Association of epicardial adipose tissue thickness by echocardiography and hypertension

Ekokardiyografik olarak ölçülen epikardiyal yağ dokusu kalınlığı ve hipertansiyon ilişkisi

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ABSTRACT

Objectives: Epicardial adipose tissue (EAT) is a component of visceral adiposity with endocrine and paracrine effects. It is also associated with metabolic syndrome (MetS). In this study, we investigated the relationship between EAT thickness and hypertension that is a component of MetS.

Study design: Enrolled in this study were 140 hypertensive patients and 60 age- and sex-similar normotensive controls. EAT thickness was measured using 2-D echocardiography from the parasternal long- and short-axis views. EAT thicknesses were compared between patients with hypertension and controls. The effects of hypertension on EAT thickness were evaluated like other components of MetS.

Results: EAT thickness was increased in hypertensive patients compared to normotensive controls (6.3±1.7 mm *vs.* 5.3±1.6 mm; p<0.001). EAT thickness correlated with systolic and diastolic blood pressures (r=0.233, p=0.001; r=0.144, p=0.047, respectively). EAT thickness was further increased in patients with uncontrolled hypertension than in those with controlled hypertension (6.6±1.7 mm *vs.* 5.9±1.8 mm, p=0.046). When linear regression analysis was performed to assess the effect of hypertension on EAT thickness like the other components of MetS, hypertension (p=0.009, 95% CI 0.236-1.619), waist circumference (p=0.003, 95%CI 0.339-1.640), HDL-cholesterol (p=0.046, 95% CI, -0.054 - 0.001) and blood glucose levels (p=0.007, 95% CI, 0.003-0.002) were found to be independent correlates of EAT thickness.

Conclusion: EAT thickness is associated with hypertension. Hypertension could be contributing factor for the development of EAT thickness like the other components of MetS.

ÖZET

Amaç: Epikardın yağ dokusu (EYD) içorgan yağlanmasının bir parçasıdır. Endokrin ve parakrin etkilere sahip olup metabolik sendrom (MetS) ile ilişkilidir. Bu çalışmada, EYD kalınlığının MetS'nin bir parçası olan hipertansiyon ile ilişkisi araştırıldı.

Çalışma planı: Çalışmaya hipertansiyonlu 140 hasta, yaş ve cinsiyet yönünden benzer normal kan basınçlı 60 olgu kontrol grubu olarak alındı. EYD iki boyutlu ekokardiyografi ile parasternal kısa ve uzun akstan ölçüldü. EYD kalınlığı hipertansiyon ve kontrol grupları arasında karşılaştırıldı. EYD kalınlığı üzerine hipertansiyonun etkisi MetS'nin diğer bileşenleriyle değerlendirildi.

Bulgular: Epikardın yağ dokusu kalınlığı hipertansiyonlu hastalarda normal kan basınçlı kontrol grubuna göre artmıştı (6.3±1.7 mm ve 5.3±1.6 mm; p<0.001). EYD kalınlığı sistolik ve diyastolik kan basıncı ile korelasyon göstermekte idi (sırasıyla, r=0.233, p=0.001; r=0.144, p=0.047). Kontrolsüz hipertansiyonlu hastalarda EYD kalınlığı kan basıncı kontrollü olanlara göre daha fazla artmıştı (6.6±1.7 mm ve 5.9±1.8 mm, p=0.046). MetS bileşenlerini içeren çok değişkenli lineer regresyon analizinde hipertansiyon (p=0.009, %95 GA 0.236-1.619), bel çevresi (p=0.003, %95 GA, 0.339-1.640), HDL-kolesterol (p=0.046, %95 GA -0.054 - 0.001) ve kan glukoz düzeyleri (p=0.007, %95 GA 0.003-0.002) EYD kalınlığını etkileyen bağımsız faktörler olarak bulundu.

