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Epicardial Adipose Tissue and Metabolic Syndrome in Hypertensive Patients With Normal Body Weight and Waist Circumference

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BACKGROUND

Metabolic syndrome (MetS) is a cluster of risk factors, related to visceral adiposity, which is frequently observed in overweight patients. However, it has also been reported in normal weight subjects. Epicardial adipose tissue (EAT) is a visceral fat. The aim of the study was to evaluate whether EAT is associated with MetS in hypertensive patients with normal weight and waist.

METHODS

We studied 174 Caucasian hypertensive patients, aged ≥40 years, with body mass index (BMI) <25 kg/m^2 and waist circumference <102 cm in men and 88 cm in women. MetS was defined according to NCEP ATP III criteria, not including waist circumference. EAT was measured by echocardiography above the free wall of the right ventricle, at end diastole.

RESULTS

MetS was present in 21 (12%) patients. EAT was significantly higher in patients with MetS than in those without MetS, 4.0 ± 0.8 vs 2.5 ± 0.9 mm, $P < 0.01$, respectively, but BMI and waist circumference were not. Multivariate analysis showed that EAT was independently associated with MetS. Receiver operating characteristic (ROC) curve analysis showed that EAT significantly improved prediction of MetS when added to BMI and waist circumference. Indeed, the area under the curve improved from 0.63 (0.50–0.76) to 0.91 (0.87–0.96), and resulted significantly higher ($P < 0.01$). ROC curve for EAT alone indicated that the cutoff value of 3.1 mm had the best performance in predicting MetS, that is, 100% sensitivity and 79% specificity.

CONCLUSION

EAT thickness is associated with MetS in hypertensive patients with normal weight and waist.

Keywords: *blood pressure; epicardial fat; essential hypertension; hypertension; metabolic syndrome; normal-weight*

American Journal of Hypertension, advance online publication 4 August 2011; doi:10.1038/ajh.2011.134

Metabolic syndrome (MetS) is a cluster of risk factors[1–3] that is associated with increased cardiovascular risk in different clinical settings.[4–6] It is usually defined as the presence of at least three features among high blood pressure (BP), abdominal obesity, high fasting glucose, high triglycerides, and low high-density lipoprotein cholesterol. Excess of visceral fat and insulin resistance, which are mainly observed in overweight and obese subjects, seem to play a major role in this condition.[1–3]

MetS, however, has also been reported in normal-weight subjects,[7,8] who have also been defined as metabolically obese, normal-weight individuals. Despite normal body weight, and frequently normal waist circumference, it has been reported that these subjects show higher visceral adiposity and lower insulin sensitivity in comparison with normal-weight subjects without MetS.[9,10]

Epicardial adipose tissue (EAT) is a layer of visceral fat between the myocardium and the epicardium that has the same embryological origin of mesenteric and omental fat.[11–14] It produces several bioactive molecules and has some biochemical peculiarities, such as fatty acid composition and high rates of fatty acid incorporation, synthesis, and breakdown.[11–14]

Recently, echocardiographic examination has been proposed as an easy and suitable method to evaluate EAT.[15–22]

Some reports[16–22] have evaluated the association between echocardiographic EAT and MetS or its components. Two studies[17,18] did not report significant correlation between EAT thickness and components of MetS. Conversely, others[16,19–21] reported higher EAT thickness on the free wall of the right ventricle in patients with MetS than in those without MetS. Previous studies evaluated populations with high prevalence of overweight and obesity[16,17,20,21] and included normotensive subjects.[16–21] A recent report has suggested that the association between EAT and MetS could be affected by body mass index (BMI).[22] Indeed, it has been reported that EAT was a stronger predictor of MetS in normal weight and mildly overweight Asian subjects than in those with higher overweight and obesity.[22]

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Received 30 April 2011; first decision 22 May 2011; accepted 25 June 2011.

The aim of this study was to evaluate the association between EAT thickness and MetS in Caucasian hypertensive patients with normal body weight and waist circumference.

