philips, Eindhoven, The Netherlands) using a body coil for signal transmission and reception. Respiratory triggering was used for the sequences, whereby repetition time was dependent on respiratory frequency. During the examination, patients were not given special breathing commands.

The areas of abdominal VAT, sc (SAT), and total (TAT) adipose tissue were measured at the L4–L5 level. We obtained TFET1-weighted sequences with axial and sagittal orientation, antero-posterior phase-encoding direction, 10-mm-thick section with 1-mm intersection gap, with a 364 field of view and a 256 × 256 matrix. The entire VAT and SAT volumes were measured by MRI while the subjects were lying supine on their abdomens, with arms elevated above the head, as described by Ross *et al.* (18). The SAT and VAT volumes were summed to obtain the TAT volume. Then VAT was calculated as TAT minus SAT. Epicardial adipose tissue scans were obtained by TSET1-weighted sequences with oblique axial orientation for a correct study of the four cardiac chambers, 10-mm-thick section with 1-mm intersection gap, 370 field of view, 256 × 256 matrix. We measured epicardial fat thickness on the free wall of the right ventricle, following the same echocardiographic points and views. The sagittal abdominal diameter was measured at the L4–L5 level. The intraclass correlation for repeated VAT, sagittal abdominal diameter, and epicardial adipose tissue determinations in our laboratory was 0.95.

Statistical analysis

Data in the text and tables are expressed as the mean ± SD. Linear regression analysis was performed on all anthropometric and clinical variables to identify correlates of epicardial adipose tissue, and variables found to be $P < 0.1$ by univariate analysis were entered into a stepwise multiple linear regression analysis to determine their independent relationship to epicardial adipose tissue. A Mann-Whitney *U* test with 95% confidence interval (CI) was applied to evaluate the differences between men and women. A Kruskal-Wallis test with 95% CI was used to evaluate the differences among the groups of patients with different conditions of fat tissue distribution in men and women, respectively. To assess the agreement between MRI and echocardiographic measurements, we used the method described by Bland and Altman. Two-tailed $P < 0.05$ indicated statistical significance. Analysis was performed using Stata 5.0 (Stata Corp., College Station, TX).

Results

Subject characteristics

The main anthropometric and clinical characteristics of the subjects studied are summarized in Table 1.

Echocardiographic study of epicardial adipose tissue

The thickness of the epicardial adipose tissue on the right ventricle varies between 1.8 and 16.5 mm. Subjects with predominant visceral fat accumulation and at least two clinical and metabolic parameters of metabolic syndrome showed higher epicardial adipose tissue than subjects with predominant peripheral fat distribution and no clinical or metabolic alterations [9.87 ± 2.55 *vs.* 4.12 ± 1.67 (95% CI, 4.06–7.18; $P < 0.01$) and 7.58 ± 3.02 *vs.* 3.13 ± 1.87 (95% CI, 2.19–5.76; $P < 0.01$) in men and women, respectively]. No significant differences in age and BMI among subjects with predominant visceral fat accumulation and subjects with peripheral fat occurred.

TABLE 1. Body composition and clinical parameters in men and women

	Men (n = 36)	Women (n = 36)	*P*
Age (yr)	48.2 ± 13.7	45.8 ± 15.7	NS
BMI (kg/m^2)	33.8 ± 13.7	34.3 ± 15.4	NS
Waist (cm)	107.7 ± 15.8	104.8 ± 15.1	NS
FM (kg)	42.3 ± 15.7	38.3 ± 21.5	NS
FFM (kg)	53.8 ± 17.2	45.0 ± 17.2	NS
Epicardial fat (cm)	7.60 ± 3.55	6.94 ± 3.71	NS
Syst BP (mm Hg)	138.8 ± 18.6	137.7 ± 15.9	NS
Diast BP (mm Hg)	88.6 ± 9.0	87.9 ± 8.0	NS
Glucose (mg/dl)	98.2 ± 18.6	98.5 ± 19.9	NS
Insulin (μIU)	20.5 ± 12.7	19.8 ± 14.5	NS
Leptin (ng/ml)	19.4 ± 11.5	26.4 ± 13.5	0.01
Adiponectin (mg/liter)	9.4 ± 6.5	15.9 ± 6.7	0.03
Total cholesterol (mg/dl)	191.8 ± 44.6	189.5 ± 42.4	NS
HDL (mg/dl)	38.6 ± 10.4	40.2 ± 10.8	NS
LDL (mg/dl)	121 ± 15.4	121.4 ± 14.7	NS
Triglycerides (mg/dl)	148 ± 54.6	140 ± 53.2	NS
CRP (mg/liter)	2.8 ± 1.6	2.0 ± 1.7	0.05
Fibrinogen (mg/dl)	178 ± 50.4	165 ± 57.5	NS