Sonuç: Epikardın yağ dokusu kalınlığı hipertansiyonla ilişkilidir. Hipertansiyon MetS'nin diğer bileşenleri gibi EYD kalınlığına katkıda bulunan bir faktör olabilir.

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Visceral adipose tissue is not only a fat deposition around internal organs. It performs endocrine and metabolic functions, representing an important source of a number of bioactive molecules that can profoundly affect energy metabolism as well as vascular, immunologic, and inflammatory responses.[1-4] Epicardial adipose tissue (EAT) is a true visceral fat deposited around the heart; its presumed physiologic functions include lipid storage and hormone, cytokine and chemokine secretion.[5,6] It has been found to be associated with metabolic syndrome (MetS).[7] Hypertension is an important risk factor for atherosclerosis and coronary artery disease.[8,9] It is also a component of MetS as akin to dyslipidemia, abdominal obesity, and insulin resistance.[10]

In this study, we investigated the relationship between the EAT thickness and hypertension, a component of MetS.

PATIENTS AND METHODS

Study population

Enrolled in this study were 140 hypertensive patients and 60 age- and sex-similar normotensive controls. Previous medical history and demographic and clinical characteristics, including smoking status, coronary artery disease, diabetes mellitus, and other systemic disease and drug treatment were noted. Hypertension was defined as a mean systolic blood pressure (BP) ≥140 mmHg or a mean diastolic BP ≥90 mmHg, or as the use of any antihypertensive drug.[11] Coronary artery disease was defined as any coronary arterial narrowing ≥ %50 with coronary angiography, history of percutaneous coronary intervention, or coronary bypass surgery. Diabetes mellitus was defined a fasting plasma glucose level ≥126 mg/dl, symptoms of hyperglycemia and causal plasma glucose level ≥200 mg/dl, plasma glucose ≥200 mg/dl at 2 hours after a 75 g oral glucose loading or glucose tolerance test, or use of any anti-diabetic drug or insulin treatment. MetS was diagnosed according to AHA/NHLBI 2005 criteria.[10] A participant had MetS if three or more of the following features were present: (i) abdominal obesity: waist circumference >102 cm in men, and >88 cm in women; (ii) plasma triglycerides: ≥150 mg/dL; or drug treatment for elevated triglycerides (iii) plasma HDL cholesterol: <40 mg/dL in men, and <50 mg/dL in women; or drug treatment for reduced HDL cholesterol; (iv) systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg, or use of antihypertensive medicine; or (v) plasma glucose ≥110 mg/dL or use of drug treatment for elevated glucose.

Abbreviations:

BMI	*Body mass index*
BP	*Blood pressure*
CRP	*C-reactive protein*
EAT	*Epicardial adipose tissue*
FFA	*Free fatty acids*
HDL	*High-density lipoprotein*
LDL	*Low-density lipoprotein*
LV	*Left ventricle*
MetS	*Metabolic syndrome*

Patients were excluded if they had severe valvular disease, heart failure, cardiomyopathy, chronic renal disease, thyroid diseases, and active infectious or inflammatory disease.

All the patients underwent physical examination. Height, weight, and body fat ratio (Tanita TBF 534, Japan) were measured during fasting. Body mass index (BMI) was calculated as body weight divided by height squared. Waist circumference was measured at the smallest circumference between the rib cage and anterior superior iliac crest in standing position and during mild expiration. Systolic and diastolic BP were measured twice after a five-minute resting period and the two values were averaged. Uncontrolled hypertension was defined if the patient had systolic BP >140 mmHg, diastolic BP >90 mmHg, despite the use of antihypertensive treatment.

Laboratory measurements

Fasting blood samples were obtained and plasma glucose, creatinine, triglyceride, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, C-reactive protein (CRP) levels were measured. LDL cholesterol was evaluated with directly homogenous enzymatic calorimetric method (Roche diagnostics, GMbH, Mann Heim, Germany) using PP moduler kits and CRP measured by immunoturbidimetric method (Roche diagnostics, GMbH, Mannheim, Germany).