METHODS

Subjects. We studied 174 Caucasian hypertensive patients with BMI <25 kg/m^2 and waist circumference <102 cm in men and <88 cm in women, aged ≥40 years. Subjects with antihypertensive therapy at baseline, secondary hypertension, valvular heart disease, heart failure, known coronary artery disease, and poor acoustic window were excluded.

Patients underwent clinical evaluation, electrocardiogram, routine laboratory tests, echocardiographic examination, and noninvasive ambulatory BP monitoring. Laboratory tests were performed by using standard methods; the coefficient of variation of various examinations was low as documented by quality controls. In this study, MetS was defined according NCEP ATP III[1] criteria, excluding waist circumference, that is, hypertension plus any two of the following factors: (i) blood glucose ≥100 mg/dl, (ii) triglycerides ≥150 mg/dl and (iii) high-density lipoprotein cholesterol <40 mg/dl in men or <50 mg/dl in women. Study population came from the same geographical area (Chieti and Pescara, Abruzzo, Italy). The study was in accordance with the Second Declaration of Helsinki and was approved by the institutional review committee. Subjects gave informed consent.

BP measurements. Clinic systolic and diastolic BP recordings were performed by a physician by using a mercury sphygmomanometer. Measurements were performed in triplicate, 2 min apart, and the average value was used as the BP for the visit. Clinic hypertension was defined as BP ≥140 and/or 90 mm Hg in repeated visits.

Ambulatory BP monitoring was performed with a portable noninvasive recorder (SpaceLabs 90207; Spacelabs, Redmond, WA) on a day of typical activity. Technical aspects have been previously reported.[23] All recordings had >70% valid readings.

Echocardiography. Two-dimensionally guided M-mode echocardiograms of the left ventricle were taken at the chordal level, and measurements were made according to the American Society of Echocardiography recommendations.[24] Left ventricular mass was calculated using the formula introduced by Devereux *et al.*[25] and was indexed by height$^{2.7}$ in each subject.[26]

EAT appears as an echo-free space between the free wall of the right ventricle and the pericardium and was measured in this area from parasternal long-axis view,[15–22] at end diastole.[17–19,21,22] EAT was measured from long-axis images (**Figure 1**) at the point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus, used as an anatomic landmark.[15–22]

Reproducibility of EAT measurement was evaluated in a subsample of 30 subjects, 1 week later. The coefficient of variation was 7.1%. All measurements were performed by the same observer who was unaware of the other patients' characteristics.

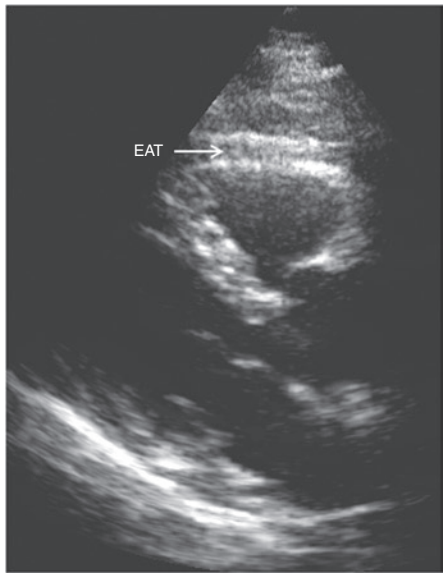

Figure 1 | Long-axis two-dimensional echocardiographic image showing epicardial adipose tissue (EAT).

Statistical analysis. Data are expressed as mean ± s.d. or %. Groups were compared with unpaired *t*-test, Mann–Whitney *U*-test, and χ^2-test, where appropriate. Comparison of EAT values according to MetS score was performed using Kruskal–Wallis test. Correlation of EAT with other variables was evaluated by Spearman's correlation analysis. Univariate and multivariate logistic regression analysis was performed to investigate the association of EAT and other variables with MetS. A receiver operating characteristic (ROC) curve analysis was used to assess the discrimination of MetS by BMI plus waist circumference and by BMI plus waist circumference plus EAT.[27] The cutoff value, where appropriate, with the best sensitivity and specificity to predict MetS was also calculated.[27] Statistical significance was defined as $P < 0.05$. Analyses were made with the SPSS 12 software package (SPSS, Chicago, IL), except for comparison between the area under the curves that was performed with the MedCalc 11.5.1 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Characteristics of study groups are reported in **Table 1**. By definition, glucose level, prevalence of subjects with glucose ≥100 mg/dl, prevalence of diabetes, triglyceride level, and prevalence of subjects with triglycerides ≥150 mg/dl were significantly higher in patients with MetS than in those without MetS. Likewise, high-density lipoprotein cholesterol level was significantly lower, and prevalence of subjects with high-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women was significantly higher, in patients with MetS than in those without MetS.