Data are presented as the mean ± SD.

Waist circumference (Waist), fat mass (FM), and fat free mass (FFM) were measured by the BIA method; systolic blood pressure (Syst BP), diastolic blood pressure (Diast BP), fasting glucose (Glucose), fasting insulin (Insulin), fasting leptin (Leptin), total cholesterol, high density lipoprotein cholesterol (HDL), LDL cholesterol (LDL), and CRP were also determined.

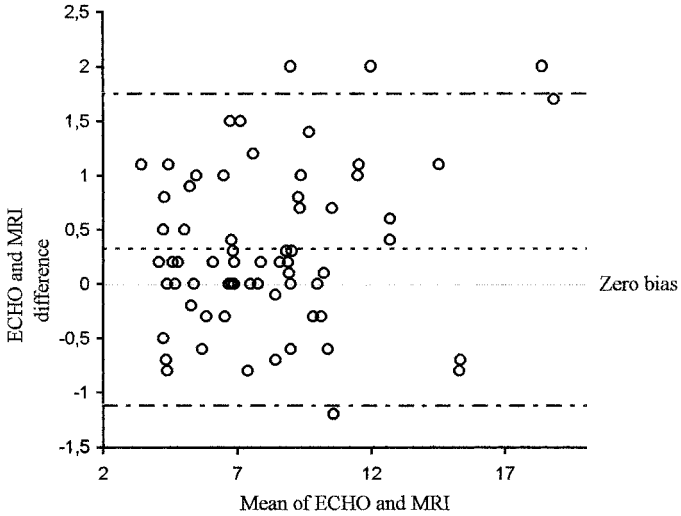

FIG. 1. Bland-Altman plot regression showed a very good agreement of echocardiographic epicardial adipose tissue with MRI epicardial fat measurement.

Anthropometric correlates of epicardial adipose tissue

Bland-Altman plot regression showed a very good agreement of echocardiographic epicardial adipose tissue with MRI epicardial fat measurement (Fig. 1).

In a simple linear regression analysis, MRI epicardial fat, waist circumference, and MRI VAT showed an excellent correlation with epicardial adipose tissue obtained from the echocardiogram (Table 2). Epicardial adipose tissue was also related to BMI and fat mass. No correlation among age, MRI SAT, and epicardial adipose tissue measurement was found. Multiple regression analysis confirmed that waist circumference and MRI VAT were the strongest independent variables related to epicardial adipose tissue (Table 2).

TABLE 2. Anthropometric correlates of echocardiographic epicardial adipose tissue

	Simple regression analysis	
	r	*P*
MRI epicardial fat	0.91	0.001
Waist	0.845	0.01
MRI VAT	0.840	0.01
BMI	0.567	0.05
FM	0.455	0.03
Hip	0.433	0.09
Sex	0.342	0.10
Age	0.219	0.14
	Multiple regression analysis	
	t	*P*
Waist	2.69	0.01
MRI VAT	2.48	0.01
BMI	1.53	0.05
FM	0.78	0.10

$r^2 = 0.428$

Waist, Waist circumference; FM, fat mass calculated by BLA.