Transthoracic echocardiography

All patients underwent transthoracic echocardiography in the left lateral decubitus position. Echocardiographic examinations were performed using Acuson Sequoia C-256 (Acuson Corporation, California, USA) cardiac ultrasound machine. Echocardiograms were recorded on videotapes. Left ventricle (LV) volumes and ejection fraction were measured using modified Simpson's method.[12] LV mass was calculated using the area length method as previously described,[12] and LV mass index was obtained and

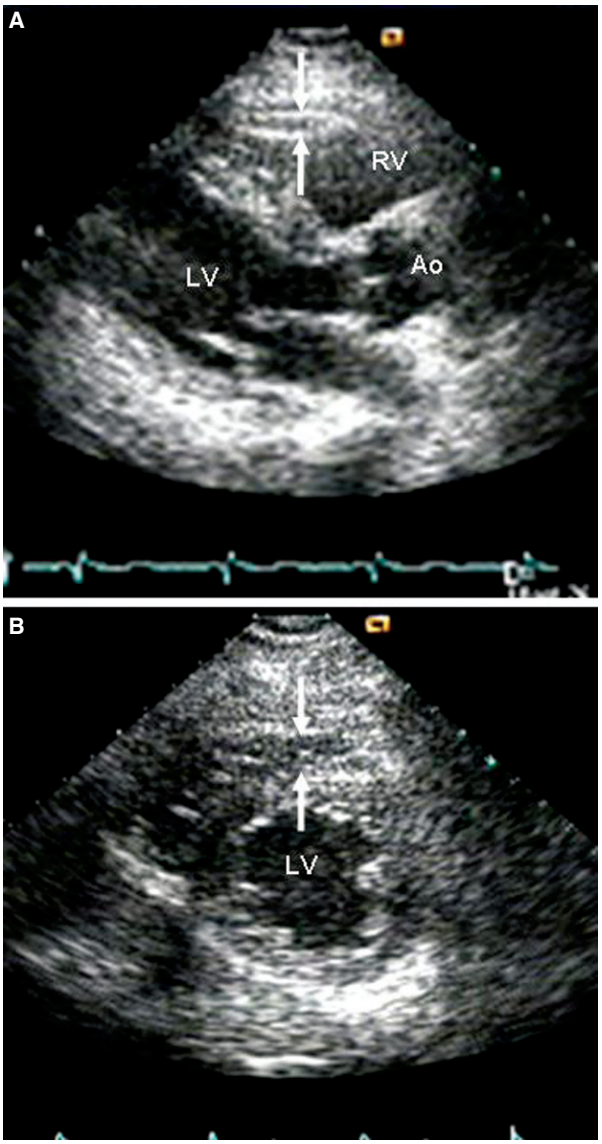

Figure 1. Epicardial adipose tissue in transthoracic 2-dimensonal echocardiography in parasternal **(A)** long and **(B)** short axis views.

corrected for body surface area. LV hypertrophy was defined as the LV mass index > 47 gr/m^2 in women and 50 gr/m^2 in men.[13]

EAT appears as an echo-free space in the pericardial layers on 2-D echocardiography. EAT thickness was measured on the free wall of right ventricle at end-diastole from the parasternal long- and short-axis views, in B mode's still-frame images, by echocardiographers blinded to clinical data (Fig. 1). Measurements from the parasternal long- and short-axis were averaged. EAT thicknesses were compared between patients with hypertension and controls. The effects of hypertension on EAT thickness were evaluated like other components of MetS.