Creatinine, estimated glomerular filtration rate and left ventricular mass index were significantly higher in subjects with MetS. BMI and waist circumference were not significantly different between the groups, whereas EAT thickness was

Table 1 | Characteristics of study groups

Parameter	No MetS ($n = 153$)	MetS ($n = 21$)	P
Age, years	61 ± 13	64 ± 12	0.31
Men, *n* (%)	64 (42)	9 (43)	1.00
Body mass index, kg/m^2	22.9 ± 1.6	23.5 ± 1.4	0.10
Waist, cm	84.5 ± 6.7	86 ± 7	0.32
Smokers, *n* (%)	19 (12)	2 (9.5)	1.00
Glucose, mg/dl	89 ± 9	111 ± 33	<0.01
Glucose ≥100 mg/dl, *n* (%)	14 (9)	13 (62)	<0.01
Diabetes, *n* (%)	0 (0)	2 (9.5)	0.01
Creatinine, mg/dl	0.88 ± 0.17	0.96 ± 0.24	0.03
eGFR, ml/min/1.73 m^2	82 ± 18	73 ± 14	0.03
Total cholesterol, mg/dl	212 ± 30	216 ± 39	0.58
HDL cholesterol, mg/dl	55 ± 11	43 ± 7	<0.01
HDL cholesterol <40 or 50 mg/dl, *n* (%)	8 (5)	15 (71)	<0.01
Triglycerides, mg/dl	115 ± 38	181 ± 50	<0.01
Triglycerides ≥150 mg/dl, *n* (%)	26 (17)	16 (76)	<0.01
LDL cholesterol, mg/dl	134 ± 26	136 ± 35	0.70
Clinic systolic BP, mm Hg	154 ± 12	156 ± 10	0.46
Clinic diastolic BP, mm Hg	96 ± 7	94 ± 9	0.32
24 hour systolic BP, mm Hg	137 ± 9	139 ± 6	0.35
24 hour diastolic BP, mm Hg	85 ± 8	83 ± 9	0.26
LVMI, g/m$^{2.7}$	42 ± 8	46 ± 7	0.04
EAT, mm	2.5 ± 0.9	4.0 ± 0.8	<0.01

BP, blood pressure; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate by MDRD study equation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVMI, left ventricular mass index; MetS, metabolic syndrome.

Table 2 | Correlations of epicardial adipose tissue with anthropometric data and different components of the metabolic syndrome

	r_s	P
Age	0.26	<0.01
Gender	0.14	0.06
Body mass index	0.34	<0.01
Waist	0.30	<0.01
Glucose	0.15	<0.05
HDL cholesterol	−0.20	<0.01
Triglycerides	0.32	<0.01
Clinic systolic BP	0.28	<0.01
Clinic diastolic BP	0.05	0.50

BP, blood pressure; HDL, high density lipoprotein.

significantly higher in patients with MetS than in those without MetS. Age, gender distribution, prevalence of smokers, total and low-density lipoprotein cholesterol levels and clinic and ambulatory BP were not significantly different between the groups.

Table 3 | Univariate logistic regression analysis evaluating the association of anthropometric data, epicardial adipose tissue, left ventricular mass index, and renal function with metabolic syndrome

	OR (95% CI)	P
Age	1.02 (0.98–1.06)	0.32
Gender	1.04 (0.41–2.62)	0.93
Body mass index	1.35 (0.94–1.94)	0.10
Waist	1.04 (0.96–1.10)	0.32
EAT	3.86 (2.27–6.57)	<0.01
LVMI	1.06 (1.01–1.12)	<0.05
eGFR	0.96 (0.93–0.99)	< 0.05

OR refers to 1 unit variation of continuous variables and to men vs. women for gender. CI, confidence interval; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; OR, odds ratio.