Correlates of MRI VAT

Taking into account echocardiographic epicardial fat and waist circumference as measures of VAT, MRI VAT was correlated better with the echocardiographic measurement than with waist circumference (r = 0.840, $P = 0.01$; and r = 0.750, $P = 0.02$, respectively; Fig. 2).

Cardiac and metabolic correlates of epicardial adipose tissue

Simple linear regression analysis showed a good correlation among diastolic blood pressure, fasting insulin, and epicardial adipose tissue (Table 3 and Fig. 3). Epicardial fat was also related to LDL cholesterol, plasma adiponectin, glucose, high-density lipoprotein cholesterol, and systolic blood pressure. No correlation between epicardial adipose tissue measurement and triglycerides, leptin, LVM, CRP, fibrinogen, heart rate, uric acid, and microalbuminuria was found.

Multiple regression analysis confirmed that diastolic blood pressure and fasting insulin were the strongest independent variables correlated with epicardial adipose tissue. (Table 3).

Discussion

Our data showed that epicardial adipose tissue measured by echocardiography is related to the main anthropometric and clinical parameters of metabolic syndrome. In fact, we found a very good correlation between epicardial adipose tissue and waist circumference, diastolic blood pressure, fasting plasma insulin, LDL cholesterol, and plasma adiponectin. Moreover, echocardiographic calculation of epicardial fat was easily reproducible and showed an excellent reliability with the MRI epicardial and visceral adipose tissue measurements. Echocardiographic assessment of visceral fat could be an easy method to indicate patients with high cardiovascular risk.

Recent studies suggested that visceral fat may be an independent predictor of metabolic risk (26–28). These observations supported the growing interest in a better definition

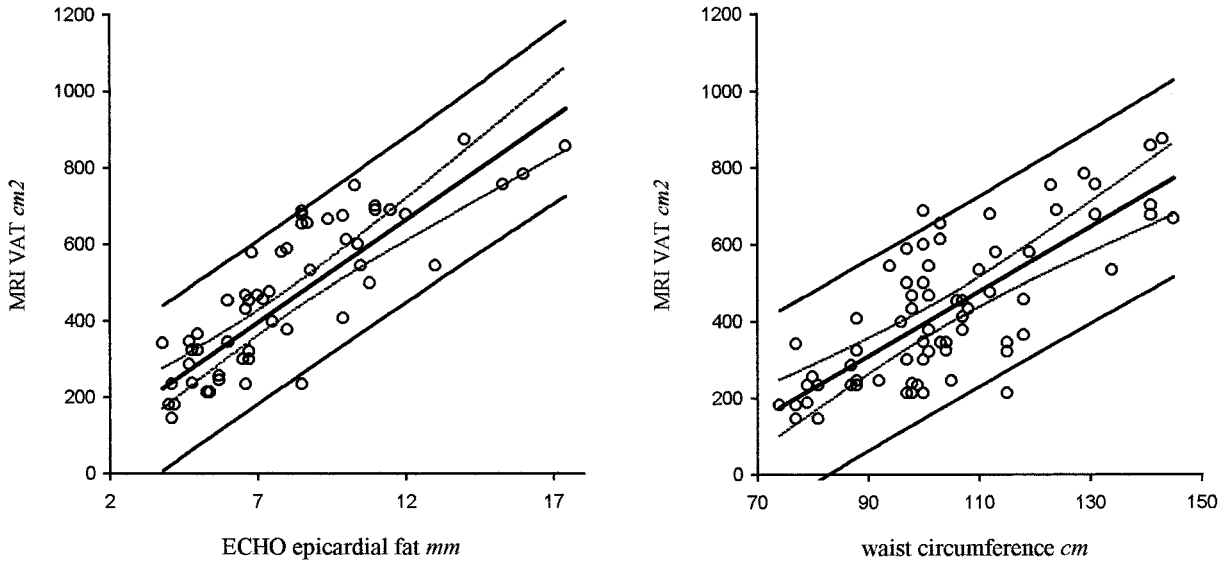

FIG. 2. Taking into account echocardiographic epicardial fat and waist circumference as measures of VAT, MRI VAT was correlated better with the echocardiographic measurement than with waist circumference (r = 0.840; $P = 0.01$ and r = 0.750; $P = 0.02$, respectively).