Statistical analysis

Kolmogorow-Smirnow test was used to test the normality of distribution. Continuous variables are expressed as means±SD or median (interquartile range). Categorical variables are given as group percentages. Variables with a normal distribution were compared by independent sample t-test. Variables that were nonparametrically distributed were compared by the Mann-Whitney U-test. Correlations were established by Pearson correlation test. Prediction of independent variables related to hypertension was obtained by multiple regression model including components of MetS. To assess the reproducibility of the echocardiographic measurements, EAT thickness was measured by two independent echocardiographers in 20 randomly selected patients, and inter-observer correlation coefficient was calculated. A p value of less than 0.05 was considered statistically significant. SPSS software (Statistical Package for the Social Sciences, version 10.0, SSPS Inc, Chicago, IL, USA) was used for all statistical calculations.

The study complied with the Declaration of Helsinki, and the study protocol was approved by the local ethics committee.

RESULTS

Age, gender, BMI, waist circumference, coronary artery disease, diabetes mellitus, lipid profile, blood

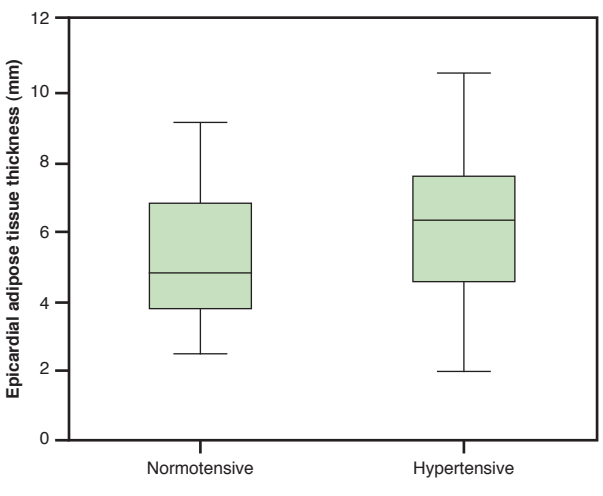

Figure 2. Comparison of epicardial adipose tissue thickness between the groups.

Table 1. Demographic, laboratory and echocardiographic characteristics of subjects by study groups

Variable	Hypertensive		Control		*p*
	(n=140)	Mean±SD	(n=60)	Mean±SD	
Demographic characteristics					
Age (years)		56.7±7.9		54.9 ± 9.6	0.156
Sex (Female / Male)	74/66		24/36		0.096
Blood pressure					
Systolic (mmHg)		141.5±21.4		123.1±12.62	**<0.001**
Diastolic (mmHg)		82.8±11.2		76.5±6.8	**<0.001**
BMI (kg/m^2)		29.3±4.2		28.1±4.1	0.066
Waist circumference (cm)		95.3±11.0		94.2±12.7	0.571
Body fat ratio (%)		34.0±8.0		33.3±7.0	0.742
Smoker (%)	41.0		41.7		0.931
CAD (%)	53.2		48.3		0.525
Diabetes mellitus (%)	24.5		18.3		0.343
Metabolic syndrome (%)	64.3		36.7		**<0.001**
Laboratory findings					
Fasting plasma glucose (mg/dL)		112.2±36.0		104.7±35.7	0.202
Total-cholesterol (mg/dL)		198.2±36.8		184.2±43.8	0.081
LDL-cholesterol (mg/dL)		119.2±28.0		118.2±34.7	0.837
HDL-cholesterol(mg/dL)		45.6±11.8		44.3±10.8	0.521
Triglyceride (mg/dL)	133.0 (97-213)		138 (105-178)		0.708
CRP (mg/L)	3.6 (1.7-6.4)		3.4 (1.5-6.7)		0.948
Creatinine (mg/dL)		0.90±0.21		0.92±0.21	0.545
Two-dimensional echocardiography findings					
Ejection fraction (%)		50.3±7.6		51.6±7.2	0.290
LV end-diastolic volume (mL)		94.5±25.2		90.1±22.7	0.243
LV end-systolic volume (mL)		44.5±15.1		47.5±19.2	0.239
Stroke volume (mL)		46.7±9.8		46.7±9.2	0.993
IVS thickness (cm)		1.19±0.15		1.12±0.16	0.002
Posterior wall thickness (cm)		1.13±0.17		1.09±0.15	0.095
LV mass (g)		111.5±32.3		102.5±25.7	0.041
LV mass index (g/m^2)		59.8±18.0		55.6±12.8	0.073
EAT thickness					
PSLX (mm)		6.4±1.8		5.4±1.7	**0.001**
PSSX (mm)		6.2±1.8		5.2±1.7	**0.001**
Average (mm)		6.3±1.7		5.3±1.6	**<0.001**
Drug treatment					
Statins (%)	25.2		31.0		0.401
Antihypertensive drugs					
Beta blockers (%)			44.3		
Ca channel blockers (%)			13.5		
ACE inhibitors (%)			25.5		
AT II receptor blockers (%)			14.5		
Diuretics (%)			25.5		
Combination (%)			38.0		