When EAT thickness was investigated according to the number of MetS components, a gradual increase of EAT was observed with increasing number of MetS components. Indeed, in subjects with 1, 2, 3, and 4 MetS components, EAT thickness was 2.4 ± 0.9 (median 2.3), 2.8 ± 0.8 (median 2.8), 3.9 ± 0.6 (median 3.8), and 4.9 ± 0.2 (median 4.9) mm, respectively ($P < 0.01$).

Correlations of EAT with anthropometric data and different MetS components are reported in **Table 2**. Significant correlation was observed between EAT and various variables, except for gender and clinic diastolic BP.

Results of univariate logistic regression analysis evaluating the association of EAT and other variables with MetS are reported in **Table 3**. EAT, left ventricular mass index, and estimated glomerular filtration rate were significantly associated with MetS, whereas age, gender, BMI, and waist circumference were not.

Results of multivariate analyses are reported in **Table 4**. Various models showed that EAT was independently associated with MetS.

Figure 2 shows ROC curves, obtained from logistic regression analysis, for BMI plus waist circumference and BMI plus waist circumference plus EAT, in predicting MetS. The area under the curve for BMI plus waist circumference was 0.63 (0.50–0.76), $P = 0.055$. When EAT was added to BMI and waist circumference, the area under the curve improved to 0.91 (0.87–0.96), $P < 0.01$, and resulted significantly higher ($P < 0.01$).

According to the ROC curve for EAT alone, the cutoff value of 3.1 mm had the best performance in predicting MetS, that is, 100% sensitivity and 79% specificity.

DISCUSSION

This is the first study, to our knowledge, to show that EAT thickness on the free wall of the right ventricle is significantly higher in normal-weight and waist hypertensive patients with MetS than in those without MetS.

Table 4 | Multivariate logistic regression analysis evaluating the association of anthropometric data, epicardial adipose tissue, left ventricular mass index, and renal function with metabolic syndrome

	OR (95% CI)	*P*
Model 1		
Age	0.98 (0.94–1.03)	0.53
Body mass index	0.94 (0.55–1.62)	0.83
Waist	0.98 (0.88–1.09)	0.72
EAT	4.30 (2.32–7.95)	<0.01
Model 2		
Age	1.02 (0.98–1.06)	0.40
Body mass index	1.33 (0.84–2.11)	0.23
Waist	0.99 (0.90–1.08)	0.76
LVMI	1.04 (0.98–1.11)	0.22
Model 3		
Age	1.01 (0.97–1.05)	0.64
Body mass index	1.30 (0.82–2.06)	0.27
Waist	1.03 (0.93–1.13)	0.60
eGFR	0.96 (0.93–0.99)	<0.05
Model 4		
EAT	3.69 (2.10–6.50)	<0.01
LVMI	1.01 (0.93–1.09)	0.84
eGFR	0.97 (0.93–1.01)	0.10

OR refers to 1 unit variation of covariates.
CI, confidence interval; EAT, epicardial adipose tissue; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; OR, odds ratio.

Iacobellis *et al.*[16,20] reported higher EAT thickness on the right ventricular free wall in Caucasian subjects with MetS than in those without MetS, both in men (9.5 vs. 4.5 mm) and women (7.5 vs. 3.5 mm). More than 50% of subjects were obese and <50% had hypertension. EAT thickness was measured at end-systole.[16,20] Ahn *et al.*[19] reported higher EAT thickness in subjects with MetS than in those without MetS (3.5 vs. 1.6 mm, at end-diastole) in a Korean population undergoing coronary angiography. Normal weight and overweight subjects were studied and ~50% of the population had hypertension.[19] Sade *et al.*[21] observed higher EAT thickness in subjects with MetS than in those without MetS (5.2 vs. 4.4 mm, at end-diastole) in Turkish women who underwent coronary angiography. More than 40% of subjects had obesity and about 50% had hypertension.[21]