TABLE 3. Metabolic correlates of epicardial adipose tissue

	Simple regression analysis[a]			
	Men		Women	
	r	*P*	r	*P*
Diast BP	0.745	0.001	0.744	0.001
Insulin	0.698	0.01	0.695	0.01
LDL	0.600	0.02	0.594	0.02
Adiponectin	−0.535	0.03	−0.590	0.02
Glucose	0.518	0.03	0.522	0.04
HDL	−0.507	0.04	−0.510	0.04
Syst BP	0.384	0.05	0.388	0.05
Triglycerides	0.386	0.06	0.377	0.06
CRP	0.358	0.06	0.359	0.07
Leptin	0.379	0.11	0.397	0.10
LVM	0.381	0.13	0.354	0.14
Fibrinogen	0.210	0.16	0.211	0.16

	Multiple regression analysis		
	t	*P*	$r^2 = 0.387$
Diast BP	2.67	0.02	
Insulin	2.00	0.03	
LDL cholesterol	1.31	0.06	
Adiponectin	−1.20	0.06	
HDL cholesterol	−1.14	0.07	
Glucose	1.13	0.09	
Syst BP	0.98	0.10	
Tryglicerides	0.86	0.11	
CRP	0.80	0.11	

Glucose, Fasting glucose; Insulin, fasting insulin; Syst BP, systolic blood pressure; Diast BP, diastolic blood pressure; HDL, high-density lipoprotein.

[a] Taking into account gender.

of imaging studies of adipose tissue (29). In fact, imaging measurements provide a more accurate quantification of adipose tissue and multicompartment body fat distribution than simple anthropometric indexes (30, 31). Particularly, ultrasound procedure has been reported to be an excellent method for visceral abdominal fat prediction, with the great advantage of being less expensive and less invasive than MRI and computed tomography techniques (32). In the present study, epicardial fat showed a correlation with abdominal VAT higher or similar to that with ultrasound intraabdominal thickness reported in previous studies (32–34). In addition, we validated our echocardiographic measurements by MRI, which is considered the gold standard technique for VAT estimation.

Epicardial adipose tissue is a true visceral fat tissue, deposited around the heart on the free wall of the right ventricle and on the left ventricular apex, but also around the atria. Obesity seems to be a predisposing factor for the accumulation of excess epicardial fat (23). Nevertheless, our data suggest that body fat distribution, particularly abdominal fat tissue, is more strongly correlated to epicardial fat. A possible common pathway during embryogenesis could explain this finding. In fact, epicardial fat and intraabdominal fat seem to be originally in brown adipose tissue in infancy. The biochemical proprieties of epicardial adipose tissue suggest its possible role as a cardiovascular and metabolic risk indicator. In fact, it was reported that in young adult guinea pigs the rate of free fatty acid release by epicardial adipose tissue was twice that of the perirenal fat depots, indicating increased lipolytic activity (35). This is probably due to several mechanisms: the antilipolytic effect of insulin is low in VAT; β-adrenergic receptors, especially β_3-receptors, are increased; and their stimulation activates lipolysis (36). The correlation of LDL cholesterol, fasting insulin, adiponectin, and arterial blood pressure with epicardial fat thickness in our subjects seems to support these observations. The relationship of epicardial fat to plasma insulin and adiponectin levels strongly suggests that it should be considered a highly insulin-resistant adipose tissue. In fact, subjects with impaired insulin sensitivity and lower adiponectin levels, independently from BMI, showed the highest epicardial fat thickness. In addition, recent observations reported that mRNA expression of resistin, a novel adipocyte-secreted factor strongly linked with insulin resistance, is increased in human epicardial fat (37). In the consolidate conviction that insulin resistance together with visceral obesity are the major de-