ACE: Angiotensin converting enzyme inhibitors; AT: Angiotensin; BMI: Body mass index; Ca: Calcium; CAD: Coronary artery disease; CRP: C-reactive protein; EAT: Epicardial adipose tissue thickness; HDL: High-density lipoprotein; IVS: Interventricular septum; LDL: Low-density lipoprotein; LV: Left ventricle; PSLX: Parasternal long axis; PSSX: Parasternal short axis.

fasting glucose, and CRP levels were similar in the hypertensive and control groups. MetS was higher in hypertensive group than normotensive group. LV mass was increased in patients with hypertension. Patient characteristics and laboratory and echocardiographic findings are presented in Table 1.

EAT thickness was increased in hypertensive patients compared to normotensive controls (6.3±1.7 mm *vs.* 5.3±1.6 mm; p<0.001) (Table 1, Fig. 2). EAT thickness correlated with systolic and diastolic BPs (r=0.233, p=0.001; r=0.144, p=0.047, respectively), LV mass (r=0.419, p<0.001), and mass index (r=0.346,

Table 2. Demographic, clinic, laboratory and echocardiographic characteristics of subjects according to metabolic syndrome

	Metabolic syndrome (+)		Metabolic syndrome (–)		*p*
	(n=112)	Mean±SD	(n=88)	Mean±SD	
Demographic characteristics					
Age (Years)		56.9±8.5		55.1±8.3	0.137
Sex (Female / Male)	48/64		50/38		0.069
BMI (kg/m^2)		30.1±3.7		27.4±4.3	**<0.001**
Waist circumference (cm)		99.2±8.7		88.8±11.7	**<0.001**
Hypertension (%)	80.4		56.8		**<0.001**
CAD (%)	62.5		37.9		**0.001**
Diabetes mellitus (%)	36.6		4.6		**<0.001**
Smoker (%)	40.2		42.5		0.738
Laboratory findings					
Fasting plasma glucose (mg/dL)		119.9±41.9		95.0±15.1	**<0.001**
LDL-cholesterol (mg/dL)		117.6±30.2		120.7±29.9	0.486
HDL-cholesterol (mg/dL)		41.6±9.5		49.9±12.1	**<0.001**
Triglyceride (mg/dL)		196.8±116.8		112.3±64.0	**<0.001**
Creatinine (mg/dL)		0.94±0.20		0.88±0.21	0.051
CRP (mg/L)	3.9 (1.9-6.7)		3.1 (1.4-6.1)		0.193
Two-dimensional echocardiography findings					
Ejection fraction (%)		48.8±8.1		53.2±5.8	**<0.001**
LV mass (g)		116.0±29.1		99.6±30.5	**<0.001**
LV mass index (g/m^2)		61.1±15.9		55.2±17.1	0.016
EAT thickness					
PSLX (mm)		6.6±1.8		5.4±1.6	**<0.001**
PSSX (mm)		6.5±1.8		5.2±1.6	**<0.001**
Average (mm)		6.6±1.7		5.3±1.6	**<0.001**
Drug treatment					
Statins (%)	33.0		19.0		0.030
Antihypertensive drugs					
Beta blockers (%)	49.1		38.1		0.127
Ca channel blockers (%)	18.2		8.3		0.079
ACE inhibitors (%)	32.7		17.9		0.020
AT II receptor blockers (%)	21.8		6.0		0.020
Diuretics (%)	35.8		14.3		**0.001**
Combination (%)	64.4		44.4		0.028