Recently, Park *et al.*[22] attempted to evaluate whether BMI could affect the link between EAT and MetS. EAT thickness was found to be significantly higher in subjects with MetS than in those without MetS (3.5 vs. 1.9 mm, at end-diastole) among patients in the nonhigh BMI group, whereas no difference was found in the high BMI group.[22] However, the nonhigh BMI group included subjects with BMI <27 kg/m^2. Thus, both subjects with normal weight and those with mild overweight were included in the nonhigh BMI group and ~65% of them had hypertension.[22]

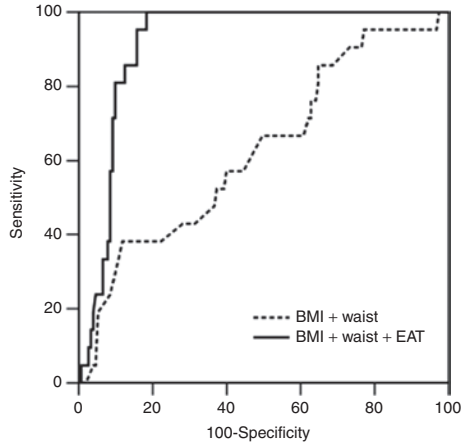

Figure 2 | Receiver operating characteristic curves of body mass index (BMI) plus waist circumference and BMI plus waist circumference plus epicardial adipose tissue (EAT), in predicting metabolic syndrome.

Chaowalit *et al.*[17] and Jeong *et al.*[18] did not find significant correlation between EAT thickness and single components of MetS. However, they did not report EAT values in patients with and without MetS, neither in the global population nor in subsets with normal weight, overweight, and obesity. Thus, our data cannot be compared with the aforesaid works.[17,18]

Globally, our data are essentially in line with the abovementioned studies.[16,19–22] However, previous reports[16,19–22] evaluated populations including selected patients, higher prevalence of overweight and obesity and lower prevalence of hypertension. Thus, our data extend previous findings to the specific setting of normal weight and waist hypertensive patients.

The relevance of EAT in normal-weight and mildly overweight subjects is reinforced by other reports[28,29] showing association between EAT and coronary artery disease in this context. An exclusion criterion of our study was known coronary artery disease and subjects were not specifically investigated about this aspect. Thus, our conclusions cannot be applied to this issue.

It could be speculated that higher EAT thickness might be implicated in the pathophysiology of MetS in normal weight and waist hypertensive subjects. Indeed, EAT produces some adipokines that have been implicated in insulin resistance.[11–14] However, it could also be speculated that, in these subjects, higher EAT thickness may be an indicator of an initial increase of global visceral adipose tissue or of a relative increase of visceral fat with respect to lean body mass. Indeed, EAT, mesenteric, and omental fat share the same embryological origin[11–14] and it has been reported higher visceral adiposity in normal weight subjects with MetS than in those without MetS.[9,10] This aspect, however, cannot be detected by BMI and waist circumference assessment, and the use of radiological techniques does not seem viable. Thus, the evaluation of EAT by echocardiography appears feasible and helpful in this setting.

This study has some limitations. First, echocardiography is less accurate than radiological techniques in evaluating EAT, although good correlation with magnetic resonance has been

reported.[15,16] Second, EAT thickness is a linear measure at a single point and does not necessarily reflect epicardial fat volume which is greater in the perivascular grooves. However, a moderate correlation between EAT thickness and epicardial fat volume has been observed.[30] In any case, EAT thickness might not reflect the regional variation of EAT, such as that present in the left atrio-ventricular groove, which has been reported to be associated with MetS together with, and similarly to, BMI.[31] It should be considered that radiological techniques are less available and more expensive than echocardiography, thus limiting their use on a large scale. On the contrary, echocardiography is far less expensive and frequently performed to study hypertensive patients, thus giving the opportunity to evaluate EAT at no extra cost. Third, HOMA index was not measured in this study. Fourth, we studied only Caucasian subjects and our data cannot be extrapolated to other ethnic groups.

The present study shows that EAT thickness is associated with MetS in normal weight and waist hypertensive patients. Its assessment, when echocardiographic examination is performed in these subjects, might help explain metabolic findings or suggest a thorough metabolic evaluation.

Disclosure: The authors declared no conflict of interest.

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