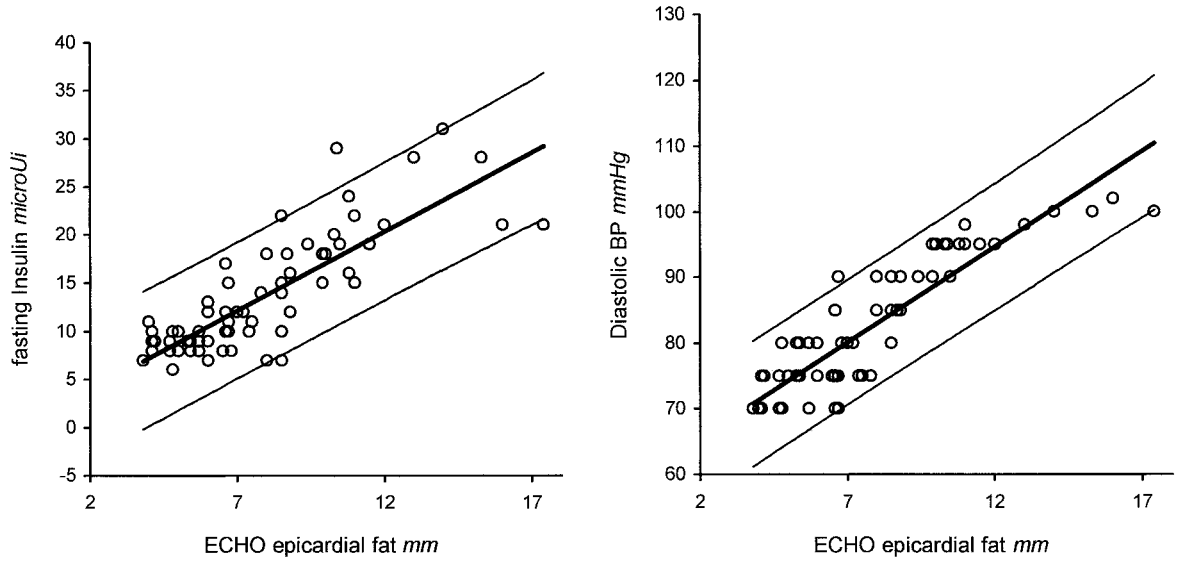

FIG. 3. Simple linear regression analysis showed a good correlation among diastolic blood pressure, fasting insulin, and epicardial adipose tissue.

terminants of metabolic syndrome, this imaging indicator of visceral fat could be useful and appropriate. The good correlation of epicardial fat with diastolic blood pressure can be intuitively inserted and explained in the context of physiopathological mechanisms of insulin resistance syndrome. In fact, the link among insulin resistance, visceral fat, and hypertension is well known (8–10, 13, 14). Finally, epicardial fat does not seem to be influenced by age, and previous autoptical studies confirmed our data (23).

In the present study, MRI VAT was correlated better with echocardiographic epicardial fat than with waist circumference. We believe that this is an important issue in favor of this new method. Although waist circumference is widely accepted as a marker of adverse metabolic profile and high cardiovascular risk, it can be confounded by large amounts of sc fat, particularly in severely obese subjects. Echocardiographic measurement of VAT would not be affected by this. In fact, we can obtain a true VAT measurement, avoiding the possible confounding effect of increased sc abdominal fat thickness.

This may also explain the advantage of echocardiography over other ultrasound abdominal fat measurements. Our finding seems to support the observation that this echocardiographic measure could be a good imaging predictor of visceral fat mass and could justify its higher cost compared with a simpler measure, such as waist circumference. In any case, echocardiography requires lower costs than existing methodologies, such as MRI and computed tomography, also providing data on cardiac parameters that can be useful in the clinical management of patients with metabolic syndrome.

Furthermore, echocardiography could have its greatest utility as a less expensive method for precise quantification of visceral fat for research and risk stratification purposes. We suggest that echocardiographic epicardial adipose tissue could be applied as an easy and reliable imaging indicator of cardiovascular risk. Further investigations with a larger population will be necessary to create threshold values of mild and severe visceral fat deposition.

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