ACE: Angiotensin converting enzyme inhibitors; AT: Angiotensin; BMI: Body mass index; Ca: Calcium; CAD: Coronary artery disease; CRP: C-reactive protein; EAT: Epicardial adipose tissue thickness; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LV: Left ventricle; PSLX: Parasternal long axis; PSSX: Parasternal short axis.

p<0.001). EAT thickness was higher in patients with LV hypertrophy than those without LV hypertrophy (6.6±1.7 mm *vs.* 5.2±1.6 mm, respectively p<0.001). There were 88 patients with uncontrolled hypertension in hypertension group. Interestingly, EAT thickness was further increased in patients with uncontrolled hypertension than in those with controlled hypertension (6.6±1.7 mm *vs.* 5.9±1.8 mm, p=0.046).

In addition, EAT thickness also correlated with waist circumference (r=0.316, p<0.001), fasting glucose (r=0.244, p=0.001), triglyceride (r=0.176, p=0.021), HDL cholesterol (r= -0.217, p=0.008), creatinine (r=0.273, p<0.001), and serum CRP levels (r=0.280, p= 0.001).

Of the 200 subjects, 112 had MetS. Patients' characteristics which correspond to MetS are presented in Table 2. In patients with MetS, EAT thickness was significantly higher than those without MetS (Table 2). When the linear regression analysis was performed to assess the effect of hypertension on EAT thickness like the other components of MetS, hypertension, waist circumference, HDL-cholesterol, and

Table 3. Multivariate linear regression analysis according to metabolic syndrome components on EAT thickness

MetS components	β	(%95 CI)	*p*
Waist circumference (cm)	0.247	0.013-0.069	0.004
Hypertension	0.236	0.339-1.640	0.003
Fasting plasma glucose	0.219	0.003-0.019	0.007
HDL-cholesterol	-0.170	-0.054 - -0.001	0.046
Triglyceride	-0.028	-0.003-0.002	0.753

B: Beta; CI: Confidence interval; HDL: High-density lipoprotein; MetS: Metabolic syndrome.

blood glucose levels were found to be independent correlates of EAT thickness (Table 3).

Correlation coefficients of inter-observer and intra-observer measurements of EAT thickness were 0.96 and 0.94, respectively.

DISCUSSION

The current study shows that there is a relationship between hypertension and EAT thickness. Hypertension could be a contributing factor for the development of EAT thickness and other components of MetS.

In humans, free fatty acids (FFA) are important energy supplements for the myocardium,[14] and their principal sources are systemic fat stores.[1] EAT stores triglyceride to supply FFA for myocardial energy generation, and also produces adipokines.[5] In animal models, the rate of FFA synthesis, release, and breakdown in response to catecholamines by the rather small amount of EAT was markedly higher as compared with other adipose tissues.[15] Lipogenesis and lipolysis in the epicardial fat of guinea-pigs were almost two-fold increased as compared with other body fat depots.[15,16] The reduced antilipolytic effect of insulin in visceral adipose tissue and the increased activity of β-adrenergic receptors, especially β3 receptors, were postulated to be responsible for the high lipolysis rate in EAT.[17] Marchington et al.[15,16] proposed that EAT serves to capture and store intravascular FFA to protect cardiomyocytes from exposure to excessive coronary arterial FFA concentrations during increased energy intake and, at other times, to release FFA as an immediate ATP source for the myocardium during periods of need. FFA released from hypertrophied adipocytes in EAT can diffuse directly into the myocardium, together with myocardial uptake of plasma FFA, exacerbating myocardial steatosis and lipotoxicity.[18] Structurally and functionally, the consequences of intracardiac lipotoxicity and extracardiac adiposity include increased heart weight that compromises the mechanical pumping effort, and impaired myocardial energy metabolism.[5,19] Sironi et al.[20] showed that higher blood pressure correlated with EAT, which was measured by magnetic resonance imaging (MRI). The authors speculated that EAT was highly lipolytic and could be related to alterations in energy substrate metabolism contributing to LV remodeling and cardiac hypertrophy.

EAT thickness measurement by echocardiography has been first validated by Iacobellis et al., who reported a good correlation between MRI and echocardiographic measurements of epicardial fat.[21] An echocardiographic study found a significant correlation between epicardial fat thickness in the parasternal long- and short-axis views and LV mass.[22] In the present study, we found significant correlations between EAT thickness and both LV mass and mass index, and EAT thickness was increased in patients with LV hypertrophy. Autopsy series support our data: Sons et al.[23] and Corradi et al.[24] reported that average amount of EAT is about 20% of total heart weight or total LV weight. Furthermore, autopsy data have shown significant correlations between epicardial fat and both total heart weight and ventricular weight.[23,25] LV hypertrophy is the result of an interaction between chronic hemodynamic overload and non-hemodynamic factors (renin angiotensin system, nitric oxide, etc.). Long term pressure overload causes myocyte cellular hyperplasia and capillary proliferation in an attempt to increase the thickness of the ventricular wall and, consequently, to decrease the magnitude of systolic and diastolic wall stress generated

by the elevation of ventricular systolic and end-diastolic pressures.[26,27] As a result, hypertension leads to hemodynamic overload, inducing LV hypertrophy which, in turn, increases myocardial energy requirement. Therefore, we thought as EAT provides energy supplement to myocardium via FFA, EAT thickness could be increased in hypertension as an adaptation to incremental needs of the hypertrophied LV, although this seems to be a maladaptive process. Interestingly, we found that EAT thickness was greater in patients with uncontrolled hypertension than in those with controlled hypertension. Uncontrolled hypertension causes more LV hypertrophy, and EAT could increase as an adaptation process for energy supplementation to the myocardium.

We found that EAT thickness correlates with systolic and diastolic BP, as found in previous studies.[20,28] Natale et al.[28] found a positive correlation between EAT, systolic BP and duration of hypertension. Subjects with EAT >7 mm had higher systolic and diastolic BP and LV mass index, compared with those with EAT ≤7 mm ($p<0.001$). Another study which measured EAT thickness using MRI showed a correlation between high blood pressure and EAT.[20] In the different study EAT was found to be related to altered BP responses to exercise stress testing.[29]

In an echocardiographic study, Iacobellis et al.[7] showed that EAT was associated with MetS and components of MetS. Our study is compatible with this study. We found that EAT was thicker in patients with MetS than in patients without MetS. When investigating the components of MetS, EAT thickness was independently associated with hypertension, waist circumference, blood glucose, and HDL-cholesterol levels.

Limitations

Hypertension is a component of MetS and EAT thickness is associated with MetS, therefore associations between EAT thickness and hypertension did not exclude effects of MetS. Only patients without MetS could be enrolled in our study in order to investigate the association between EAT and hypertension.

In conclusion, we know that EAT is not a simple fat deposit and has a complex function. Multiple factors, especially the components of MetS, may influence EAT thickness. Our study showed that hypertension is associated with EAT thickness. We thought that hypertension could be a contributing factor for the development of EAT thickness, like the other components of MetS. Increased LV mass as a result of hypertension may be a responsible mechanism for the relationship between hypertension and EAT thickness, which enhances myocardium's energy demand. But the mechanisms of increased EAT thickness in hypertension should be investigated in larger studies.

Conflict-of-interest issues regarding the authorship or article: None declared

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